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Forced Vital Capacity and Six-Minute Walk Test as Indicators of Interstitial Lung Disease Extent on High-Resolution Computed Tomography in Systemic Sclerosis

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Running head: FVC and 6MWT in SSc-ILD

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WHAT IS NEW / WHAT IS IMPORTANT

- Six-minute walk test distance alone is insufficient to identify extensive interstitial lung disease in systemic sclerosis.
- Exertional oxygen desaturation (≥4%) and forced vital capacity below 70% predicted are strongly associated with extensive pulmonary involvement on high-resolution computed tomography.
- FVC alone provides discriminatory performance essentially comparable to the combined FVC–6MWT distance model, while the 6MWT retains complementary value for assessing functional capacity and exertional desaturation.

ABSTRACT

Introduction. Interstitial lung disease (ILD) is a leading cause of morbidity and mortality in systemic sclerosis (SSc). High-resolution computed tomography (HRCT) is the gold standard for assessing ILD extent but is limited by cost, availability, and radiation exposure. Practical functional tools are thus needed to identify extensive ILD in routine practice.

Methods. This cross-sectional study enrolled adult patients with SSc-associated ILD at a tertiary referral hospital in Jakarta, Indonesia. All participants underwent spirometry and the six-minute walk test (6MWT). Forced vital capacity (FVC), 6MWT distance, and exertional oxygen desaturation were evaluated. ILD extent on HRCT was classified as non-extensive (<20%) or extensive (≥20%). Associations were analyzed using bivariate analysis, receiver operating characteristic (ROC) curves, and multivariable Poisson regression with robust standard errors.

Results. A total of 83 patients were included; 21 (25%) had extensive ILD. Six-minute walk test distance did not differ significantly between groups (p = 0.492; AUC 0.550). Exertional oxygen desaturation ≥4% and FVC <70% predicted were each significantly associated with extensive ILD. FVC alone achieved an AUC of 0.795, whereas adding 6MWT distance resulted in only a marginal

improvement in discrimination (AUC 0.799; ΔAUC 0.005), with adequate calibration and stable internal validation.

Conclusion. FVC alone may serve as a practical functional indicator of ILD extent, particularly where HRCT access is limited. Routine addition of 6MWT distance is not justified solely for estimating ILD extent, although the 6MWT remains valuable for assessing functional capacity and exertional desaturation.

Key words: systemic sclerosis; interstitial lung disease; forced vital capacity; six-minute walk test; high-resolution computed tomography

INTRODUCTION

Interstitial lung disease (ILD) comprises a heterogeneous group of disorders characterized by involvement of the alveolar walls and supporting pulmonary structures, commonly presenting with progressive exertional dyspnea and chronic non-productive cough [1]. More than 200 distinct disease entities fall within the ILD spectrum, encompassing both primary pulmonary disorders and secondary manifestations of systemic diseases, particularly systemic connective tissue diseases [1,2]. Systemic sclerosis (SSc) is among the connective tissue diseases most frequently complicated by ILD, with pulmonary involvement occurring in approximately 40–60% of patients. ILD represents the leading cause of disease-related mortality in this population [3]. Data from the European Scleroderma Trials and Research (EUSTAR) registry indicate that the prevalence of SSc-associated ILD in Asia reached 60.9% between 2009 and 2020, exceeding rates reported in Western cohorts [4]. A systematic review and meta-analysis of East Asian cohorts similarly reported ILD in up to 56% of patients with SSc, with longer disease duration and diffuse cutaneous

subtype identified as key risk factors [5]. Furthermore, registry data indicate that pulmonary fibrosis has been reported to account for approximately 35% of SSc-related deaths [6,7].

High-resolution computed tomography (HRCT) is the gold standard for assessing pulmonary involvement in SSc-ILD. Based on HRCT findings, ILD can be classified as extensive (≥20% lung involvement) or non-extensive, with extensive disease being associated with a poorer prognosis and increased mortality risk [8]. A recent meta-analysis reported that 34.3% of patients with SSc-ILD have extensive disease [9]. Despite its diagnostic value, accurate characterization of SSc-ILD extent on HRCT remains challenging, and several diagnostic approaches have been proposed to improve identification of extensive disease in clinical practice [10]. Although HRCT is essential for accurate disease assessment, its routine use is limited by cost, availability, and radiation exposure, particularly in resource-limited settings.

Current guidelines recommend screening for SSc-ILD using pulmonary function tests in combination with HRCT [11]. However, spirometric parameters such as forced vital capacity (FVC) and diffusing capacity for carbon monoxide may fail to detect extensive disease as standalone screening tools and can be influenced by disease-related factors in SSc [12–15]. As a result, there remains a need for practical functional tools that can improve identification of extensive ILD. The six-minute walk test (6MWT) is a simple, widely available functional assessment that evaluates the integrated cardiopulmonary response during physical activity. Parameters derived from the 6MWT, including walking distance and exertional oxygen desaturation, have been shown to correlate with pulmonary function and gas exchange impairment in connective tissue disease-associated ILD [12]. We hypothesized that combining spirometric and exercise-derived parameters would improve discrimination of ILD extent compared with either modality alone. This study therefore aimed to evaluate whether the combined use of spirometry

and 6MWT parameters could improve identification of extensive ILD on HRCT in patients with SSc.

MATERIALS AND METHODS

Study Design and Setting

This was an observational analytic study with a cross-sectional design, reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The study was conducted at the Pulmonology and Rheumatology outpatient clinics and internal medicine inpatient wards of a tertiary national referral hospital in Jakarta, Indonesia, between June and July 2025. No additional interventions were performed beyond routine clinical care.

Study Population

The target population consisted of adult patients diagnosed with SSc with evidence of ILD. Diagnosis of systemic sclerosis was confirmed according to the 2013 ACR/EULAR classification criteria [31], based on medical record review by the attending rheumatologist. Eligible participants were consecutively enrolled from patients receiving outpatient or inpatient care during the study period. Inclusion criteria were: age 18–60 years, confirmed diagnosis of systemic sclerosis, willingness to participate, and availability of chest HRCT performed within three months before or after study enrollment. HRCT was not performed at a standardized interval for all patients but rather as part of routine clinical care, typically prompted by respiratory symptoms or clinical suspicion of pulmonary involvement; this indication-based ascertainment may have enriched the cohort for patients with a higher pre-test likelihood of ILD and is addressed further in the Discussion. Exclusion criteria included incomplete medical records, pulmonary arterial hypertension, heart failure, acute or chronic respiratory infection, chronic obstructive pulmonary

disease, overlapping autoimmune diseases, significant mobility limitation precluding ambulation, and inability to perform spirometry or the 6MWT.

Clinical and Functional Assessment

All participants underwent standardized clinical evaluation, including medical interview and physical examination. Disease severity was assessed using the modified Rodnan Skin Score (mRSS), evaluated at the time of study enrollment by a team comprising a rheumatologist and a pulmonologist. Smoking history was classified according to the Brinkman Index (cigarettes smoked per day × duration of smoking in years); patients were categorized as non-smokers or moderate smokers (index 200–599). Erythrocyte sedimentation rate (ESR; laboratory reference range 0–15 mm/h) and C-reactive protein (CRP, quantitative assay; laboratory reference range <5.0 mg/L) were measured from venous blood samples collected at enrollment, on the same study visit as the functional assessments described below, and processed at the hospital's central clinical laboratory. Pulmonary function testing was performed using spirometry (Cosmed Pony FX®, Cosmed, Rome, Italy) in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [29]. Measurements were performed by a trained nurse in the Division of Respirology, Department of Internal Medicine, under the supervision of a respirology consultant, on the same study visit as clinical evaluation. Forced vital capacity (FVC) was expressed as a percentage of the predicted value. Functional exercise capacity was assessed using the six-minute walk test, conducted along a 15-meter corridor in accordance with American Thoracic Society (ATS) guidelines [30], by a physiatrist (rehabilitation medicine consultant with cardiorespiratory subspecialty training) from the Department of Physical Medicine and Rehabilitation, on the same study visit as spirometry. Walking distance was recorded in meters, and peripheral oxygen saturation (SpO_2) was continuously monitored before and after the test

using a pulse oximeter (Elitech®, Elitech Group, Puteaux, France). Exertional oxygen desaturation was defined as a decline in SpO_2 of ≥4% from baseline, a threshold widely used as a clinically meaningful marker of impaired gas exchange in interstitial lung disease [22,26].

HRCT Assessment and ILD Classification

Chest HRCT was acquired using 128-detector-row multidetector CT scanners (Philips Ingenuity CT and Philips Incisive CT, Philips Healthcare, Best, the Netherlands), obtained within the predefined three-month window. Images were reviewed by two experienced radiologists blinded to the functional test results and to each other's assessments. Inter-rater agreement was evaluated using Cohen's kappa coefficient; discrepancies in interpretation were resolved by consensus discussion. The extent of ILD was quantified as the percentage of lung volume affected by interstitial disease using 3D Slicer software (slicer.org), following the visual scoring approach described by Goh et al. [8], and classified as non-extensive (<20% lung involvement) or extensive (≥20% lung involvement), which served as the primary reference standard for analysis.

Statistical Analysis

Data analysis was performed using STATA software (StataCorp, College Station, TX, USA). Continuous variables are presented as mean with standard deviation (SD) for normally distributed data, or as median with interquartile range (IQR) for non-normally distributed data. Categorical variables are expressed as frequencies and proportions. Comparisons between the extensive and non-extensive ILD groups were performed using the unpaired t-test or Mann–Whitney U test for continuous variables, and the chi-square test for categorical variables or Fisher's exact test when expected cell counts were below 5. Associations were expressed as prevalence ratios (PR) with 95% confidence intervals (CI). Receiver operating characteristic (ROC) curve

analysis was used to evaluate the discriminatory performance of functional parameters and to determine optimal cutoff values. Age, disease duration, and mRSS were selected a priori as candidate confounders based on their plausible clinical association with both functional impairment and ILD severity; each was retained in the final model if adjustment changed the crude PR by ≥10% (ΔPR), consistent with a change-in-estimate approach to confounder selection. Multivariable analysis was conducted to assess independent associations after adjustment for these potential confounders, using Poisson regression with robust standard errors to estimate adjusted PRs; this approach was used in place of conventional logistic regression because oxygen desaturation ≥4% occurred exclusively among patients with extensive ILD, producing quasi-complete separation that precludes stable maximum-likelihood estimation. Statistical significance was defined as a two-tailed p-value of <0.05. Internal validation was performed using bootstrap resampling with 1,000 iterations to evaluate model stability and correct for optimism bias. Reporting of diagnostic accuracy analyses followed the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines.

Ethical Considerations

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (Approval No. KET-205/UN2.F1/ETIK/PPM.00.02/2025). All participants received a full explanation of the study objectives and procedures and provided written informed consent prior to enrollment.

RESULTS

Patient Characteristics

A total of 83 adult patients with SSc-ILD fulfilled the inclusion criteria and were included in the final analysis. Based on HRCT, 21 patients (25%) were classified as having extensive ILD and 62 patients (75%) as non-extensive ILD. The mean age was 41.19 ± 10.84 years and did not

differ significantly between groups (Table 1). Most participants were female (94%), and all patients with extensive ILD were women. Diffuse cutaneous SSc was the predominant subtype in both groups. Patients with extensive ILD tended to have longer disease duration (median 70 vs 28 months) and lower mean FVC (47.0 ± 13.6 vs 64.7 ± 15.2% predicted) compared with those with non-extensive ILD. Other demographic and clinical characteristics are presented in Table 1, and functional, laboratory, and treatment characteristics are presented in Table 2.

Association Between 6MWT Distance and ILD Extent

The median 6MWT distance was 330 m (IQR 281–392) in patients with extensive ILD and 349 m (IQR 307–390) in those with non-extensive ILD (Table 2). ROC analysis demonstrated poor discriminatory performance of 6MWT distance alone for differentiating extensive from non-extensive ILD, with an AUC of 0.550. The optimal cutoff was 338.35 m; however, this threshold did not significantly discriminate between ILD extent groups (PR 1.579, 95% CI 0.743–3.353; p = 0.311, Fisher's exact test) (Table 3).

Exertional Oxygen Desaturation and ILD Extent

Exertional oxygen desaturation of ≥4% during the 6MWT was observed in three patients (4%), all of whom were classified in the extensive ILD group; no cases were observed in the non-extensive ILD group (Table 3). A significant association was found between desaturation ≥4% and extensive ILD (PR 4.444, 95% CI 2.95–6.69; p = 0.015, Fisher's exact test), indicating a significantly higher probability of extensive ILD in patients with exertional desaturation.

Forced Vital Capacity and ILD Extent

Mean FVC (% predicted) was significantly lower in patients with extensive ILD compared with those with non-extensive ILD (47.0 ± 13.6 vs 64.7 ± 15.2%; mean difference −17.7, 95% CI −24.5 to −10.9; p = 0.001) (Table 2).

No patient with FVC ≥70% predicted had extensive ILD. FVC <70% predicted was significantly associated with extensive ILD (PR 1.553, 95% CI 1.284–1.877; p < 0.001) (Table 3).

Analysis of Potential Confounders

Potential confounding variables — including age, sex, smoking history, modified Rodnan Skin Score (mRSS), and disease duration — were evaluated as part of the demographic and clinical comparison (Table 1). No statistically significant differences were observed between groups for any of these variables (all p ≥0.32), indicating that they did not materially influence the observed associations.

Multivariable Analysis

In multivariable analysis adjusted for age, disease duration, and mRSS (Table 4), 6MWT distance was not independently associated with extensive ILD. FVC (% predicted) remained a consistent and significant predictor across all adjusted models, with each 1% increase in FVC associated with a 5% reduction in the prevalence of extensive ILD (adjusted PR 0.948, 95% CI 0.931–0.965). Oxygen desaturation ≥4% remained strongly and independently associated with extensive ILD after adjustment (adjusted PR 4.33, 95% CI 2.53–7.43), with no evidence of confounding by age, disease duration, or mRSS (ΔPR <10% at each step).

Diagnostic Performance of Combined Functional Models

ROC analysis was used to compare the discriminatory performance of combined functional models with that of individual parameters. Among categorical models, the three-variable model

(AUC 0.759) outperformed the two-variable model (AUC 0.724), but showed poorer calibration and instability on internal validation. Continuous-variable models demonstrated better overall performance. FVC alone, modeled continuously, achieved an AUC of 0.795. The two-variable continuous model incorporating FVC and 6MWT distance achieved the best balance of discrimination and stability, with an AUC of 0.799 (apparent AUC 0.800), representing only a marginal improvement over FVC alone (ΔAUC 0.005). The final model was: logit(P) = 3.093 − 0.0853 × FVC(%) + 0.0018 × 6MWT distance(m), where P is the predicted probability of extensive ILD. On bootstrap internal validation (1,000 iterations), the optimism-corrected AUC was 0.785, with a calibration slope of 0.93 and a non-significant Hosmer-Lemeshow test ($\chi^2 = 1.88$, df = 3, p = 0.599), indicating good calibration and acceptable, though not perfect, internal validity.

DISCUSSION

This study demonstrates that functional parameters derived from spirometry and the six-minute walk test show differing abilities to reflect the extent of ILD in patients with SSc. While 6MWT distance alone was not significantly associated with ILD extent, exertional oxygen desaturation and reduced FVC were strongly associated with extensive pulmonary involvement. Importantly, combining functional parameters improved model discrimination; however, simpler models with fewer variables demonstrated better overall stability and performance.

The absence of a significant association between 6MWT distance and ILD extent underscores the limitations of walking distance as a surrogate for structural lung disease in SSc. Although reduced walking distance reflects impaired global functional capacity, it is influenced by multiple extra-pulmonary factors commonly present in SSc, including musculoskeletal involvement, joint pain, Raynaud phenomenon, peripheral vascular disease, and physical deconditioning [8,16,17]. Previous studies have similarly reported weak correlations between

6MWT distance and radiological extent of ILD, indicating that walking distance alone does not reliably reflect parenchymal lung involvement [16,19,20].

In contrast, exertional oxygen desaturation emerged as a sensitive functional indicator of extensive ILD. Exercise-induced desaturation reflects impaired gas exchange caused by thickening of the alveolar–capillary membrane and ventilation–perfusion mismatch — hallmark features of advanced interstitial fibrosis [16,17]. While resting oxygen saturation may remain preserved, the increased oxygen demand during physical activity unmasks diffusion limitation. Consistent with previous reports, desaturation of ≥4% during the 6MWT has been shown to correlate with reduced FVC, lower diffusing capacity for carbon monoxide (DLCO), greater extent of fibrosis on HRCT, and worse clinical outcomes [17,20–22].

Notably, all three patients with desaturation ≥4% belonged to the extensive-ILD group, producing quasi-complete separation that precluded stable estimation by conventional logistic regression. Adjusted prevalence ratios were therefore estimated using Poisson regression with robust standard errors, and the association remained statistically significant after adjustment for age, disease duration, and mRSS. However, this association is derived from only three events. The magnitude of the prevalence ratio should therefore be interpreted with caution, as estimates based on such sparse data are inherently imprecise and can be strongly influenced by chance findings, even when the associated confidence interval excludes the null. The very low event rate further limits the precision of this estimate and warrants replication in larger cohorts before exertional desaturation is used in isolation for clinical decision-making.

Forced vital capacity remains a cornerstone of functional assessment in SSc-ILD. Reduced FVC reflects ventilatory restriction resulting from diffuse interstitial fibrosis and loss of lung compliance, and has been consistently associated with greater disease extent and poorer prognosis

[19,23,24]. It should be noted, however, that musculoskeletal involvement — a common extra-pulmonary manifestation of SSc — may also contribute to restrictive ventilatory impairment, and therefore FVC should be interpreted in clinical context rather than as an isolated metric. Several longitudinal studies have demonstrated that baseline FVC <70% predicted or a decline of ≥10% over time predicts ILD progression and increased mortality in patients with SSc [12,19,24,25].

A key finding of this study was the limited incremental value of adding exercise-derived parameters to FVC. Although FVC, 6MWT distance, and exertional desaturation represent distinct physiological domains, increasing the number of predictors did not meaningfully improve model performance. The two-variable continuous model (FVC and 6MWT distance) demonstrated the best balance of discrimination and stability, underscoring the value of parsimony in clinical prediction. FVC alone achieved discrimination essentially equivalent to that of the combined model (AUC 0.795 vs 0.799–0.800). Moreover, 6MWT distance was not an independent predictor in the multivariable analysis. From a practical clinical standpoint, routine addition of 6MWT distance is therefore not justified solely for estimating ILD extent. FVC alone may be sufficient for this specific purpose, particularly in resource-limited settings. Nevertheless, the 6MWT retains complementary value for assessing functional capacity and exertional desaturation. The inferior stability of the three-variable model likely reflects the very low event rate for oxygen desaturation in this cohort, which limited its contribution to a regression model with bootstrap resampling [8,19,25,26].

It is also noteworthy that HRCT patterns differed between groups, with UIP being more prevalent in extensive ILD (57% vs 32%). The extent to which HRCT pattern independently influences functional impairment — and whether it acts as a confounder in the association between functional parameters and ILD extent — warrants further investigation.

From a clinical perspective, these findings carry particular relevance for healthcare settings with limited access to HRCT. Spirometry and the 6MWT are inexpensive, widely available, and repeatable tools that can support risk stratification and guide decisions regarding closer monitoring, referral for advanced imaging, or intensification of therapy. This is especially pertinent in resource-limited settings across Asia, where ILD affects up to 56% of patients with SSc [5] but access to high-quality HRCT may be inconsistent. This approach aligns with current expert recommendations that advocate for the integration of radiological and physiological assessments in SSc-ILD management [7,20,28].

Several limitations should be acknowledged. The cross-sectional design precludes assessment of causality and disease progression over time. The single-center setting and modest sample size may limit external generalizability. With 21 extensive-ILD events and two predictors in the final model (approximately 10.5 events per variable), the prediction model is at the lower bound of conventional adequacy. This increases the risk of overfitting, despite the small optimism observed on bootstrap validation (apparent AUC 0.800 versus optimism-corrected AUC 0.785; calibration slope 0.93). External validation in larger, independent cohorts is therefore needed before clinical implementation.

FVC was expressed as percentage of predicted value using local reference equations rather than Global Lung Function Initiative (GLI) z-scores, which were not available for this cohort. Z-scores may provide more precise, age- and height-adjusted estimates of restriction. Diffusing capacity for carbon monoxide (DLCO) was not performed in this cohort, and serum biomarkers were not measured. Both may have provided additional insight into gas exchange impairment and disease activity, and their absence should be considered when interpreting the functional findings

reported here. Data on glucocorticoid and biologic agent use were also not collected and could not be accounted for as potential confounders or effect modifiers.

Participants were recruited from a tertiary referral center among patients already known to have SSc-ILD, and HRCT was obtained as clinically indicated rather than at a standardized interval. This may have selected for patients with a higher pre-test likelihood of pulmonary involvement. This indication-based selection may also explain the low frequency of anti-centromere antibody positivity observed in this cohort (3.6% overall) relative to unselected SSc populations, in which anti-centromere positivity is typically more common and is associated with a lower risk of ILD. These findings therefore apply to risk stratification of ILD extent within an already HRCT-referred population, rather than to screening of all SSc patients for ILD.

Patients with extensive ILD had numerically longer disease duration than those with non-extensive ILD (median 70 versus 28 months), although this difference did not reach statistical significance ($p = 0.423$). Given the modest sample size, this may represent a clinically relevant trend rather than true equivalence between groups, and should be interpreted with caution. Prospective multicenter studies with larger samples and longer follow-up are needed to address these limitations.

CONCLUSION

FVC alone provides discrimination for extensive ILD that is essentially comparable to a combined model incorporating 6MWT distance, and may serve as a practical, low-cost tool for risk stratification where HRCT access is limited; the 6MWT retains complementary value for assessing functional capacity and exertional desaturation rather than for estimating ILD extent per se. These findings are most applicable to patients with established SSc-ILD undergoing HRCT evaluation,

rather than to screening of the general systemic sclerosis population. Prospective multicenter studies are warranted to validate these findings and determine their prognostic value in SSc-ILD.

Introducere. *Boala pulmonară interstițială (BPI) reprezintă una dintre principalele cauze de morbiditate și mortalitate la pacienții cu scleroză sistemică (SSc). Tomografia computerizată de înaltă rezoluție (HRCT) reprezintă standardul de referință pentru evaluarea extensiei BPI, însă utilizarea sa este limitată de costuri, disponibilitate și expunerea la radiații. Prin urmare, sunt necesare instrumente funcționale practice pentru identificarea formelor extinse de BPI în practica curentă.*

Metode. *Acest studiu transversal a inclus pacienți adulți cu BPI asociată sclerozei sistemice, evaluați într-un spital terțiar de referință din Jakarta, Indonezia. Toți participanții au efectuat spirometrie și testul de mers de 6 minute (6MWT). Au fost evaluate capacitatea vitală forțată (FVC), distanța parcursă la 6MWT și desaturarea la efort. Extensia BPI la HRCT a fost clasificată ca non-extinsă (<20%) sau extinsă (≥20%). Asocierile au fost analizate prin analiză bivariată, curbe ROC și regresie Poisson multivariată cu erori standard robuste.*

Rezultate. *Au fost incluși 83 de pacienți, dintre care 21 (25%) prezentau BPI extinsă. Distanța parcursă la testul de mers de 6 minute nu a diferit semnificativ între grupuri (p = 0,492; AUC 0,550). Desaturarea la efort ≥4% și FVC <70% din valoarea prezisă au fost fiecare asociate semnificativ cu prezența unei BPI extinse. FVC utilizată individual a avut o AUC de 0,795, iar adăugarea distanței la 6MWT a determinat doar o îmbunătățire marginală a capacității de discriminare (AUC 0,799; ΔAUC 0,005), cu calibrare adecvată și rezultate stabile la validarea internă.*

Concluzii. *FVC utilizată individual poate reprezenta un indicator funcțional practic al extensiei BPI, în special în situațiile în care accesul la HRCT este limitat. Utilizarea de rutină a distanței parcurse la 6MWT nu se justifică exclusiv pentru estimarea extensiei BPI, deși testul de mers de 6 minute își păstrează valoarea pentru evaluarea capacității funcționale și a desaturării la efort.*

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Table 1. Demographic and clinical characteristics of patients with systemic sclerosis according to ILD extent on HRCT.

Variable	Extensive ILD (n=21)	Non-extensive ILD (n=62)	Total (n=83)	p
Age (years), mean (SD)	41.90 (10.07)	40.95 (11.16)	41.19 (10.84)	0.730
Sex — Male, n (%)	0 (0)	5 (8)	5 (6)	0.323
Sex — Female, n (%)	21 (100)	57 (92)	78 (94)	0.323
Smoking history — Non-smoker, n (%)	21 (100)	57 (92)	78 (94)	0.323
Smoking history — Moderate smoker*, n (%)	0 (0)	5 (8)	5 (6)	0.323
SSc subtype — Diffuse cutaneous (dcSSc), n (%)	13 (62)	42 (68)	55 (66)	0.709
SSc subtype — Limited cutaneous (lcSSc), n (%)	8 (38)	19 (31)	27 (33)	0.709
SSc subtype — Sine scleroderma (ssSSc), n (%)	0 (0)	1 (2)	1 (1)	0.709
Organ involvement — Musculoskeletal, n (%)	8 (38)	28 (45)	36 (43)	0.619
Organ involvement — Renal, n (%)	1 (5)	0 (0)	1 (1)	0.253
Organ involvement — Gastrointestinal, n (%)	10 (48)	14 (23)	24 (29)	0.049
mRSS, median (IQR)	8 (3–10)	7 (3–15)	7 (3–15)	0.459
Disease duration (months), median (IQR)	70 (12–114)	28 (10–90)	38 (11–95)	0.423
Predominant HRCT pattern — NSIP, n (%)	9 (43)	42 (68)	51 (61)	0.068
Predominant HRCT pattern — UIP, n (%)	12 (57)	20 (32)	32 (39)	0.068

*ILD = interstitial lung disease; HRCT = high-resolution computed tomography; SD = standard deviation; IQR = interquartile range; mRSS = modified Rodnan Skin Score; SSc = systemic sclerosis; NSIP = non-specific interstitial pneumonia; UIP = usual interstitial pneumonia. *Moderate smoker was defined as a Brinkman Index of 200–599 (cigarettes smoked per day × years of smoking). p-values: unpaired t-test (age); Mann-Whitney U test (mRSS, disease duration); chi-square test or Fisher's exact test as appropriate (categorical variables).*

Table 2. Functional, laboratory, and treatment characteristics of patients with systemic sclerosis according to ILD extent on HRCT.

Variable	Extensive ILD (n=21)	Non-extensive ILD (n=62)	Total (n=83)	p
6MWT distance (m), median (IQR)	330 (281–392)	349 (307–390)	348 (300–390)	0.492
Oxygen desaturation ≥4% during 6MWT, n (%)	3 (14)	0 (0)	3 (4)	0.015
FVC (% predicted), mean (SD)	47.0 (13.6)	64.7 (15.2)	60.2 (16.7)	0.001
FEV1/FVC (%), median (IQR)	90.5 (83–93)	87.8 (85–92)	88.4 (84–92)	0.480
ESR (mm/h), median (IQR)†	28 (12–59)	41 (27–62)	41 (25–61)	0.242
CRP (mg/L), median (IQR)‡	1.65 (0.77–5.42)	1.65 (0.77–6.72)	1.65 (0.77–6.07)	0.950
Anti-Scl-70 antibody, n (%)	4 (19)	12 (19)	16 (19)	1.000
Anti-centromere antibody, n (%)	0 (0)	3 (5)	3 (4)	0.568
Treatment — Treatment-naïve, n (%)	1 (5)	7 (11)	8 (10)	0.423
Treatment — Methotrexate, n (%)	1 (5)	7 (11)	8 (10)	0.423
Treatment — Mycophenolate mofetil, n (%)	19 (90)	48 (77)	67 (81)	0.423

ILD = interstitial lung disease; HRCT = high-resolution computed tomography; SD = standard deviation; IQR = interquartile range; 6MWT = six-minute walk test; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein. †ESR available for 82/83 patients. ‡CRP available for 78/83 patients. Data on glucocorticoid and biologic agent use were not collected. p-values: unpaired t-test (FVC); Mann-Whitney U test (6MWT distance, FEV1/FVC, ESR, CRP); chi-square test or Fisher's exact test as appropriate (categorical variables).

Table 3. Univariate association between functional parameters and ILD extent on HRCT.

Variable	Extensive ILD (n=21)	Non-extensive ILD (n=62)	PR (95% CI)	p
6MWT distance ≤338.35 m, n (%)	12 (57)	26 (42)	1.579 (0.743–3.353)	0.311
6MWT distance >338.35 m, n (%)	9 (43)	36 (58)	Reference	—
Oxygen desaturation ≥4%, n (%)	3 (14)	0 (0)	4.444 (2.95–6.69)	0.015
Oxygen desaturation <4%, n (%)	18 (86)	62 (100)	Reference	—
FVC <70% predicted, n (%)	21 (100)	38 (61)	1.553 (1.284–1.877)	<0.001
FVC ≥70% predicted, n (%)	0 (0)	24 (39)	Reference	—

PR = prevalence ratio; CI = confidence interval; 6MWT = six-minute walk test; FVC = forced vital capacity; ILD = interstitial lung disease; HRCT = high-resolution computed tomography. p-values were calculated using Fisher's exact test given the small expected cell counts.

Table 4. Multivariable analysis of functional parameters associated with extensive ILD.

Variable	Crude PR (95% CI)	p	Adjusted PR (95% CI)*	p
FVC (% predicted)	0.952 (0.936–0.970)	<0.001	0.948 (0.931–0.965)	<0.001
Oxygen desaturation ≥4%	4.444 (2.959–6.675)	<0.001	4.333 (2.528–7.427)	<0.001
6MWT distance (m)	0.998 (0.995–1.002)	0.376	0.997 (0.993–1.002)	0.234

PR = prevalence ratio, estimated using Poisson regression with robust standard errors; CI = confidence interval; FVC = forced vital capacity; ILD = interstitial lung disease; mRSS = modified Rodnan Skin Score; 6MWT = six-minute walk test.

Adjusted for age, disease duration, and mRSS. Age, disease duration, and mRSS were selected a priori as candidate confounders; none changed the crude PR by ≥10% (ΔPR), the pre-specified threshold for confounding.