CHEST

Quantitative CT Imaging in Progressive Pulmonary Fibrosis

Clinical Usefulness and Meaningful Threshold Definition

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BACKGROUND: Although quantitative CT imaging offers objective evaluation of radiologic progression in non-idiopathic pulmonary fibrosis (IPF) fibrosing interstitial lung disease (ILD), clinically meaningful thresholds for defining progressive pulmonary fibrosis (PPF) remain unclear.

RESEARCH QUESTION: What are the minimal clinically important differences (MCIDs) in quantitative CT imaging-based fibrosis score (FS) changes over 1 year and 6 months, and do these thresholds predict outcomes and enhance risk stratification in defining PPF among patients with non-IPF fibrosing ILD?

STUDY DESIGN AND METHODS: This retrospective study included patients with non-IPF fibrosing ILD who underwent volumetric CT imaging at baseline and the 1-year follow-up. FS was calculated using a deep learning-based quantitative CT imaging algorithm. The MCID for FS change was determined using anchor-based methods, referencing absolute 1-year FVC change. The association of FS change MCID with transplant-free survival (TFS) and its alignment with PPF criteria were analyzed using Cox regression. Concordance between quantitative CT imaging-based and visual assessments was also assessed.

RESULTS: Among 476 patients, the 1-year and 6-month MCIDs were 2.24% and 1.34%, respectively. Exceeding the 1-year MCID was independently associated with poorer TFS (adjusted hazard ratio [HR], 3.01; 95% CI, 2.19-4.14). Quantitative CT imaging-based progression provided additional risk stratification in patients with discordant PPF criteria, including those with disagreement on visual progression ($P = .02$). Patients with both visual and quantitative CT imaging-based progression showed worse outcomes than those with visual progression alone ($P < .001$). FS changes of more than the 6-month MCID were also associated with worse outcome (adjusted HR, 2.82; 95% CI, 1.57-5.04).

INTERPRETATION: Quantitative CT imaging-based PPF definition using 1-year change in FS was prognostic across patients with non-IPF fibrosing ILDs and enhanced risk stratification in patients with discordant PPF assessments. CHEST 2026; 169(5):1255-1266

KEY WORDS: CT imaging; interstitial lung disease; progressive pulmonary fibrosis; quantification

FOR EDITORIAL COMMENT, SEE PAGE 1165

Take-Home Points

Research Question: What are the minimal clinically important differences (MCIDs) in quantitative CT imaging-based fibrosis score (FS) changes over 1 year, and do these thresholds predict outcomes and enhance risk stratification in defining progressive pulmonary fibrosis (PPF) among patients with non-idiopathic pulmonary fibrosis (IPF) fibrosing interstitial lung disease (ILD)?

Results: The 1-year MCID for FS was 2.24%, and exceeding this threshold was associated independently with reduced transplant-free survival (adjusted hazard ratio, 3.01; 95% CI, 2.19-4.14) while also improving risk stratification in patients with discordant PPF assessments.

Interpretation: This study supports the use of quantitative CT imaging for defining PPF, demonstrating prognostic value across non-IPF fibrosing ILDs and complementing existing physiologic and visual criteria.

Progressive pulmonary fibrosis (PPF) is a clinical phenotype formally defined in 2022 by an international guideline from the American Thoracic Society, the European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax,[1] in recognition of a subset of patients with non-idiopathic pulmonary fibrosis (IPF) fibrosing interstitial lung diseases (ILDs) who exhibit a progressive disease course resembling IPF. Although IPF traditionally has represented the archetype of progressive fibrosing ILD, accumulating evidence shows that variable proportions of other fibrosing ILDs—such as connective tissue disease (CTD)-associated ILD, fibrotic hypersensitivity pneumonitis (HP), and unclassifiable ILD—also can undergo relentless progression, regardless of etiology or initial presentation.[1,2] These patients typically experience worse outcomes and may benefit from antifibrotic therapies originally developed for IPF.[3-5] As such, timely and accurate detection of disease progression is essential to guide treatment.

The PPF definition incorporates clinical, physiologic, and radiologic criteria for identifying progression within a 1-year period.[1] However, few studies have validated these criteria across diverse populations with non-IPF ILD, and those have focused primarily on physiologic decline.[4,6] Radiologic progression remains particularly difficult to assess because of its subjective interpretation and the lack of consensus on what constitutes a clinically meaningful change. This variability limits the reproducibility of PPF assessments and hinders cross-study comparisons. In this context, quantitative CT imaging has emerged as a promising tool, offering objective and reproducible measurement of fibrotic burden and its progression.[7-9] By providing continuous and observer-independent metrics, quantitative CT imaging may improve consistency in disease monitoring and may reduce interobserver variability. Previous work has demonstrated the usefulness of quantitative CT imaging in IPF, estimating the minimal clinically important difference (MCID) for disease progression to be 3.4% to 6.4%.[10] However, non-IPF ILDs often exhibit varying degrees of inflammation, which may influence disease behavior.[11] Therefore, validating quantitative CT imaging thresholds in non-IPF ILD is necessary to ensure their clinical relevance. Identifying a quantitative CT imaging-based threshold for meaningful progression could link imaging changes with outcomes and could support standardized monitoring strategies.

Current guidelines do not define a standardized interval for imaging follow-up, and in clinical

ABBREVIATIONS: CTD = connective tissue disease; DLCO = diffusing capacity of the lungs for carbon monoxide; FS = fibrosis score; HP = hypersensitivity pneumonitis; HR = hazard ratio; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; IQR = interquartile range; MCID = minimal clinically important difference; PPF = progressive pulmonary fibrosis; PFT = pulmonary function testing; TFS = transplant-free survival; UIP = usual interstitial pneumonia

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practice, CT imaging often is performed at roughly 12-month intervals or earlier when clinically indicated. However, the role of 6-month quantitative CT imaging follow-up in capturing early progression has not been well explored. One prior study of IPF found that a 6-month increase in quantitative lung fibrosis of ≥ 4% predicted poorer progression-free survival.[12]

Accordingly, this study aimed to determine the MCID for a 1-year quantitative CT imaging-based fibrosis score (FS) change that reflects clinically meaningful progression in non-IPF ILD. We further evaluated its association with transplant-free survival (TFS), as well as the usefulness of 6-month quantitative CT imaging follow-up in identifying early progression.

Study Design and Methods

This retrospective study was approved by the institutional review board of Asan Medical Center, Seoul, South Korea (Identifier: 2024-0462), which waived the requirement for written informed consent.

Study Sample and Data Collection

A retrospective search of the electronic medical records of patients with non-IPF fibrosing ILD who were followed up at Asan Medical Center between January 2011 and April 2020 was performed. Patients were eligible if they had undergone both baseline and 1-year follow-up volumetric CT scans. Patients were excluded if they lacked baseline or follow-up pulmonary function testing (PFT) within 3 months of each CT scan or the CT images showed overlapping diffuse lung parenchymal abnormalities or poor image quality that precluded accurate quantitative analysis (e-Fig 1).

Clinical data extracted from the electronic medical records included age, sex, BMI, smoking history, baseline and 1-year follow-up PFT results, use of antifibrotic or immunosuppressive therapy within the first year, multidisciplinary ILD diagnosis, and dates of lung transplantation. Pulmonary function metrics included FVC and diffusing capacity of the lungs for carbon monoxide (DLCO). Symptom worsening was defined as increased respiratory symptoms within 2 weeks of follow-up CT imaging or PFT. Dates of death were obtained from the Ministry of the Interior and Safety (Seoul, South Korea). TFS was calculated from the date of baseline CT imaging to the date of death or lung transplantation (event) or last known follow-up (censored).

High-Resolution CT Imaging Analysis

All patients underwent high-resolution CT imaging of the chest at full inspiration without IV contrast using multidetector CT imaging scanners. Axial volumetric images were acquired with 1-mm section thickness and 1-mm intervals. Detailed CT imaging protocols are detailed in e-Appendix 1.

Two thoracic radiologists (J. C. and S. P., with 13 and 9 years of experience, respectively), masked to all clinical information, independently assessed radiologic progression using predefined criteria from the 2022 American Thoracic Society, the European Respiratory Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax Clinical Practice guidelines: increased extent or severity of traction bronchiectasis and bronchiolectasis, new ground-glass opacities with traction bronchiectasis, new fine reticulation, increased extent or coarseness of reticular abnormality, new or increased honeycombing, or increased lobar volume loss. For patients with 6-month follow-up scans, the same criteria were applied. An usual interstitial pneumonia (UIP) pattern was classified according to IPF diagnostic guidelines by 1 thoracic radiologist (J. C.). FS, defined as the sum of the extent of reticulation and honeycombing, was calculated using a deep learning-based quantitative CT imaging tool (Aview version 1.1.44.27; Coreline Soft) at baseline, 6-month, and 1-year high-resolution CT imaging of the chest.[13,14]

Statistical Analysis

Baseline characteristics were summarized using standard descriptive statistics. MCID thresholds for FS changes were evaluated at 6 and 12 months using both anchor-based and distribution-based approaches.[10] For anchor-based analysis, FS changes were analyzed relative to established thresholds for FVC and DLCO decline. FVC change was categorized as improvement (> 5%), stable (≤ 5% to > –5%), slight decline (≤ –5% to > –10%), or marked decline (≤ –10%). DLCO similarly was categorized using thresholds of ± 10% and –15%. The mean FS changes in the group showing slight decline was used to estimate the MCID. The effect size (mean FS change divided by the baseline SD[15]) also was calculated to quantify the magnitude of change. Measurement stability was evaluated using intraclass correlation coefficients between baseline and follow-up FS in patients

classified as stable. The distribution-based approach MCIDs were estimated using the SEM, calculated as SD of baseline FS × √(1 – intraclass correlation coefficient) or 0.5 × SD of baseline FS.

The association between 1-year FS change MCID and TFS was evaluated using univariable and multivariable Cox proportional hazards models, adjusting for age, smoking status, baseline FVC, and ILD subtype (CTD-associated ILD, idiopathic nonspecific interstitial pneumonia, fibrotic HP, and other or unclassifiable ILDs). The association of different PPF criteria with TFS was also examined, including visual and quantitative CT imaging-based radiologic progression, physiologic decline, and symptom worsening, and their discriminatory ability was assessed using Harrell's concordance index. Subgroup analyses were conducted to assess concordance and discordance between criteria. The prognostic significance of 6-month FS change MCID was assessed similarly using Cox regression. Analyses were performed with overall TFS as the primary outcome, and additionally using 5-year TFS as a secondary outcome measure. Interaction terms were used to test whether the prognostic impact of MCID differed by ILD subtype. Serial FVC and DLCO values over the 3 years after the 1-year follow-up CT scan (corresponding to the 2-year, 3-year, and 4-year time points from baseline [time point 0]) were analyzed using a general linear mixed-effects model, adjusting for baseline PFT values and testing group-by-time interactions. Interobserver agreement between 2 radiologists for radiologic progression (at 6 months and 1 year) was evaluated using Cohen's κ. Kaplan-Meier survival curves were used to compare TFS across groups, with log-rank tests for group comparisons. Multiple comparisons between subgroups were adjusted using the Bonferroni method. All statistical analyses were performed using SAS version 9.1.3 software (SAS Institute) and R version 4.1.0 software (R Foundation for Statistical Computing). A 2-sided P value of $< .05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics

Of 539 patients with baseline and 1-year follow-up volumetric high-resolution CT scans of the chest, 34 patients who lacked corresponding PFT findings and 29 patients who had overlapping lung abnormalities or poor-quality CT scan were excluded, leaving 476 patients (mean age, 61 years; 228 male [47.9%]) with complete data (e-Fig 1, Table 1).

ILD subtypes included CTD-associated ILD (41.6% [198/476]), idiopathic nonspecific interstitial pneumonia (17.0% [81/476]), fibrotic HP (10.3% [49/476]), and other or unclassifiable ILD (31.1% [148/476]) (Table 1). Median baseline FVC and DLCO were 73% predicted (interquartile range [IQR], 59%-84%) and 58% predicted (IQR, 46%-70%), respectively.

The median baseline FS was 5.57% (IQR, 2.68%-10.24%). Corticosteroids or immunosuppressants were administered in 86.3% of patients (411/476), with 62.8% of patients (299/476) initiating treatment within the first year. Antifibrotic therapy was given to 16.0% of patients (76/476), including 2.3% of patients (11/476) within the first year. A total of 131 patients (27.5%) underwent 6-month follow-up CT imaging before the 1-year scan; these patients showed lower baseline FVC and DLCO, and the proportion receiving steroids, immunosuppressants, or both within 6 months after diagnosis was marginally higher ($P = .07$) (e-Table 1).

MCID for Quantitative CT Imaging-Based FS Changes

e-Table 2 presents anchor-based MCID estimates for FS changes on the 1-year and 6-month follow-up CT scans. At 1 year, mean FS changes differed significantly across all anchor-based categories ($P < .001$), showing a linear trend. At 6 months, significant differences were observed only in DLCO-based categories ($P = .03$-$.04$). Effect sizes in the groups showing slight decline were modest at 6 months (range, -0.01-0.15), but were higher at 1 year (range, 0.10-0.28).

Distribution-based MCID estimates were 3.69% at 1 year and 4.22% at 6 months (e-Table 3), whereas SEM-based estimates ranged from 2.23% to 2.38% (1 year) and 2.51% to 2.93% (6 months). Given the clinical relevance of FVC and its largest effect size among anchor variables (e-Table 2), we selected MCID thresholds derived from absolute FVC decline: 2.24% (1 year) and 1.34% (6 months).

Prognostic Significance of MCID for Change in FS

The median follow-up for TFS was 8.49 years (IQR, 6.05-10.44 years), during which 1.9% of patients (9/476) underwent lung transplantation and 36.3% of patients (173/476) died before lung transplantation. For the analysis of 5-year TFS, a total of 84 events occurred. Univariable analysis showed worse TFS was associated with older age ($P < .001$), male sex ($P = .001$), ever smoking ($P = .02$), smoking amount ($P = .01$), fibrotic

TABLE 1] Baseline Characteristics of Study Patients

Variable	All Patients (n = 476)
Age, y	61 (54-68)
Sex	
Male	228 (47.9)
Female	248 (52.1)
Smoking history	
Never	267 (56.1)
Former or current	209 (43.9)
Smoking duration, pack-years	0.0 (0.0-24.0)
ILD subtype	
CTD associated	198 (41.6)
Rheumatoid arthritis associated	83 (17.4)
Systemic sclerosis associated	34 (7.1)
Sjögren syndrome associated	29 (6.1)
Myositis associated	19 (4.0)
Systemic lupus erythematosus associated	17 (3.6)
Other or mixed CTD-associated ILD	16 (3.4)
Idiopathic NSIP	81 (17.0)
Fibrotic HP	49 (10.3)
Others (including unclassifiable ILD)	148 (31.1)
Baseline pulmonary function testing results	
FVC, % predicted	73 (59-84)
D_{LCO}, % predicted	58 (46-70)
HRCT imaging UIP pattern	
UIP or probable UIP	128 (26.9)
Indeterminate for UIP	80 (16.8)
Alternative diagnosis	268 (56.3)
Baseline CT quantification, % of entire lung volume	
Fibrosis score	5.57 (2.68-10.24)
Reticulation	5.02 (2.33-9.03)
Honeycombing	0.11 (0.01-0.79)
Ground-glass opacity	1.32 (0.33-3.95)
Emphysema	0.04 (0.00-0.22)
Treatment exposure	
Corticosteroid or immunosuppressant therapy	411 (86.3)
Corticosteroids	408 (85.7)
Immunosuppressant therapy	335 (70.4)
Antifibrotic therapy	76 (16.0)

Data are presented as No. (%) or median (interquartile range). Percentages may not sum to 100 because of rounding. CTD = connective tissue disease; D_{LCO} = diffusing capacity of the lungs for carbon monoxide; HP = hypersensitivity pneumonitis; HRCT = high-resolution CT; ILD = interstitial lung disease; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

HP ($P = .004$ with CTD-associated ILD as a reference), UIP or probable UIP pattern ($P = .005$), and lower baseline FVC ($P < .001$) (e-Table 4).

At the 1-year follow-up, both continuous FS changes (hazard ratio [HR], 1.10 [95% CI, 1.08-1.13]; $P < .001$) and quantitative CT imaging MCID-based progression (FS changes > 2.24%: HR, 3.74 [95% CI, 2.78-5.02]; $P < .001$) were associated with shorter TFS. These associations persisted in multivariable models adjusted for smoking status, baseline FVC, and ILD subtype (continuous FS changes: adjusted HR, 1.06 [95% CI,

1.04-1.09]; $P < .001$; quantitative CT imaging MCID-based progression: adjusted HR, 3.01 [95% CI, 2.19-4.14]; $P < .001$) (Table 2). Both also significantly were associated with 5-year TFS (e-Tables 5, 6).

TFS rates at 2, 5, and 10 years were 97.9%, 88.3%, and 68.5%, respectively, for patients with FS changes of ≤ 2.24% and 87.1%, 60.4%, and 26.5%, respectively, for those with FS changes of > 2.24% ($P < .001$, log-rank test) (Fig 1A). Stratification into 4 FS changes groups using twice the MCID threshold (≤ 0.00%, 0.00%-2.24%, 2.24%-4.48%, and > 4.48%) showed stepwise TFS decline ($P < .001$, log-rank test), with 10-year TFS rates of 70.7%, 65.5%, 35.2%, and 17.2%, respectively. Patients with FS changes of > 4.48% showed significantly worse TFS than those with FS changes of 2.24% to 4.48% ($P = .01$, Bonferroni corrected) (Fig 1B). Radiologic progression defined by 1-year MCID was associated significantly with shorter TFS across ILD subtypes (HR, 3.34-5.61; $P < .001$ for all), with no significant interaction between ILD subtype and progression category ($P = .75$ for interaction) (e-Table 7). In addition, patients who met the quantitative CT imaging-MCID criterion for progression exhibited significantly greater subsequent declines in both FVC and DLCO over 2 to 4 years compared with those without progression at 1 year ($P = .03$ for interaction for FVC; $P = .005$ for interaction for DLCO) (e-Table 8, e-Fig 2).

Among 131 patients with available 6-month follow-up CT imaging, radiologic progression assessed by radiologist 2 was associated significantly with shorter TFS (adjusted HR, 1.83; $P = .02$); however, the HRs were lower than those observed at 1 year, and radiologic progression assessed by radiologist 1 was not associated

TABLE 2] Multivariable Analysis for Transplant-Free Survival Based on Different Progressive Pulmonary Fibrosis Criteria at 1-Year Follow-Up

Variable (reference)	Adjusted HR (95% CI)[a]	*P* Value	Concordance Index
Absolute FVC decline ≥ 5%	2.62 (1.90-3.62)	< .001	0.785
Absolute DLCO decline ≥ 10%	1.69 (1.19-2.39)	.004	0.766
Symptom worsening	2.60 (1.68-4.03)	< .001	0.771
Visual radiologic progression			
Radiologist 1	2.04 (1.50-2.77)	< .001	0.767
Radiologist 2	1.94 (1.43-2.64)	< .001	0.771
FS changes			
ΔFS at 1 y[b]	1.06 (1.04-1.09)	< .001	0.772
ΔFS > 1-y MCID (2.24%)	3.01 (2.19-4.14)	< .001	0.783
ΔFS > 1-y MCID × 2 (4.48%)	4.19 (2.85-6.17)	< .001	0.782
Absolute FVC decline ≥ 5% with visual radiologic progression	3.07 (2.09-4.49)	< .001	0.778
Absolute FVC decline ≥ 5% with ΔFS > 1-y MCID	3.90 (2.68-5.68)	< .001	0.782
Absolute DLCO decline ≥ 10% with visual radiologic progression[c]	2.02 (1.29-3.14)	.002	0.765
Absolute DLCO decline ≥ 10% with ΔFS > 1-y MCID	3.44 (2.25-5.27)	< .001	0.776
Symptom worsening with visual radiologic progression[b]	2.99 (1.77-5.05)	< .001	0.768
Symptom worsening with ΔFS > 1-y MCID	3.05 (1.76-5.28)	< .001	0.769
At least 2 criteria			
Visual radiologic progression[c], symptom worsening, and absolute PFT results decline (≥ 5% FVC or ≥ 10% DLCO decline)	2.67 (1.88-3.79)	< .001	0.777
ΔFS > 1-y MCID, symptom worsening, and absolute PFT results decline (≥ 5% FVC or ≥ 10% DLCO decline)	3.06 (2.16-4.33)	< .001	0.780

ΔFS = fibrosis score change; DLCO = diffusing capacity of the lungs for carbon monoxide; FS = fibrosis score; HR = hazard ratio; MCID = minimal clinically important difference; PFT = pulmonary function testing.
[a]Adjusted by age, smoking status, baseline FVC, and interstitial lung disease subtype.
[b]Analyzed as a continuous variable.
[c]Visual progression defined by radiologist 1.

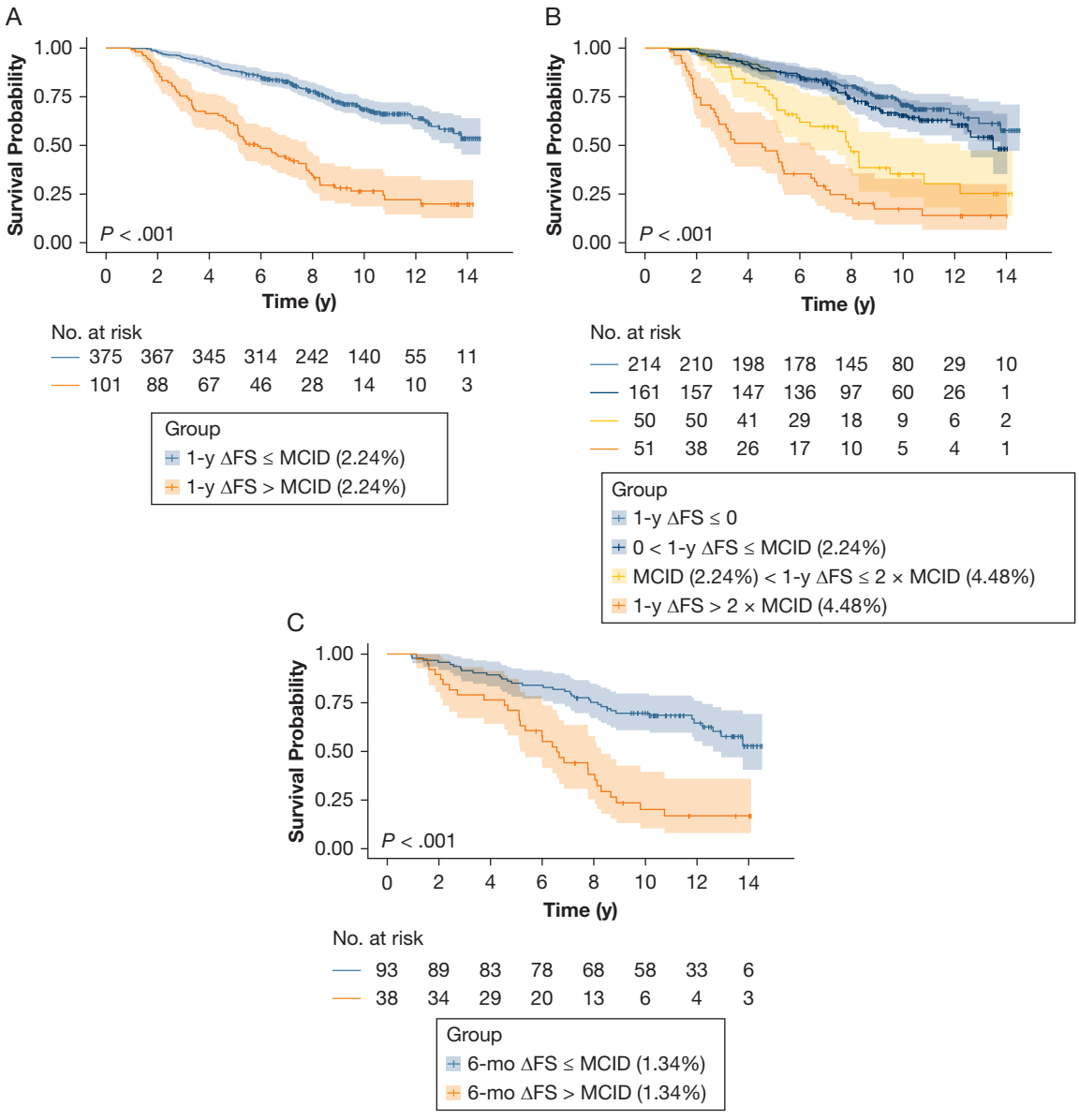

Figure 1 – *Kaplan-Meier transplant-free survival (TFS) curves stratified by MCID in ΔFS on quantitative CT imaging at the 1-y and 6-mo follow-up. A, TFS differed significantly between groups stratified by the 1-y MCID threshold for ΔFS (ΔFS > 2.24%; P < .001, log-rank test). B, Further stratification into 4 groups—ΔFS ≤ 0.00%, 0.00% < ΔFS ≤ 2.24%, 2.24% < ΔFS ≤ 4.48% (MCID × 2), and ΔFS > 4.48—demonstrated stepwise separation in TFS (P < .001 overall, log-rank test). Pairwise comparison showed significantly worse outcome in patients with ΔFS of > 4.48% compared with those with 2.24% < ΔFS ≤ 4.48% (P = .01, Bonferroni correction). C, TFS also differed significantly between groups based on the 6-mo MCID threshold (ΔFS > 1.34%; P < .001, log-rank test). ΔFS = fibrosis score change; MCID = minimal clinically important difference.*

significantly with TFS ($P = .08$). An FS increase exceeding the 6-month MCID threshold (> 1.34%) was associated significantly with reduced TFS (adjusted HR, 2.82; $P = .001$) (Table 3). Stratified by this threshold, patients with FS changes of ≤ 1.34% showed 2-year, 5-year, and 10-year TFS rates of 95.6%, 85.7%, and 70.1%, respectively, whereas those with FS changes of > 1.34% showed rates of 90.0%, 70.0%, and 21.8%. The survival difference between groups was statistically significant ($P < .001$, log-rank test) (Fig 1C). The association between 6-month change in FS and 5-year TFS did not remain significant in the multivariable analysis, and the interpretation is limited because of the small number of events (e-Table 9).

Evaluation of PPF Criteria

The proportion of patients meeting PPF definitions varied substantially depending on the specific criteria

TABLE 3] Evaluation of Associations of 6-Month Change in Fibrosis Score on Follow-Up Quantitative CT Imaging With Transplant-Free Survival (n = 131)

Variable	Univariable Analysis		Multivariable Analysis	
	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)[a]	*P* Value
Visual radiologic progression				
Radiologist 1	1.96 (1.13-3.42)	.02	1.71 (0.94-3.12)	.08
Radiologist 2	2.40 (1.47-3.93)	.001	1.83 (1.10-3.06)	.02
6-mo ΔFS	1.10 (1.04-1.16)	< .001	1.07 (1.01-1.13)	.03
6-mo ΔFS > MCID (1.34%)	3.42 (2.08-5.62)	< .001	2.82 (1.57-5.04)	.001

ΔFS = fibrosis score change; HR = hazard ratio; MCID = minimal clinically important difference.
[a]Adjusted by age, smoking status, baseline FVC, and interstitial lung disease subtype.

applied (e-Fig 3). An absolute FVC decline of ≥ 5% was observed in 20.0% of patients (95 of 476). PPF was identified in 29.0% of patients (138 of 476) by visual assessment (radiologist 1) and 21.2% of patients (101 of 476) by quantitative CT imaging-defined progression, with considerable overlap between radiologic and physiologic decline. Composite definitions requiring at least 2 PPF criteria yielded lower rates: 16.2% (77 of 476; visual) and 15.8% (75 of 476; quantitative CT imaging). Venn diagrams (Fig 2) illustrate the differences in overlap with other criteria when radiologic progression was defined using either visual or quantitative CT imaging assessment. Among patients showing radiologic progression, those classified by quantitative CT imaging more frequently exhibited concurrent PFT results worsening than those identified visually (54.5% [55 of 101] vs 45.7% [63 of 138]), although this was not statistically significant ($P = .18$). A higher proportion of patients met radiologic criteria alone using visual CT imaging vs quantitative CT imaging (50.0% [69 of 138] vs 37.6% [38 of 101]; $P = .06$). Direct comparison (Fig 2C) showed that most patients with quantitative CT imaging-defined progression also met the visual criterion (62.3% [63 of 101]), whereas visual CT imaging alone identified a broader group (54.3% [75 of 138]). Among those with visual progression alone,

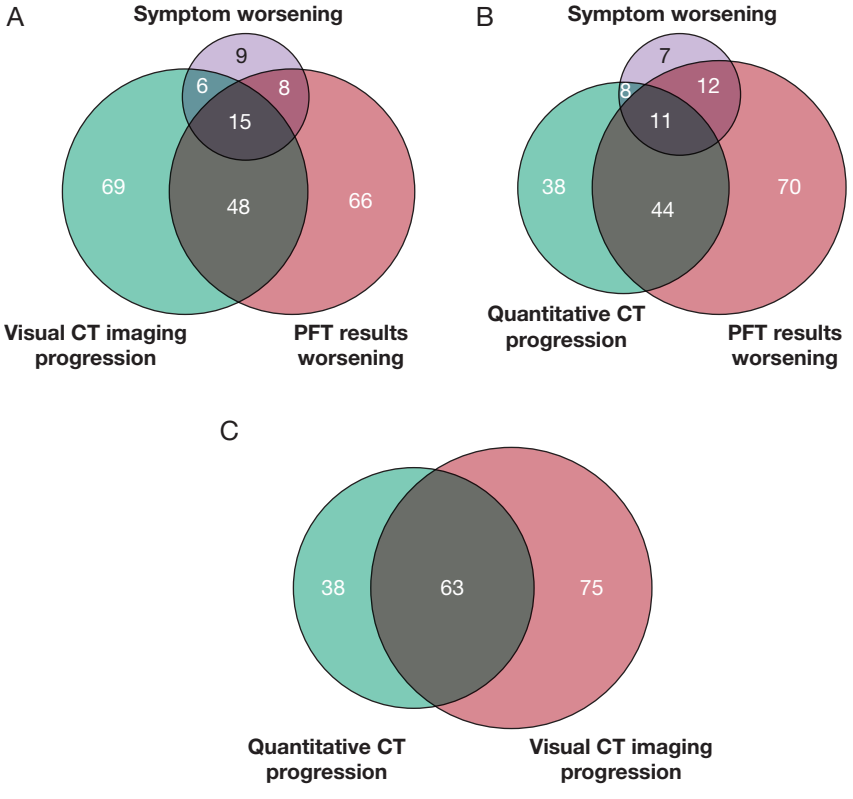

Figure 2 – *A-C, Venn diagrams illustrating the overlap of patients meeting different progressive pulmonary fibrosis criteria: symptom worsening, physiologic worsening (defined as ≥ 5% absolute FVC decline or ≥ 10% absolute decline in diffusing capacity of the lungs for carbon monoxide), and visual CT progression assessed by radiologist 1 (A); symptom worsening, physiologic worsening, and quantitative CT imaging progression defined by the minimal clinically important difference threshold (fibrosis score changes > 2.24%) (B); and comparison between visual CT progression (radiologist 1) and quantitative CT imaging progression (C). Each circle represents the number of patients meeting a given criterion; overlapping areas indicate patients who met > 1 criterion. PFT = pulmonary function testing.*

more than one-half also demonstrated an increase in FS changes (42 of 75 [56.0%]; median, 1.25% increase [IQR, 0.4%-1.7%]) that did not exceed the predefined quantitative CT imaging progression threshold (> 2.24% increase).

Despite differences in classification, all 3 PPF components—PFT decline, symptom worsening, and radiologic progression (visual or quantitative CT imaging-based)—were associated independently with TFS in multivariable analysis, both as individual predictors and in combination (Table 2). Among all definitions, the strongest prognostic performance (concordance index ≥ 0.770) was observed for absolute FVC decline of ≥ 5%, symptom worsening, visual progression (radiologist 2), and FS changes exceeding 1-year MCID or twice the MCID threshold. Composite criteria combining FVC decline with either visual or quantitative CT imaging-based progression, or any 2 of the 3 components (radiologic progression, symptom worsening, and PFT results decline) also demonstrated high prognostic performance. Notably, patients with both FVC and FS exceeding 1-year MCID showed substantially elevated risk (adjusted HR, 3.90), as did those with FS changes exceeding twice the MCID threshold (adjusted HR, 4.19). The multivariable analysis with 5-year TFS as the outcome is presented in e-Table 6.

Role of Quantitative CT Imaging in Concordant and Discordant PPF

Interreader agreement for visual radiologic progression was moderate at 1 year (κ = 0.42) and fair at 6 months (κ = 0.35). Based on 1-year assessments, patients were classified into concordant progression (n = 113), discordant assessment (n = 135), and concordant stable or improved (n = 228). Kaplan-Meier analysis showed significant differences in TFS across groups ($P < .001$, log-rank test; $P < .001$-.05, pairwise Bonferroni correction) (Fig 3), with the poorest outcomes observed in the concordant progression group. Within the discordant group, patients with quantitative CT imaging-defined progression (FS changes > 2.24%) showed significantly worse TFS ($P = .02$, Bonferroni correction).

Stratification by concordance between quantitative CT imaging and visual progression also revealed significant TFS differences ($P < .001$, log-rank test) (e-Fig 4). Patients with concordant quantitative CT imaging and visual progression showed worse TFS than those with visual progression alone ($P < .001$, Bonferroni correction), whereas survival did not differ significantly between concordant progressors and quantitative CT imaging-only progressors ($P = .24$, Bonferroni correction). When stratified by concordance between

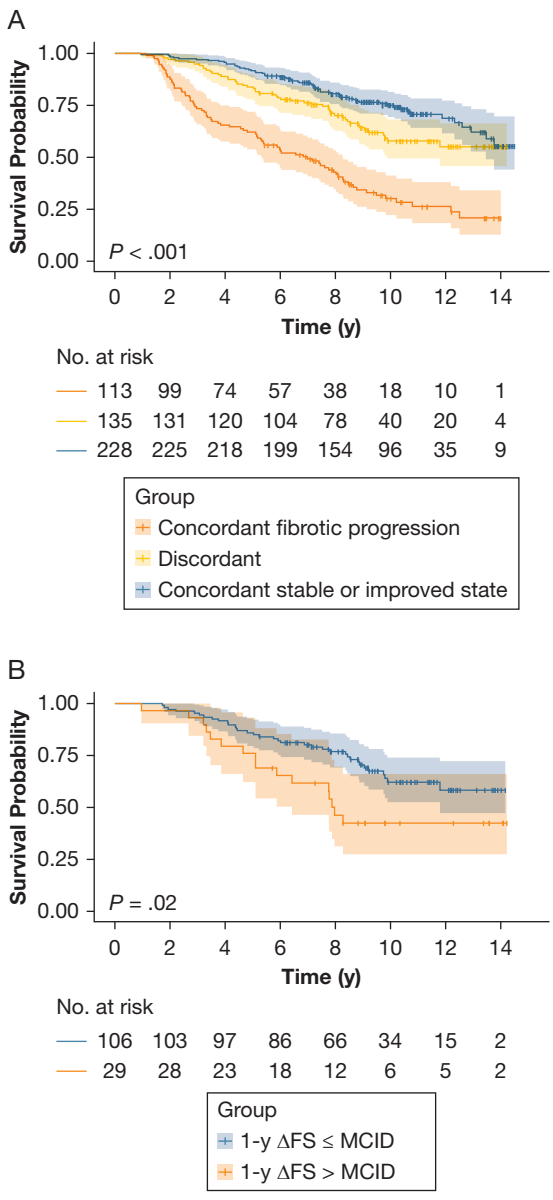

Figure 3 – *Kaplan-Meier estimates of transplant-free survival (TFS) based interreader concordance for visual assessment of radiologic progression at 1 y. A, Patients were categorized into 3 groups: concordant progression (n = 113), discordant (n = 135), and concordant stable or improved (n = 228). TFS differed significantly across groups (P < .001, log-rank test), with 2-y, 5-y, and 10-y TFS rates being 87.6%, 61.9%, and 30.0%, respectively, in the concordant progression group; 97.0%, 83.7%, and 57.8%, respectively, in the discordant group; and 98.7%, 91.7%, and 75.0%, respectively, in the concordant stable or improved group. B, The discordant group was stratified further by the 1-y MCID threshold (ΔFS > 2.24% vs ΔFS ≤ 2.24%). TFS differed significantly between these subgroups (P < .001, log-rank test), with patients showing ΔFS of > 2.24% having significantly worse TFS (P = .02). ΔFS = fibrosis score change; MCID = minimum clinically important difference.*

quantitative CT imaging progression and each of the other PPF criteria (FVC, DLCO, symptom worsening), TFS again differed significantly across groups ($P < .001$, log-rank test) (e-Fig 5). Concordant progressors showed the poorest prognosis, followed by the quantitative CT imaging-only progression group, the physiologic or symptom-only progression group, and the concordant stable or improved group. Notably, the DLCO-only progression group and the symptom-only progression group showed limited prognostic separation from stable patients, suggesting lower discriminatory value compared with other criteria.

Discussion

This study established clinically meaningful thresholds for quantitative CT imaging-based fibrosis progression in patients with non-IPF ILD and highlighted the prognostic usefulness of quantitative CT imaging-derived metrics in defining PPF. A 1-year increase in FS exceeding the MCID threshold of 2.24% was associated independently with worse TFS, with an even higher risk observed in patients with FS changes exceeding 4.48%—twice the MCID threshold. These findings underscore the value of quantitative CT imaging-derived progression as a meaningful marker for risk stratification in non-IPF fibrosing ILD. Notably, quantitative CT imaging-based progression remained prognostically informative even in patients with discordant visual assessments, supporting its role as an independent prognostic indicator. FS progression exceeding the 6-month MCID threshold also was associated significantly with worse outcome, suggesting the potential usefulness of short-interval imaging as an early indicator of disease worsening. Together, these findings support the integration of fully automated quantitative CT imaging metrics into both clinical practice and the design of future clinical trials, including for patient selection and monitoring disease progression.

Progression occurs in a subset of patients with fibrosing ILDs other than IPF,[16,17] and several criteria have been proposed to characterize this trajectory.[1,3,18] Among these, the definition of PPF has been relatively well validated and is increasingly used as a standardized framework for identifying progression.[19,20] Physiologic variables such as FVC and DLCO have been studied extensively, with various thresholds validated across different ILD cohorts.[20] These measures long have served as primary clinical trial end points, reinforcing their central role in both research and clinical care.[21] However, FVC is known to be variable,[22] and DLCO can be confounded by comorbidities such as pulmonary hypertension,[23] limiting their reliability. Radiologic assessment may offer a more objective and reproducible measure of fibrotic extent on chest CT imaging.[24] Prior studies in IPF using texture-based analysis have demonstrated good performance, with an MCID for quantitative CT imaging-based FS change of approximately 3.4%.[10] Building on this, we derived and validated anchor-based thresholds of 2.24% at 1 year and 1.34% at 6 months in patients with non-IPF ILD. Patients exceeding twice the 1-year MCID threshold (FS changes $> 4.48\%$) showed substantially worse outcomes, with an adjusted HR of > 4. These findings suggest that MCID-based radiologic progression can serve as both a component of the broader PPF framework and as an independent prognostic marker. Clinically, patients exceeding these thresholds may warrant closer monitoring and consideration for earlier intervention.

A recent systematic review noted only moderate interobserver agreement among thoracic radiologists in evaluating ILD features and UIP patterns, with even less evidence supporting agreement in assessing disease extent, or progress.[25] Consistent with this, we observed substantial interreader discordance in visual CT scan assessments. In such discordant cases, quantitative CT imaging-defined progression (FS changes $> 2.24\%$) successfully stratified survival outcomes, supporting its potential usefulness in standardizing disease monitoring. Although quantitative CT imaging and visual progression often overlapped, quantitative CT imaging-identified progressors more frequently demonstrated concurrent physiologic worsening, although this did not reach statistical significance. Additionally, prognosis was similar between patients with concordant quantitative CT imaging and visual progression and those with quantitative CT imaging progression alone, whereas visual-only progressors showed more favorable outcomes. Regarding the discordance between visually defined and quantitative CT imaging-defined progression, most patients with quantitative CT imaging-defined progression also met the visual criterion (62.3% [63 of 101]), whereas visual CT alone identified a broader group of patients (54.3% [75 of 138]). This discordance can be explained by several factors. Visual evaluation tends to capture a broader spectrum of qualitative or focal changes—such as conversion of reticulation into traction bronchiolectasis, bronchiectasis, or honeycombing cysts or aggravation of

localized traction bronchiectasis—even when the overall extent of fibrosis changes minimally. In contrast, given that the degree of visual progression is inherently variable and difficult to quantify objectively, quantitative CT imaging may help to distinguish patients with definite increases in fibrosis from those without, thereby providing more consistent categorization and clearer prognostic separation in survival. Conversely, a relatively small subset of patients were identified as showing quantitative CT imaging progression alone, and certain technical factors (eg, inspiratory variation or pattern misclassification) may have led to erroneous classification as false quantitative CT imaging-defined progression. Taken together, these findings suggest that although visual assessment may capture subtle or focal progression not exceeding the quantitative CT imaging threshold, quantitative CT imaging—despite certain technical limitations—may offer a more reliable, objective, and clinically relevant method for tracking disease progression than visual assessment alone.

Although annual CT follow-up is practiced commonly in ILD management, this approach lacks high-level evidence. Small cohort studies in IPF have shown that radiologic progression at 6 months can predict further progression at 12 months and worse outcomes.[12,26] In our study, 6-month follow-up CT imaging was available in 27.5% of patients (131 of 476). Despite the smaller effect size at this earlier interval, FS progression exceeding the 6-month MCID threshold (1.34%) was associated independently with poorer survival (adjusted HR, 3.42; $P < .001$), supporting its potential role as an early prognostic marker. However, given the modest magnitude of change at this interval, further validation is warranted, and whether early intervention guided by 6-month quantitative CT imaging changes improves clinical outcomes remains to be determined in future studies.

This study has several limitations. First, because this was a single-center study, CT imaging protocols were relatively uniform, potentially limiting generalizability and necessitating further multicenter validation. However, prior multicenter data using the same quantitative CT imaging software demonstrated minimal measurement variability (–0.9% to 1.0% absolute FS change) across same-day scans with identical parameters, smaller than the MCID defined in our study.[27] Measurement variability increases when CT imaging protocols differ, emphasizing the importance of standardization between baseline and follow-up imaging. Advanced deep learning-based image harmonization algorithms may enhance reproducibility across heterogeneous scan protocols.[28,29] Second, because of the retrospective nature of the study, symptom worsening was based on review of medical records and may have been underreported. Third, patients undergoing 6-month follow-up CT imaging showed significantly worse baseline pulmonary function, suggesting potential clinical indications for earlier imaging and possible selection bias. Finally, our current study focused on quantitative CT imaging-derived FS and did not evaluate the potential clinical impact of other radiologic features, including ground-glass opacities or increased lobar volume loss.[30,31] However, we chose to evaluate changes in FS because it represents a more practical, reproducible, and simple measure that demonstrated a significant association with TFS as a single index, rather than requiring a composite score.

Interpretation

In conclusion, quantitative CT imaging-defined progression at 1 year was associated independently with worse TFS across non-IPF fibrosing ILDs and enhanced risk stratification even in cases with discordant PPF assessments. Quantitative CT imaging-defined progression at 6 months also demonstrated an association with TFS, supporting the potential usefulness of shorter-interval imaging in selected patients. These findings highlight the value of quantitative CT imaging metrics in augmenting clinical evaluation and guiding clinical trial frameworks for non-IPF ILD. Prospective multicenter validation in independent cohorts is warranted to confirm generalizability and to strengthen clinical applicability.

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Additional information: The e-Appendix, e-Figures, and e-Tables are available online under "Supplementary Data."

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2022;205(9):e18-e47.
2. Oldham JM, Lee CT, Wu Z, et al. Lung function trajectory in progressive fibrosing interstitial lung disease. *Eur Respir J*. 2022;59(6):2101396.
3. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med*. 2019;381(18):1718-1727.
4. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med*. 2021;9(5):476-486.
5. Ghazipura M, Mammen MJ, Bissell BD, et al. Pirfenidone in progressive pulmonary fibrosis: a systematic review and meta-analysis. *Ann Am Thorac Soc*. 2022;19(6):1030-1039.
6. Pugashetti JV, Adegunsoye A, Wu Z, et al. Validation of proposed criteria for progressive pulmonary fibrosis. *Am J Respir Crit Care Med*. 2023;207(1):69-76.
7. Felder FN, Walsh SLF. Exploring computer-based imaging analysis in interstitial lung disease: opportunities and challenges. *ERJ Open Res*. 2023;9(4):00145-02023.
8. Jacob J, Bartholmai BJ, van Moorsel CHM, et al. Longitudinal prediction of outcome in idiopathic pulmonary fibrosis using automated CT analysis. *Eur Respir J*. 2019;54(3):1802341.
9. Maldonado F, Moua T, Rajagopalan S, et al. Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis. *Eur Respir J*. 2013;43(1):204-212.
10. Humphries SM, Swigris JJ, Brown KK, et al. Quantitative high-resolution computed tomography fibrosis score: performance characteristics in idiopathic pulmonary fibrosis. *Eur Respir J*. 2018;52(3):1801384.
11. Behr J, Salisbury ML, Walsh SLF, et al. The role of inflammation and fibrosis in interstitial lung disease treatment decisions. *Am J Respir Crit Care Med*. 2024;210(4):392-400.
12. Kim GHJ, Weigt SS, Belperio JA, et al. Prediction of idiopathic pulmonary fibrosis progression using early quantitative changes on CT imaging for a short term of clinical 18-24-month follow-ups. *Eur Radiol*. 2020;30(2):726-734.
13. Kim GB, Jung KH, Lee Y, et al. Comparison of shallow and deep learning methods on classifying the regional pattern of diffuse lung disease. *J Digit Imaging*. 2018;31(4):415-424.
14. Park B, Park H, Lee SM, Seo JB, Kim N. Lung segmentation on HRCT and volumetric CT for diffuse interstitial lung disease using deep convolutional neural networks. *J Digit Imaging*. 2019;32(6):1019-1026.
15. Roux A, Mourin G, Fastenackels S, et al. CMV driven CD8(+) T-cell activation is associated with acute rejection in lung transplantation. *Clin Immunol*. 2013;148(1):16-26.
16. Singer D, Bengtson LGS, Conoscenti CS, et al. Claims-based prevalence of disease progression among patients with fibrosing interstitial lung disease other than idiopathic pulmonary fibrosis in the United States. *Ann Am Thorac Soc*. 2022;19(7):1112-1121.
17. Wells AU. Patterns of progression in non-IPF fibrotic interstitial lung disease. *Curr Opin Pulm Med*. 2023;29(5):459-464.
18. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ. What's in a name? That which we call IPF, by any other name would act the same. *Eur Respir J*. 2018;51(5):1800692.
19. Erçen Diken Ö, Güngör Ö, Akkaya H. Evaluation of progressive pulmonary fibrosis in non-idiopathic pulmonary fibrosis-interstitial lung diseases: a cross-sectional study. *BMC Pulm Med*. 2024;24(1):403.
20. Wells AU, Walsh SLF, Adegunsoye A, et al. Identification of progressive pulmonary fibrosis: consensus findings from a modified Delphi study. *Respir Res*. 2024;25(1):448.
21. Raghu G, Ghazipura M, Fleming TR, et al. Meaningful endpoints for idiopathic pulmonary fibrosis (IPF) clinical trials: emphasis on 'feels, functions, survives'. Report of a collaborative discussion in a symposium with direct engagement from representatives of patients, investigators, the National Institutes of Health, a patient advocacy organization, and a regulatory agency. *Am J Respir Crit Care Med*. 2024;209(6):647-669.
22. Nathan SD, Wanger J, Zibrak JD, Wencel ML, Burg C, Stauffer JL. Using forced vital capacity (FVC) in the clinic to monitor patients with idiopathic pulmonary fibrosis (IPF): pros and cons. *Expert Rev Respir Med*. 2021;15(2):175-181.
23. Rose L, Prins KW, Archer SL, et al. Survival in pulmonary hypertension due to chronic lung disease: Influence of low diffusion capacity of the lungs for carbon monoxide. *J Heart Lung Transplant*. 2019;38(2):145-155.
24. Walsh SLF, De Backer J, Prosch H, et al. Towards the adoption of quantitative computed tomography in the management of interstitial lung disease. *Eur Respir Rev*. 2024;33(171):230055.
25. Delaney L, Alabed S, Maiter A, et al. Meta-analysis of interobserver agreement in assessment of interstitial lung disease using high-resolution CT. *Radiology*. 2024;313(1):e240016.
26. Oda K, Ishimoto H, Yatera K, et al. High-resolution CT scoring system-based grading scale predicts the clinical outcomes in patients with idiopathic pulmonary fibrosis. *Respir Res*. 2014;15(1):10.
27. Lee JH, Chae KJ, Park J, et al. Measurement variability of same-day CT quantification of interstitial lung disease: a multicenter prospective study. *Radiol Cardiothorac Imaging*. 2024;6(2):e230287.
28. Choe J, Hwang HJ, Kim MS, et al. Improving functional correlation of quantification of interstitial lung disease by reducing the vendor difference of CT using generative adversarial network (GAN) style conversion. *Eur J Radiol*. 2025;183:111899.
29. Hwang HJ, Kim H, Seo JB, et al. Generative adversarial network-based image conversion among different computed tomography protocols and vendors: effects on accuracy and variability in quantifying regional disease patterns of interstitial lung disease. *Korean J Radiol*. 2023;24(8):807-820.
30. Ahn Y, Kim HC, Lee JK, et al. Usefulness of CT quantification-based assessment in defining progressive pulmonary fibrosis. *Acad Radiol*. 2024;31(11):4696-4708.
31. Wang JM, Adegunsoye A, Pugashetti JV, et al. A quantitative imaging measure of progressive pulmonary fibrosis. *Am J Respir Crit Care Med*. 2025;211(10):1785-1793.