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Extent of lung fibrosis is of greater prognostic importance than HRCT pattern in patients with progressive pulmonary fibrosis: data from the ILD-PRO registry

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Abstract

Background The prognostic value of patterns and quantitative measures of lung fibrosis on high-resolution computed tomography (HRCT) in patients identified as having progressive pulmonary fibrosis (PPF) has not been established. We investigated whether HRCT patterns and quantitative scores were associated with risk of progression in patients with PPF.

Methods Patients enrolled in the ILD-PRO Registry had an interstitial lung disease (ILD) other than idiopathic pulmonary fibrosis, reticular abnormality and traction bronchiectasis, and met criteria for ILD progression. HRCT images taken between 24 months prior to enrollment and 90 days after enrollment were analyzed using a machine learning algorithm to derive quantitative scores. Associations were assessed between HRCT pattern (usual interstitial pneumonia [UIP]-like versus other patterns) and tertiles of quantitative scores and measures of disease severity at enrollment, and between these patterns/tertiles at enrollment and ILD progression (relative decline in forced vital capacity [FVC] % predicted ≥ 10%, lung transplant, or death) over a median follow-up of 17.3 months.

Results Among 395 patients, 178 (45.1%) had a UIP-like pattern on HRCT. A UIP-like pattern did not associate with worse disease severity at enrollment or an increased risk of ILD progression (HR 1.01 [95% CI: 0.71, 1.44]). The highest quantitative lung fibrosis (QLF) score tertile (≥ 20.5%) was associated with worse disease severity. In unadjusted analyses, patients with QLF scores in the highest tertile had a significantly increased risk of ILD progression versus the middle tertile (HR [95% CI] 1.63 [1.07, 2.49] and a numerically increased risk versus the lowest tertile (HR 1.46 [0.97, 2.18]); however, after adjustment for sex, age, FVC % predicted and oxygen use at enrollment, there were no significant differences. There were no significant associations between tertiles of quantitative ILD score, quantitative ground glass score, or quantitative honeycomb cysts score and risk of ILD progression in unadjusted or adjusted analyses.

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Conclusions In a real-world cohort of patients with PPF, QLF score associated with subsequent risk of ILD progression, while HRCT pattern did not. The QLF score did not provide additional prognostic information beyond clinical variables.

Trial registration ClinicalTrials.gov; No: NCT01915511; registered August 5, 2013; URL: www.clinicaltrials.gov.

Keywords Disease progression, Interstitial lung disease

Background

A subset of patients with fibrosing interstitial lung disease (ILD) develop progressive pulmonary fibrosis [1]. The term progressive pulmonary fibrosis, or PPF, is generally used to describe progressive lung fibrosis in patients with an ILD other than idiopathic pulmonary fibrosis (IPF) [2]. Various criteria have been proposed to define PPF, based on decline in lung function, worsening radiologic abnormalities, and worsening symptoms [2, 3, 4, 5, 6]. All these criteria identify patients with poor outcomes [7]; however, the rate at which PPF progresses is variable [8, 9, 10]. Identification of patients with PPF who are at the highest risk of continued progression may help to inform management decisions such as referral for lung transplant evaluation or palliative care.

High-resolution computed tomography (HRCT) scans provide valuable prognostic information in patients with ILDs. A usual interstitial pattern (UIP) pattern on HRCT has been associated with worse outcomes in patients with several types of ILD [9, 11, 12, 13, 14, 15, 16, 17, 18]. In addition, a greater extent of fibrosis evident on HRCT has been shown to be predictive of worse outcomes in patients with IPF [19, 20, 21, 22, 23], ILD associated with systemic sclerosis (SSc-ILD) [24, 25], unclassifiable ILD [26], and in a mixed population of patients with various fibrosing ILDs [17]. However, it is uncertain whether associations between quantitative measures of lung fibrosis on HRCT and progression persist in patients who meet criteria for PPF, and whether the extent of ILD on HRCT provides prognostic information beyond commonly measured clinical variables.

The ILD-PRO Registry is a prospective multicenter US registry of patients with PPF [27]. We used data from this registry to evaluate associations between HRCT patterns and quantitative scores derived from HRCT scans and the severity and progression of pulmonary fibrosis. We believe that this is the first study to investigate associations between HRCT-derived patterns and scores and clinical outcomes in a population of patients identified as having PPF.

Methods

The ILD-PRO registry

Patients were enrolled into the ILD-PRO Registry at 45 sites across the US. Participants had an ILD other than IPF that was diagnosed or confirmed at the enrolling center (listed in the Acknowledgments) and reticular abnormality and traction bronchiectasis confirmed by HRCT and/or lung biopsy [27]. Participants had to meet ≥ 1 of the following criteria for ILD progression at any time within the past 24 months: relative decline in forced vital capacity (FVC) % predicted ≥ 10%; relative decline in diffusing capacity of the lungs for carbon monoxide (DLco) % predicted ≥ 10%; relative decline in FVC % predicted ≥ 5–<10% plus worsened respiratory symptoms; relative decline in FVC % predicted ≥ 5–<10% plus increased extent of fibrotic changes on HRCT; worsened respiratory symptoms plus increased extent of fibrotic changes on HRCT. Investigators (listed in the Acknowledgments) were asked to select the criterion for ILD progression that best applied to the patient. Patients were followed prospectively while receiving usual care. The study was approved by the Duke University Institutional Review Board (Pro00046131) and the protocol was approved by the relevant Institutional Review Boards and/or local Independent Ethics Committees prior to enrolment at each site. All participants provided written informed consent.

HRCT

Thin section non-contrast volumetric chest HRCT scans obtained for clinical purposes within the 24 months prior to enrollment and up to 90 days post-enrollment were analyzed using a previously developed machine learning algorithm [28, 29] following lobar segmentation [30]. On a denoised HRCT image, texture features were calculated by sampling each pixel from a 4-by-4 grid within the segmented lung. A support vector machine classifier was then used to classify pixels as fibrotic or non-fibrotic reticulation. The following quantitative scores, expressed as percentages of total lung involvement, were derived: quantitative lung fibrosis (QLF) (fibrotic reticulation patterns with architectural distortion), quantitative ground glass (QGG), quantitative honeycomb cysts (QHC) and quantitative ILD (QILD: sum of QLF, QGG and QHC scores). Some of these quantitative scores have been associated with measures of disease severity and/or risk of clinically relevant outcomes in patients with various ILDs [20, 24, 25, 31, 32]. The margin of measurement variation for the QLF score has been estimated as ± 0.14% (i.e., 2 × SD) [33].

HRCT patterns were categorized according to international guidelines [2, 34] as UIP, probable UIP, indeterminate for UIP, or suggestive of an alternative diagnosis by a single reader. For the purposes of this analysis, patterns of UIP or probable UIP were categorized as a UIP-like pattern. Classifications of the extent and pattern of ILD were made independently.

Analyses

Associations between HRCT pattern (UIP-like pattern versus other patterns) and measures of disease severity, and between tertiles of each quantitative score and measures of disease severity, all assessed at enrollment, were assessed using linear or proportional odds logistic regression. The measures of disease severity were FVC % predicted, DLco % predicted, GAP stage (I, II, III) [35], composite physiologic index (CPI) [36] and supplemental oxygen use (at rest, with exertion, none). Quantitative measures were analyzed as tertiles rather than as continuous scores in order to evaluate associations between extreme scores and outcomes, and because it was suspected that the relationships between scores and outcomes would be non-linear, but that the sample size would be insufficient to distinguish the shape of the non-linearity.

Associations between HRCT pattern (UIP-like pattern versus other patterns) and between tertiles of each quantitative score and ILD progression (relative decline in FVC % predicted ≥ 10%, lung transplant, or death), and death, following enrollment were analyzed using Cox proportional hazard models. Models were unadjusted or adjusted for sex, and age, FVC % predicted and oxygen use (at rest, with exertion, none) at enrollment. The proportional hazards assumption was checked by testing the correlation between the weighted Schoenfeld residuals for a covariate and failure time. Missing values for the adjustment covariates were imputed using the fully conditional specification method. Missing data were filled in 20 times to generate 20 complete data sets. Each of the complete data sets were analyzed using standard statistical analyses. The final inferential results were generated by averaging the results across the 20 imputed datasets. For the association analyses, a sensitivity analysis was performed that was limited to HRCT scans taken between 6 months pre-enrollment and 90 days post-enrollment. Analyses were performed in SAS 9.4.

Table 1 Quantitative scores by HRCT pattern at enrollment

	UIP-like pattern (*n* = 178)	Other patterns (*n* = 217)
QLF, %	15.1 (9.4, 24.2)	14.2 (6.8, 25.5)
QGG, %	21.1 (15.7, 28.0)	24.2 (17.1, 31.7)
QHC, %	0.2 (0.0, 3.9)	0.0 (0.0, 0.7)
QILD, %	40.7 (28.2, 54.1)	44.0 (28.1, 59.3)

Data are median (Q1, Q3)

Results

Patients

A total of 395 patients were included in the primary analysis. At enrollment, median (Q1, Q3) age was 67 (57, 74) years; 47.2% were current or former smokers. The most common ILDs were autoimmune disease-associated ILDs (50.9%, not including interstitial pneumonia with autoimmune features [IPAF]) and hypersensitivity pneumonitis (18.2%). Overall, 68.4% of patients were taking immunosuppressant/cytotoxic drugs and 21.8% were taking nintedanib.

HRCT findings

Median (Q1, Q3) time from the HRCT scan to enrollment was 5.1 (2.2, 9.4) months. A total of 178 patients (45.1%) had a UIP-like pattern (53 [13.4%] UIP, 125 [31.6%] probable UIP) and 217 patients (54.9%) had other patterns on HRCT (87 [22.0%] a pattern that was indeterminate for UIP, 130 [32.9%] a pattern suggestive of an alternative diagnosis). Median (Q1, Q3) QLF, QGG, QHC and QILD scores (%) were 14.3 (8.0, 24.9), 22.7 (16.2, 29.7), 0.1 (0.0, 2.0) and 42.3 (28.1, 57.3), respectively. Median (Q1, Q3) quantitative scores were generally similar between patients with a UIP-like pattern or other HRCT patterns (Table 1).

The characteristics of patients at enrollment by tertile of QLF score and by HRCT pattern are shown in Table 2 and Table S1, respectively. There were no differences in the inclusion criteria for ILD progression selected by the investigator between patients with a UIP-like pattern versus other HRCT patterns. The inclusion criterion of a relative decline in FVC % predicted ≥ 10% was chosen for a greater proportion of patients in the highest tertile of QLF score than the other tertiles. Among patients with versus without a UIP pattern, median FVC % predicted, DLco % predicted, and supplemental oxygen use was similar. In contrast, patients in the highest versus lowest tertiles of QLF, QGG, and QILD scores had lower median FVC % predicted, DLco % predicted, and more frequently used supplemental oxygen. Nintedanib use was more common among patients with versus without a UIP pattern as well as in the highest versus lowest tertiles of QLF, QHC, and QILD scores.

Associations between HRCT findings and measures of disease severity at enrollment

There were no significant associations between the presence of a UIP-like pattern and measures of disease severity at enrollment except for FVC % predicted, which was higher in patients with a UIP-like pattern (mean difference: 5.11 [95% CI: 1.56, 8.67]) (Table 3). Tertiles of QLF score were significantly associated with all measures of disease severity (Table 4). The mean difference in FVC % predicted between the highest versus lowest

Table 2 Patient characteristics at enrollment by tertile of QLF score

	Lowest QLF tertile (< 10.7%) (*n* = 132)	Middle QLF tertile (≥ 10.7% to < 20.5%) (*n* = 131)	Highest QLF tertile (≥ 20.5%) (*n* = 132)	Overall (*n* = 395)
Age, years	67.5 (56.0, 75.0)	66.0 (56.0, 74.0)	66.0 (59.0, 73.0)	67.0 (57.0, 74.0)
Female	76 (57.6)	88 (67.2)	66 (50.0)	230 (58.2)
Race				
White	102 (79.7)	91 (70.0)	95 (76.0)	288 (75.2)
Black/African-American	20 (15.6)	32 (24.6)	20 (16.0)	72 (18.8)
Other	6 (4.7)	7 (5.4)	10 (8.0)	23 (6.0)
Body mass index, kg/m^2	29.0 (25.4, 33.1)	30.0 (25.8, 33.8)	30.0 (26.2, 35.1)	29.7 (25.8, 34.2)
Current or former smoker	59 (44.7)	55 (42.3)	72 (54.5)	186 (47.1)
Type of ILD				
Autoimmune disease-associated ILDs	73 (55.3)	72 (55.0)	56 (42.4)	201 (50.9)
Hypersensitivity pneumonitis	20 (15.2)	18 (13.7)	34 (25.8)	72 (18.2)
IPAF	10 (7.6)	19 (14.5)	9 (6.8)	38 (9.6)
Idiopathic non-specific interstitial pneumonia	8 (6.1)	8 (6.1)	14 (10.6)	30 (7.6)
Unclassifiable ILD	11 (8.3)	9 (6.9)	8 (6.1)	28 (7.1)
Other ILDs	10 (7.6)	4 (3.1)	11 (8.3)	25 (6.3)
Inclusion criteria related to ILD progression*				
Relative decline in FVC % predicted ≥ 10%	60 (45.5)	63 (48.1)	83 (62.9)	206 (52.2)
Worsened respiratory symptoms plus increased extent of fibrotic changes on HRCT	31 (23.5)	30 (22.9)	19 (14.4)	80 (20.3)
Relative decline in DLco % predicted ≥ 10%	28 (21.2)	21 (16.0)	17 (12.9)	66 (16.7)
Relative decline in FVC % predicted ≥ 5–<10% plus worsened respiratory symptoms	11 (8.3)	14 (10.7)	10 (7.6)	35 (8.9)
Relative decline in FVC % predicted ≥ 5–<10% plus increased extent of fibrotic changes on HRCT	2 (1.5)	3 (2.3)	3 (2.3)	8 (2.0)
Time since HRCT scan, months	5.4 (2.2, 9.6)	5.1 (2.3, 9.9)	5.0 (1.9, 8.7)	5.1 (2.2, 9.4)
FVC % predicted	68.9 (59.5, 81.1)	60.8 (50.4, 70.7)	51.3 (40.7, 63.8)	61.0 (49.4, 71.7)
DLco % predicted	48.1 (39.6, 56.3)	38.1 (31.4, 46.7)	31.1 (24.9, 38.7)	38.8 (30.6, 49.1)
GAP stage				
I	69 (56.6)	39 (33.1)	17 (15.3)	125 (35.6)
II	49 (40.2)	71 (60.2)	62 (55.9)	182 (51.9)
III	4 (3.3)	8 (6.8)	32 (28.8)	44 (12.5)
CPI	47.6 (40.5, 55.0)	56.4 (50.5, 61.8)	62.7 (57.4, 67.4)	55.8 (47.0, 62.6)
Nintedanib use	16 (12.1)	30 (22.9)	40 (30.3)	86 (21.8)
Immunosuppressant/ cytotoxic use†	70 (58.8)	91 (75.2)	88 (71.0)	249 (68.4)
Oral steroid use	55 (46.2)	68 (57.1)	83 (68.6)	206 (57.4)
Oxygen use with activity	11 (8.6)	24 (18.6)	36 (27.7)	71 (18.3)
Oxygen use at rest	14 (10.9)	22 (17.1)	61 (46.9)	97 (25.1)

Data are median (Q1, Q3) or n (%) of patients with available data

*Investigators were asked to select the criterion that best applied to the patient

†Not including oral steroids

tertile of QLF score was – 18.62 [95% CI: –22.61, – 14.63]. The odds of increased oxygen usage (defined by usage at rest or with exertion vs. no use, or usage at rest vs. with exertion or never) was 10.39 [95% CI: 5.98, 18.05] times higher than in those with a QLF score in the highest versus lowest tertile. Findings were similar for the QILD score (Table S2) and inconsistent for the QGG score (Table S3). There were no significant associations between tertiles of QHC scores and measures of disease severity at enrollment (Table S4). Findings from the sensitivity analyses that were limited to patients with HRCT scans taken between 6 months pre-enrollment and 90

Table 3 Associations between HRCT pattern and measures of disease severity at enrollment

	Unadjusted primary analysis		Unadjusted sensitivity analysis*	
	Effect size for UIP-like pattern (95% CI)	*P*-value	Effect size for UIP-like pattern (95% CI)	*P*-value
FVC % predicted	5.11 (1.56, 8.67)	< 0.01	2.67 (– 2.00, 7.34)	0.26
DLco % predicted	1.90 (– 1.34, 5.15)	0.25	–1.39 (– 5.44, 2.66)	0.50
GAP stage	1.02 (0.68, 1.52)	0.93	1.48 (0.86, 2.56)	0.16
CPI	–1.79 (– 4.35, 0.78)	0.17	1.26 (– 2.05, 4.58)	0.45
Oxygen use	0.80 (0.55, 1.19)	0.28	0.94 (0.55, 1.58)	0.80

Data for GAP stage and oxygen use are OR (95% CI) and parameterized as "worse" versus "better" health status. Other data are mean difference (95% CI)

*Based on HRCT scans taken from 6 months pre-enrollment to 90 days post-enrollment

CPI, composite physiologic index

Table 4 Associations between QLF tertiles and measures of disease severity at enrollment

	Unadjusted primary analysis		Unadjusted sensitivity analysis*	
	Effect size for QLF tertile (95% CI)	*P*-value	Effect size for QLF tertile (95% CI)	*P*-value
FVC % predicted		< 0.001		< 0.001
Highest vs. lowest tertile	–18.62 (– 22.61, – 14.63)		–18.27 (– 23.45, – 13.08)	
Middle vs. lowest tertile	–9.71 (– 13.65, – 5.76)		–7.64 (– 12.81, – 2.47)	
DLco % predicted		< 0.001		< 0.001
Highest vs. lowest tertile	–17.49 (– 20.99, – 13.98)		–15.70 (– 20.05, – 11.36)	
Middle vs. lowest tertile	–11.11 (– 14.59, – 7.62)		–10.35 (– 14.76, – 5.94)	
GAP stage		< 0.001		< 0.001
Highest vs. lowest tertile	9.13 (5.15, 16.21)		10.41 (4.81, 22.53)	
Middle vs. lowest tertile	2.48 (1.51, 4.10)		2.80 (1.40, 5.59)	
Composite physiologic index		< 0.001		< 0.001
Highest vs. lowest tertile	15.87 (13.22, 18.51)		14.96 (11.54, 18.38)	
Middle vs. lowest tertile	9.98 (7.36, 12.59)		9.36 (5.92, 12.81)	
Oxygen use		< 0.001		< 0.001
Highest vs. lowest tertile	10.39 (5.98, 18.05)		11.38 (5.28, 24.51)	
Middle vs. lowest tertile	2.22 (1.26, 3.88)		2.07 (0.94, 4.55)	

Data for GAP stage and oxygen use are OR (95% CI). These were parameterized as "worse" versus "better". Other data are mean difference (95% CI). Lowest tertile: QLF score < 10.7%, middle tertile: QLF score ≥ 10.7% to < 20.5%, highest tertile: QLF score ≥ 20.5%. *Based on HRCT scans taken between 6 months pre-enrollment and 90 days post-enrollment

days post-enrollment were generally similar to those from the primary analysis (Tables 3 and 4 and Tables S2–4), although the association between a UIP-like pattern and FVC % predicted in the primary analysis was no longer significant in the sensitivity analysis.

Associations between HRCT findings and time to ILD progression

Time to ILD progression following enrollment by HRCT pattern is depicted in Fig. 1. Over a median follow-up of 17.3 months, among patients with a UIP-like pattern and other patterns, respectively, 61 (34.3%) and 72 (33.2%) patients had ILD progression and 32 (18.0%) and 32 (14.7%) patients died. In unadjusted and adjusted analyses, there was no significant difference in the risk of ILD progression or death in patients with a UIP-like pattern versus other patterns (adjusted HR 1.01 [95% CI: 0.71, 1.44] for ILD progression and adjusted HR 1.15 [95% CI: 0.69, 1.91] for death) (Table 5).

Time to ILD progression by tertile of QLF score is shown in Fig. 2. Among patients in the lowest, middle and highest tertiles of QLF score, respectively, 42 (31.8%), 36 (27.5%) and 55 (41.7%) had ILD progression and 18 (13.6%), 16 (12.2%) and 30 (22.7%) patients died. In the unadjusted analysis, patients with QLF scores in the highest tertile had an increased risk of ILD progression or death compared with patients in the middle or lowest tertiles (HR [95% CI] 1.63 [1.07, 2.49] and 1.46 [0.97, 2.18], respectively, for ILD progression; HR [95% CI] 2.01 [1.09, 3.69] and 1.84 [1.03, 3.32], respectively, for death). However, after adjustment for sex, age, FVC % predicted and oxygen use at enrollment, there was no significant difference in the risk of progression or death by QLF tertile (Table 6). There were no significant associations between tertiles of QILD score, QGG score, or QHC score and risk of ILD progression or death (Tables S5–7). Findings from the unadjusted sensitivity analysis were generally similar to those from the unadjusted primary analysis (Tables 5 and 6, Tables S5–6).

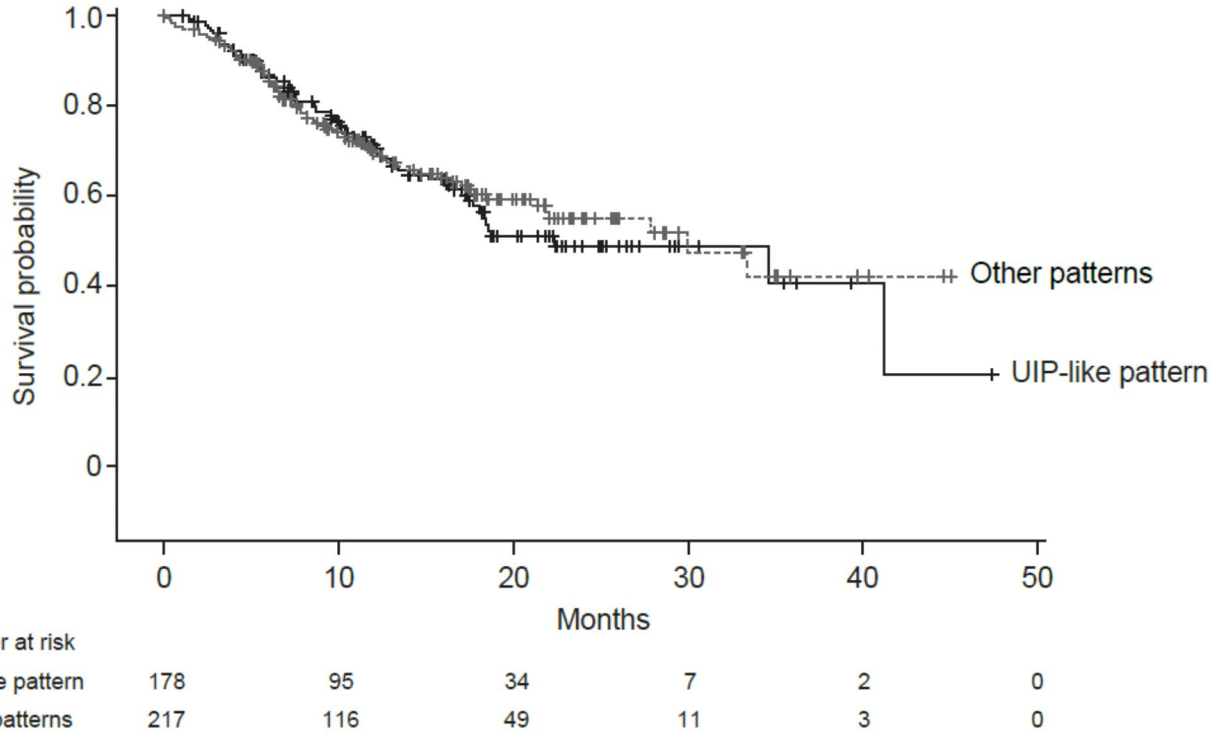

Fig. 1 Kaplan-Meier curves of time to ILD progression (relative decline in FVC % predicted ≥ 10%, death, or lung transplant) by HRCT pattern at enrollment

Table 5 Associations between HRCT pattern at enrollment and time to ILD progression or death

	Unadjusted primary analysis		Adjusted primary analysis		Unadjusted sensitivity analysis*	
	HR (95% CI)	*p*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Relative decline in FVC % predicted ≥ 10%, death, or lung transplant						
UIP-like vs. other patterns	1.07 (0.76, 1.51)	0.68	1.01 (0.71, 1.44)	0.94	1.31 (0.83, 2.06)	0.25
Death						
UIP-like vs. other patterns	1.26 (0.77, 2.05)	0.36	1.15 (0.69, 1.91)	0.60	1.53 (0.80, 2.92)	0.20

Adjusted for sex, and age, FVC % predicted and oxygen use (at rest, with exertion, none) at enrollment

*Based on HRCT scans taken between 6 months pre-enrollment and 90 days post-enrollment

Discussion

To our knowledge, this is the first study to evaluate associations between HRCT patterns and quantitative scores and ILD severity and progression in a real-world cohort of patients with PPF. In contrast to prior studies in patients with ILDs that were not limited to patients with PPF [9, 11, 13, 14, 15, 16, 17, 18], we did not identify an association between a UIP-like pattern on HRCT and ILD severity or progression. In unadjusted analyses, we observed associations between a higher QLF score and both disease severity and progression during follow-up. This suggests that in patients who have already developed PPF, the extent of ILD may be prognostically more relevant than the presence of a UIP-like pattern. However, the associations between QLF score and progression were no longer significant after adjustment for age, sex, FVC % predicted, and oxygen use, implying that among patients known to have PPF, the QLF score does not add to the prognostic information provided by commonly assessed clinical variables.

The association that we observed between higher QLF score and worse disease severity is consistent with prior studies in patients with ILDs [20, 31, 32, 37, 38] and supports a structure–function relationship between lung fibrosis and lung function. Given these strong associations, it is not surprising that the association between QLF score and the risk of ILD progression was attenuated after adjusting for other measures of disease severity. However, our results differ from prior studies conducted in patients with IPF and other fibrosing ILDs that identified associations between quantitative HRCT scores and ILD progression independent of lung function [17, 23, 39]. This difference may be because our study was limited to patients who already had PPF. Our findings suggest that in patients with PPF, either the extent of fibrosis on

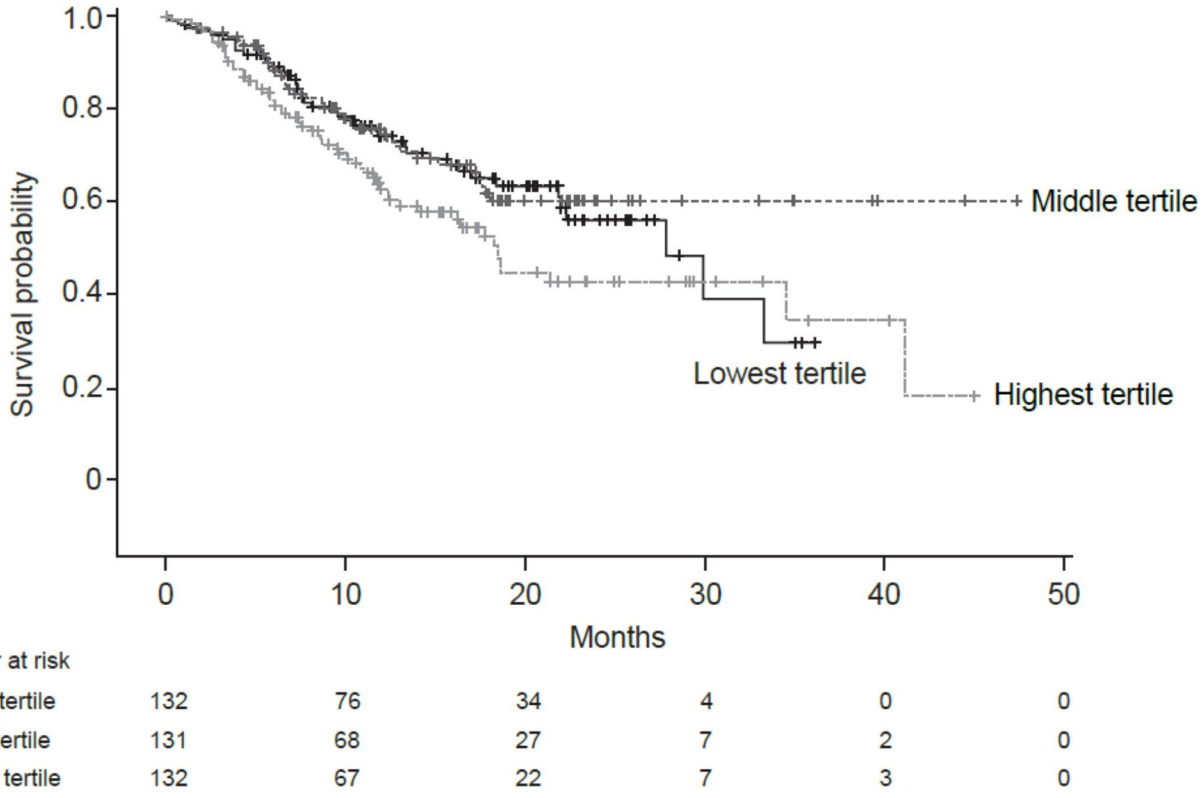

Fig. 2 Kaplan-Meier curves of time to ILD progression (relative decline in FVC % predicted ≥ 10%, death, or lung transplant) by QLF tertile at enrollment

Table 6 Associations between QLF tertiles at enrollment and time to ILD progression or death

	Unadjusted primary analysis		Adjusted primary analysis		Unadjusted sensitivity analysis*	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Relative decline in FVC % predicted ≥ 10%, death, or lung transplant		0.046		0.73		0.036
Highest vs. lowest tertile	1.46 (0.97, 2.18)		1.01 (0.64, 1.61)		1.62 (0.95, 2.78)	
Middle vs. lowest tertile	0.89 (0.57, 1.39)		0.86 (0.54, 1.37)		0.81 (0.44, 1.50)	
Death		0.033		0.40		0.09
Highest vs. lowest tertile	1.84 (1.03, 3.32)		0.99 (0.49, 2.00)		1.66 (0.78, 3.53)	
Middle vs. lowest tertile	0.92 (0.47, 1.80)		0.67 (0.33, 1.36)		0.68 (0.27, 1.70)	

Adjusted for sex, and age, FVC % predicted and oxygen use (at rest, with exertion, none) at enrollment. Lowest tertile: QLF score < 10.7%, middle tertile: QLF score ≥ 10.7% to < 20.5%, highest tertile: QLF score ≥ 20.5%. *Based on HRCT scans taken between 6 months pre-enrollment and 90 days post-enrollment

HRCT or physiologic measures of disease severity can be used to inform the risk of progression.

We did not observe significant associations between quantitative CT measures other than the QLF score and the risk of ILD progression or death. Several studies in patients with IPF have found that a greater extent of honeycombing on HRCT was associated with higher mortality [21, 40, 41]. The lack of association between QHC score and measures of disease severity or the risk of ILD progression or death in our study might be explained by the low QHC scores (median of 0.1%) in our cohort, in whom only a small number of patients had definite UIP, and/or might reflect that the overall extent of lung fibrosis has more of an impact on progression than the extent of honeycombing. Previous studies in patients with ILD associated with rheumatoid arthritis or systemic sclerosis have reported an increased risk of ILD progression or death in patients with worse QILD scores at baseline [13, 24, 25]; however, the patients in these studies generally had lower mean QILD scores than the patients in our study. Our study was underpowered to look for associations in subgroups with specific diagnoses, and it is possible that the QILD score is more relevant as a predictor of ILD progression in patients with systemic autoimmune disease-related ILDs.

In contrast to prior studies in patients with ILDs [9, 11, 13, 14, 15, 16, 17, 18], we did not observe worse disease severity or higher risk of ILD progression or death in

patients with a UIP-like pattern compared with patients with other patterns on HRCT. This may be because in our study, quantitative HRCT scores were generally similar between patients with a UIP-like pattern and other patterns, whereas in prior studies, patients with a UIP-like pattern also had a greater extent of fibrosis [17, 18, 42]. In interpreting our findings, it is important to bear in mind that the ILD-PRO Registry did not enroll all-comers with ILDs, but a selected population of patients who met criteria for PPF. Our data suggest that once patients have developed PPF, progression of fibrosis drives poor outcomes irrespective of whether they have a UIP-like pattern. This finding emphasizes the importance of close monitoring and prompt management of patients with PPF, regardless of HRCT pattern, and the need to continue to investigate risk factors for progression of pulmonary fibrosis beyond a UIP-like pattern, including quantitative radiological biomarkers [4, 43].

Strengths of our analysis include the heterogeneous cohort of patients with PPF with a variety of ILD diagnoses and the prospective data collection. Limitations include the relatively short time frame over which ILD progression was assessed and the small sample size, which may have reduced our ability to detect associations between HRCT patterns/scores and outcomes. The HRCT scans were acquired as part of clinical care and were not standardized. The time lag between the HRCT scan being taken and PFTs being assessed may have hindered detection of associations between HRCT patterns/scores and measures of disease severity or progression; however, a sensitivity analysis limited to patients who had an HRCT scan within 6 months of enrollment provided similar findings. HRCT pattern was determined by a single radiologist, but visual assessment of a UIP pattern is subject to inter-observer variation [44] and has been shown to be less sensitive as a prognostic marker in patients with IPF/PPF than the probability of UIP based on an artificial intelligence algorithm [15]. A lack of power meant that we were unable to assess associations between HRCT patterns and quantitative scores and outcomes in subgroups based on ILD diagnosis. We did not adjust for treatment with antifibrotic or immunosuppressive medications due to limitations in power and variability in treatment patterns, which may have confounded our findings.

In conclusion, in patients with PPF in the ILD-PRO Registry, the extent of lung fibrosis on HRCT was prognostically more important than the pattern on HRCT, but did not provide additional prognostic information beyond established clinical variables. Future studies will evaluate change in QLF score as a prognostic biomarker in patients with PPF.

Plain language summary

- The ILD-PRO Registry is collecting information on patients with progressive (worsening) fibrosis (scarring) of the lungs who are receiving care at centers across the US.
- The patterns and amounts of disease in a patient's lungs can be seen on a scan known as a high-resolution computed tomography or "HRCT" scan. Computer programs can generate scores that measure how much of a patient's lungs are affected by different types of damage. For example, a "quantitative lung fibrosis" score of 20% means that 20% of a patient's lungs is affected by lung fibrosis.
- In this study, researchers used data from 395 patients in the ILD-PRO Registry to look at whether patients who had a greater amount of damage to their lungs had worse lung function when they were enrolled, or were more likely to experience progression (worsening) of their disease during follow-up.
- Over an average follow-up of about 17 months, about a third of the patients in the study had progression of their disease, which was defined as a significant loss of lung function, lung transplant, or death. Patients who had the largest amount of their lungs affected by fibrosis (i.e. who were in the top third of the "quantitative lung fibrosis" scores) had worse lung function at enrollment and were more likely to experience progression of their disease during follow-up than patients who had a lower amount of lung fibrosis.
- Further information collected in the ILD-PRO Registry will help improve our understanding of the course and impact of lung fibrosis.

Abbreviations

CPI	Composite physiologic index
DLco	Diffusing capacity of the lungs for carbon monoxide
FVC	Forced vital capacity
HRCT	High-resolution computed tomography
ILD	Interstitial lung disease
IPAF	Interstitial pneumonia with autoimmune features
IPF	Idiopathic pulmonary fibrosis
PPF	Progressive pulmonary fibrosis
QGG	Quantitative ground glass
QHC	Quantitative honeycomb cysts
QILD	Quantitative interstitial lung disease
QLF	Quantitative lung fibrosis
SSc-ILD	Systemic sclerosis-associated interstitial lung disease
UIP	Usual interstitial pneumonia

Supplementary Information

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Supplementary Material 1

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Author contributions
A.C.S., J.M.W., S.M.P., M.L.N. and T.B.L. contributed to the study design. T.P.W. contributed to data acquisition as a site investigator. J.M.W. and M.L.N. conducted the data analysis. A.C.S., J.M.W., J.L.T., S.M.P., M.L.N., T.P.W., G.H.J.K., T.B.L. and J.G. contributed to the interpretation of the data and to the writing and critical review of this manuscript. All authors have approved the final manuscript.

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Data availability
The datasets analyzed during the current study are not publicly available, but they are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Duke University Institutional Review Board (Pro00046131) and at every enrolling center (listed in the Acknowledgments). The protocol was approved by the relevant Institutional Review Boards and/or local Independent Ethics Committees prior to patient enrolment at every site. All patients provided written consent prior to entering the registry.

Consent for publication
Not applicable.

Competing interests
ACS, JMW, JLT, SMP and MLN are employed by the Duke Clinical Research Institute, which receives funding support from Boehringer Ingelheim Pharmaceuticals, Inc to coordinate the IPF-PRO/ILD-PRO Registry. ACS also reports consulting fees from United Therapeutics. JLT also reports grants from AstraZeneca and CareDx and has participated on advisory boards for Altavant, Avalyn, Natera, Sanofi, Theravance. SMP reports research funding paid to the Duke Clinical Research Institute from Bristol Myers Squibb and Genentech and has participated on advisory boards for Altavant and Bristol Myers Squibb. TPW is a site investigator for the IPF-PRO/ILD-PRO Registry. GHJK reports grants from Boehringer Ingelheim and Genentech; consulting fees from Voiant Clinical (formerly MedQIA); and holds patent UC-2015-0324982-A1. TBL was an employee of Boehringer Ingelheim Pharmaceuticals, Inc at the time that these analyses were performed. JG is the founder of MedQIA, now Voiant Clinical, which received funding support from Boehringer Ingelheim Pharmaceuticals, Inc, to analyze HRCT scans for this project; he also reports grants from Boehringer Ingelheim. The University of California Los Angeles has a patent for the machine learning algorithm used in this project.

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References

1. Selman M, Pardo A. From pulmonary fibrosis to progressive pulmonary fibrosis: a lethal pathobiological jump. Am J Physiol Lung Cell Mol Physiol. 2021;321:L600–7.
2. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, 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:e18–47.
3. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019;381:1718–27.
4. George PM, Spagnolo P, Kreuter M, Altinisik G, Bonifazi M, Martinez FJ, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med. 2020;8:925–34.
5. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med. 2020;8:147–57.
6. Behr J, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F, 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;9:476–86.
7. Pugashetti JV, Adegunsoye A, Wu Z, Lee CT, Srikrishnan A, Ghodrati S, et al. Validation of proposed criteria for progressive pulmonary fibrosis. Am J Respir Crit Care Med. 2023;207:69–76.
8. Maher TM, Brown KK, Kreuter M, Devaraj A, Walsh SLF, Lancaster LH, et al. Effects of nintedanib by inclusion criteria for progression of interstitial lung disease. Eur Respir J. 2022;59:2004587.

9. Oldham JM, Lee CT, Wu Z, Bowman WS, Pugashetti JV, Dao N, et al. Lung function trajectory in progressive fibrosing interstitial lung disease. Eur Respir J. 2022;59:2101396.
10. Buschulte K, Kabitz HJ, Hagmeyer L, Hammerl P, Esselmann A, Wiederhold C, et al. Disease trajectories in interstitial lung diseases - data from the EXCITING-ILD registry. Respir Res. 2024;25:113.
11. Yunt ZX, Chung JH, Hobbs S, Fernandez-Perez ER, Olson AL, Huie TJ, et al. High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: relationship to survival. Respir Med. 2017;126:100–4.
12. Brown KK, Inoue Y, Flaherty KR, Martinez FJ, Cottin V, Bonella F, et al. Predictors of mortality in subjects with progressive fibrosing interstitial lung diseases. Respirology. 2022;27:294–300.
13. Oh JH, Kim GHJ, Cross G, Barnett J, Jacob J, Hong S, et al. Automated quantification system predicts survival in rheumatoid arthritis-associated interstitial lung disease. Rheumatology (Oxford). 2022;61:4702–10.
14. Solomon JJ, Danoff SK, Woodhead FA, Hurwitz S, Maurer R, Glaspole I, et al. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet Respir Med. 2023;11:87–96.
15. Walsh SLF, Mackintosh JA, Calandriello L, Silva M, Sverzellati N, Larici AR, et al. Deep learning-based outcome prediction in progressive fibrotic lung disease using high-resolution computed tomography. Am J Respir Crit Care Med. 2022;206:883–91.
16. Humphries SM, Thieke D, Baraghoshi D, Strand MJ, Swigris JJ, Chae KJ, et al. Deep learning classification of usual interstitial pneumonia predicts outcomes. Am J Respir Crit Care Med. 2024;209:1121–31.
17. Oh AS, Lynch DA, Swigris JJ, Baraghoshi D, Dyer DS, Hale VA, et al. Deep learning-based fibrosis extent on CT predicts outcome of fibrosing interstitial lung disease independent of visually assessed CT pattern. Ann Am Thorac Soc. 2024;21:218–27.
18. Zheng B, Marinescu DC, Hague CJ, Muller NL, Murphy D, Churg A et al. Lung imaging patterns in connective tissue disease-associated interstitial lung disease impact prognosis and immunosuppression response. Rheumatology (Oxford) 2024:keae076.
19. Maldonado F, Moua T, Rajagopalan S, Karwoski RA, Raghunath S, Decker PA, et al. Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis. Eur Respir J. 2014;43:204–12.
20. Kim HJ, Brown MS, Chong D, Gjertson DW, Lu P, Kim HJ, et al. Comparison of the quantitative CT imaging biomarkers of idiopathic pulmonary fibrosis at baseline and early change with an interval of 7 months. Acad Radiol. 2015;22:70–80.
21. Jacob J, Bartholmai BJ, Rajagopalan S, Kokosi M, Nair A, Karwoski R, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. Eur Respir J. 2017;49:1601011.
22. Salisbury ML, Lynch DA, van Beek EJ, Kazerooni EA, Guo J, Xia M, et al. Idiopathic pulmonary fibrosis: the association between the adaptive multiple features method and fibrosis outcomes. Am J Respir Crit Care Med. 2017;195:921–9.
23. Humphries SM, Mackintosh JA, Jo HE, Walsh SLF, Silva M, Calandriello L, et al. Quantitative computed tomography predicts outcomes in idiopathic pulmonary fibrosis. Respirology. 2022;27:1045–53.
24. Goldin JG, Kim GHJ, Tseng CH, Volkmann E, Furst D, Clements P, et al. Longitudinal changes in quantitative interstitial lung disease on computed tomography after immunosuppression in the Scleroderma Lung Study II. Ann Am Thorac Soc. 2018;15:1286–95.
25. Volkmann ER, Tashkin DP, Roth MD, Goldin J, Kim GHJ. Early radiographic progression of scleroderma: lung disease predicts long-term mortality. Chest. 2022;161:1310–9.
26. Jacob J, Bartholmai BJ, Rajagopalan S, Egashira R, Brun AL, Kokosi M, et al. Unclassifiable-interstitial lung disease: outcome prediction using CT and functional indices. Respir Med. 2017;130:43–51.
27. Lobo LJ, Liu Y, Li P, Ramaswamy M, Swaminathan AC, Veeraraghavan S, et al. Design and baseline characteristics of the ILD-PRO Registry in patients with progressive pulmonary fibrosis. BMC Pulm Med. 2024;24:468.
28. Kim HJ, Li G, Gjertson DW, Elashoff R, Shah SK, Ochs R, et al. Classification of parenchymal abnormality in scleroderma lung using a novel approach to denoise images collected via a multicenter study. Acad Radiol. 2008;15:1004–16.
29. Kim HG, Tashkin DP, Clements P, Li G, Brown MS, Elashoff R, et al. A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients. Clin Exp Rheumatol. 2010;28(5 Suppl 62):S26–35.
30. Wang X, Teng P, Lo P, Banola A, Kim G, Abtin F, Goldin J, Brown M. High throughput lung and lobar segmentation by 2D and 3D CNN on chest CT with diffuse lung disease. In: Stoyanov, et al. editors. Image Analysis for Moving Organ, breast, and thoracic images. D.; 2018.
31. Tashkin DP, Volkmann ER, Tseng CH, Kim HJ, Goldin J, Clements P, et al. Relationship between quantitative radiographic assessments of interstitial lung disease and physiological and clinical features of systemic sclerosis. Ann Rheum Dis. 2016;75:374–81.
32. Roofeh D, Lin CJF, Goldin J, Kim GH, Furst DE, Denton CP, et al. Tocilizumab prevents progression of early systemic sclerosis-associated interstitial lung disease. Arthritis Rheumatol. 2021;73:1301–10.
33. Kim HJ, Brown MS, Elashoff R, Li G, Gjertson DW, Lynch DA, et al. Quantitative texture-based assessment of one-year changes in fibrotic reticular patterns on HRCT in scleroderma lung disease treated with oral cyclophosphamide. Eur Radiol. 2011;21:2455–65.
34. Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society white paper. Lancet Respir Med. 2018;6:138–53.
35. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012;156:684–91.
36. Wells AU, Desai SR, Rubens MB, Goh NS, Cramer D, Nicholson AG, et al. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. Am J Respir Crit Care Med. 2003;167:962–9.
37. Salaffi F, Carotti M, Di Donato E, Di Carlo M, Ceccarelli L, Giuseppetti G. Computer-aided tomographic analysis of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc). Correlation with pulmonary physiologic tests and patient-centred measures of perceived dyspnea and functional disability. PLoS ONE. 2016;11:e0149240.
38. Yeo J, Yoon SH, Kim JY, Lee JS, Lee EY, Goo JM, et al. Quantitative interstitial lung disease scores in idiopathic inflammatory myopathies: longitudinal changes and clinical implications. Rheumatology (Oxford). 2023;62:3690–9.
39. Lee SM, Seo JB, Oh SY, Kim TH, Song JW, Lee SM, et al. Prediction of survival by texture-based automated quantitative assessment of regional disease patterns on CT in idiopathic pulmonary fibrosis. Eur Radiol. 2018;28:1293–300.
40. Nakagawa H, Ogawa E, Fukunaga K, Kinose D, Yamaguchi M, Nagao T, et al. Quantitative CT analysis of honeycombing area predicts mortality in idiopathic pulmonary fibrosis with definite usual interstitial pneumonia pattern: a retrospective cohort study. PLoS ONE. 2019;14:e0214278.
41. Kunihiro Y, Matsumoto T, Murakami T, Shimokawa M, Kamei H, Tanaka N, et al. A quantitative analysis of long-term follow-up computed tomography of idiopathic pulmonary fibrosis: the correlation with the progression and prognosis. Acta Radiol. 2023;64:2409–15.
42. Barnett JL, Maher TM, Quint JK, Adamson A, Wu Z, Smith DJF, et al. Combination of BAL and computed tomography differentiates progressive and non-progressive fibrotic lung diseases. Am J Respir Crit Care Med. 2023;208:975–82.
43. Walsh SLF, De Backer J, Prosch H, Langs G, Calandriello L, Cottin V, et al. Towards the adoption of quantitative computed tomography in the management of interstitial lung disease. Eur Respir Rev. 2024;33:230055.
44. Walsh SL, Calandriello L, Sverzellati N, Wells AU, Hansell DM. UIP observer consort. Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT. Thorax. 2016;71:45–51.

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