Supporting Information

Appendix S1.

Quantitative computed tomography (QCT) Analysis

Volumetric non-contrast chest CT scans were acquired during full inspiration in the supine position using three different scanners; Somatom Drive, Somatom Perspective, or Somatom Definition AS (Siemens Healthineers, Forchheim, Germany). The scanning protocol adhered to ATS/ERS guidelines for IPF diagnosis [1], with non-contrast, reduced-dose acquisition using a tube voltage of 120 kVp, tube current-time product of 24–28 mAs, and high-frequency algorithm reconstruction (Br51, I50s, B45f). Images were reconstructed at a 1.5 mm slice thickness.

Quantitative CT (QCT) analysis was performed using a commercially available deep learning software (A-view Lung Texture, version 1.1.44.21; Coreline Soft, Seoul, South Korea) [2, 3]. The software automatically classified lung parenchymal patterns and quantified their volumetric extent as percentages of total lung volume. Fibrosis extent was the volumetric sum of reticulation and honeycombing, and total ILD extent as the sum of ground-glass opacity (GGO), reticulation, and honeycombing [2, 3]. Inflammation extent was defined as the sum of GGO and reticulation excluding honeycombing as an indicator of end-stage fibrosis [4] This definition acknowledges that both GGO and reticulation may represent a broad spectrum of abnormalities ranging from acute lung injury to fine fibrosis [1].

QCT progression was assessed by calculating the absolute change in fibrosis extent between baseline and follow-up exams. Fibrotic progression was defined as an absolute increase of ≥3% in fibrosis extent, based on a previously reported 1-year minimal clinically meaningful threshold of 2.24% [5].

All CT images were reviewed by a thoracic radiologist (J.Y.H., 13 years of experience) to exclude superimposed acute abnormalities, including pneumonia, acute exacerbation, pleural effusion, or pneumothorax, and to validate suitability for quantitative analysis.

Visual CT assessment

CT patterns were classified as typical, probable, or indeterminate for usual interstitial pneumonia according to the 2022 ATS/ERS/JRS/ALAT guidelines [6]. Visual ILD progression was assessed by the same radiologist (J.Y.H.) using binary criteria (progression vs. stability) based on established visual criteria, including new or increased traction bronchiectasis/bronchiolectasis; new GGO with traction bronchiectasis; new fine reticulation; increased reticular coarseness; new or increased honeycombing; and increased lobar volume loss. All assessments were blinded, without access to clinical or QCT data, and repeated after a 2-month interval. Discrepancies were resolved by a senior thoracic radiologist (S.J.C., with 30 years of experience).

Figures

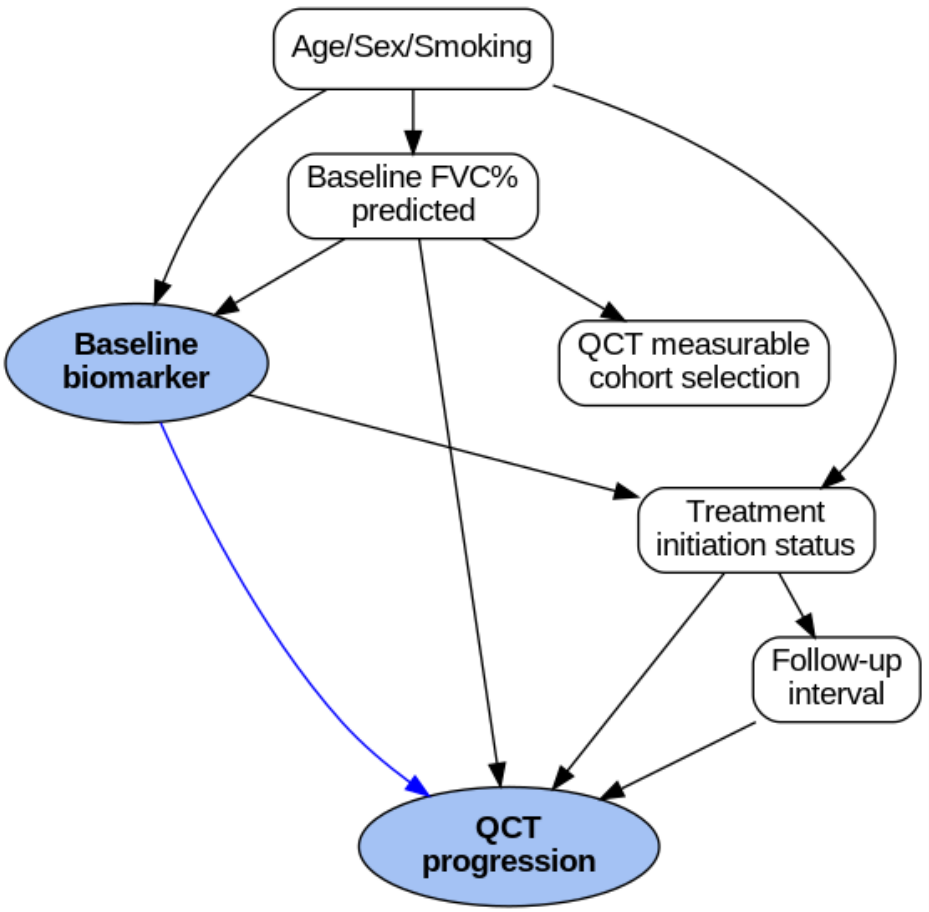

Figure S1. Directed acyclic graph illustrating the assumed causal structure of the study

The directed acyclic graph (DAG) depicts hypothesized relationships among the baseline serum biomarkers, quantitative CT–defined fibrotic progression, and potential confounders. The minimal sufficient adjustment set included age, sex, smoking status, baseline forced vital capacity (% predicted), and CT follow-up interval. Treatment initiation status was considered in sensitivity analyses. The blue arrow indicates the primary association of interest.

Abbreviations: QCT, quantitative CT; FVC, forced vital capacity

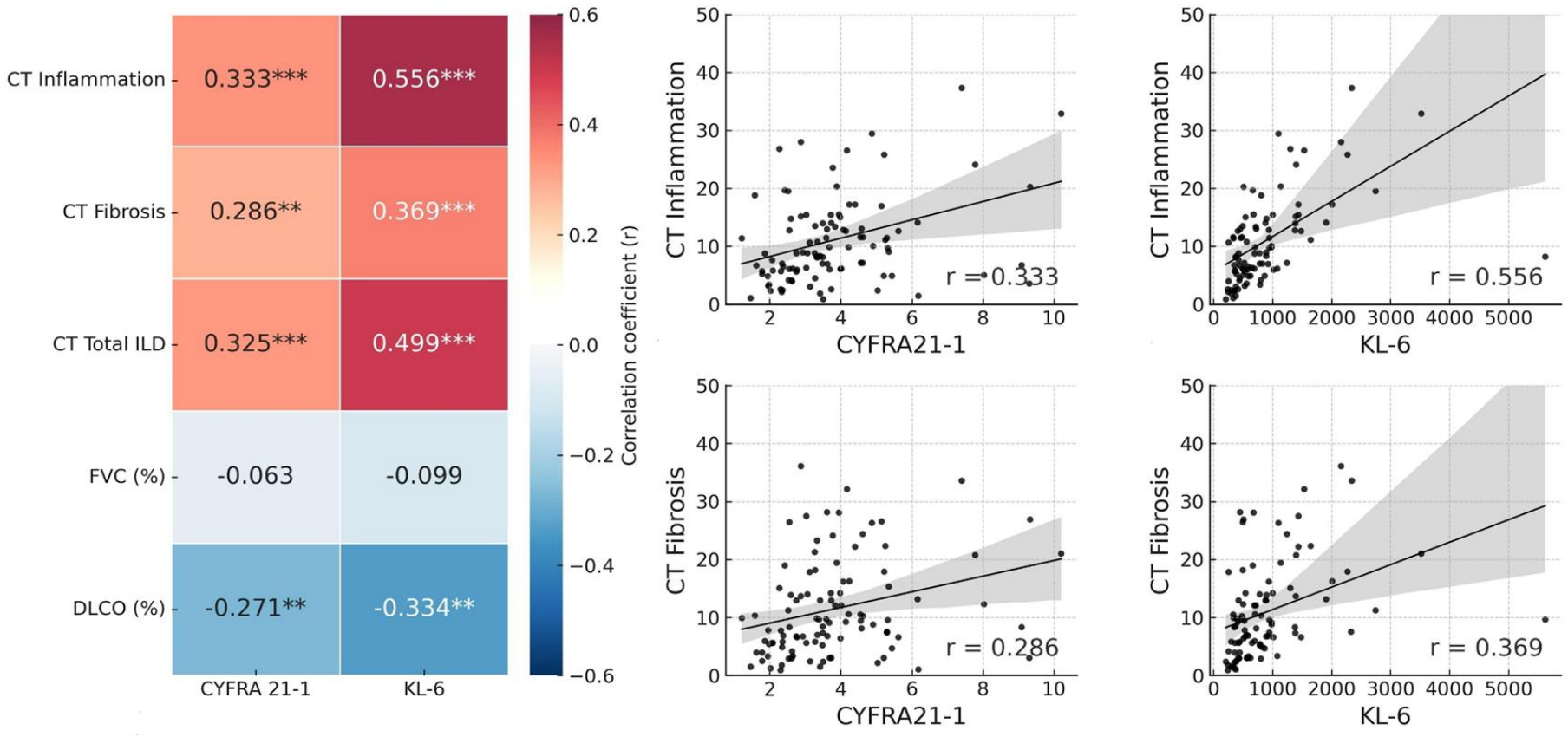

Figure S2. Cross-sectional correlations between baseline serum biomarkers, quantitative CT measures, and pulmonary function.

Heatmap (A) indicating Pearson correlation coefficients between the baseline serum biomarkers (CYFRA 21-1 and KL-6), quantitative CT measures (fibrosis, inflammation, and total ILD extent), and pulmonary function parameters. Color intensity reflects the strength and direction of the correlations. Statistical significance is indicated by asterisks (** $p < 0.01$; *** $p < 0.001$).

Scatter plots illustrating cross-sectional correlations between the baseline serum biomarkers and QCT-defined inflammation extent: CYFRA 21-1 (B) and KL-6 (C).

Scatter plots illustrating cross-sectional correlations between the baseline serum biomarkers and QCT-defined fibrosis extent: CYFRA 21-1 (D) and KL-6 (E).

In panels B–E, solid lines indicate linear regression fits, and shaded areas represent 95% confidence intervals. Overall, KL-6 demonstrated higher correlation coefficients with both QCT-defined inflammation and fibrosis measures compared with CYFRA 21-1 in cross-sectional analyses.

Abbreviations: QCT, quantitative CT; ILD, interstitial lung disease; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide

Tables

Table S1. Sensitivity Analysis Including Antifibrotic Treatment Initiation Status

	Cyfra21-1 (per 1ng/mL)		KL-6 (per 100U/mL)	
	Adjusted OR (CI)	P value	Adjusted OR (CI)	P value
Sex	0.961 (0.144 to 6.404)	0.968	1.004 (0.144 to 6.981)	0.997
Age	0.960 (0.901 to 1.023)	0.213	0.981 (0.920 to 1.047)	0.566
Smoking	0.558 (0.104 to 2.996)	0.496	0.672 (0.113 to 3.989)	0.661
Baseline FVC (%)	0.925 (0.887 to 0.965)	<0.001	0.927 (0.887 to 0.968)	<0.001
CT follow up duration	1.312 (1.063 to 1.619)	0.011	1.243 (0.996 to 1.551)	0.054
Serum biomarker	1.397 (1.025 to 1.903)	0.034	1.084 (1.011 to 1.163)	0.024
Antifibrotics at baseline	0.602 (0.120 to 3.424)	0.602	0.729 (0.144 to 3.686)	0.702

Models were additionally adjusted for antifibrotic treatment initiation status to assess the robustness of the primary associations between serum biomarkers and QCT-defined fibrotic progression.

Abbreviations: OR, odds ratio; CI, confidence interval

Table S2. Predictive Performance of Serum Biomarkers for Disease Progression Assessed by Receiver Operating Characteristic Analysis

	AUC	CI	P value
Clinical progression* (n = 94)			
CYFRA 21-1	0.574	0.456, 0.692	0.242
KL-6	0.484	0.359, 0.609	0.802
Visual CT progression			
CYFRA 21-1	0.666	0.551, 0.781	0.004
KL-6	0.653	0.527, 0.778	0.017
QCT Fibrosis progression†			
CYFRA 21-1	0.693	0.580, 0.806	0.001
KL-6	0.754	0.645, 0.863	<0.001

The values represent the area under the curve (AUC) with 95% confidence intervals.

The optimal cut-off values for predicting QCT-defined fibrotic progression (≥ 3% increase) were 3.98 ng/mL for CYFRA 21-1 (sensitivity 57.7%, specificity 77.5%) and 636.7 U/mL for KL-6 (sensitivity 88.5%, specificity 52.4%).

*Clinical progression was defined as a > 10% decline in FVC or DLCO or death within one year.

†QCT-defined fibrosis progression was defined as a > 3% increase in fibrosis extent.

Abbreviations: AUC, area under the curve; CI, confidence interval; QCT, quantitative CT; ILD, interstitial lung disease; ROC, receiver operating characteristic

References

1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018; 198: e44-e68.
2. Koh SY, Lee JH, Park H, Goo JM. Value of CT quantification in progressive fibrosing interstitial lung disease: a deep learning approach. Eur Radiol. 2024; 34: 4195-4205.
3. Ahn Y, Kim HC, Lee JK, et al. Usefulness of CT Quantification-Based Assessment in Defining Progressive Pulmonary Fibrosis. Acad Radiol. 2024; 31: 4696-4708.
4. Arakawa H, Honma K. Honeycomb lung: history and current concepts. AJR Am J Roentgenol. 2011; 196: 773-782.
5. Park S, Kim MJ, Lee JH, et al. Quantitative CT Imaging in Progressive Pulmonary Fibrosis: Clinical Usefulness and Meaningful Threshold Definition. Chest. 2025.
6. 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: e18-e47.