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HRCT-assessed fibrosis burden predicts mortality better than pulmonary function decline in progressive pulmonary fibrosis

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Abstract:

BACKGROUND AND AIM: Progressive pulmonary fibrosis (PPF) is a clinically significant phenotype observed across fibrotic interstitial lung diseases (ILDs), characterized by pulmonary functional decline, radiologic progression, and worsening symptoms. While declines in forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) are widely used to define progression, the prognostic value of baseline radiologic fibrosis burden in real-world PPF cohorts remains incompletely defined. We aimed to evaluate the relationships among HRCT-derived fibrosis extent, pulmonary function decline, and overall survival in patients with PPF.

METHODS: In this retrospective single-center study, 99 patients with progressive fibrotic ILD who were followed between 2010 and 2019 were included. PPF was defined according to accepted criteria, including functional, radiologic, and symptomatic progression. The extent of fibrosis on HRCT was assessed by two independent radiologists using a semi-quantitative visual scoring method. Cox regression models were used to identify predictors of mortality.

RESULTS: Baseline HRCT fibrosis extent was independently associated with mortality. In a multivariable analysis adjusted for age, sex, smoking status, and diagnosis, each 1% increase in fibrotic involvement was associated with a 5% higher risk of death (HR 1.050, 95% CI 1.025–1.076; $p < 0.001$). In contrast, categorical declines in FVC or DLCO ($\geq 5\%$ or $\geq 10\%$) were not independently associated with survival. Baseline DLCO impairment and smoking history were also associated with reduced survival.

CONCLUSIONS: In patients with PPF, radiological fibrosis burden on HRCT outperformed conventional spirometric decline thresholds in predicting mortality. These findings support an integrated prognostic approach combining standardized HRCT quantification with longitudinal functional assessment to improve risk stratification and clinical decision-making in PPF.

Keywords:

Diffuse parenchymal lung diseases, high resolution computerized tomography, fibrotic interstitial lung diseases, progressive pulmonary fibrosis

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Introduction

Interstitial lung diseases (ILDs) comprise a heterogeneous group of disorders characterized by varying etiologies, clinical courses, and prognoses. Among them, idiopathic pulmonary fibrosis (IPF) represents the most aggressive fibrotic phenotype and is defined by the radiologic and histopathologic pattern of usual interstitial pneumonia (UIP).^[1] However, it has become increasingly recognized that a progressive fibrotic course is not exclusive to IPF. Several other fibrotic ILDs, including fibrotic hypersensitivity pneumonitis (fHP), connective tissue disease-associated ILDs (CTD-ILDs), and some idiopathic interstitial pneumonias, may also develop a similar progressive phenotype.^[2]

This clinical behavior has been defined as progressive pulmonary fibrosis (PPF) in the 2022 ATS/ERS/JRS/ALAT guideline, characterized by worsening respiratory symptoms, radiological progression, and/or pulmonary functional decline within a one-year period in patients with underlying fibrotic ILD.^[2] The development of PPF is associated with substantial deterioration in quality of life, progressive loss of lung function, and increased mortality. Consequently, early identification of patients at risk for PPF has become an important clinical objective. Functional parameters such as declines in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) are widely used indicators of disease progression, and several threshold values have been proposed to define clinically meaningful deterioration.^[3–5] In addition, radiological progression and the extent of fibrotic involvement on high-resolution computed tomography (HRCT) provide important information regarding disease behavior.^[6]

Although both pulmonary functional decline and radiologic progression are recognized markers of disease worsening, the prognostic significance of baseline fibrotic burden on HRCT for predicting PPF has not been fully clarified. In this study, we retrospectively evaluated patients meeting the diagnostic criteria for PPF by analyzing pulmonary function parameters and HRCT findings to investigate whether the extent of fibrotic involvement on HRCT may provide additional prognostic information on disease progression.

Materials and Methods

This study was designed as a retrospective case-control study. The patient cohort consisted of individuals with

ILD who were followed at our center between January 1, 2010, and December 31, 2019. After approval for the study was obtained from the Ethics Committee of Pamukkale University (Approval Number: 60116787-020/72294, Date: October 27, 2020), patient data were analyzed. Our study was conducted in accordance with the Declaration of Helsinki. Patients were included if they demonstrated a PPF and had sufficient clinical data for analysis. Cases with incomplete medical records or those lacking serial HRCT or pulmonary function tests (PFTs) were excluded.

The data were obtained from the hospital's electronic medical records system. Survival data were obtained through the hospital information system and the national health system's mortality records. HRCT images and PFTs were performed in our outpatient clinic using the same standard equipment throughout the study period, ensuring consistency in data acquisition. As this was a retrospective study, HRCT and PFT assessments were performed according to the timing and clinical judgment of the treating pulmonologists. The time interval between radiologic and functional assessments was recorded for each patient and included in the analysis.

PPF was defined based on at least two of the following during follow-up:

1. Physiological evidence of disease progression (either of the following):
 - a. Absolute decline in FVC $\geq 5\%$ predicted within 1 year of follow-up,
 - b. Absolute decline in DLCO (corrected for Hb) $\geq 10\%$ predicted within 1 year of follow-up.
2. Radiologic evidence of fibrotic progression on HRCT, or
3. Documentation of worsening respiratory symptoms by the treating physician in the clinical notes.

The study population included patients with IPF, CTD-ILD, and fHP, as determined by a multidisciplinary team evaluation.

HRCT images were evaluated using a simplified semi-quantitative visual scoring system based on the method described by Goh et al.^[7] At each predefined anatomical level, the extent of fibrotic involvement was visually estimated to the nearest 5%, and the average of these estimates was used to determine global fibrosis. Reticulation grading was not performed; only the percentage of fibrotic

Table 1: Baseline demographic and clinical characteristics of the study population

Variable	Category	All patients	Censored	Exitus	p
Age	Mean±SD	66.97±9.84	66±10.87	68.34±8.1	0.313
	Median (IQR)	67 (62–74)	66 (60.75–73.25)	70 (62–75)	
	Min–max	34–86	34–86	47–83	
Sex, n (%)	Male	65 (65.66)	35 (60.3)	30 (73.2)	0.186
	Female	34 (34.34)	23 (39.7)	11 (26.8)	
Occupational exposure, n (%)	No risk	50 (50.51)	33 (56.9)	17 (41.5)	0.13
	Risk present	50 (49.49)	25 (43.1)	24 (58.5)	
Smoking status, n (%)	Never smoker	43 (43.43)	29 (50)	14 (34.1)	0.117
	Former smoker	56 (56.57)	29 (50)	27 (65.9)	
Rheumatologic disease, n (%)	No	78 (78.79)	43 (74.1)	35 (85.4)	0.178
	Yes	21 (21.21)	15 (25.9)	6 (14.6)	
Diagnosis, n (%)	CTD-ILD	34 (34.34)	24 (41.4)	10 (24.4)	0.155
	IPF	51 (51.52)	28 (48.3)	23 (56.1)	
	fHP	14 (14.14)	6 (10.3)	8 (19.5)	

SD: Standard deviation, CTD-ILD: Connective tissue disease–associated ILD, IPF: Idiopathic pulmonary fibrosis, fHP: Fibrotic hypersensitivity pneumonitis.

involvement was assessed. All HRCT scans were obtained at our center and met predefined standards for technical quality. Two experienced radiologists independently scored each scan while blinded to both clinical data and each other's evaluations. The interobserver agreement was calculated and found to be high, supporting the reliability and reproducibility of the visual scoring approach.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY). Continuous variables were presented as mean±standard deviation, and categorical variables as n (%). When parametric test assumptions were met, Student's t-test was used to compare two means; when parametric test assumptions were not met, the Mann-Whitney U test was used to compare independent groups. Furthermore, relationships between continuous variables were analyzed using Spearman or Pearson correlation analyses, and survival associations were assessed using Cox proportional hazards regression models. Comparisons of categorical variables, including those across multiple diagnostic subgroups, were performed using the chi-square test, with Fisher's exact test applied when appropriate. Interobserver agreement between the two thoracic radiologists for the visual fibrosis scores was assessed using the intraclass correlation coefficient (ICC). Statistical significance was defined as $p < 0.05$.

Results

A total of 99 patients diagnosed with PPF were included in the study. The baseline demographic and clinical characteristics are summarized in Table 1.

Interobserver agreement for visual HRCT fibrosis scoring was excellent, with an intraclass correlation coefficient (ICC) of 0.882, supporting the reproducibility of the semi-quantitative assessment method.

Kaplan–Meier survival analysis demonstrated significant differences across diagnostic subgroups (log-rank $p = 0.026$); patients with IPF exhibited the poorest survival among fibrotic ILD subtypes (Fig. 1, Table 2). Baseline pulmonary function parameters were also associated with survival: both baseline DLCO and baseline FVC showed significant differences in survival distributions ($p = 0.018$ and $p = 0.045$, respectively). In contrast, longitudinal declines in DLCO and FVC at predefined thresholds ($\geq 5\%$ and $\geq 10\%$) were not significantly associated with survival outcomes.

Among patients with available longitudinal data, declines in DLCO and FVC were frequently observed; however, these changes did not differ significantly between survival groups (Table 3) or across ILD subtypes (Table 4). Although a trend toward earlier decline was observed in patients with IPF, these differences did not reach statistical significance.

In univariate Cox regression analyses, smoking status, diagnostic subtype, baseline DLCO $\geq 80\%$ predicted, baseline FVC $\geq 80\%$ predicted, and HRCT-derived fibrosis extent were significantly associated with mortality (Table 5). In contrast, longitudinal declines in DLCO and FVC were not predictive of survival.

In multivariable models, HRCT fibrosis extent remained the only consistent independent predictor of mortality.

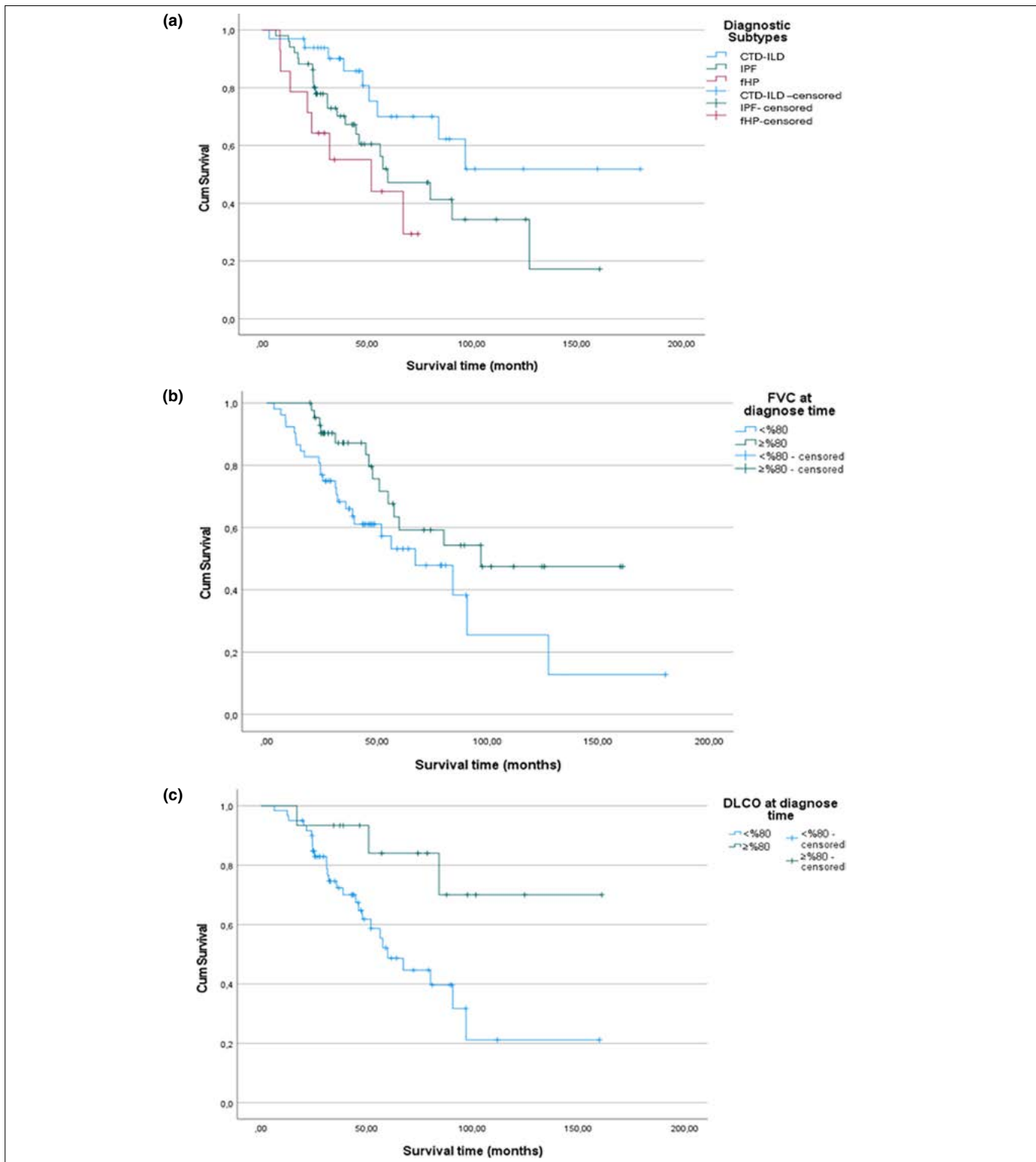


Figure 1: Kaplan–Meier survival curves according to diagnosis and baseline pulmonary function parameters. Kaplan–Meier survival curves showing overall survival according to (a) diagnostic subgroup, (b) baseline FVC status, and (c) baseline DLCO status. Survival differed significantly among fibrotic ILD subtypes, with patients with IPF showing poorer survival than those with CTD-ILD and fHP (log-rank $p=0.025$). Patients with impaired baseline DLCO had significantly different survival compared with those with preserved DLCO (log-rank $p=0.018$). Baseline FVC status was also significantly associated with survival outcomes (log-rank $p=0.045$). Tick marks indicate censored observations. DLCO: Diffusing capacity of the lung for carbon monoxide, FVC: Forced vital capacity, ILD: Interstitial lung disease, IPF: Idiopathic pulmonary fibrosis, CTD-ILD: Connective tissue disease-associated ILD, fHP: Fibrotic hypersensitivity pneumonitis

Table 2: Survival analysis according to clinical variables and pulmonary function parameters

Variable	Total (n)	Event n (%)	Censored n (%)	Mean±SE (months)	%95 CI (Lower–Upper)	Log-rank p
Diagnostic subgroups						
CTD-ILD	34	10 (29.4)	24 (70.6)	118.31±14.64	89.62–147.00	0.026*
IPF	51	23 (45.1)	28 (54.9)	79.18±10.16	59.27–99.09	
fHP	14	8 (57.1)	6 (42.9)	45.76±7.21	31.61–59.9	
Baseline DLCO status						
<80	60	27 (45)	33 (55)	76.89±9.68	57.92–95.85	0.018*
≥80	15	3 (20)	12 (80)	130.38±15.22	100.55–160.21	
≥5% decline in DLCO						
No	18	7 (38.9)	11 (61.1)	64.51±9.53	45.83–83.18	0.329
Yes	47	18 (38.3)	29 (61.7)	97.9±10.34	77.63–118.18	
≥10% decline in DLCO						
No	27	12 (44.4)	15 (55.6)	71.66±9.67	52.7–90.62	0.189
Yes	37	13 (35.1)	24 (64.9)	102.39±11.77	79.32–125.46	
Baseline FVC						
<80	52	25 (48.1)	27 (51.9)	75.37±11.86	52.12–98.63	0.045*
≥80	43	14 (32.6)	29 (67.4)	104.67±11.04	83.02–126.31	
≥5% decline in FVC						
No	54	19 (35.2)	35 (64.8)	93.96±13.19	68.11–119.8	0.546
Yes	40	19 (47.5)	21 (52.5)	87.68±11.12	65.89–109.47	
≥10% decline in FVC						
No	66	23 (34.8)	43 (65.2)	95.48±12.61	70.77–120.18	0.359
Yes	28	15 (53.6)	13 (46.4)	81.57±12.6	56.88–106.27	

*p<0.05: Statistically significant, Kaplan Meier Survival Analysis. SE: Standard error, %95 CI: %95 Confidence interval, IPF: Idiopathic pulmonary fibrosis, DLCO: Diffusing capacity of the lung for carbon monoxide, FVC: Forced vital capacity.

Table 3: Longitudinal pulmonary function changes and their distribution by survival status

Variable	Category	All patients n (%)	Censored n (%)	Exitus n (%)	p
Baseline DLCO status	<80	61 (80.26)	33 (73.3)	28 (90.3)	0.067
	≥80	15 (19.74)	12 (26.7)	3 (9.7)	
≥5% decline in DLCO	No	18 (27.69)	11 (27.5)	7 (28)	0.965
	Yes	47 (72.31)	29 (72.5)	18 (72)	
≥10% decline in DLCO	No	27 (42.19)	15 (38.5)	12 (48)	0.451
	Yes	37 (57.81)	24 (61.5)	13 (52)	
Baseline FVC	<80	53 (55.2)	27 (48.2)	26 (65)	0.103
	≥80	43 (44.8)	29 (51.8)	14 (35)	
≥5% decline in FVC	No	54 (57.4)	35 (62.5)	19 (50)	0.229
	Yes	40 (42.6)	21 (37.5)	19 (50)	
≥10% decline in FVC	No	66 (70.2)	43 (76.8)	223 (60.5)	0.091
	Yes	28 (29.8)	13 (23.2)	15 (39.5)	

DLCO: Diffusing capacity of the lung for carbon monoxide, FVC: Forced vital capacity.

In Model 1, each 1% increase in fibrosis extent (Observer 1 – Scan 1) was associated with a 4.8% increase in the risk of death (HR 1.048, 95% CI 1.021–1.076; p<0.001). Similarly, in Model 2, fibrosis extent measured on the second scan remained independently associated with mortality (HR 1.082, 95% CI 1.037–1.129; p<0.001).

After adjustment for age, sex, smoking status, and diagnostic subtype, neither baseline FVC nor baseline DLCO,

and none of the predefined thresholds for longitudinal decline in these parameters, remained independently associated with mortality.

Discussion

In this study, we evaluated the clinical, functional, and radiological characteristics of 99 patients diagnosed with PPF and investigated factors associated with overall

Table 4: Distribution of baseline pulmonary function and longitudinal functional decline by ILD diagnostic subgroup

Variable	Category	CTD-ILD n (%)	IPF n (%)	fHP n (%)	p
Baseline DLCO status	<80	17 (70.8)	38 (88.4)	6 (66.7)	0.125
	≥80	7 (29.2)	5 (11.6)	3 (33.3)	
≥5% decline in DLCO	No	5 (25)	8 (22.2)	5 (55.6)	0.157
	Yes	15 (75)	28 (77.8)	4 (44.4)	
≥10% decline in DLCO	No	8 (40)	13 (37.1)	6 (66.7)	0.273
	Yes	12 (60)	22 (62.9)	3 (33.3)	
Baseline FVC	<80	17 (53.1)	28 (56)	8 (57.1)	0.956
	≥80	15 (46.9)	22 (44)	6 (42.9)	
≥5% decline in FVC	No	19 (59.4)	28 (57.1)	8 (57.1)	0.979
	Yes	13 (40.6)	21 (42.9)	6 (42.9)	
≥10% decline in FVC	No	20 (62.5)	38 (77.6)	9 (64.3)	0.297
	Yes	12 (37.5)	11 (22.4)	5 (35.7)	

CTD-ILD: Connective tissue disease-associated ILD, IPF: Idiopathic pulmonary fibrosis, fHP: Fibrotic hypersensitivity pneumonitis, DLCO: Diffusing capacity of the lung for carbon monoxide, FVC: Forced vital capacity.

Table 5: Cox proportional hazards regression analyses of factors associated with mortality in patients with fibrotic ILDs

Model	Variable	Wald	p	HR	95% CI (Lower–Upper)
Univariate	Age	0.724	0.395	1.014	0.982–1.047
	Sex (Female; Reference: Male)	2.913	0.088	0.547	0.273–1.094
	Smoking status (Present; Reference: Absent)	4.912	0.027*	2.124	1.091–4.137
	Diagnostic subtype (IPF; Reference: CTD-ILD)	3.852	0.05*	2.172	1.001–4.713
	Diagnostic subtype (IPF; Reference: fHP)	6.481	0.011*	3.537	1.337–9.354
	Baseline DLCO ≥80% (Present; Reference: Absent)	4.842	0.028*	0.258	0.077–0.863
	≥5% decrease in DLCO (Present; Reference: Absent)	0.940	0.332	0.645	0.265–1.566
	≥10% decrease in DLCO (Present; Reference: Absent)	1.689	0.194	0.591	0.268–1.306
	Baseline FVC ≥80% (Present; Reference: Absent)	3.899	0.048*	0.512	0.264–0.995
	≥5% decrease in FVC (Present; Reference: Absent)	0.444	0.505	1.243	0.656–2.354
	≥10% decrease in FVC (Present; Reference: Absent)	0.941	0.332	1.383	0.718–2.662
Model 1	HRCT fibrotic extent	15.953	<0.0001*	1.050	1.025–1.076
	Age	0.125	0.723	1.007	0.969–1.047
	Sex (Female; Reference: Male)	0.355	0.551	1.519	0.384–6.01
	Smoking status (Present; Reference: Absent)	1.813	0.178	2.484	0.661–9.341
	Diagnostic subtype (IPF; Reference: CTD-ILD)	0.103	0.748	1.176	0.436–3.174
	Diagnostic subtype (IPF; Reference: fHP)	3.557	0.059	3.181	0.956–10.586
Model 2	HRCT fibrotic extent	12.329	<0.0001*	1.048	1.021–1.076
	Age	0.899	0.343	1.023	0.976–1.072
	Sex (Female; Reference: Male)	0.071	0.790	1.381	0.129–14.81
	Smoking status (Present; Reference: Absent)	1.118	0.290	3.752	0.324–43.513
	Diagnostic subtype (IPF; Reference: CTD-ILD)	1.494	0.222	2.178	0.625–7.588
	Diagnostic subtype (IPF; Reference: fHP)	4.219	0.04*	5.212	1.078–25.194
	HRCT fibrotic extent	12.989	<0.0001*	1.082	1.037–1.129

*: p<0.05 statistically significant. HR: Hazard ratio, CI: confidence interval, IPF: Idiopathic pulmonary fibrosis, CTD-ILD: Connective tissue disease-associated ILD, fHP: Fibrotic hypersensitivity pneumonitis, DLCO: Diffusing capacity of the lung for carbon monoxide, FVC: Forced vital capacity, HRCT: High-resolution computed tomography, ILD: Interstitial lung disease.

survival. A central finding of our analysis was that the extent of fibrotic involvement on baseline HRCT was independently associated with mortality. In both univariate and multivariate Cox regression models, each 1% increase in visually scored fibrotic extent was associated with an increased risk of death (multivariable HR 1.050, 95% CI 1.025–1.076; p<0.001) and this association

remained significant after adjustment for age, sex, smoking status, and diagnosis. These findings highlight the critical prognostic role of radiological fibrosis burden in PF-ILD, suggesting that quantitative or semi-quantitative assessment of fibrosis on HRCT is a more robust predictor of survival than baseline pulmonary function parameters in our cohort. Conversely, declines in DLCO

and FVC of $\geq 5\%$ and $\geq 10\%$ were not significantly associated with mortality in either univariate and multivariate analyses. The observed effect size is clinically meaningful and supports the concept that radiological fibrosis burden captures irreversible structural lung damage more reliably than isolated spirometric measures.

In a recent multicenter analysis from the ILD-PRO registry, investigators reported that the extent of lung fibrosis on HRCT was a stronger predictor of disease progression than fibrotic pattern descriptors, such as a UIP pattern; however, the quantitative CT score did not provide additional prognostic information beyond clinical variables.^[8] Similarly, in CTD-ILD baseline HRCT fibrosis extent has been independently associated with mortality, reinforcing the concept that total fibrotic burden captures disease severity beyond functional decline alone.^[9] In our study, fibrotic burden on HRCT was quantified by two experienced thoracic radiologists who independently assessed scans while blinded to each other's evaluations, and their assessments showed high interobserver agreement. Although this approach ensured methodological rigor, we acknowledge that intercenter variability in image acquisition and reader interpretation may influence visual scoring in real-world settings. Rapid advances in deep learning and radiomics now provide more standardized, reproducible, and potentially more sensitive methods for quantifying fibrotic changes on HRCT. Recent studies suggest that AI-driven approaches may reduce observer dependency and enhance prognostic precision, particularly in heterogeneous diseases such as PPF.^[10,11] Therefore, while our findings support the prognostic value of expert visual scoring, we anticipate that future AI-based quantitative imaging tools could further refine and potentially surpass the accuracy of semi-quantitative methods, enabling more individualized risk stratification and treatment planning in PPF.

In our cohort, baseline fibrotic burden on HRCT emerged as a strong and independent predictor of mortality, whereas categorical declines in FVC or DLCO ($\geq 5\%$ or $\geq 10\%$) were not significantly associated with overall survival. Although this finding may appear to contrast with a substantial body of literature demonstrating the prognostic value of pulmonary function decline in PPF, it should not be interpreted as negating the clinical relevance of changes in FVC and DLCO. Although Kaplan-Meier analyses suggested that patients with baseline DLCO or FVC $< 80\%$ had significantly shorter

survival compared with those with higher values, these associations did not remain significant in multivariable Cox regression models. This discrepancy indicates that baseline pulmonary function is influenced by other clinical factors and radiological disease burden, and highlights that the extent of fibrosis on HRCT, a measure of structural lung damage, is a more robust independent predictor of mortality than baseline spirometric values. The 2022 ERS/ATS clinical practice guideline for PPF appropriately recognizes FVC and DLCO decline as a central criterion for defining disease progression and a key component of longitudinal assessment.^[2] Accordingly, our results should not be interpreted as diminishing the importance of FVC and DLCO in monitoring disease progression. Rather, they suggest that pulmonary function measures alone may not fully capture prognosis, and that the extent of fibrotic involvement on HRCT provides additional and potentially stronger prognostic information regarding survival.

Longitudinal changes in pulmonary function are influenced by multiple factors beyond fibrotic progression, including acute exacerbations, pulmonary hypertension, cardiac dysfunction, concomitant airway disease, and measurement variability, all of which may attenuate their prognostic signal in real-world heterogeneous cohorts.^[12-14] Pulmonary hypertension and left heart disease can reduce DLCO and FVC through mechanisms independent of parenchymal fibrosis, potentially confounding the relationship between functional decline and mortality.^[13,15] Furthermore, our cohort included not only patients with IPF but also individuals with fHP and CTD-ILD conditions characterized by distinct biological behaviors and variable physiological trajectories. The relatively limited sample size may have further reduced our statistical power to detect independent associations between functional decline and survival.

In contrast, the strong prognostic performance of quantitative HRCT fibrosis extent observed in our study underscores the central role of structural disease burden in determining outcomes in PPF. These findings suggest that while FVC and DLCO remain essential clinical tools, their prognostic utility is likely optimized when interpreted in conjunction with the extent of radiological fibrosis rather than used as standalone thresholds. An integrated, patient-level assessment combining imaging and lung function may therefore provide more accurate risk stratification, particularly in cohorts enriched for PPF.

In subgroup analyses, we observed that a $\geq 5\%$ decline in DLCO occurred more rapidly in patients with IPF, indicating a more aggressive disease course compared with other subtypes. Although patients with fHP experienced a $\geq 5\%$ decline in DLCO at a similar rate to those with CTD-ILD, the time to reach a 10% decline appeared shorter in the fHP group; however, this difference was not statistically significant. In our study, occupational or environmental exposures were identified in nearly half of the patients, suggesting that such exposures may negatively impact disease progression and survival. Smoking was found to have a significantly negative effect on survival across all patient groups ($p=0.027$), consistent with the literature and supporting its role in accelerating disease progression by increasing inflammation and tissue damage. These findings highlight the importance of thoroughly investigating exposures in patients diagnosed with ILD and of prioritizing smoking cessation efforts.

In the retrospective cohort study by Lee *et al.*,^[16] involving a one-year follow-up of 319 patients with IPF, a 10% decline in DLCO was emphasized as a significant prognostic marker for monitoring fibrotic progression. This study differs from ours in that it included all patients diagnosed with IPF, rather than only those with PPF. However, in patients with IPF and well-defined disease trajectories, such monitoring provides valuable insights into which parameters should be followed in clinical practice. Moreover, because IPF constituted the largest subgroup in our study, the finding that a 10% decline in DLCO is an important prognostic marker is relevant to our results.

In the study by Cen *et al.*,^[17] a baseline DLCO level of $<50\%$ and the presence of a UIP-like pattern on thoracic HRCT emerged as the variables most strongly associated with the development of PPF. The inclusion of patients with CTD-ILD in their cohort reflects a patient profile similar to that of our study. However, their approach was based on categorizing patients into those who developed PPF and those who did not, and directly comparing the clinical and radiological characteristics of these two groups. While our study does not include this exact stratification, the findings of Cen *et al.* suggest that parameters such as low DLCO and the presence of a UIP pattern may be valuable both diagnostically and in predicting progressive fibrotic behavior. In this respect, their findings are informative in identifying early markers relevant to the definition of PPF and are consistent with the results we obtained.

Although the time to 5% and 10% declines in FVC appeared shorter in patients with IPF than in those with CTD-ILD or fHP, the differences did not reach statistical significance. This trend, however, may still carry clinical relevance, as earlier functional deterioration in patients with IPF aligns with the known progressive nature of the disease. The lack of statistical significance might be partly attributable to a relatively small sample size, particularly in the fHP group, which may have limited statistical power to detect meaningful differences. Future studies with larger and more balanced subgroup populations are warranted to better clarify the trajectory of lung function decline across different ILD phenotypes.

In the study by Jang *et al.*,^[18] advanced age and low FVC were identified as independent predictors of mortality following the development of PPF in patients with non-IPF ILDs. This study is noteworthy because it evaluates factors influencing both the development of PPF and subsequent survival among patients with and without PPF. In contrast, our study did not find a statistically significant association between FVC and mortality. This discrepancy may be attributed to differences in patient profiles, follow-up durations, or assessment methodologies between the studies.

The demographic characteristics of our cohort are largely consistent with the literature. The mean age was 66.97 ± 9.84 years, with most patients being over 60 years old. This aligns with large-scale studies such as PROGRESS (68.4 ± 15.0 years)^[19] and ILD-PRO (median 68 years),^[20] which indicate that ILDs predominantly affect older individuals. Cellular senescence, telomere shortening, and genetic predispositions, including mutations in telomere-related genes such as TERT, TERC, RTEL1, and PARN, play significant roles in the development of fibrotic ILD.^[21,22] These mutations have been identified not only in IPF but also in other fibrotic ILD subtypes, such as nonspecific interstitial pneumonia (NSIP) and fHP. Notably, rare variants in genes such as TERT and TERC have been reported in 8–12% of patients with fHP and are associated with shortened telomere length.^[21]

The gender distribution showed a male predominance (65.7%). This ratio was more pronounced in the IPF (72.5%) and fibrotic HP (78.6%) subgroups, while the CTD-ILD group showed a balanced gender distribution. Although the PROGRESS study also reported

a higher male ratio, Nasser *et al.*^[19] described a slight female predominance (48.1%) but demonstrated that male sex was significantly associated with increased mortality risk. It is well established in the literature that males have a 1.5 to 2 times higher risk of developing IPF compared with females.^[23] Conversely, CTD-ILD is more common among younger, non-smoking women. Our study reflected this classic distribution, with male predominance in the IPF subgroup and female predominance in the CTD-ILD subgroup. Although male predominance was notable in the fHP group, the limited number of patients reduces the generalizability of this finding. In the real-life data study conducted by Nashatyreva *et al.*,^[24] no significant differences were reported between PF and PPF patient groups in terms of age, sex, symptom severity, or pulmonary function. Similarly, our study found no statistically significant differences in age or sex between the groups. However, among pulmonary function parameters, DLCO emerged as a significant predictor of mortality. Consistent with the findings of Nashatyreva *et al.*, cigarette smoking and a history of harmful occupational or domestic exposures were more frequently observed in the PPF group. Notably, our results suggest that occupational exposure may be associated with disease progression. Furthermore, shorter survival time was clearly associated with smoking, highlighting its detrimental impact on the disease course.

This study has several notable strengths. First, it was conducted in a well-characterized cohort of patients with PPF who were evaluated within a multidisciplinary framework, thereby increasing diagnostic accuracy and internal validity. Second, all HRCT scans used for semi-quantitative fibrosis assessment were obtained at a single center and were evaluated by experienced thoracic radiologists using a standardized visual scoring method, thereby minimizing variability related to imaging protocols and interpretation. The high interobserver agreement (ICC 0.882) further supports the reliability and reproducibility of our radiological assessments. Third, unlike many retrospective series that rely solely on baseline pulmonary function tests, our study incorporated both radiological fibrosis burden and longitudinal changes in DLCO and FVC, allowing a more comprehensive evaluation of structural and functional disease progression. Finally, by including three major fibrotic ILD subtypes (IPF, CTD-ILD, and fHP), our findings have broader applicability

across the spectrum of fibrotic lung diseases rather than being limited to IPF.

Our study also has important limitations that should be acknowledged. First, the relatively small sample size, particularly in the fibrotic HP subgroup, may have reduced statistical power and limited our ability to detect significant differences in the time to FVC and DLCO decline between diagnostic categories. This may partly explain why some clinically relevant trends did not reach statistical significance. Second, the retrospective design introduces potential sources of bias, including missing data, variability in follow-up duration, and heterogeneity in clinical management over time. Third, because this was a single-center study, our findings may not be fully generalizable to other populations or healthcare settings with different patient profiles or imaging practices. Fourth, although we used a validated semi-quantitative HRCT scoring system, visual assessment remains inherently subjective compared with fully automated quantitative or AI-based methods; thus, some degree of measurement variability is unavoidable. Finally, we did not systematically analyze genetic markers such as telomere length or fibrosis-related gene mutations, which could have provided additional prognostic insight and mechanistic context.

In this study, we demonstrate that the extent of fibrotic involvement on baseline HRCT is a robust and independent predictor of mortality in patients with PPF, outperforming conventional spirometric thresholds of FVC decline. Each incremental increase in visually scored fibrosis was associated with a significantly higher risk of death, underscoring the central role of radiological assessment in prognostic stratification. Although categorical declines in FVC and DLCO of $\geq 5\%$ and $\geq 10\%$ were not independently associated with mortality, DLCO, particularly when assessed longitudinally, remains clinically informative and should be interpreted alongside imaging findings rather than in isolation. Collectively, our results support an integrated approach in which early, standardized quantification of fibrotic burden on HRCT, combined with serial DLCO monitoring, can improve risk stratification, guide the timing of antifibrotic therapy, and facilitate more personalized follow-up strategies. Future multicenter studies incorporating quantitative imaging and genetic biomarkers are warranted to refine prognostic models and optimize management pathways for patients with fibrotic ILD.

Ethics Committee Approval

The study was approved by the Pamukkale University Ethics Committee (No: 60116787-020/72294, Date: 27/10/2020).

Informed Consent

Written informed consent was not required for this study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

Concept – N.Y., G.A.; Design – N.Y., G.A.; Supervision – G.A., E.U., F.U.; Resource – N.Y.; Materials – N.Y., G.A., H.G.Y., F.U.; Data collection and/or processing – N.Y., H.G.Y., F.U.; Analysis and/or interpretation – H.Ş.; Literature search – N.Y., G.A., F.U.; Writing – N.Y.; Critical review – G.A., E.U., F.U.

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