Mortality surrogates in combined pulmonary fibrosis and emphysema

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Abstract

Background: Idiopathic pulmonary fibrosis (IPF) with co-existent emphysema, termed combined pulmonary fibrosis and emphysema (CPFE) may associate with reduced FVC declines compared to non-CPFE IPF patients. We examined associations between mortality and functional measures of disease progression in two IPF cohorts.

Methods: Visual emphysema extent (CPFE:non-CPFE: derivation cohort=317:183; replication cohort=358:152), scored on computed tomography imaging subgrouped CPFE patients using either a) 10%, or b) 15% visual emphysema threshold, or c) an unsupervised machine learning model considering emphysema and ILD extents. Baseline characteristics, 1-year forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLco) decline (linear mixed effects models), and their associations with mortality (multivariable Cox regression models) were compared across CPFE and non-CPFE subgroups.

Results: In both IPF cohorts, CPFE patients with >10% emphysema had a greater smoking history and lower baseline DLco compared to CPFE patients with <10% emphysema. Using multivariable Cox regression analyses in patients with >10% emphysema, 1-year DLco decline was a better indicator of mortality than 1-year FVC decline. Results were maintained in patients suitable for therapeutic IPF trials.

Results were replicated in the >15% emphysema population and using unsupervised machine learning. Importantly, the unsupervised machine learning approach identified CPFE patients in whom FVC decline did not associate strongly with mortality. In non-CPFE IPF patients, 1-year FVC declines >5% and >10% showed comparable mortality associations.

Conclusion: When assessing disease progression in IPF, DLco decline should be considered in patients with >10% emphysema and a >5% 1-year FVC decline threshold considered in non-CPFE IPF patients.

KEYWORDS: Combined pulmonary fibrosis and emphysema, mortality surrogates, idiopathic pulmonary fibrosis, computed tomography.

Introduction

Emphysema is a common pulmonary finding on computed tomography (CT) imaging of idiopathic pulmonary fibrosis (IPF) patients [1]. The term combined pulmonary fibrosis and emphysema (CPFE) describes a potential clinical endotype characterized by the coexistence of upper lobe-predominant emphysema, lower lobe-predominant fibrosis and relative preservation of forced vital capacity (FVC) in the context of a disproportionately reduced gas transfer (DLco) [1–3]. CPFE is highly heterogeneous in terms of the distribution and relative extents of fibrosis and emphysema seen on CT.

CPFE patients are typically categorised using visual thresholds of emphysema extent: >0%, >5%, >10%, >15%. It has been suggested that a subset of CPFE patients (>15% emphysema) may manifest slower rates of FVC decline than CPFE patients with lesser amounts of emphysema [4]. Despite the importance of fibrosis in driving FVC decline, fibrosis extent hasn't been considered in prior definitions of CPFE [5]. Categorisation of CPFE patients using a combination of fibrosis and emphysema is possible using data-driven machine learning methods. SuStaIn [6] is a machine learning method initially proposed for subtyping and modelling disease progression behaviour in dementia, which has been extended to COPD [7]. SuStaIn can identify disease subtypes with different progression patterns and can reconstruct their progression trajectories from cross-sectional data. A by-product of this approach would be the identification of patients in different CPFE subtypes who may benefit

from different forms of disease progression monitoring, which in turn could inform clinical trial design.

In our study, we therefore aimed to assess whether FVC decline, the most widely used surrogate for mortality prediction in IPF associated with mortality in independent CPFE populations with >10% and >15% emphysema scored visually on CT imaging, and in CPFE subgroups categorised by considering relative extents of interstitial lung disease (ILD) and emphysema. We further examined whether DLco decline could represent an alternative surrogate for mortality in IPF patients with CPFE [5, 8].

Methods

Cohorts

Two independent IPF cohorts diagnosed by multidisciplinary teams were studied. The derivation cohort (n=500) derived from three centres: Ege University Hospital, Izmir, Turkey; St Antonius Hospital, Nieuwegein, Netherlands; Piza University Hospital, Italy. The replication cohort (n=510) derived from four centres: University Hospital Southampton NHS Foundation Trust, UK; University College London Hospitals NHS Foundation Trust, UK; University Hospitals Leuven, Belgium; Australian IPF registry, Australia. Approval for this retrospective study of clinically indicated pulmonary function and CT data were obtained from the local research ethics committees and Leeds East Research Ethics Committee: 20/YH/0120.

Visual CT Scoring of Emphysema and ILD

Patients with infection or cancer on baseline CT or who died within 3 months of the baseline CT were excluded from the study. Emphysema extent and fibrosis extent were visually scored in 6 lobes (the lingula was counted as the sixth lobe) by an experienced radiologist (JJ). Fibrosis extent comprised the sum of ground glass density (with overlying reticulation or traction bronchiectasis), reticulation, traction bronchiectasis and honeycomb cysts. Lobar extents of emphysema/ILD were summed and divided by 6 to obtain a lung percentage of emphysema/ILD. CPFE patients were

subdivided in a primary analysis into those >10% emphysema, and in a secondary analysis into those >15% emphysema. A subset of 122 cases were evaluated independently by two radiologists (GC and JB: 3 and 4 years imaging experience respectively) to provide an estimate of observer variation in CT scores.

FVC/DLco Decline Modelling

Linear mixed-effects (LME) models estimated absolute and relative 1-year FVC decline and 1-year DLco decline. The trajectory of FVC for patients from different countries/centres was modelled separately by using the LME model. Fixed effects included: age at baseline CT date, gender, smoking history (never vs. ever), antifibrotics (never vs. ever), baseline percent predicted FVC (nearest to and within 3 months of baseline CT date), and time since baseline CT imaging date. Each subject had a random intercept and random slope. FVC measurements between baseline FVC date and 18 months after baseline CT date were used to build the LME model. Patients required at least two FVC measurements during this period and an FVC measurement within 3 months of baseline CT for study inclusion. Absolute and relative 1-year FVC declines were calculated. For relative 1-year FVC decline, each follow-up FVC measurement (mls) was divided by baseline FVC (mls) and multiplied by 100 [9] and LME-predicted relative FVC percentage calculated at 1 year. 1-year DLco decline was estimated using similar methods, with longitudinal DLco and baseline percent predicted DLco used in the LME models. LME models were implemented with MATLAB (version R2019b, Mathworks, Natick, Massachusetts,

US).

Machine learning delineation of CPFE subtypes

Only patients with emphysema scored visually in any lobe were considered for SuStaIn CPFE analysis. Using baseline data alone, SuStaIn can identify disease subtypes with distinct progression trajectories that describe the z-score evolution of multiple biomarkers. Z-scores for fibrosis and emphysema were calculated separately and were based on the interobserver variability (measured using the single determination standard deviation) between two radiologists visually estimating fibrosis and emphysema extent. For an individual CPFE subtype, fibrosis and emphysema within each of the six lobes was modelled as a monotonically increasing piece-wise linear function [6, 7]. The trained SuStaIn model, by reconstructing disease progression trajectories of each subtype, can predict probabilities that an individual belongs to a particular subtype and stage [6].

Statistical analysis

Data are presented as means and standard deviations unless otherwise stated. Two-sample t-tests were used for continuous variables, and chi-squared tests were used for categorical variables. Kaplan-Meier survival plots and the log-rank test were used to test for differences in survival between non-CPFE IPF patients, and CPFE patients in different subgroups (using emphysema thresholds or SuStaIn subtype) in both IPF

cohorts. Subanalyses were performed for patients satisfying lung function criterion for inclusion into IPF therapeutic trials (percent predicted DLco >30%, percent predicted FVC >50%, and forced expiratory volume in the first second/FVC ratio >0.7).

In multivariable mixed-effects Cox regression models associations of FVC decline and DLco decline with mortality were examined across IPF subtypes. Models were adjusted for age, gender, smoking history (never vs. ever), antifibrotic use (never vs. ever), and baseline disease severity (using percent predicted DLco at baseline). Differences between different countries/centres in each cohort were modelled by assigning a random intercept for each centre. Cox models were used with a minimum of 8 outcome events per predictor covariant [10]. The Concordance index (C-index) compared the goodness of fit of Cox regression models. P-values <0.01 were considered statistically significant. All mixed-effects Cox regression analyses were implemented by R (version 4.0.3 with Rstudio version 1.3.1093, Rstudio, Boston, Massachusetts, US).

To investigate the impact of emphysema on FVC and DLco decline in the different IPF subgroups (non-CPFE patients; CPFE patients classified using emphysema thresholds or SuStaIn), proportions of patients with >5% and >10% relative FVC decline in 1-year and >10% and >15% relative DLco decline in 1-year were calculated. Mean absolute 1-year FVC decline (mls) and DLco decline (mls) was also calculated for the three subgroups. Analyses were performed in both IPF cohorts, with

subanalyses in subjects fulfilling criteria for inclusion into IPF therapeutic trials. Chi-squared tests with Bonferroni-adjusted p-values were calculated for categorical variables. A one-way ANOVA test examined differences in mean absolute FVC decline (ml/year) with a post hoc Tukey Honest Significant Difference (HSD) test used to compare pairwise differences in subtypes.

Results

Baseline characteristics

317/500 (63%) IPF patients in the derivation cohort had emphysema and were defined as CPFE compared to 358/510 (70%) IPF patients with CPFE in the replication cohort. CPFE patients were more likely to be smokers, had a higher percent-predicted FVC and lower percent-predicted DLco than non-CPFE patients.

Across the derivation and replication cohorts, CPFE patients with >10% emphysema comprised greater numbers of smokers and had lower baseline percent predicted DLco compared to CPFE patients with <10% emphysema (Table 1). To power analyses, patients in both IPF cohorts fulfilling entry criteria for therapeutic trials were combined into a single cohort (Supplementary Table 1). Baseline characteristics of CPFE patients with emphysema above or below 15% in derivation and replication cohorts are shown in Supplementary Table 2-3.

The interobserver variation in visual emphysema scores, measured using Cohens Kappa for 0%, 5%, 10%, and 15% emphysema thresholds was: 0.2, 0.5, 0.61, 0.69, respectively demonstrating substantial agreement for a 10% visual emphysema threshold.

Machine Learning Model

Machine learning analyses of ILD and emphysema extents in the CPFE population identified two distinct CPFE subtypes. One subtype (*Fibrosis Dominant CPFE*; 60% of derivation cohort CPFE patients and 61% of replication cohort CPFE patients) had much more extensive fibrosis at an early stage followed by a later emergence of emphysema (Supplementary Figure 3 and 4). The second subtype (*Matched CPFE*) demonstrated fibrosis and emphysema worsening together, with later stages showing relatively more extensive emphysema and less fibrosis compared to the fibrosis-dominant CPFE subtype (Supplementary Table 4 and 5).

PFT decline analyses

Fewer CPFE patients with >10% emphysema reached the >10% or >5% 1-year FVC decline thresholds and had lower mean absolute FVC declines, though differences between groups did not reach statistical significance (Table 2). Greater numbers of CPFE patients with >10% emphysema demonstrated 1-year DLco declines >15%, though again results did not reach statistical significance (Table 3). Similar trends were found in the replication cohort, patients fulfilling criteria to enter IPF therapeutic trials (Table 2 and 3), and when CPFE was categorized using a 15% emphysema threshold or machine learning analyses (Supplementary Table 6 and 7).

Survival Analyses

Kaplan-Meier survival plots (Figure 1**Error! Reference source not found.**) demonstrated that in both cohorts, non-CPFE and CPFE patients with <10% emphysema had a significantly better prognosis than CPFE patients with >10% emphysema. Results were maintained in patients fulfilling criteria to enter IPF therapeutic trials and were similar when CPFE patients were separated using a 15% emphysema threshold or machine learning analyses (Supplementary Figure 1 and 2).

Mortality analysis for visual emphysema thresholds

Multivariable Cox regression models adjusted for patient age, gender, smoking history (never vs. ever), antifibrotic use (never vs. ever), and baseline percent predicted DLco showed that across both study cohorts, in non-CPFE patients, a 5% 1-year FVC decline threshold showed equivalent associations with mortality as compared to a 10% 1-year FVC decline threshold (Table 4 and 5). A 5% 1-year FVC decline threshold identified more non-CPFE patients (derivation cohort=59%; replication cohort=108%) than a 10% 1-year FVC decline threshold (Table 2). Associations with mortality were maintained in patients fulfilling criteria to enter IPF therapeutic trials (Supplementary Table 8), where 78% more non-CPFE patients had >5% 1-year FVC declines compared to patients with >10% 1-year FVC decline (Table 2).

For CPFE patients with >10% emphysema (derivation cohort n=103/352 (29%);

replication cohort n=115/382 (30%)), 1-year DLco decline showed a much stronger association with mortality than 1-year FVC decline in derivation and replication cohorts (Table 4 and 5). 1-year FVC decline did not associate significantly with mortality in the replication cohort (Table 5). When DLco thresholds were examined in CPFE patients with >10% emphysema in both cohorts, >15% 1-year DLco decline showed stronger associations with mortality than >10% 1-year FVC decline. In subjects eligible for inclusion into IPF therapeutic trials (where 144/589 (24%) patients had >10% emphysema) DLco decline showed stronger associations with mortality than FVC decline (Supplementary Table 8). Similar trends were observed in multivariable analyses performed in CPFE patients with >15% emphysema (Supplementary Table 9-11).

Mortality analyses of machine learning derived CPFE subgroups

Trends seen for the 10% visual emphysema threshold were again replicated when CPFE patients were separated using machine learning analyses that considered ILD and emphysema extents. The *Matched CPFE* cohort better delineated patients in whom FVC decline proved a poor surrogate for mortality compared to visual emphysema thresholds of >10% and >15%. Importantly, in the *Matched CPFE* cohort, DLco decline, whether measured as absolute decline or a >15% DLco threshold remained a strong surrogate for mortality (Supplementary Table 12-14).

Discussion

Our study evaluated functional indicators of disease progression in IPF patients with emphysema that have been the key mortality surrogates used in clinical care and therapeutic trials. We identified three important findings across two IPF populations: Firstly, we demonstrated the limited associations between FVC decline and mortality in CPFE patients with >10% and >15% emphysema, and conversely the strong associations with mortality for DLco decline in the same subgroups. Second, our machine learning model identified a subgroup of CPFE patients where a relatively greater amount of emphysema compared to ILD accentuated the limited associations between ILD-driven FVC decline and mortality in these CPFE patients. Lastly, in non-CPFE patients we showed that FVC decline is a powerful measure of IPF progression showing comparable associations with mortality for both >5% and >10% 1-year FVC decline thresholds. Using a >5% 1-year FVC decline threshold in non-CPFE patients identified over 50% more subjects with real declines than when using a >10% 1-year FVC decline threshold.

FVC decline occupies a cardinal role in the assessment of disease progression in IPF as it has been shown to be a strong surrogate for mortality [11]. The demonstration however that FVC decline may be curtailed in IPF patients with >15% [4] emphysema raised the question of whether FVC decline remained a surrogate for mortality in IPF patients with more extensive emphysema. Only one other study, by

Schmidt et al [8], which was relatively underpowered (n=42) for subjects with moderate/severe emphysema (defined as emphysema at least as extensive as ILD), addressed this question and found that FVC decline did not associate with mortality at 12 months. Other studies considering IPF patients regardless of emphysema presence/extent have shown strong associations between mortality and other functional decline measures/thresholds including: DLco decline thresholds of >10% [12] and 15% [13], and FVC declines of >5% [14–16].

An explanation for the poor association between FVC decline and mortality in patients with more extensive emphysema may relate to the impact of fibrosis when encroaching on areas of emphysema. Emphysematous regions of lung commonly demonstrate air trapping as thickened small airways collapse on expiration. Fibrotic processes however can irreversibly pull open small airways. The supervening traction bronchiolectasis can result in emphysematous airspaces being ventilated, thereby artificially preserving FVC. In IPF patients with emphysema, as fibrosis progresses and extends to involve the upper zones of the lungs, more emphysematous lung may become incorporated into the expiratory lung volume over time. A consequence may more heterogeneity in expiratory volumes superimposing considerable noise to the overarching pattern of progressive FVC decline. This effect is likely to be more pronounced in patients with more extensive emphysema.

One limitation in prior definitions of CPFE has been the focus on emphysema extent

alone as the sole arbiter for categorising a CPFE endotype. A recent ATS/ERS/ALAT/JRS research statement identified a 5% emphysema threshold as a research definition for CPFE patients, whilst suggesting a 15% emphysema threshold for classifying a CPFE clinical syndrome [5]. In our study we found that a 10% emphysema threshold (which showed substantial CT observer agreement) may represent a better cut-off than a 15% emphysema threshold to identify a CPFE population disenfranchised by the use of FVC as a sole measure of disease progression.

A further challenge with CPFE definitions being determined by emphysema thresholds is that FVC decline is primarily driven by ILD progression rather than emphysema progression. Our novel unsupervised machine learning model (SuStaIn) considered both fibrosis and emphysema when subtyping patients and replicated the strong association of DLco decline and mortality in patients with more extensive emphysema seen in CPFE patients with >10% emphysema. By considering ILD extent in relation to emphysema extent, the SuStaIn model improved delineation of a subgroup of CPFE patients, fulfilling criteria to enter IPF therapeutic trials, where FVC decline did not associate strongly with mortality. This could have implications for assessing disease progression in future IPF clinical trials.

Prior studies have shown associations between DLco decline and mortality in IPF [8, 12, 13, 17–19] but have not analysed the impact of emphysema on DLco trends. DLco

decline has generally been less consistent in its links with mortality than FVC decline in IPF patients [20]. Yet DLco decline may have particular relevance in subsets of IPF patients [21]. For example, the strong mortality signal for DLco decline seen in CPFE patients with more extensive emphysema could reflect progressive localised pulmonary hypertension complicating CPFE patients with more extensive emphysema [22, 23].

There were limitations to the current study. A single observer scored the CTs for fibrosis and emphysema. For studies to be clinically meaningful, they have to be suitably powered, and this requires the careful evaluation of large IPF populations which is challenging with limited availability of radiologists. The single read of CTs in this study aligns with other large scale IPF studies where pragmatic considerations required assessment of CTs by a single specialist [24, 25]. Similar functional measures and IPF subgroups proportions across both study cohorts provides reassurance for the validity of the visual CT scores. The improvement in observer agreement at higher emphysema thresholds (even amongst less experienced radiologists) adds confidence to the reliability of visual scores at higher emphysema extents and aligns with prior work [26] demonstrating improved agreement for emphysema extent categories at higher emphysema extents. Lastly, whilst we would have liked to have fully automated our machine learning model, using computationally quantified emphysema as an objective measure of disease. Yet no computer algorithms can reliably distinguish emphysema from honeycomb cysts and

traction bronchiectasis. Accordingly, there will remain a reliance on visual CT reads for assessing the emphysematous component of CPFE in the near future.

In conclusion, annual DLco decline was shown to be a better mortality surrogate for patients with more than 10% emphysema than FVC decline. Findings were validated by a data-driven machine learning method that considers emphysema and ILD extents when defining patients with more extensive emphysema. These observations may be useful in clinical trial design to identify subjects where FVC decline is a poor disease progression measure. A 5% 1-year FVC decline threshold however was found to be a comparable mortality indicator to a 1-year 10% FVC decline threshold in non-CPFE IPF patients.

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Disclosure of Conflicts of Interest

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Author Contributions

AZ, EG, IS, ALY, DB, DCA, AUW, and JJ contributed to study design and data interpretation. AZ, EG, NM, MGJ, CvM, TJC, CR, RC, TJMW, ED, TG, RS, AA, CJB, HWvE, HJ, ADL, MD, KP, LDS, FvB, JB, GC, AP, MV, PH, YM, AT, MT, SV, LT, MV, AN, SMJ, JP, MGJ, WW and JJ were responsible for data acquisition. AZ, EG, IS, and JJ contributed to the statistical analysis. AZ and JJ prepared the first draft of the manuscript. AZ and JJ were responsible for study data integrity. All authors reviewed the manuscript and approved the final submitted version.

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Table 1. Baseline characteristics of non-CPFE IPF patients and CPFE patients with emphysema below or above 10% in the derivation and replication cohorts.

Cohort	Variable	Non-CPFE IPF patients	CPFE patients with emphysema < 10%	CPFE patients with emphysema ⩾ 10%	P value
Derivation cohort	Subjects (%)	183 (36.6)	174 (34.8)	143 (28.6)	-
	Age (years)	67.8±9.2	66.9±9.1	65.0±9.1	0.06
	Male (%)	110/183 (60.1)	143/174 (82.2)	132/143 (92.3)	0.01
	Never-/ever-smokers (ever %)	92/91 (49.7)	38/133 (77.8) *	8/134 (94.4) **	< 0.0001
	Visual fibrosis extent (%, n)	38.68±14.62	36.34±14.12	40.84±13.51	0.004
	Visual emphysema extent (%)	0±0	4.7557±2.26	20.4225±8.8366	< 0.0001
	FVC (% predicted, n)	77.14±20.78 (158)	80.11±20.23 (150)	79.05±21.87 (122)	0.68
	DLco (% predicted, n)	52.21±16.48 (151)	51.62±15.13 (138)	40.43±13.28 (116)	< 0.0001
Validation cohort	Subjects (%)	152 (29.8)	206 (40.4)	152 (29.8)	-
	Age (years)	71.6±8.4	71.9±8.3	70.5±8.0	0.12
	Male (%)	96/152 (63.2)	168/206 (81.6)	128/152 (84.2)	0.60
	Never-/ever-smokers (ever %)	78/74 (48.7)	51/152 (74.9) †	22/129 (85.4) ††	0.02
	Visual fibrosis extent (%, n)	34.0±14.9 (152)	34.6±12.8 (206)	37.8±12.4 (152)	0.02
	Visual emphysema extent (%)	0±0 (152)	4.9±2.4 (206)	21.1±11.1 (152)	< 0.0001
	FVC (% predicted, n)	84.5±21.1 (137)	84.4±20.5 (184)	86.6±18.9 (137)	0.32
	DLco (% predicted, n)	55.2±15.1 (121)	51.2±16.0 (176)	40.7±11.2 (126)	< 0.0001

FVC: forced vital capacity; DLco: diffusing capacity for carbon monoxide; * 171 patients and ** 142 patients had smoking data available in derivation cohort; † 203 patients and †† 151 patients had smoking data available in replication cohort; P-value shows the significance of the difference between CPFE patients with emphysema above or below 10%.

Table 2. FVC decline analysis in different subgroups of IPF patients

Cohort	Subgroup	FVC data available cases/all case	Relative 1-year FVC decline (%)		Absolute 1-year FVC decline (mls/year)
			Number of >10% (proportion)	Number of >5% (proportion)	Mean
Derivation cohort	Non-CPFE	150/183	51 (34%)	81 (54%)	163.50
	CPFE with emphysema <10%	136/174	39 (28.68%)	69 (50.74%)	180.12
	CPFE with emphysema ⩾10%	115/143	27 (23.48%)	49 (42.61%)	97.43
Replication cohort	Non-CPFE	124/152	24 (19.35%)	50 (40.32%)	110.65
	CPFE with emphysema <10%	170/206	37 (21.76%)	75 (44.12%)	132.62
	CPFE with emphysema ⩾10%	130/152	21 (16.15%)	44 (33.85%)	87.71
Combined drug trial cohort	Non-CPFE	222/236	59 (26.58%)	105 (47.30%)	142.94
	CPFE with emphysema <10%	240/261	57 (23.75%)	113 (47.08%)	164.81
	CPFE with emphysema ⩾10%	150/157	29 (19.33%)	56 (37.33%)	112.19

The proportions of patients with more than 10% and 5% relative 1-year FVC decline, and the mean of absolute 1-year FVC decline in derivation, replication cohorts and combined drug trial cohort (patients fulfilling criteria to enter IPF therapeutic trials in derivation and replication cohorts) are shown in this table. The number of subjects with available FVC decline versus the number of all subjects belonging to a certain subgroup is shown in n/n format. We also compared non-CPFE with CPFE with emphysema ⩾10%, and CPFE with emphysema ⩾10% with CPFE with emphysema <10% in terms of the relative decline and absolute decline. None of them are significantly different. CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity.

Table 3. DLco decline analysis in different subgroups of IPF patients

Cohort	Subgroup	DLco data available cases/all case	Relative 1-year DLco decline (%)		Absolute 1-year DLco decline (mls/year)
			Number of >15% (proportion)	Number of >10% (proportion)	Mean
Derivation cohort	Non-CPFE	132/183	52 (39.39%)	73 (55.30%)	645.39
	CPFE with emphysema <10%	125/174	42 (33.60%)	60 (48%)	1020.97
	CPFE with emphysema ⩾10%	107/143	42 (39.25%)	59 (55.14%)	870.88
Replication cohort	Non-CPFE	108/152	30 (27.78%)	43 (39.81%)	769.10
	CPFE with emphysema <10%	161/206	38 (23.60%)	67 (41.61%)	615.04
	CPFE with emphysema ⩾10%	117/152	42 (35.90%)	64 (54.70%)	581.21
Combined drug trial cohort	Non-CPFE	213/236	71 (33.33%)	100 (46.95%)	748.91
	CPFE with emphysema <10%	238/261	66 (27.73%)	112 (47.06%)	863.75
	CPFE with emphysema ⩾10%	146/157	54 (36.99%)	80 (54.79%)	814.72

The proportions of patients with more than 15% and 10% relative 1-year DLco decline, and the mean of absolute 1-year DLco decline in derivation, replication cohorts and combined drug trial cohort (patients fulfilling criteria to enter IPF therapeutic trials in derivation and replication cohorts) are shown in this table. The number of subjects with available DLco decline versus the number of all subjects belonging to a certain subgroup is shown in n/n format. CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; DLCO: diffusion capacity for carbon monoxide.

Table 4. Multivariable mixed-effects Cox proportional hazards regression models in non-CPFE patients and the two CPFE subgroups in the derivation IPF cohorts.

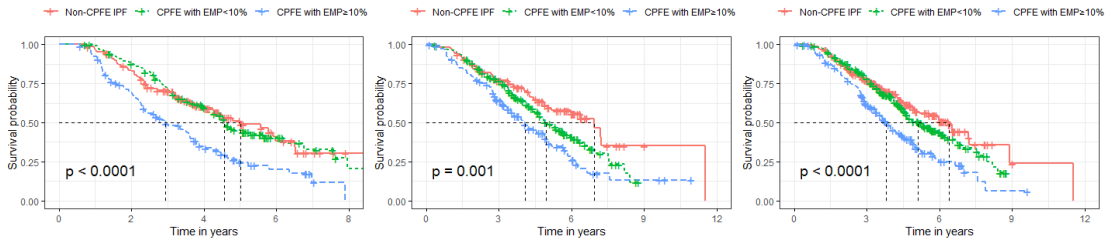
Subgroup	Baseline severity and PFTs changes models	Entire study population					
		N (N-observed)	C-index	p-Value	Hazard ratio	95% CI	
						Lower	Upper
Non-CPFE IPF patients	DLCO % predicted 1-year FVC relative decline	130 (61)	0.821	1.94E-06 3.02E-08	0.942 1.082	0.919 1.052	0.966 1.113
	DLCO % predicted Binary 1-year FVC decline (5%)	130 (61)	0.805	7.65E-08 1.09E-05	0.935 3.824	0.912 2.104	0.958 6.953
	DLCO % predicted Binary 1-year FVC decline (10%)	130 (61)	0.811	4.33E-06 4.96E-07	0.945 4.261	0.923 2.422	0.968 7.497
	DLCO % predicted 1-year DLCO relative decline	130 (61)	0.803	1.62E-07 = 0.0001	0.937 1.038	0.914 1.018	0.960 1.058
	DLCO % predicted Binary 1-year DLco decline (10%)	130 (61)	0.800	4.03E-07 0.0010	0.940 2.764	0.918 1.511	0.963 5.055
	DLCO % predicted Binary 1-year DLco decline (15%)	130 (61)	0.811	9.11E-08 4.69E-07	0.936 4.211	0.913 2.407	0.959 7.366
CPFE patients with emphysema < 10%	DLCO % predicted 1-year FVC relative decline	119 (63)	0.716	6.88E-06 6.46E-05	0.953 1.051	0.933 1.026	0.973 1.077
	DLCO % predicted Binary 1-year FVC decline (5%)	119 (63)	0.721	1.21E-05 = 0.0001	0.956 3.000	0.937 1.705	0.976 5.279
	DLCO % predicted Binary 1-year FVC decline (10%)	119 (63)	0.685	=0.0001 = 0.025	0.961 1.983	0.942 1.091	0.981 3.604
	DLCO % predicted 1-year DLCO relative decline	119 (63)	0.727	2.04E-06 = 0.0003	0.948 1.035	0.927 1.016	0.969 1.055
	DLCO % predicted Binary 1-year DLco decline (10%)	119 (63)	0.682	3.38E-05 = 0.173	0.957 1.453	0.938 0.849	0.977 2.486
	DLCO % predicted Binary 1-year DLco decline (15%)	119 (63)	0.696	1.47E-05 = 0.017	0.956 1.979	0.936 1.131	0.976 3.464
CPFE patients with emphysema ⩾ 10%	DLCO % predicted 1-year FVC relative decline	103 (73)	0.714	1.34E-05 = 0.008	0.950 1.034	0.928 1.009	0.972 1.061
	DLCO % predicted Binary 1-year FVC decline (5%)	103 (73)	0.714	3.09E-05 = 0.016	0.954 1.868	0.932 1.126	0.975 3.100
	DLCO % predicted Binary 1-year FVC decline (10%)	103 (73)	0.715	7.64E-05 = 0.002	0.956 2.540	0.934 1.421	0.977 4.539
	DLCO % predicted 1-year DLCO relative decline	103 (73)	0.732	3.26E-05 1.24E-05	0.951 1.033	0.928 1.018	0.974 1.049
	DLCO % predicted Binary 1-year DLco decline (10%)	103 (73)	0.703	4.95E-05 = 0.058	0.955 1.619	0.933 0.983	0.976 2.665
	DLCO % predicted Binary 1-year DLco decline (15%)	103 (73)	0.732	4.09E-05 7.61E-05	0.953 2.674	0.932 1.643	0.975 4.353

Multivariable mixed-effects Cox regression models were used to investigate associations with mortality for 1-year FVC decline and 1-year DLCO decline after adjusting for patient age, gender, smoking status (never versus ever), antifibrotic use (never versus ever) and baseline disease severity estimated using DLco. Binary 1-year FVC decline uses 5% abd 10% relative decline as thresholds, and binary 1-year DLco decline uses 10% and 15% relative decline as threshold. Separate centres/countries within the derivation and replication cohorts were modelled as multilevel with random effects between centres/countries (a random intercept per centre/country). N: number of patients in mixed-effects Cox model. N-observed: number of deaths observed in N patients; C-index: concordance index; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; CI: confidence interval.

Table 5. Multivariable mixed-effects Cox proportional hazards regression models in non-CPFE patients and the two CPFE subgroups in the replication IPF cohorts.

Subgroup	Baseline severity and PFTs changes models	Entire study population					
		N (N-observed)	C-index	p-Value	Hazard ratio	95% CI	
						Lower	Upper
Non-CPFE IPF patients	DLCO % predicted 1-year FVC relative decline	108 (45)	0.823	2.51E-05 8.65E-05	0.940 1.086	0.913 1.042	0.967 1.132
	DLCO % predicted Binary 1-year FVC decline (5%)	108 (45)	0.827	3.35E-05 = 0.002	0.942 2.719	0.916 1.425	0.969 5.187
	DLCO % predicted Binary 1-year FVC decline (10%)	108 (45)	0.817	5.17E-05 = 0.004	0.944 2.733	0.918 1.374	0.971 5.437
	DLCO % predicted 1-year DLCO relative decline	108 (45)	0.822	3.28E-06 = 0.019	0.933 1.032	0.906 1.005	0.960 1.059
	DLCO % predicted Binary 1-year DLco decline (10%)	108 (45)	0.835	1.56E-05 = 0.013	0.938 2.373	0.911 1.201	0.966 4.688
	DLCO % predicted Binary 1-year DLco decline (15%)	108 (45)	0.835	2.69E-05 = 0.006	0.941 2.693	0.915 1.336	0.968 5.428
CPFE patients with emphysema < 10%	DLCO % predicted 1-year FVC relative decline	159 (83)	0.754	1.86E-09 = 0.001	0.942 1.055	0.924 1.022	0.961 1.089
	DLCO % predicted Binary 1-year FVC decline (5%)	159 (83)	0.763	1.51E-09 = 0.004	0.942 1.960	0.924 1.246	0.960 3.083
	DLCO % predicted Binary 1-year FVC decline (10%)	159 (83)	0.767	8.65E-10 9.27E-05	0.940 2.704	0.922 1.642	0.959 4.453
	DLCO % predicted 1-year DLCO relative decline	159 (83)	0.776	5.69E-11 2.87E-05	0.936 1.032	0.918 1.017	0.955 1.047
	DLCO % predicted Binary 1-year DLco decline (10%)	159 (83)	0.772	1.74E-10 = 0.0005	0.937 2.252	0.919 1.424	0.956 3.561
	DLCO % predicted Binary 1-year DLco decline (15%)	159 (83)	0.768	1.78E-09 = 0.0001	0.940 2.781	0.921 1.659	0.959 4.661
CPFE patients with emphysema ⩾ 10%	DLCO % predicted 1-year FVC relative decline	115 (70)	0.705	1.23E-05 = 0.130	0.946 1.024	0.922 0.993	0.970 1.056
	DLCO % predicted Binary 1-year FVC decline (5%)	115 (70)	0.689	3.05E-05 = 0.707	0.950 1.105	0.927 0.656	0.973 1.863
	DLCO % predicted Binary 1-year FVC decline (10%)	115 (70)	0.706	9.84E-05 = 0.035	0.952 2.028	0.929 1.053	0.976 3.906
	DLCO % predicted 1-year DLCO relative decline	115 (70)	0.720	7.79E-06 = 0.001	0.945 1.030	0.922 1.012	0.969 1.049
	DLCO % predicted Binary 1-year DLco decline (10%)	115 (70)	0.716	1.15E-05 = 0.0004	0.948 2.672	0.925 1.546	0.971 4.617
	DLCO % predicted Binary 1-year DLco decline (15%)	115 (70)	0.729	1.52E-05 1.04E-05	0.948 3.883	0.925 2.124	0.971 7.097

Multivariable mixed-effects Cox regression models were used to investigate associations with mortality for 1-year FVC decline and 1-year DLCO decline after adjusting for patient age, gender, smoking status (never versus ever), antifibrotic use (never versus ever) and baseline disease severity estimated using DLco. Binary 1-year FVC decline uses 5% and 10% relative decline as thresholds, and binary 1-year DLco decline uses 10% and 15% relative decline as threshold. Separate centres/countries within the derivation and replication cohorts were modelled as multilevel with random effects between centres/countries (a random intercept per centre/country). N: number of patients in mixed-effects Cox model. N-observed: number of deaths observed in N patients; C-index: concordance index; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; CI: confidence interval.



(a) (b) (c)

Figure 1. Kaplan-Meier curves of non-CPFE IPF patients (red), CPFE patients with emphysema <10% (green) and CPFE patients with emphysema ⩾ 10% (blue) in the derivation cohort (a), the replication cohort (b), combined derivation and replication cohort patients qualifying for therapeutic trials (c). Log-rank tests show a significant difference in mortality between the three subtypes in all three analyses.

Supplementary Appendix

Supplementary Table 1. Baseline characteristics of non-CPFE IPF patients and CPFE patients fulfilling criteria to enter IPF therapeutic trials and with emphysema below or above 10% in the combined cohorts.

Variable	Non-CPFE IPF patients	CPFE patients with emphysema < 10%	CPFE patients with emphysema ⩾ 10%	P value
Subjects (%)	236 (36.1)	261 (39.9)	157 (24.0)	-
Age (years)	69.8±8.2	69.8±8.8	67.5±9.0	0.009
Male (%)	141/236 (59.7)	209/261 (80.1)	142/157 (90.4)	0.008
Never-/ever-smokers (ever %)	121/115 (48.7)	64/192 (75) *	15/140 (90.3) **	0.0002
Visual fibrosis extent (%, n)	34.4±13.9	33.9±12.9	37.5±13.0	0.007
Visual emphysema extent (%)	0±0	4.7±2.3	18.7±8.4	< 0.0001
FVC (% predicted, n)	83.9±19.1	85.2±17.7	85.7±17.9	0.81
DLco (% predicted, n)	55.7±14.1	53.1±13.7	45.7±9.8	< 0.0001
FVC: forced vital capacity; DLco: diffusing capacity for carbon monoxide; * 256 patients and ** 155 patients had smoking data available. P-value shows the significance of the difference between CPFE patients with emphysema above or below 10%.				

Supplementary Table 2. Baseline characteristics of non-CPFE IPF patients and CPFE patients with emphysema below or above 15% in the derivation and replication cohorts.

Cohort	Variable	Non-CPFE IPF patients	CPFE patients with emphysema < 15%	CPFE patients with emphysema ⩾ 15%	P value
Derivation cohort	Subjects (%)	183 (36.6)	218 (43.6)	99 (19.8)	-
	Age (years)	67.8±9.2	66.3±9.1	65.4±9.2	0.39
	Male (%)	110/183 (60.1)	185/218 (84.9)	90/99 (90.9)	0.20
	Never-/ever-smokers (ever %)	92/91 (49.7)	40/174 (81.3) *	6/93 (93.9)	0.006
	Visual fibrosis extent (%, n)	38.7±14.6	37.3±13.9	40.8±14.0	0.04
	Visual emphysema extent (%)	0±0	6.2±3.6	24.2±8.2	< 0.0001
	FVC (% predicted, n)	77.1±20.8 (158)	78.7±20.4 (189)	81.7±22.1 (83)	0.30
	DLco (% predicted, n)	52.2±16.5 (151)	50.1±14.7 (174)	38.7±13.9 (80)	< 0.0001
Validation cohort	Subjects (%)	152 (29.8)	258 (50.59)	100 (19.6)	-
	Age (years)	71.6±8.4	71.7±8.1	70.3±8.6	0.17
	Male (%)	96/152 (63.2)	211/258 (81.8)	85/100 (85)	0.57
	Never-/ever-smokers (ever %)	78/74 (48.7)	60/195 (76.5) †	13/86 (86.9) ††	0.04
	Visual fibrosis extent (%, n)	34.0±14.9 (152)	35.2±12.9	37.7±11.9	0.08
	Visual emphysema extent (%)	0±0 (152)	6.3±3.6	26.0±10.9	< 0.0001
	FVC (% predicted, n)	84.5±21.1 (137)	84.3±20.4 (227)	87.8±18.3 (94)	0.13
	DLco (% predicted, n)	55.2±15.1 (121)	49.7±15.5 (215)	39.6±11.4 (87)	< 0.0001

FVC: forced vital capacity; DLco: diffusing capacity for carbon monoxide; * 214 patients had smoking data available in derivation cohort; † 255 patients and †† 99 patients had smoking data available in replication cohort. P-value shows the significance of the difference between CPFE patients with emphysema above or below 15%.

Supplementary Table 3. Baseline characteristics of non-CPFE IPF patients and CPFE patients fulfilling criteria to enter IPF therapeutic trials and with emphysema below or above 15% in the combined cohorts.

Variable	Non-CPFE IPF patients	CPFE patients with emphysema < 15%	CPFE patients with emphysema ⩾ 15%	P value
Subjects (%)	236 (36.1)	318 (48.6)	100 (15.3)	-
Age (years)	69.8±8.2	69.4±8.9	67.4±8.9	0.06
Male (%)	141/236 (59.7)	260/318 (81.8)	91/100 (91)	0.04
Never-/ever-smokers (ever %)	121/115 (48.7)	71/241 (77.2) *	8/91 (91.9) **	0.002
Visual fibrosis extent (%, n)	34.4±13.9	35.0±13.1	36.1±12.8	0.43
Visual emphysema extent (%)	0±0	6.0±3.5	22.6±8.2	< 0.0001
FVC (% predicted, n)	83.9±19.1	84.7±17.7	87.5±17.8	0.18
DLco (% predicted, n)	55.7±14.1	52.0±13.1	45.0±10.4	< 0.0001
FVC: forced vital capacity; DLco: diffusing capacity for carbon monoxide; * 312 patients and ** 99 patients had smoking data available. P-value shows the significance of the difference between CPFE patients with emphysema above or below 15%.				

Supplementary Table 4. Baseline characteristics of non-CPFE IPF patients and CPFE patients in the fibrosis-dominant and Matched-CPFE subtypes in the derivation and replication cohorts.

Cohort	Variable	Non-CPFE IPF patients	CPFE patients with emphysema < 15%	CPFE patients with emphysema ⩾ 15%	P value
Derivation cohort	Subjects (%)	183 (36.6)	191 (38.2)	126 (25.2)	-
	Age (years)	67.8±9.2	66.7±9.1	65.0±9.1	0.09
	Male (%)	110/183 (60.1)	159/191 (83.2)	116/126 (92.1)	0.04
	Never-/ever-smokers (ever %)	92/91 (49.7)	40/148 (78.7) *	6/119 (95.2) **	0.0001
	Visual fibrosis extent (%, n)	38.7±14.6	38.6±14.2	38.1±13.7	0.77
	Visual emphysema extent (%)	0±0	5.6±3.4	21.3±9.1	< 0.0001
	FVC (% predicted, n)	77.1±20.8 (158)	78.3±19.9 (167)	81.8±22.5 (105)	0.19
	DLco (% predicted, n)	52.2±16.5 (151)	50.2±15.4 (153)	40.9±13.4 (101)	< 0.0001
Validation cohort	Subjects (%)	152 (29.8)	227 (44.5)	131 (25.7)	-
	Age (years)	71.6±8.4	71.8±8.3	70.5±8.1	0.14
	Male (%)	96/152 (63.2)	187/227 (82.4)	109/131 (83.2)	0.96
	Never-/ever-smokers (ever %)	78/74 (48.7)	56/168 (75) †	17/113 (86.9) ††	0.01
	Visual fibrosis extent (%, n)	34.0±14.9 (152)	37.2±12.6	33.8±12.6	0.01
	Visual emphysema extent (%)	0±0 (152)	5.8±3.6	22.1±11.7	< 0.0001
	FVC (% predicted, n)	84.5±21.1 (137)	83.1±20.4 (200)	88.9±18.4 (121)	0.01
	DLco (% predicted, n)	55.2±15.1 (121)	49.8±16.1 (189)	41.8±11.7 (113)	< 0.0001

FVC: forced vital capacity; DLco: diffusing capacity for carbon monoxide; **188 patients and **125 patients had smoking data available in derivation cohort; †224 patients and ††130 patients had smoking data available in replication cohort. P-value shows the significance of the difference between CPFE patients in the fibrosis-dominant and Matched-CPFE subtypes.

Supplementary Table 5. Baseline characteristics of non-CPFE IPF patients and Fibrosis-dominant and Matched-CPFE subtypes fulfilling criteria to enter IPF therapeutic trials in the combined cohorts.

Variable	Non-CPFE IPF patients	Fibrosis-dominant CPFE subtype	Matched-CPFE subtype	P value
Subjects (%)	236 (36.1)	281 (43.0)	137(20.9)	-
Age (years)	69.8±8.2	69.6±8.9	67.5±8.8	0.02
Male (%)	141/236 (59.7)	230/281 (81.9)	121/137 (88.3)	0.12
Never-/ever-smokers (ever %)	121/115 (48.7)	66/210 (76.1) *	13/122 (90.4) **	0.0009
Visual fibrosis extent (%, n)	34.4±13.9	36.5±13.1	32.6±12.6	0.004
Visual emphysema extent (%)	0±0	5.4±3.4	19.2±9.0	< 0.0001
FVC (% predicted, n)	83.9±19.1	84.3±17.6	87.7±17.7	0.06
DLco (% predicted, n)	55.7±14.1	52.1±13.7	46.7±10.0	< 0.0001
FVC: forced vital capacity; DLco: diffusing capacity for carbon monoxide; * 276 patients and ** 135 patients had smoking data available. P-value shows the significance of the difference between CPFE patients in the fibrosis-dominant and Matched-CPFE subtypes.				

Supplementary Table 6. FVC decline analysis in different subgroups of IPF patients.

Cohort	Subgroup	FVC data available cases/all case	Relative 1-year FVC decline (%)		Absolute 1-year FVC decline (mls/year)
			Number of >10% (proportion)	Number of >5% (proportion)	Mean
Derivation cohort	Non-CPFE	150/183	51 (34%)	81 (54%)	163.50
	CPFE with emphysema <15%	174/218	51 (29.31%)	90 (51.72%)	165.21
	CPFE with emphysema ⩾15%	77/99	15 (19.48%)	28 (36.36%)	90.31
	Fibrosis-dominant CPFE	153/191	46 (30.07%)	77 (50.33%)	159.50
	Matched-CPFE	98/126	20 (20.41%)	41 (41.84%)	115.27
Replication cohort	Non-CPFE	124/152	24 (19.35%)	50 (40.32%)	110.65
	CPFE with emphysema <15%	211/258	43 (20.38%)	91 (43.13%)	127.95
	CPFE with emphysema ⩾15%	89/100	15 (16.85%)	28 (31.46%)	78.10
	Fibrosis-dominant CPFE	187/227	41 (21.93%)	83 (44.39%)	135.32
	Matched-CPFE	113/131	17 (15.04%)	36 (31.86%)	76.48
Combined drug trial cohort	Non-CPFE	222/236	59 (26.58%)	105 (47.30%)	142.94
	CPFE with emphysema <15%	295/318	71 (24.07%)	141 (47.80%)*	161.88
	CPFE with emphysema ⩾15%	95/100	15 (15.79%)	28 (29.47%)*	90.84
	Fibrosis-dominant CPFE	262/281	65 (24.81%)	124 (47.33%)	163.21
	Matched-CPFE	128/137	21 (16.41%)	45 (35.16%)	106.42

The proportions of patients with more than 10% and 5% relative 1-year FVC decline, and the mean of absolute 1-year FVC decline in different subgroups in derivation, replication cohorts and combined drug trial cohort (patients fulfilling criteria to enter IPF therapeutic trials in derivation and replication cohorts) are shown in this table. The number of subjects with available FVC decline versus the number of all subjects belonging to a certain subgroup is shown in n/n format. CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity. *=$p<0.01$ when comparing CPFE subgroup with non-CPFE.

Supplementary Table 7. DLco decline analysis in different subgroups of IPF patients

Cohort	Subgroup	DLco data available cases/all case	Relative 1-year DLco decline (%)		Absolute 1-year DLco decline (mls/year)
			Number of >15% (proportion)	Number of >10% (proportion)	Mean
Derivation cohort	Non-CPFE	132/183	52 (39.39%)	73 (55.30%)	645.39
	CPFE with emphysema <15%	157/218	51 (32.48%)	75 (47.77%)	950.61
	CPFE with emphysema ⩾15%	75/99	33 (44.00%)	44 (58.67%)	954.13
	Fibrosis-dominant CPFE	140/191	48 (34.29%)	67 (47.86%)	957.04
	Matched-CPFE	92/126	36 (39.13%)	52 (56.52%)	943.68
Replication cohort	Non-CPFE	108/152	30 (27.78%)	43 (39.81%)	769.10
	CPFE with emphysema <15%	197/258	51 (25.89%)	86 (43.65%)	617.02
	CPFE with emphysema ⩾15%	81/100	29 (35.80%)	45 (55.56%)	561.34
	Fibrosis-dominant CPFE	175/227	48 (27.43%)	81 (46.29%)	623.83
	Matched-CPFE	103/131	32 (31.07%)	50 (48.54%)	561.68
Combined drug trial cohort	Non-CPFE	213/236	71 (33.33%)	100 (46.95%)	748.91
	CPFE with emphysema <15%	291/318	83 (28.52%)	139 (47.77%)	832.87
	CPFE with emphysema ⩾15%	93/100	37 (39.78%)	53 (56.99%)	883.39
	Fibrosis-dominant CPFE	260/281	79 (30.38%)	128 (49.23%)	844.65
	Matched-CPFE	124/137	41 (33.06%)	64 (51.61%)	846.06

The proportions of patients with more than 15% and 10% relative 1-year DLco decline, and the mean of absolute 1-year DLco decline in different subgroups in derivation, replication cohorts and combined drug trial cohort (patients fulfilling criteria to enter IPF therapeutic trials in derivation and replication cohorts) are shown in this table. The number of subjects with available DLco decline versus the number of all subjects belonging to a certain subgroup is shown in n/n format. CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; DLCO: diffusion capacity for carbon monoxide.

Supplementary Table 8. Multivariable mixed-effects Cox proportional hazards regression models in non-CPFE patients and the two CPFE subgroups (10% emphysema threshold) who fulfill criteria to enter IPF therapeutic trials in combined derivation and replication IPF cohorts.

Subgroup	Baseline severity and PFTs changes models	Entire study population					
		N (N-observed)	C-index	p-Value	Hazard ratio	95% CI	
						Lower	Upper
Non-CPFE IPF patients	DLCO % predicted 1-year FVC relative decline	212 (87)	0.812	2.63E-06 1.29E-11	0.952 1.088	0.933 1.062	0.972 1.115
	DLCO % predicted Binary 1-year FVC decline (5%)	212 (87)	0.805	9.97E-07 9.94E-07	0.952 3.268	0.933 2.034	0.971 5.252
	DLCO % predicted Binary 1-year FVC decline (10%)	212 (87)	0.807	1.40E-05 2.13E-09	0.957 4.36	0.938 2.693	0.976 7.06
	DLCO % predicted 1-year DLCO relative decline	212 (87)	0.800	7.88E-08 4.25E-06	0.946 1.042	0.927 1.024	0.965 1.06
	DLCO % predicted Binary 1-year DLco decline (10%)	212 (87)	0.805	5.09E-07 6.23E-05	0.950 2.697	0.931 1.659	0.969 4.384
	DLCO % predicted Binary 1-year DLco decline (15%)	212 (87)	0.808	4.65E-07 5.74E-07	0.949 3.337	0.93 2.081	0.969 5.352
CPFE patients with emphysema < 10%	DLCO % predicted 1-year FVC relative decline	233 (114)	0.711	6.76E-08 6.70E-07	0.954 1.049	0.938 1.03	0.971 1.069
	DLCO % predicted Binary 1-year FVC decline (5%)	233 (114)	0.710	3.62E-08 = 0.0003	0.954 2.007	0.938 1.376	0.970 2.928
	DLCO % predicted Binary 1-year FVC decline (10%)	233 (114)	0.699	2.53E-07 = 0.0001	0.955 2.282	0.939 1.502	0.972 3.469
	DLCO % predicted 1-year DLCO relative decline	233 (114)	0.735	1.27E-09 6.20E-09	0.948 1.04	0.931 1.027	0.964 1.054
	DLCO % predicted Binary 1-year DLco decline (10%)	233 (114)	0.710	6.00E-09 = 0.0002	0.952 2.110	0.936 1.429	0.968 3.116
	DLCO % predicted Binary 1-year DLco decline (15%)	233 (114)	0.719	6.84E-09 5.87E-07	0.951 2.885	0.935 1.904	0.968 4.372
CPFE patients with emphysema ⩾ 10%	DLCO % predicted 1-year FVC relative decline	144 (89)	0.710	1.26E-06 = 0.0006	0.936 1.051	0.912 1.022	0.961 1.082
	DLCO % predicted Binary 1-year FVC decline (5%)	144 (89)	0.700	3.23E-06 = 0.022	0.940 1.693	0.916 1.077	0.965 2.660
	DLCO % predicted Binary 1-year FVC decline (10%)	144 (89)	0.708	4.02E-05 = 0.001	0.948 2.363	0.924 1.412	0.972 3.955
	DLCO % predicted 1-year DLCO relative decline	144 (89)	0.723	6.70E-06 5.45E-08	0.941 1.041	0.916 1.026	0.966 1.056
	DLCO % predicted Binary 1-year DLco decline (10%)	144 (89)	0.691	3.07E-06 = 0.003	0.939 1.987	0.914 1.272	0.964 3.105
	DLCO % predicted Binary 1-year DLco decline (15%)	144 (89)	0.730	2.43E-06 2.33E-07	0.939 3.376	0.914 2.129	0.964 5.353

Multivariable mixed-effects Cox regression models were used to investigate associations with mortality for 1-year FVC decline and 1-year DLCO decline after adjusting for patient age, gender, smoking status (never versus ever), antifibrotic use (never versus ever) and baseline disease severity estimated using DLco. Binary 1-year FVC decline uses 5% and 10% relative decline as thresholds, and binary 1-year DLco decline uses 10% and 15% relative decline as thresholds. Separate centres/countries within the derivation and replication cohorts were modelled as multilevel with random effects between centres/countries (a random intercept per centre/country). N: number of patients in mixed-effects Cox model. N-observed: number of deaths observed in N patients; C-index: concordance index; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; CI: confidence interval.

Supplementary Table 9. Multivariable mixed-effects Cox proportional hazards regression models in non-CPFE patients and the two CPFE subgroups (15% emphysema threshold) in the derivation IPF cohorts.

Subgroup	Baseline severity and PFTs changes models	Entire study population					
		N (N-observed)	C-index	p-Value	Hazard ratio	95% CI	
						Lower	Upper
Non-CPFE IPF patients	DLCO % predicted 1-year FVC relative decline	130 (61)	0.821	1.94E-06 3.02E-08	0.942 1.082	0.919 1.052	0.966 1.113
	DLCO % predicted Binary 1-year FVC decline (5%)	130 (61)	0.805	7.65E-08 1.09E-05	0.935 3.824	0.912 2.104	0.958 6.953
	DLCO % predicted Binary 1-year FVC decline (10%)	130 (61)	0.811	4.33E-06 4.96E-07	0.945 4.261	0.923 2.422	0.968 7.497
	DLCO % predicted 1-year DLCO relative decline	130 (61)	0.803	1.62E-07 = 0.0001	0.937 1.038	0.914 1.018	0.960 1.058
	DLCO % predicted Binary 1-year DLco decline (10%)	130 (61)	0.800	4.03E-07 0.0010	0.940 2.764	0.918 1.511	0.963 5.055
	DLCO % predicted Binary 1-year DLco decline (15%)	130 (61)	0.811	9.11E-08 4.69E-07	0.936 4.211	0.913 2.407	0.959 7.366
CPFE patients with emphysema < 15%	DLCO % predicted 1-year FVC relative decline	149 (87)	0.719	6.46E-09 = 0.0003	0.945 1.037	0.927 1.016	0.963 1.057
	DLCO % predicted Binary 1-year FVC decline (5%)	149 (87)	0.722	2.52E-08 0.0002	0.949 2.487	0.931 1.546	0.966 4.001
	DLCO % predicted Binary 1-year FVC decline (10%)	149 (87)	0.707	2.24E-07 = 0.016	0.953 1.847	0.935 1.122	0.970 3.039
	DLCO % predicted 1-year DLCO relative decline	149 (87)	0.742	7.69E-10 7.87E-06	0.939 1.038	0.920 1.021	0.958 1.055
	DLCO % predicted Binary 1-year DLco decline (10%)	149 (87)	0.707	3.98E-08 0.0746	0.949 1.510	0.931 0.960	0.967 2.377
	DLCO % predicted Binary 1-year DLco decline (15%)	149 (87)	0.725	4.72E-09 = 0.0009	0.946 2.213	0.929 1.380	0.964 3.548
CPFE patients with emphysema ⩾ 15%	DLCO % predicted 1-year FVC relative decline	73 (49)	0.729	= 0.0003 = 0.002	0.949 1.055	0.923 1.020	0.977 1.090
	DLCO % predicted Binary 1-year FVC decline (5%)	73 (49)	0.723	0.0011 0.0202	0.957 2.169	0.932 1.128	0.983 4.170
	DLCO % predicted Binary 1-year FVC decline (10%)	73 (49)	0.730	= 0.010 = 0.001	0.964 4.305	0.938 1.756	0.991 10.551
	DLCO % predicted 1-year DLCO relative decline	73 (49)	0.742	= 0.0005 7.28E-05	0.948 1.034	0.920 1.017	0.977 1.051
	DLCO % predicted Binary 1-year DLco decline (10%)	73 (49)	0.720	0.0012 0.0566	0.956 1.842	0.930 0.983	0.982 3.451
	DLCO % predicted Binary 1-year DLco decline (15%)	73 (49)	0.738	= 0.0008 = 0.0005	0.952 2.931	0.925 1.598	0.980 5.375

Multivariable mixed-effects Cox regression models were used to investigate associations with mortality for 1-year FVC decline and 1-year DLCO decline after adjusting for patient age, gender, smoking status (never versus ever), antifibrotic use (never versus ever) and baseline disease severity estimated using DLco. Binary 1-year FVC decline uses 5% and 10% relative decline as thresholds, and binary 1-year DLco decline uses 10% and 15% relative decline as thresholds. Separate centres/countries within the derivation and replication cohorts were modelled as multilevel with random effects between centres/countries (a random intercept per centre/country). N: number of patients in mixed-effects Cox model. N-observed: number of deaths observed in N patients; C-index: concordance index; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; CI: confidence interval.

Supplementary Table 10. Multivariable mixed-effects Cox proportional hazards regression models in non-CPFE patients and the two CPFE subgroups (15% emphysema threshold) in the replication IPF cohorts.

Subgroup	Baseline severity and PFTs changes models	Entire study population					
		N (N-observed)	C-index	p-Value	Hazard ratio	95% CI	
						Lower	Upper
Non-CPFE IPF patients	DLCO % predicted 1-year FVC relative decline	108 (45)	0.823	2.51E-05 8.65E-05	0.940 1.086	0.913 1.042	0.967 1.132
	DLCO % predicted Binary 1-year FVC decline (5%)	108 (45)	0.827	3.35E-05 = 0.002	0.942 2.719	0.916 1.425	0.969 5.187
	DLCO % predicted Binary 1-year FVC decline (10%)	108 (45)	0.817	5.17E-05 = 0.004	0.944 2.733	0.918 1.374	0.971 5.437
	DLCO % predicted 1-year DLCO relative decline	108 (45)	0.822	3.28E-06 = 0.019	0.933 1.032	0.906 1.005	0.960 1.059
	DLCO % predicted Binary 1-year DLco decline (10%)	108 (45)	0.835	1.56E-05 = 0.013	0.938 2.373	0.911 1.201	0.966 4.688
	DLCO % predicted Binary 1-year DLco decline (15%)	108 (45)	0.835	2.69E-05 = 0.006	0.941 2.693	0.915 1.336	0.968 5.428
CPFE patients with emphysema < 15%	DLCO % predicted 1-year FVC relative decline	194 (102)	0.750	1.93E-10 = 0.0005	0.944 1.053	0.927 1.023	0.961 1.085
	DLCO % predicted Binary 1-year FVC decline (5%)	194 (102)	0.754	1.23E-10 0.0021	0.943 1.890	0.926 1.260	0.960 2.835
	DLCO % predicted Binary 1-year FVC decline (10%)	194 (102)	0.760	1.85E-10 2.44E-05	0.944 2.657	0.927 1.688	0.961 4.183
	DLCO % predicted 1-year DLCO relative decline	194 (102)	0.776	3.01E-11 4.21E-06	0.943 1.032	0.926 1.018	0.959 1.047
	DLCO % predicted Binary 1-year DLco decline (10%)	194 (102)	0.766	8.95E-11 0.0002	0.944 2.181	0.928 1.454	0.961 3.272
	DLCO % predicted Binary 1-year DLco decline (15%)	194 (102)	0.767	8.49E-10 7.76E-06	0.946 2.798	0.929 1.782	0.963 4.393
CPFE patients with emphysema ⩾ 15%	DLCO % predicted 1-year FVC relative decline	80 (51)	0.722	= 0.001 = 0.122	0.952 1.027	0.923 0.993	0.981 1.063
	DLCO % predicted Binary 1-year FVC decline (5%)	80 (51)	0.688	0.0031 0.8652	0.956 1.056	0.928 0.565	0.985 1.973
	DLCO % predicted Binary 1-year FVC decline (10%)	80 (51)	0.706	= 0.007 = 0.079	0.959 2.052	0.930 0.920	0.988 4.576
	DLCO % predicted 1-year DLCO relative decline	80 (51)	0.720	= 0.0003 = 0.01	0.946 1.026	0.917 1.006	0.975 1.047
	DLCO % predicted Binary 1-year DLco decline (10%)	80 (51)	0.709	0.0002 0.0025	0.947 2.767	0.920 1.430	0.975 5.353
	DLCO % predicted Binary 1-year DLco decline (15%)	80 (51)	0.724	= 0.0006 = 0.0003	0.950 3.846	0.922 1.866	0.978 7.925

Multivariable mixed-effects Cox regression models were used to investigate associations with mortality for 1-year FVC decline and 1-year DLCO decline after adjusting for patient age, gender, smoking status (never versus ever), antifibrotic use (never versus ever) and baseline disease severity estimated using DLco. Binary 1-year FVC decline uses 5% and 10% relative decline as thresholds, and binary 1-year DLco decline uses 10% and 15% relative decline as thresholds. Separate centres/countries within the derivation and replication cohorts were modelled as multilevel with random effects between centres/countries (a random intercept per centre/country). N: number of patients in mixed-effects Cox model. N-observed: number of deaths observed in N patients; C-index: concordance index; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; CI: confidence interval.

Supplementary Table 11. Multivariable mixed-effects Cox proportional hazards regression models in non-CPFE patients and the two CPFE subgroups (15% emphysema threshold) who fulfill criteria to enter IPF therapeutic trials in combined derivation and replication IPF cohorts.

Subgroup	Baseline severity and PFTs changes models	Entire study population					
		N (N-observed)	C-index	p-Value	Hazard ratio	95% CI	
						Lower	Upper
Non-CPFE IPF patients	DLCO % predicted 1-year FVC relative decline	212 (87)	0.812	2.63E-06 1.29E-11	0.952 1.088	0.933 1.062	0.972 1.115
	DLCO % predicted Binary 1-year FVC decline (5%)	212 (87)	0.805	9.97E-07 9.94E-07	0.952 3.268	0.933 2.034	0.971 5.252
	DLCO % predicted Binary 1-year FVC decline (10%)	212 (87)	0.807	1.40E-05 2.13E-09	0.957 4.36	0.938 2.693	0.976 7.06
	DLCO % predicted 1-year DLCO relative decline	212 (87)	0.800	7.88E-08 4.25E-06	0.946 1.042	0.927 1.024	0.965 1.06
	DLCO % predicted Binary 1-year DLco decline (10%)	212 (87)	0.805	5.09E-07 6.23E-05	0.950 2.697	0.931 1.659	0.969 4.384
	DLCO % predicted Binary 1-year DLco decline (15%)	212 (87)	0.808	4.65E-07 5.74E-07	0.949 3.337	0.93 2.081	0.969 5.352
CPFE patients with emphysema < 15%	DLCO % predicted 1-year FVC relative decline	285 (147)	0.721	4.27E-11 4.51E-07	0.948 1.045	0.933 1.028	0.963 1.064
	DLCO % predicted Binary 1-year FVC decline (5%)	285 (147)	0.720	3.60E-11 0.0001	0.948 1.913	0.933 1.370	0.963 2.671
	DLCO % predicted Binary 1-year FVC decline (10%)	285 (147)	0.714	2.96E-10 6.63E-06	0.949 2.356	0.934 1.623	0.965 3.42
	DLCO % predicted 1-year DLCO relative decline	285 (147)	0.760	1.71E-13 5.28E-13	0.941 1.046	0.926 1.034	0.956 1.059
	DLCO % predicted Binary 1-year DLco decline (10%)	285 (147)	0.730	4.37E-12 1.50E-05	0.946 2.127	0.931 1.511	0.961 2.994
	DLCO % predicted Binary 1-year DLco decline (15%)	285 (147)	0.739	1.74E-12 2.99E-10	0.944 3.199	0.929 2.228	0.959 4.593
CPFE patients with emphysema ⩾ 15%	DLCO % predicted 1-year FVC relative decline	92 (56)	0.735	0.0001 0.0004	0.935 1.071	0.904 1.031	0.968 1.112
	DLCO % predicted Binary 1-year FVC decline (5%)	92 (56)	0.722	0.0005 0.0253	0.944 2.030	0.913 1.091	0.975 3.777
	DLCO % predicted Binary 1-year FVC decline (10%)	92 (56)	0.717	0.008 0.009	0.957 2.764	0.926 1.295	0.989 5.899
	DLCO % predicted 1-year DLCO relative decline	92 (56)	0.714	0.0009 0.0009	0.945 1.029	0.914 1.012	0.977 1.047
	DLCO % predicted Binary 1-year DLco decline (10%)	92 (56)	0.689	0.0009 0.0765	0.945 1.701	0.914 0.945	0.977 3.061
	DLCO % predicted Binary 1-year DLco decline (15%)	92 (56)	0.720	0.002 0.001	0.948 2.623	0.917 1.478	0.98 4.657

Multivariable mixed-effects Cox regression models were used to investigate associations with mortality for 1-year FVC decline and 1-year DLCO decline after adjusting for patient age, gender, smoking status (never versus ever), antifibrotic use (never versus ever) and baseline disease severity estimated using DLco. Binary 1-year FVC decline uses 5% and 10% relative decline as thresholds, and binary 1-year DLco decline uses 10% and 15% relative decline as thresholds. Separate centres/countries within the derivation and replication cohorts were modelled as multilevel with random effects between centres/countries (a random intercept per centre/country). N: number of patients in mixed-effects Cox model. N-observed: number of deaths observed in N patients; C-index: concordance index; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; CI: confidence interval.

Supplementary Table 12. Multivariable mixed-effects Cox proportional hazards regression models in non-CPFE patients and the two CPFE SuStaIn subtypes in the derivation IPF cohorts.

Subgroup	Baseline severity and PFTs changes models	Entire study population					
		N (N-observed)	C-index	p-Value	Hazard ratio	95% CI	
						Lower	Upper
Non-CPFE IPF patients	DLCO % predicted 1-year FVC relative decline	130 (61)	0.821	1.94E-06 3.02E-08	0.942 1.082	0.919 1.052	0.966 1.113
	DLCO % predicted Binary 1-year FVC decline (5%)	130 (61)	0.805	7.65E-08 1.09E-05	0.935 3.824	0.912 2.104	0.958 6.953
	DLCO % predicted Binary 1-year FVC decline (10%)	130 (61)	0.811	4.33E-06 4.96E-07	0.945 4.261	0.923 2.422	0.968 7.497
	DLCO % predicted 1-year DLCO relative decline	130 (61)	0.803	1.62E-07 = 0.0001	0.937 1.038	0.914 1.018	0.960 1.058
	DLCO % predicted Binary 1-year DLco decline (10%)	130 (61)	0.800	4.03E-07 0.0010	0.940 2.764	0.918 1.511	0.963 5.055
	DLCO % predicted Binary 1-year DLco decline (15%)	130 (61)	0.811	9.11E-08 4.69E-07	0.936 4.211	0.913 2.407	0.959 7.366
Fibrosis-dominant CPFE patients	DLCO % predicted 1-year FVC relative decline	134 (76)	0.731	1.31E-08 =0.0005	0.943 1.039	0.924 1.017	0.962 1.062
	DLCO % predicted Binary 1-year FVC decline (5%)	134 (76)	0.743	2.85E-08 7.82E-05	0.947 2.765	0.928 1.669	0.965 4.580
	DLCO % predicted Binary 1-year FVC decline (10%)	134 (76)	0.718	4.79E-07 = 0.009	0.952 2.018	0.934 1.189	0.970 3.424
	DLCO % predicted 1-year DLCO relative decline	134 (76)	0.745	6.00E-09 =0.0001	0.940 1.033	0.920 1.016	0.960 1.051
	DLCO % predicted Binary 1-year DLco decline (10%)	134 (76)	0.719	1.08E-07 0.0831	0.948 1.540	0.929 0.945	0.967 2.509
	DLCO % predicted Binary 1-year DLco decline (15%)	134 (76)	0.732	2.62E-08 = 0.003	0.946 2.168	0.928 1.313	0.965 3.577
Matched-CPFE patients	DLCO % predicted 1-year FVC relative decline	88 (60)	0.701	=0.0003 =0.0064	0.956 1.040	0.933 1.011	0.980 1.070
	DLCO % predicted Binary 1-year FVC decline (5%)	88 (60)	0.704	0.0008 0.0589	0.960 1.711	0.938 0.980	0.983 2.987
	DLCO % predicted Binary 1-year FVC decline (10%)	88 (60)	0.705	= 0.002 = 0.012	0.963 2.484	0.941 1.219	0.987 5.065
	DLCO % predicted 1-year DLCO relative decline	88 (60)	0.727	=0.0006 1.07E-05	0.957 1.036	0.933 1.020	0.981 1.053
	DLCO % predicted Binary 1-year DLco decline (10%)	88 (60)	0.688	0.0011 0.0699	0.961 1.674	0.939 0.959	0.984 2.922
	DLCO % predicted Binary 1-year DLco decline (15%)	88 (60)	0.721	= 0.001 = 0.0004	0.961 2.634	0.938 1.535	0.984 4.518

Multivariable mixed-effects Cox regression models were used to investigate associations with mortality for 1-year FVC decline and 1-year DLCO decline after adjusting for patient age, gender, smoking status (never versus ever), antifibrotic use (never versus ever) and baseline disease severity estimated using DLco. Binary 1-year FVC decline uses 5% and 10% relative decline as thresholds, and binary 1-year DLco decline uses 10% and 15% relative decline as thresholds. Separate centres/countries within the derivation and replication cohorts were modelled as multilevel with random effects between centres/countries (a random intercept per centre/country). N: number of patients in mixed-effects Cox model. N-observed: number of deaths observed in N patients; C-index: concordance index; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; CI: confidence interval.

Supplementary Table 13. Multivariable mixed-effects Cox proportional hazards regression models in non-CPFE patients and the two CPFE SuStaIn subtypes in the replication IPF cohorts.

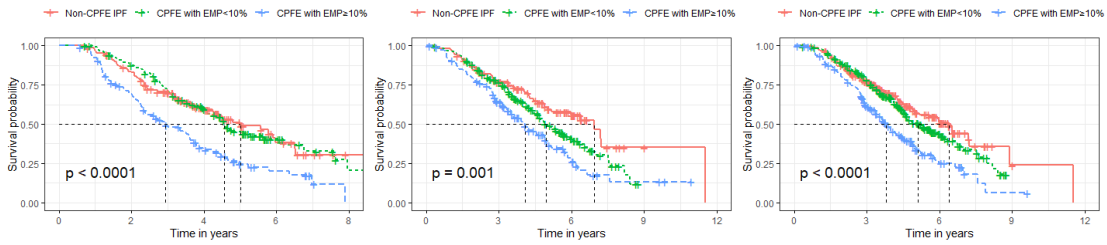
Subgroup	Baseline severity and PFTs changes models	Entire study population					
		N (N-observed)	C-index	p-Value	Hazard ratio	95% CI	
						Lower	Upper
Non-CPFE IPF patients	DLCO % predicted 1-year FVC relative decline	108 (45)	0.823	2.51E-05 8.65E-05	0.940 1.086	0.913 1.042	0.967 1.132
	DLCO % predicted Binary 1-year FVC decline (5%)	108 (45)	0.827	3.35E-05 = 0.002	0.942 2.719	0.916 1.425	0.969 5.187
	DLCO % predicted Binary 1-year FVC decline (10%)	108 (45)	0.817	5.17E-05 = 0.004	0.944 2.733	0.918 1.374	0.971 5.437
	DLCO % predicted 1-year DLCO relative decline	108 (45)	0.822	3.28E-06 = 0.019	0.933 1.032	0.906 1.005	0.960 1.059
	DLCO % predicted Binary 1-year DLco decline (10%)	108 (45)	0.835	1.56E-05 = 0.013	0.938 2.373	0.911 1.201	0.966 4.688
	DLCO % predicted Binary 1-year DLco decline (15%)	108 (45)	0.835	2.69E-05 = 0.006	0.941 2.693	0.915 1.336	0.968 5.428
Fibrosis-dominant CPFE patients	DLCO % predicted 1-year FVC relative decline	173 (95)	0.764	2.26E-11 =0.0008	0.938 1.051	0.921 1.021	0.956 1.082
	DLCO % predicted Binary 1-year FVC decline (5%)	173 (95)	0.765	2.71E-11 0.0095	0.939 1.750	0.921 1.147	0.956 2.671
	DLCO % predicted Binary 1-year FVC decline (10%)	173 (95)	0.770	2.11E-11 = 0.0003	0.938 2.396	0.921 1.497	0.956 3.836
	DLCO % predicted 1-year DLCO relative decline	173 (95)	0.782	8.97E-12 9.06E-05	0.939 1.028	0.922 1.014	0.956 1.042
	DLCO % predicted Binary 1-year DLco decline (10%)	173 (95)	0.772	0.0029 1.82E-10	1.890 0.941	1.244 0.924	2.873 0.959
	DLCO % predicted Binary 1-year DLco decline (15%)	173 (95)	0.772	1.82E-10 = 0.0003	0.941 2.363	0.924 1.480	0.959 3.771
Matched-CPFE patients	DLCO % predicted 1-year FVC relative decline	101 (58)	0.719	3.61E-05 = 0.226	0.942 1.021	0.915 0.987	0.969 1.056
	DLCO % predicted Binary 1-year FVC decline (5%)	101 (58)	0.708	7.26E-05 0.7189	0.945 1.112	0.919 0.624	0.972 1.982
	DLCO % predicted Binary 1-year FVC decline (10%)	101 (58)	0.729	= 0.0001 = 0.021	0.947 2.361	0.921 1.137	0.975 4.906
	DLCO % predicted 1-year DLCO relative decline	101 (58)	0.745	7.93E-06 = 0.0013	0.937 1.033	0.911 1.013	0.964 1.054
	DLCO % predicted Binary 1-year DLco decline (10%)	101 (58)	0.747	8.24E-06 0.0001	0.941 3.468	0.916 1.845	0.967 6.517
	DLCO % predicted Binary 1-year DLco decline (15%)	101 (58)	0.764	2.09E-05 1.33E-05	0.943 4.858	0.917 2.385	0.969 9.895

Multivariable mixed-effects Cox regression models were used to investigate associations with mortality for 1-year FVC decline and 1-year DLCO decline after adjusting for patient age, gender, smoking status (never versus ever), antifibrotic use (never versus ever) and baseline disease severity estimated using DLco. Binary 1-year FVC decline uses 5% and 10% relative decline as thresholds, and binary 1-year DLco decline uses 10% and 15% relative decline as thresholds. Separate centres/countries within the derivation and replication cohorts were modelled as multilevel with random effects between centres/countries (a random intercept per centre/country). N: number of patients in mixed-effects Cox model. N-observed: number of deaths observed in N patients; C-index: concordance index; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; CI: confidence interval.

Supplementary Table 14. Multivariable mixed-effects Cox proportional hazards regression models in non-CPFE patients and the two CPFE SuStaIn subtypes who fulfill criteria to enter IPF therapeutic trials in combined derivation and replication IPF cohorts.

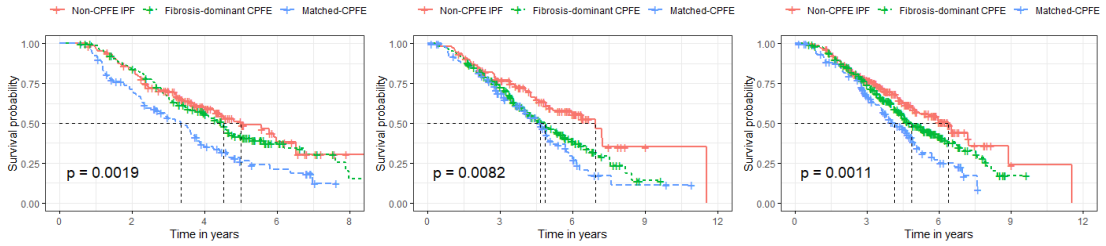
Subgroup	Baseline severity and PFTs changes models	Entire study population					
		N (N-observed)	C-index	p-Value	Hazard ratio	95% CI	
						Lower	Upper
Non-CPFE IPF patients	DLCO % predicted 1-year FVC relative decline	212 (87)	0.812	2.63E-06 1.29E-11	0.952 1.088	0.933 1.062	0.972 1.115
	DLCO % predicted Binary 1-year FVC decline (5%)	212 (87)	0.805	9.97E-07 9.94E-07	0.952 3.268	0.933 2.034	0.971 5.252
	DLCO % predicted Binary 1-year FVC decline (10%)	212 (87)	0.807	1.40E-05 2.13E-09	0.957 4.36	0.938 2.693	0.976 7.06
	DLCO % predicted 1-year DLCO relative decline	212 (87)	0.800	7.88E-08 4.25E-06	0.946 1.042	0.927 1.024	0.965 1.06
	DLCO % predicted Binary 1-year DLco decline (10%)	212 (87)	0.805	5.09E-07 6.23E-05	0.950 2.697	0.931 1.659	0.969 4.384
	DLCO % predicted Binary 1-year DLco decline (15%)	212 (87)	0.808	4.65E-07 5.74E-07	0.949 3.337	0.93 2.081	0.969 5.352
Fibrosis-dominant CPFE patients	DLCO % predicted 1-year FVC relative decline	255 (131)	0.727	9.64E-11 5.19E-06	0.947 1.045	0.932 1.025	0.963 1.064
	DLCO % predicted Binary 1-year FVC decline (5%)	255 (131)	0.730	8.67E-11 0.0005	0.948 1.877	0.932 1.319	0.963 2.671
	DLCO % predicted Binary 1-year FVC decline (10%)	255 (131)	0.721	5.41E-10 6.12E-05	0.949 2.243	0.933 1.511	0.965 3.331
	DLCO % predicted 1-year DLCO relative decline	255 (131)	0.759	1.94E-12 3.37E-10	0.942 1.042	0.926 1.028	0.958 1.055
	DLCO % predicted Binary 1-year DLco decline (10%)	255 (131)	0.734	1.28E-11 0.0001	0.945 2.028	0.930 1.417	0.961 2.901
	DLCO % predicted Binary 1-year DLco decline (15%)	255 (131)	0.741	1.19E-11 9.46E-09	0.945 3.009	0.930 2.066	0.961 4.384
Matched-CPFE patients	DLCO % predicted 1-year FVC relative decline	122 (72)	0.696	8.17E-05 = 0.0006	0.943 1.058	0.916 1.025	0.971 1.093
	DLCO % predicted Binary 1-year FVC decline (5%)	122 (72)	0.680	0.0002 0.0509	0.947 1.663	0.921 0.998	0.974 2.772
	DLCO % predicted Binary 1-year FVC decline (10%)	122 (72)	0.686	= 0.002 = 0.002	0.957 2.669	0.930 1.420	0.984 5.015
	DLCO % predicted 1-year DLCO relative decline	122 (72)	0.722	= 0.0001 1.39E-07	0.944 1.041	0.917 1.025	0.972 1.056
	DLCO % predicted Binary 1-year DLco decline (10%)	122 (72)	0.684	8.40E-05 0.0007	0.944 2.412	0.917 1.453	0.971 4.006
	DLCO % predicted Binary 1-year DLco decline (15%)	122 (72)	0.730	= 0.0004 9.58E-07	0.948 3.606	0.921 2.159	0.977 6.023

Multivariable mixed-effects Cox regression models were used to investigate associations with mortality for 1-year FVC decline and 1-year DLCO decline after adjusting for patient age, gender, smoking status (never versus ever), antifibrotic use (never versus ever) and baseline disease severity estimated using DLco. Binary 1-year FVC decline uses 5% and 10% relative decline as thresholds, and binary 1-year DLco decline uses 10% and 15% relative decline as thresholds. Separate centres/countries within the derivation and replication cohorts were modelled as multilevel with random effects between centres/countries (a random intercept per centre/country). N: number of patients in mixed-effects Cox model. N-observed: number of deaths observed in N patients; C-index: concordance index; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; CI: confidence interval.



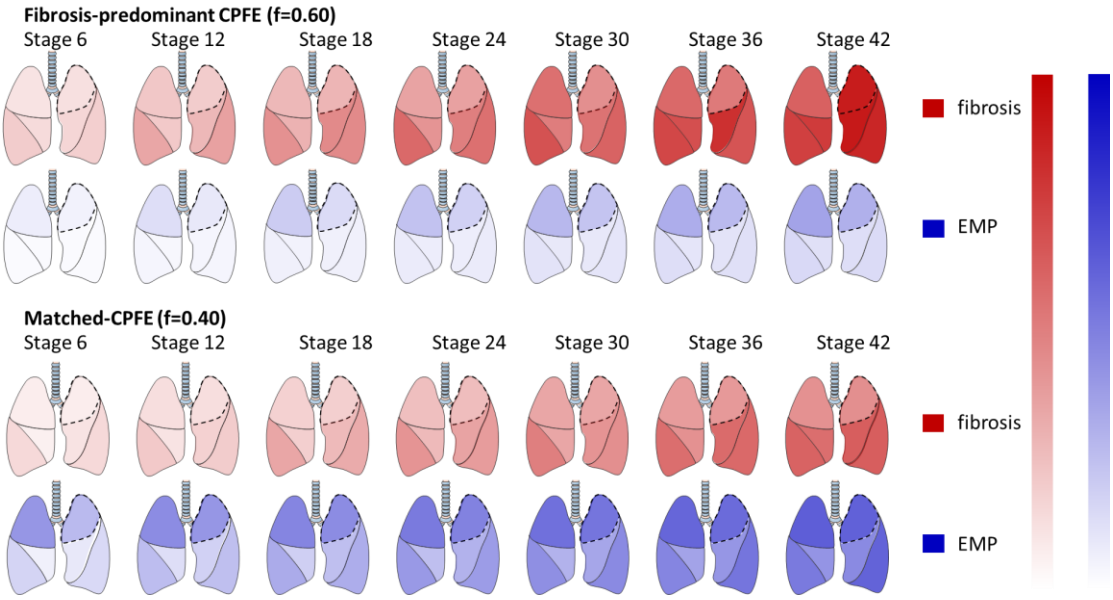
(a) (b) (c)

Supplementary Figure 1. Kaplan-Meier curves of non-CPFE IPF patients (red), CPFE patients with emphysema <15% (green) and CPFE patients with emphysema ⩾ 15% (blue) in the derivation cohort (a), the replication cohort (b), combined derivation and replication cohort patients qualifying for therapeutic trials (c). Log-rank tests show a significant difference in mortality between the three subtypes in all three analyses.

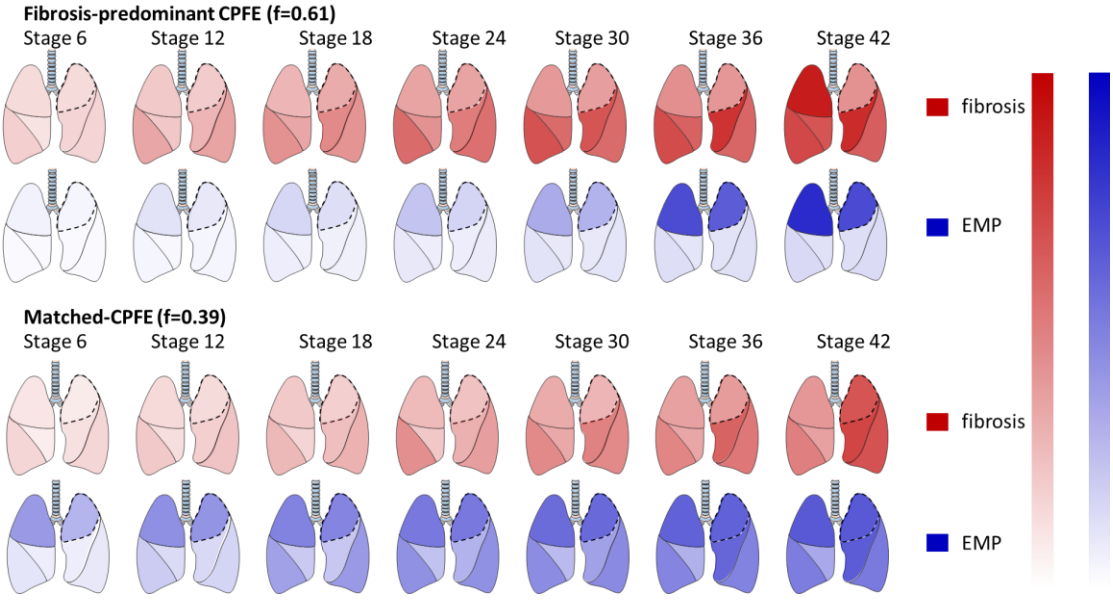


(a) (b) (c)

Supplementary Figure 2. Kaplan-Meier curves of non-CPFE IPF patients (red), fibrosis-dominant CPFE patients (green) and Matched-CPFE patients (blue) in the derivation cohort (a), the replication cohort (b), combined derivation and replication cohort patients qualifying for therapeutic trials (c). Log-rank tests show a significant difference in mortality between the three subtypes in all four analyses.



Supplementary Figure 3. Identification of CPFE subtypes and subtype disease progression modelled by SuStaIn in the derivation cohort. The rows show progression patterns of fibrosis extent (in red) and emphysema extent (in blue) in 6 lung zones (upper, middle and lower) in the two CPFE subtypes identified by SuStaIn: fibrosis-dominant CPFE and Matched-CPFE. Seven disease stages are highlighted, expressed as z-score intervals, In the fibrosis-dominant CPFE subtype comprising 60% of the cohort (top two rows), fibrosis is more severe at an early stage followed by a later emergence of emphysema. In the Matched-CPFE subtype comprising 40% of the cohort (bottom two rows), fibrosis and emphysema get worse together, with later stages showing relatively more extensive emphysema and less fibrosis compared to the fibrosis-dominant CPFE subtype. The upper lobe predominance of emphysema seen at early disease stages no longer exists in the later stages of the Matched-CPFE subtype. CPFE: Combined pulmonary fibrosis and emphysema. This figure was produced with the assistance of Servier Medical Art (https://smart.servier.com).



Supplementary Figure 4. Identification of CPFE subtypes and subtype disease progression modelled by SuStaIn in the replication cohort. The rows show progression patterns of fibrosis extent (in red) and emphysema extent (in blue) in 6 lung zones (upper, middle and lower) in the two CPFE subtypes identified by SuStaIn: Fibrosis-dominant CPFE and Matched-CPFE. Seven disease stages are highlighted, expressed as z-score intervals, In the fibrosis-dominant CPFE subtype comprising 61% of the cohort (top two rows), fibrosis is more severe at an early stage followed by a later emergence of emphysema. In the Matched-CPFE subtype comprising 39% of the cohort (bottom two rows), fibrosis and emphysema get worse together, with later stages showing relatively more extensive emphysema and less fibrosis compared to the fibrosis-dominant CPFE subtype. The upper lobe predominance of emphysema seen at early disease stages no longer exists in the later stages of the Matched-CPFE subtype. CPFE: Combined pulmonary fibrosis and emphysema. This figure was produced with the assistance of Servier Medical Art (https://smart.servier.com).