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Pulmonary function measures predict mortality differently in IPF *versus* combined pulmonary fibrosis and emphysema

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ABSTRACT: The composite physiologic index (CPI) was derived to represent the extent of fibrosis on high-resolution computed tomography (HRCT), adjusting for emphysema in patients with idiopathic pulmonary fibrosis (IPF). We hypothesised that longitudinal change in CPI would better predict mortality than forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) or diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) in all patients with IPF, and especially in those with combined pulmonary fibrosis and emphysema (CPFE).

Cox proportional hazard models were performed on pulmonary function data from IPF patients at baseline (n=321), 6 months (n=211) and 12 months (n=144). Presence of CPFE was determined by HRCT.

A five-point increase in CPI over 12 months predicted subsequent mortality (HR 2.1, p=0.004). At 12 months, a 10% relative decline in FVC, a 15% relative decline in $D_{L,CO}$ or an absolute increase in CPI of five points all discriminated median survival by 2.1 to 2.2 yrs *versus* patients with lesser change. Half our cohort had CPFE. In patients with moderate/severe emphysema, only a 10% decline in FEV_1 predicted mortality (HR 3.7, p=0.046).

In IPF, a five-point increase in CPI over 12 months predicts mortality similarly to relative declines of 10% in FVC or 15% in $D_{L,CO}$. For CPFE patients, change in FEV_1 was the best predictor of mortality.

KEYWORDS: Chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, prognosis, pulmonary function, survival

Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal diffuse parenchymal lung disease [1–4]. Progression of disease is heterogeneous. Some patients decline rapidly, others remain stable and all appear at risk of developing acute exacerbations [2, 3, 5]. Methods to assess and monitor disease status and ultimately predict mortality and response to therapy are needed. A variety of variables including pulmonary function at time of diagnosis, hypoxaemia at rest, desaturation during a 6-min walk test, longitudinal changes in forced vital capacity (FVC), longitudinal changes in diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) and performance on cardiopulmonary exercise testing have been shown to have prognostic value [6–12].

Smoking is a common risk factor for both emphysema and pulmonary fibrosis [13–15]. Therefore, patients with IPF may have combined pulmonary fibrosis and emphysema (CPFE). The presence of both pathologies could limit the ability to utilise FVC in the assessment and monitoring of disease course [16, 17]. The composite physiologic index (CPI) was developed to improve on previous prognostic measures in IPF by adjusting for emphysema and incorporating multiple measures of pulmonary function, namely forced expiratory volume in 1 s (FEV_1), FVC and $D_{L,CO}$ [18]. The CPI score at diagnosis more accurately predicted mortality than the individual pulmonary function tests (PFTs) alone in patients with concomitant emphysema [18].

We hypothesised that longitudinal changes in CPI would more accurately predict mortality than previously published longitudinal declines in FVC of 10% and $D_{L,CO}$ of 15% in all patients with IPF, and to a greater degree in patients with CPFE [7–10]. As such, we tested the CPI in a large cohort of patients diagnosed with IPF on biopsy or high-resolution computed tomography

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(HRCT). We evaluated the magnitude of CPI change required to predict an increased risk of mortality, and compared the relevant longitudinal change in CPI with changes in individual PFTs. Finally, we evaluated if the presence/absence of emphysema impacted the ability of CPI or individual measures of pulmonary function to predict mortality.

MATERIALS AND METHODS

Study population

Patients with IPF were selected from the University of Michigan (Ann Arbor, MI, USA) interstitial lung disease database. The diagnosis of IPF was made with either a surgical lung biopsy or HRCT scan diagnostic of usual interstitial pneumonia (UIP) using standard criteria [1, 3, 4, 7]. Patients were included if they had a PFT performed at the University of Michigan within 3 months of diagnosis. Mortality data were confirmed through the Social Security Death Registry Index censured by 3 months to account for reporting lag. Follow-up time was calculated from date of baseline PFT to date of death or censure. IPF patients were eligible for the analysis of CPFE if a HRCT had been performed at the University of Michigan within 1 yr before or after diagnosis.

Methods

Patients with at least one additional PFT after baseline were eligible for longitudinal analyses. For the 6-month analysis, all PFTs from 3 to 9 months after the baseline study were included to generate a regression line for each patient. An estimated 6-month PFT value was obtained from the regression. At least one PFT performed between 9 and 15 months after diagnosis was required to be included in the 12-month analysis. The same individual regression technique was used for 12-month data using all PFTs up to 15 months after baseline. The CPI was calculated from the following formula: 91 – (0.65x% predicted $D_{L,CO}$) – (0.53x% pred FVC) + (0.34x % pred FEV_1) [18]. Relative changes in PFT values were calculated as the estimated 6 or 12 month value minus the baseline value, divided by the baseline value.

The index of concordance (IOC) was used to compare predictive ability of the longitudinal change in various PFTs and CPI [19]. The IOC analysis considers each combination of two patients in the dataset and measures how accurately the model predicts which patient will live longer. The higher the IOC, the more likely the variables in the model explain the outcome, in this case mortality. Various cut-off points of relative and absolute change in CPI were studied to determine what change of CPI would yield the best IOC.

Emphysema was scored semi-quantitatively as none, mild (present but scant), moderate (notable or equivalent in extent to the fibrosis) or severe (the predominant pathology) by a thoracic radiologist experienced with HRCT scoring in prior clinical trials, blinded to tobacco history and patient outcome. Figure 1 contains representative images. Patients were grouped together for analysis as none/mild or moderate/severe emphysema.

Survival analysis

Cox proportional hazards models adjusting for age at diagnosis, sex and smoking status were used to assess the relationship of FEV_1, FVC, $D_{L,CO}$ and CPI to mortality [20]. Longitudinal models included adjustment for baseline PFT value. Time zero for median survival calculations was the last PFT, either 6 or 12 months. Therefore, the survival only applies to patients who were able to provide a 6 or 12 month PFT. Longitudinal changes in CPI were compared with longitudinal changes in each of its PFT components, including the previously published relative declines in FVC (10%) and $D_{L,CO}$ (15%) [7–10]. We also evaluated changes in CPI and PFTs in patients stratified by amount of emphysema. All statistics were performed on SAS® 9.2 software (SAS Institute Inc., Cary, NC, USA). Our institutional review board approved the study. Data on a subgroup of this patient cohort has been previously published [7, 9]. A portion of these results was presented at the 2010 American Thoracic Society International Conference [21].

RESULTS

Patient population

We identified 396 patients with IPF from 1995 to 2007. Of these, 321 patients had a baseline PFT performed at the University of Michigan, 211 patients had 6-month data and 144 had 12-month data. Of the 99 who did not have any longitudinal data, 34 died. 15 of the 67 who had 6-month but not 12-month data died. The remainder returned to the community for continuity of care. HRCT performed at the University of Michigan was available for analysis in 169 and 118 from the 6- and 12-month patients cohorts, respectively. Baseline demographics were not clinically different between patients participating in the baseline 6 or 12 month analyses or between patients with or without a HRCT available for scoring of emphysema, table 1.

Comparison at baseline

We assessed the impact of the baseline CPI and each individual component (FEV_1, FVC and $D_{L,CO}$) on risk of subsequent mortality. Each component, as well as the CPI, was predictive of subsequent mortality with all measures showing increased risk of mortality with greater physiological derangement (table 2). A lower $D_{L,CO}$ was associated with greater risk of mortality compared with similar degrees of dysfunction in FEV_1 or FVC.

Identifying relevant longitudinal change in CPI

We used IOC to compare the ability to predict mortality from longitudinal changes in CPI and the individual measures of pulmonary function. An absolute increase of five points in the CPI at 6 months yielded the highest IOC of 0.664, therefore the model would correctly predict patients at an increased risk of mortality 66.4% of the time. At 12 months, an absolute increase of 15 points had the highest IOC of 0.690 but only 6% of the cohort achieved this extent of worsening and an absolute increase in five points was within 1.2%, IOC of 0.678. Therefore, we determined an absolute increase of five points to be a clinically meaningful longitudinal change for future analyses. By comparison, a relative decline in FVC of 10% and $D_{L,CO}$ of 15% at 12 months yielded IOCs of 0.689 and 0.683 respectively, all roughly equivalent.

Longitudinal change and survival

Cox proportional hazards models of mortality with varying longitudinal changes in CPI, FEV_1, FVC and $D_{L,CO}$ over 6 and

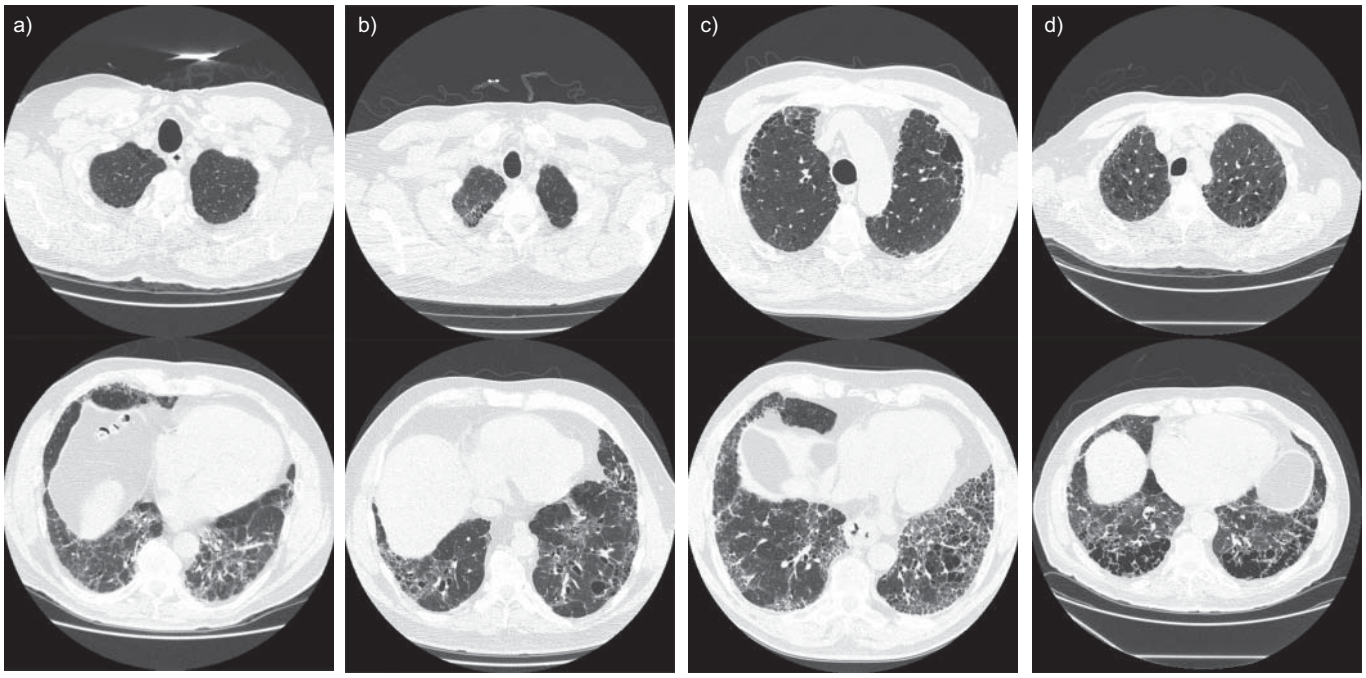

FIGURE 1. Examples of the high-resolution computed tomography scan semi-quantitative scoring system. Each panel contains a characteristic upper and lower lobe slice of a patient scored as a) none, b) mild, c) moderate and d) severe emphysema.

12 months are shown in table 3. At 6 months, only change in $D_{L,CO}$ was consistently significant. The other PFTs and the CPI exhibited variable significance and in general were insignificant at greater perturbations from baseline. This may represent the inherent variability in these physiological measures over short time periods. At 12 months, the models became more consistent as one would expect. The relative FVC decline of 10% and $D_{L,CO}$ decline of 15% yielded similar hazard ratios (HRs) at 2.4 and 2.3, respectively, with p-values <0.001. An increase in CPI of five points was similar with a HR of 2.1. An increase in CPI of 20 points yielded the highest HR at 5.2, but only applied to two patients. A CPI increase of five points was still significant after removing those patients with an increase in CPI >15 (HR 1.9; 95% CI 1.1–3.2, p=0.017).

Survival curves based on 12-month PFT and CPI data are shown in figure 2a–d. CPI performed similarly to its components FEV_1, FVC and $D_{L,CO}$. Median survival (95% CI), from the date of the last PFT for a five-point increase in CPI over 12 months was 2.63 yrs (1.63–3.93) compared with 4.75 yrs (3.53–6.81) for a less than five point change. This was similar to a 15% relative decline in $D_{L,CO}$, 2.58 yrs (1.63–3.57) *versus* 4.75 yrs (3.74–6.81). Longitudinal changes in all physiological variables discriminated median survival in this patient population by 2 to 2.2 yrs.

TABLE 1 Baseline demographics and pulmonary function data

	Baseline	6 month	6 month HRCT	12 month	12 month HRCT
Patients n	321	211	169	144	118
Age at diagnosis yrs	63.9±9.7	63.2±10.0	63.8±9.8	62.3±10.0	62.7±10.0
Male	217 (67.6)	151 (71.6)	127 (75.1)	102 (70.8)	88 (74.6)
Ever tobacco use	236 (73.5)	162 (76.8)	131 (77.5)	109 (75.7)	89 (75.4)
Tobacco pack-yrs	26.2±27.5	27.2±28.4	27.2±28.0	26.6±27.6	27.3±28.1
Surgical lung biopsy	245 (76.3)	158 (74.9)	118 (69.8)	113 (78.5)	88 (74.6)
Follow-up yrs	5.2 (4.9–6.1)	5.4 (5.1–7.0)	5.1 (4.7–6.1)	6.6 (5.3–7.7)	5.4 (5.0–7.0)
Pulmonary function					
FEV_1 % pred	79.2±19.0	79.1±17.2	79.1±17.0	80.7±18.6	80.9±18.5
FVC % pred	67.6±16.8	68.0±15.8	67.7±15.3	69.0±16.4	69.0±16.3
$D_{L,CO}$ % pred	44.5±16.2	46.2±15.3	44.9±14.8	48.0±16.1	46.6±15.6
CPI	53.2±12.4	51.8±11.7	52.8±11.2	50.7±12.1	51.6±11.7

Data are presented as mean±SD, n (%) or median (95% CI), unless otherwise stated. HRCT: high-resolution computed tomography; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity: $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; CPI: composite physiologic index.

TABLE 2 Hazard ratios (HRs) for mortality associated with discrete differences in 321 baseline individual pulmonary function tests and composite physiology index

	HR (95% CI)#	p-value
Difference in FEV_1 % pred		
5% less	1.1 (1.0–1.1)	0.015
10% less	1.1 (1.0–1.2)	0.015
15% less	1.2 (1.0–1.3)	0.015
Difference in FVC % pred		
5% less	1.1 (1.0–1.1)	0.003
10% less	1.2 (1.1–1.3)	0.003
15% less	1.2 (1.1–1.4)	0.003
Difference in $D_{L,CO}$ % pred		
5% less	1.1 (1.1–1.2)	<0.001
10% less	1.2 (1.1–1.4)	<0.001
15% less	1.4 (1.2–1.6)	<0.001
Difference in CPI		
5 points more	1.2 (1.1–1.2)	<0.001
10 points more	1.3 (1.2–1.5)	<0.001
15 points more	1.6 (1.3–1.9)	<0.001

FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; CPI: composite physiologic index. #: HRs are based on Cox models that assume a continuous change in each value. The hazards have been tabulated at clinically relevant differences. For example, a patient with a baseline FVC 10% less than another patient has a 20% increased hazard (HR 1.2).

CPFE is prevalent

CPFE was common in our cohort. Of the 169 patients with HRCT scans in the 6-month analysis, 86 (51%) had evidence of emphysema, 42 (25%) with moderate or severe emphysema. In the 12-month analysis, 55 (47%) of the 118 patients with HRCT had CPFE, 32 (27%) moderate or severe. The moderate/severe combined emphysema patients tended to have higher FEV_1, FVC and lower CPI with equivocal $D_{L,CO}$, than those with none/mild emphysema (table 4). The mean FEV_1/FVC ratios in the none/mild emphysema groups were 0.84–0.85, higher than those in the moderate/severe emphysema group (0.78–0.79); however, all were greater than the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for obstruction (0.70) [22].

CPFE and survival

A longitudinal decline in FEV_1 was the strongest and most consistent predictor of mortality for patients with moderate-to-severe emphysema on HRCT (table 5). In contrast, change in FVC, $D_{L,CO}$ and CPI were not predictive at 12 months follow-up and only FVC was predictive at 6 months. Furthermore, the HR associated with a 10% decline in FEV_1 increased for increasing levels of emphysema on HRCT. The HR (95% CI) increased from 1.8 (0.8–4.1) to 2.5 (1.2–5.1) to 3.7 (1.0–13.7) in patients with no emphysema, none/mild emphysema and moderate/severe emphysema, respectively. Cox survival curves are shown in figure 2e–h.

In the none/mild emphysema group, a five-point increase in the CPI appeared to be the best predictor with the highest HR (95% CI) at 12 months (3.6 (1.7–7.7); p=0.001) (table 5). 12-month relative declines in $D_{L,CO}$ and FVC performed similarly with HRs of 2.9 and 2.8, respectively. In a separate 12-month analysis of patients with no emphysema, a five-point increase in CPI out performed the other measures with a HR of 4.4 (1.8–10.7) compared with relative declines in $D_{L,CO}$ 2.8 (1.3–4.4) and FVC 2.6 (0.8–2.6).

Overall, grouping patients by emphysema status increased each pulmonary function model's IOC, therefore knowing emphysema status provided the best mortality prediction.

DISCUSSION

In a large cohort of patients with IPF we described that: 1) baseline individual pulmonary function parameters (FEV_1, FVC or DL,CO) and the CPI were predictive of subsequent mortality; 2) an increase in CPI of at least five points over 6 or 12 months significantly predicted mortality and was, therefore, clinically relevant; 3) longitudinal changes in $D_{L,CO}$ and CPI are more predictive than FVC and FEV_1, and comparable to each other; 4) CPFE is common in patients diagnosed with IPF; 5) longitudinal change in FEV_1 was most predictive of mortality in patients with CPFE; and 6) CPI may be the best predictor in patients without emphysema. These data confirm the value of longitudinal physiological monitoring in IPF patients but extend previous results to highlight the importance of accounting for the presence and severity of emphysema in choosing the optimal longitudinal measure of physiological derangement to predict outcome.

Comparison of CPI and individual measures of pulmonary function

Without accounting for emphysema, baseline PFT measurements and CPI were all predictive of mortality. The baseline $D_{L,CO}$ and CPI were the best predictors and were similar, which is not entirely consistent with an article describing CPI [18]. In a study by WELLS *et al.* [18] and a follow-up study by LATSI *et al.* [10], which incorporated longitudinal changes in patients with UIP and nonspecific interstitial pneumonia, the baseline CPI was reported to be a better predictor for mortality than baseline $D_{L,CO}$. These differences could be due to differences in patient population or sample size with >200 additional cases of IPF in this dataset.

To compare CPI as a longitudinal predictor, we identified the magnitude of CPI change that increases risk of subsequent mortality, a CPI increase of at least five points at 6 or 12 months follow-up. Although extreme worsening of CPI was associated with an even higher risk of mortality, the small numbers of patients with these severe changes made those cut-off points impractical. Importantly, a recent report from the IFIGENIA (Idiopathic Pulmonary Fibrosis International Group Exploring *N*-acetyl-cysteine I Annual) study group demonstrated a difference of 5.47 in CPI in placebo-treated patients compared with a change of 0.509 in *N*-acetylcysteine-treated patients [23]. This finding suggests broad applicability of the cut-off point of five; however, there were too few deaths in the study to examine the relationship of this increase on mortality. An increase in CPI of at least five points remained a significant predictor of mortality even when patients whose CPI worsened by >15 were removed highlighting that an increase of

TABLE 3 Longitudinal hazard ratios (HR) for mortality by absolute increase in composite physiologic index (CPI) and relative decrease in individual pulmonary function tests over 6 and 12 months

	6-month change[#]			12-month change[¶]		
	n (%)	HR (95% CI)	p-value	n (%)	HR (95% CI)	p-value
Decline in FEV_1 % pred						
5	81 (38)	1.6 (1.1–2.3)	0.018	72 (50)	2.3 (1.4–3.7)	<0.001
10	44 (21)	1.6 (1.0–2.4)	0.051	42 (29)	2.2 (1.3–3.5)	0.002
15	24 (11)	1.6 (0.9–2.8)	0.086	25 (17)	2.1 (1.3–3.6)	0.005
20	8 (4)	1.4 (0.6–3.5)	0.473	9 (6)	3.6 (1.6–8.1)	0.001
Decline in FVC % pred						
5	88 (42)	1.8 (1.2–2.7)	0.002	75 (52)	1.8 (1.1–2.9)	0.012
10	51 (24)	1.4 (0.9–2.1)	0.122	51 (35)	2.4 (1.5–3.8)	<0.001
15	28 (13)	1.1 (0.6–1.8)	0.857	26 (18)	2.6 (1.6–4.5)	<0.001
20	12 (6)	2.0 (1.0–4.0)	0.051	15 (10)	3.6 (1.9–6.9)	<0.001
Decline in $D_{L,CO}$ % pred						
10	74 (35)	1.7 (1.1–2.5)	0.011	68 (47)	2.2 (1.4–3.5)	0.001
15	51 (24)	1.6 (1.1–2.5)	0.029	57 (40)	2.3 (1.5–3.7)	<0.001
20	33 (16)	1.8 (1.1–3.0)	0.030	37 (26)	3.0 (1.8–4.9)	<0.001
25	20 (9)	2.3 (1.2–4.2)	0.010	26 (18)	3.5 (2.0–6.1)	<0.001
Increase in CPI						
+5	51 (24)	1.7 (1.1–2.7)	0.019	63 (44)	2.1 (1.3–3.5)	0.004
+10	20 (9)	1.3 (0.7–2.4)	0.439	21 (15)	2.3 (1.2–4.2)	0.011
+15	4 (2)	2.0 (0.6–6.6)	0.240	9 (6)	3.3 (1.4–7.7)	0.007
+20	2 (1)	1.2 (0.2–8.4)	0.884	2 (1)	5.2 (1.1–23.8)	0.036

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide. [#]: n=211; [¶]: n=144.

five in CPI is significant and not just driven by the subset of patients with extreme worsening.

Throughout our study the $D_{L,CO}$ and CPI were comparable predictors both at baseline and longitudinally. The FVC was as strong as $D_{L,CO}$ at 12 months. Median survival discrimination between these three predictors was comparable. In summary, these analyses suggest that contrary to our hypothesis, in all-comers with IPF, longitudinal change in either FVC or $D_{L,CO}$ appear equivalent to changes in CPI. However, when patients with emphysema are removed, CPI appears to be a better predictor.

Impact of CPFE

Prior studies highlight that longitudinal changes in FVC and $D_{L,CO}$ are important but imperfect predictors of subsequent mortality [2, 7, 8, 10, 24]. This imperfection could be due to concomitant emphysema. In our cohort, combined moderate-to-severe emphysema was seen in one quarter of our IPF patients with HRCT, any emphysema was seen in half of the patients. Grouping patients by emphysema status improved the ability of the models to predict mortality by IOC analysis. These results argue that CPFE is common, and identifying CPFE is important in clarifying the appropriate prognostic measure. However, identifying patients with CPFE does not appear to be feasible with spirometry alone. Our patients with moderate/severe emphysema did not have FEV_1/FVC ratios consistent with obstruction as per the GOLD criteria [22]. Less than half (42.6%) of CPFE patients from one study met GOLD criteria for chronic obstructive pulmonary disease [25]. Therefore, accurately diagnosing CPFE may require HRCT.

The differential ability of individual measures of pulmonary function to predict mortality based on the quantity of emphysema is a novel and important finding of our study. Our hypothesis predicted that CPI would be the strongest predictor of mortality in patients with CPFE. However, our data highlight that change in FEV_1 appeared to be the best surrogate for predicting subsequent mortality in IPF patients with moderate-to-severe emphysema. Interestingly, the HRs associated with declining FEV_1 increased with increasing emphysema on HRCT scan in a dose-dependent fashion. FEV_1 was not a significant predictor in the patients without emphysema just as changes in FVC, $D_{L,CO}$ or CPI at 12 months were not consistently predictive of subsequent mortality in patients with moderate/severe emphysema.

In our dataset, patients who had a decline in FVC over time almost always had a decline in FEV_1 as well. This fact underscores why CPI may not be an effective longitudinal measure in CPFE, since FEV_1 and FVC have opposite effects on the CPI: a lower FEV_1 decreases the CPI, a lower FVC increases it. Therefore, the CPI may remain balanced in the face of progressive obstruction and restriction. More surprising, the $D_{L,CO}$ did not statistically predict mortality in the emphysema patients which may be due to selection bias as more severely ill patients may not be able to perform a $D_{L,CO}$ test or increased survivorship in a small number of patients. The Cox survival curves show good separation for 4–5 yrs for both CPI and $D_{L,CO}$ with more separation for $D_{L,CO}$, but come back together with increased survivorship in a small sample.

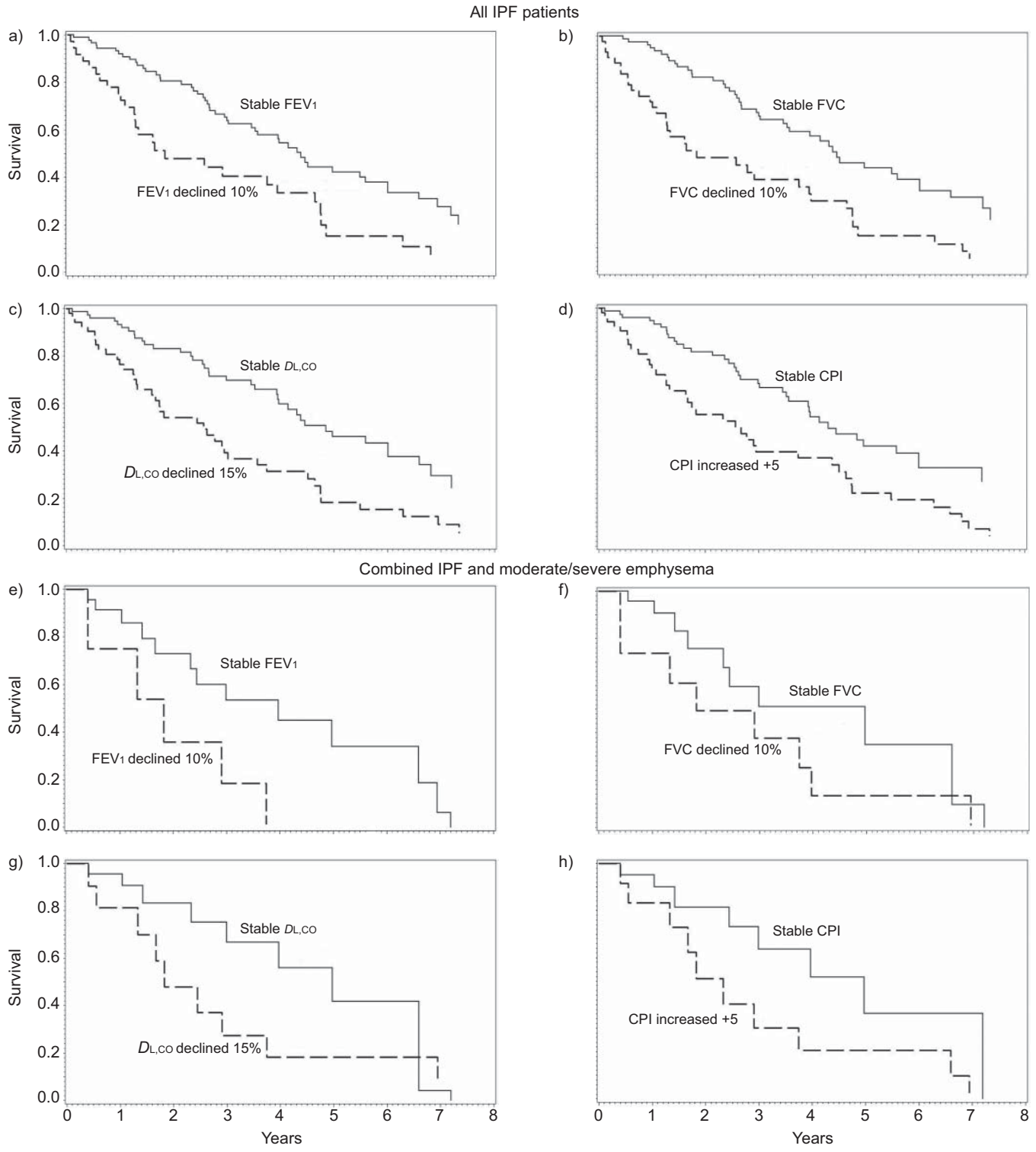

FIGURE 2. Cox model survival estimates for relevant 12 month longitudinal changes in pulmonary function tests or composite physiologic index (CPI) in all patients with a–d) idiopathic pulmonary fibrosis (IPF) and e–h) combined IPF and moderate/severe emphysema. a, e) A relative decline in forced expiratory volume in 1 s (FEV_1) % predicted of >10% (– – – – –) *versus* <10% (——), followed by b, f) a relative decline in forced vital capacity (FVC) % pred of >10% (– – – – –) *versus* <10% (——). c, g) A relative decrease in diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) % pred of 15% (– – – – –) *versus* a <15% change (——). d, h) An absolute CPI increase >5 points (– – – – –) *versus* <5 points (——). Survival is dated from the time of their last analysed pulmonary function test (PFT), the 12 month study. Therefore, this survival applies to patients able to survive 1 yr from their baseline study. These physiologic cut-off points were chosen based on prior literature and the best prognostic fit according to index of concordance. All Cox models are adjusted for the baseline average PFT or CPI value, average age at diagnosis of 62 yrs, male sex and positive smoking history, with baseline hazards stratified by whether the patient was in the stable or change group.

TABLE 4 Demographics of patients stratified by presence and severity of combined pulmonary fibrosis and emphysema

	6-month analysis		12-month analysis	
	None/mild	Moderate/severe	None/mild	Moderate/severe
Patients n	127	42	86	32
Age at diagnosis yrs	63.8±9.9	64.0±9.6	62.8±10.1	62.6±9.8
Male	94 (74.0)	33 (78.6)	65 (75.6)	23 (71.9)
Ever tobacco use	89 (70.1)	42 (100)	57 (66.3)	32 (100)
Tobacco pack-yrs	21.0±25.0	46.4±28.4	20.8±25.8	45.4±26.5
Surgical lung biopsy	98 (77.2)	20 (47.6)	71 (82.6)	17 (53.1)
Follow-up yrs	5.1 (4.7–6.1)	5.3 (3.3–7.9)	5.3 (5.0–7.0)	6.0 (2.5–6.8)
HRCT type				
Volumetric	35 (27.6)	16 (38.1)	17 (19.8)	9 (28.1)
Incremental	91 (71.1)	26 (61.9)	69 (80.2)	23 (71.9)
Emphysema				
None	83 (65.4)		63 (73.3)	
Mild	44 (34.6)		23 (26.7)	
Moderate		32 (76.2)		27 (84.4)
Severe		10 (23.8)		5 (15.6)
Pulmonary function				
FEV_1 % pred	77.4±16.9	84.0±16.2	78.1±17.4	88.5±19.6
FVC % pred	64.8±14.3	76.2±15.2	65.3±14.8	79.2±16.1
FEV_1/FVC ratio	0.84±0.06	0.78±0.07	0.85±0.05	0.79±0.07
$D_{L,CO}$ % pred	45.8±14.3	42.2±16.0	46.7±15.8	46.3±15.3
CPI	53.2±10.8	51.7±12.5	52.6±11.7	49.1±11.5

Data are presented as mean±SD, n (%) or median (95% CI), unless otherwise stated. HRCT: high-resolution computed tomography; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; CPI: composite physiologic index.

Limitations

Important limitations of this study include the possibility of selection or referral bias, the absence of data to assess for concomitant pulmonary hypertension and the lack of prospectively defined treatments which precludes our ability to evaluate any potential impact of treatment on outcome. The lack of available HRCT in all patients could lead to selection bias. However, our subset of patients with HRCT scans had

TABLE 5 Longitudinal hazard ratios (HRs) for mortality associated with absolute increases in composite physiologic index (CPI) and relative decreases in individual pulmonary function tests over 6 and 12 months in patients with combined pulmonary fibrosis and emphysema

	6-month change			12-month change		
	n (%)	HR (95% CI)	p-value	n (%)	HR (95% CI)	p-value
None-to-mild empysema#						
10% decline FEV_1	31 (24.4)	1.4 (0.8–2.6)	0.268	26 (30.2)	2.5 (1.2–5.1)	0.012
10% decline FVC	36 (28.3)	1.4 (0.8–2.6)	0.209	29 (33.7)	2.8 (1.4–5.9)	0.005
15% decline $D_{L,CO}$	31 (24.4)	2.4 (1.3–4.4)	0.005	33 (38.4)	2.9 (1.4–5.7)	0.003
+5 increase CPI	33 (26.0)	2.4 (1.3–4.4)	0.003	34 (39.5)	3.6 (1.7–7.7)	0.001
Moderate-to-severe emphysema¶						
10% decline FEV_1	4 (9.5)	8.4 (1.9–37.8)	0.006	6 (18.8)	3.7 (1.0–13.7)	0.046
10% decline FVC	5 (11.9)	4.1 (1.2–14.0)	0.025	9 (28.1)	2.1 (0.8–6.0)	0.154
15% decline $D_{L,CO}$	13 (31.0)	2.1 (0.8–5.5)	0.140	12 (37.5)	2.1 (0.7–6.0)	0.174
+5 increase CPI	11 (26.2)	1.9 (0.6–5.7)	0.279	15 (46.8)	2.4 (0.8–7.9)	0.135

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide. #: n=127 for 6-month change and n= 86 for 12-month change; ¶: n=42 for 6-month change and n=32 for 12-month change.

similar clinical characteristics to the remainder of the cohort, theoretically lessening the chance that only patients with emphysema had HRCT scans available for analysis. Also, our CPFE patient population is similar to cohorts previously described in terms of baseline FEV_1 and $D_{L,CO}$. Our patients tended to have a lower FVC and there was a higher percentage of females [25–27]. Another limitation is the lack of a computer-generated quantitative score for the HRCT scans. The available HRCT scans spanned many years during which significant advancements were made in HRCT technology. Further prospective, quantitative HRCT information on IPF patients could provide refinement to this analysis and extend these findings. Other limitations include referral bias as complicated cases with dual diagnoses may be more likely to be referred. We do not have systematic data in the CPFE cohort to control for pulmonary hypertension or treatments received in the survival analyses. Therefore, we cannot reflect on the significance that known pulmonary hypertension or a particular chronic obstructive pulmonary disease phenotype may have in an individual patient. Also, the most consistent longitudinal findings occur at 12-month follow-up PFT. Therefore applying our results would require that a patient be alive and able to perform the testing at 12 months.

In a large, well characterised cohort of patients with IPF an increase in CPI of at least five points is a meaningful predictor of subsequent mortality. Longitudinal changes in CPI were comparable to changes in FVC and $D_{L,CO}$ unless emphysema was absent wherein CPI was superior. Combined pulmonary fibrosis and emphysema is common in patients diagnosed with IPF. FEV_1 appears to be the best physiological predictor of mortality in CPFE.

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STATEMENT OF INTEREST

None declared.

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