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# **Likelihood of pulmonary hypertension in patients with idiopathic pulmonary fibrosis and emphysema**

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## **SUMMARY AT A GLANCE**

In combined pulmonary fibrosis and emphysema (CPFE), the likelihood of having pulmonary hypertension is explained by the summed baseline CT extents of interstitial lung disease and emphysema. There is no synergistic effect in CPFE increasing the likelihood of pulmonary hypertension. CPFE is therefore not associated with a malignant microvascular phenotype.

## **ABBREVIATION LIST**

CI	confidence interval
CPFE	combined fibrosis and emphysema
CPI	composite physiologic index
CT	computed tomography
DLco	diffusing capacity for carbon monoxide
FVC	forced vital capacity
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
MDT	multi-disciplinary team
PHT	pulmonary hypertension
RVSP	right ventricular systolic pressure

## **ABSTRACT**

**BACKGROUND AND OBJECTIVE:** To evaluate whether patients with combined pulmonary fibrosis and emphysema (CPFE) have an increased likelihood of pulmonary hypertension (PHT) when compared to idiopathic pulmonary fibrosis (IPF) patients without emphysema.

**METHODS:** Two consecutive IPF populations having undergone transthoracic echocardiography were examined (n=223 and n=162). Emphysema and interstitial lung disease (ILD) extent were quantified visually; ILD extent was also quantified by a software tool, CALIPER. Echocardiographic criteria categorised PHT risk.

**RESULTS:** The prevalence of an increased PHT likelihood was 29% and 31% in each CPFE cohort. Survival at 12 months was 60% across both CPFE cohorts with no significantly worsened outcome identified when compared to IPF patients without emphysema.

Using logistic regression models in both cohorts, total CT disease extent (ILD and emphysema) predicted the likelihood of PHT. After adjustment for total disease extent, CPFE had no stronger association with PHT likelihood than IPF patients without emphysema.

**CONCLUSION:** Our findings indicate that the reported association between CPFE and PHT is explained by the summed baseline CT extents of ILD and emphysema. Once baseline severity is taken into account, CPFE is not selectively associated with a

malignant microvascular phenotype, when compared to IPF patients without emphysema.

**KEY WORDS:** idiopathic pulmonary fibrosis, computer tomography, emphysema, pulmonary hypertension

**Short title:** PHT likelihood in CPFE

## INTRODUCTION

It has now been over 25 years since the initial observation that emphysema co-exists in a proportion of patients with idiopathic pulmonary fibrosis (IPF)(1). Over the intervening period, the term combined pulmonary fibrosis and emphysema (CPFE)(2) has entered the interstitial lung disease (ILD) lexicon to describe a combination of two pathologies, namely emphysema and fibrosis, which combine to increase the probability of developing of pulmonary hypertension (PHT) when compared to patients with IPF alone(3-6). Yet what remains unclear in patients with CPFE is whether a symbiotic relationship exists between emphysema and fibrosis where the combination of the two disease processes, emphysema and fibrosis, exerts an impact greater than the sum of the individual parts on the likelihood of having PHT.

We therefore examined two consecutive populations of IPF patients presenting to our institution over a seven-year period. We aimed to identify whether the combined severity of emphysema and fibrosis represents a distinct microvascular phenotype, with a vasculopathic effect greater than expected from the sum of the individual components.

## **METHODS**

### **Clinical data**

A previously reported consecutive population of 272 patients retrospectively diagnosed by a multidisciplinary team (MDT) with IPF from January 2007 to July 2011 was examined(7). A retrospective review of an ILD database subsequently identified 201 consecutive patients with an MDT diagnosis of IPF presenting to our institution between July 2011 and December 2014. Patients were defined as “ever smokers” following evaluation of clinical notes if they had smoked at least one cigarette per day for at least one year.

CT and pulmonary function test protocols are included in the supplementary appendix S1. Approval for this retrospective study of clinically indicated CT and pulmonary function data was obtained from Liverpool Research Ethics Committee (Reference: 14/NW/0028), the Institutional Ethics Committee of the Royal Brompton Hospital and Mayo Clinic and informed patient consent was not required.

### **CT evaluation**

CALIPER quantitation of total ILD extent was performed for both cohorts to provide an independent measure of ILD extent(8). CALIPER emphysema scores were not utilized in the analyses for reasons described in the Supplementary Appendix S1.

CTs were visually scored on a lobar basis with extents of ILD and emphysema estimated to the nearest 5%. Visual scoring was performed by two of four radiologists: cohort 1 (AN, SLW); cohort 2 (GC, JB). Lobar CT scores for both IPF



cohorts were adjusted using normalized lobar volumes with correction factors highlighted in Supplementary Table S1. The most disparate 5% (two standard deviations) of values were arbitrated by a third scorer (JJ). Discrepancies between scorer pairs for the presence of emphysema and emphysema extent in never-smokers was also consensed by the same third scorer (JJ).

### **CT total disease extent scores**

Total disease extent on CT at baseline was defined as the sum of ILD extent and total visual emphysema extent. Total CT disease extent was used to categorise patients as having an increased echocardiographic likelihood of PHT using two scores:

- 1) Sum of CALIPER ILD extent and visual emphysema extent (CILDemph)
- 2) Sum of Visual ILD extent and visual emphysema extent (VILDemph)

### **Definitions of echocardiographic likelihood of PHT**

Only echocardiographic examinations performed within 3 months of the initial diagnostic CT scan were considered for analysis. Two definitions of echocardiographic likelihood of PHT were considered:

Increased likelihood of PHT: defined using a threshold of right ventricular systolic pressure (RVSP)  $>50\text{mmHg}$ (9), or two of the following measures: evidence of right atrial or ventricular dilatation, evidence of right ventricular dysfunction or a pulmonary artery acceleration time  $<105\text{msec}$ .

High probability of PHT: defined using European Society of Cardiology and European Respiratory Society consensus guidelines(10). Patients required a peak tricuspid

regurgitation velocity >340m/s, or a peak tricuspid regurgitation velocity >290m/s, and two of the following signs: right atrial or ventricular dilatation, evidence of right ventricular dysfunction or a pulmonary artery acceleration time <105msec.

Use of the “Increased PHT likelihood” definition allowed evaluation of PHT likelihood in patients in whom a tricuspid regurgitation velocity could not be measured. This definition also allowed evaluation of PHT likelihood in historic cases, where all the various measurements required to satisfy the 2015 consensus guidelines for a high probability of PHT (10), had not been routinely performed. The group of patients with a “High likelihood of PHT” included patients with an “Increased probability of PHT”(10) that fulfilled the relevant inclusion criteria. As the study evaluated patients presenting for their baseline clinical assessment, no study patients had received vasodilator medication.

### **Statistical analysis**

Differences in visual CT scores between scorers were evaluated using the Kappa score for categorical variables and the single determination standard deviation for continuous variables (Supplementary Table S2). Group differences were examined using the Students T-test for continuous variables or the Chi-squared test for categorical variables and the Mann Whitney U test for non-normally distributed median values. Outcomes were examined using Kaplan Meier survival curves with differences between the curves evaluated using the Log Rank test.

The relationship between each combined morphologic score (CILDemph and VILDemph) and an increased or high likelihood of PHT was explored in separate logistic regression models with adjustment made for patient age, gender and smoking status (never versus ever). To investigate whether CPFE accords a patient an increased likelihood of PHT, beyond that explained by total disease extent on CT (CILDemph and VILDemph), a binary emphysema score (presence/absence of emphysema) was inserted into each logistic regression model alongside patient age, gender, smoking status and either CILDemph or VILDemph. DLco was not used to adjust for baseline disease extent in any logistic regression model used to identify PHT likelihood.

## RESULTS

### Baseline parameters

385/473 (81%) patients across both cohorts had echocardiographic examinations within 3 months of the diagnostic CT scan. Baseline characteristics of patients across both study cohorts are shown in Supplementary Table S3. The mean interval between echocardiography and CT imaging was  $8.7\pm 19.5$  days. No significant difference in the likelihood of CPFE ( $p=0.45$ ) or mortality (Log rank test  $p=0.63$ ) was identified between patients that did and did not undergo transthoracic echocardiography. Patients that did not undergo echocardiography had less extensive disease than patients undergoing transthoracic echocardiography, as evidenced by less ILD (scored by both CALIPER and visual analysis), less emphysema, a lower CPI score and a higher mean DLco (Supplementary Table S4). In patients that did undergo transthoracic echocardiography, emphysema was identified in 171/385 (44%) patients (Cohort 1 Kappa=0.59; Cohort 2 Kappa=0.45) with a mean emphysema extent of  $12.2\pm 13.5\%$  in patients with emphysema.

In all analyses in the study, similar results were obtained when both cohorts were examined separately. Results for Cohort 1 alone are described in the main manuscript, with detailed results for Cohort 2 included in the Supplementary Appendix. The final two Results subsections however, represent analyses performed on the combined populations of Cohorts 1 and 2.

Amongst patients with CPFE in Cohort 1, the prevalence of an increased likelihood of PHT was 27/88 (31%)[Table 1]and the prevalence of a high likelihood of PHT was

20/88 (23%). No significant difference in patient age, gender or baseline DLco values was identified between IPF and CPFE patients with an increased echocardiographic likelihood of PHT (Table 1). The results were maintained in patients with a high echocardiographic likelihood of PHT in Cohort 1, and for both PHT definitions in Cohort 2 (Supplementary Table S5).

### **CT features of patients with increased likelihood of PHT**

When patients in Cohort 1 with an increased or high likelihood of PHT were examined using the CILDemph and VILDemph scores, CPFE patients were not found to have significantly more disease on CT (sum of ILD and emphysema extents) than IPF patients (Table 1). In Cohort 2, CPFE patients with an increased and high likelihood of PHT had significantly more disease on CT (sum of ILD and emphysema extents) when the VILDemph scores were considered but not when using the CILDemph score (Supplementary Table 5). When patients with CPFE alone were subanalysed, patients with an increased likelihood of PHT had significantly more disease on CT than patients without an increased likelihood of PHT: CILDemph  $p=0.0003$ ; VILDemph  $p=0.02$ . The results were similar when CPFE patients with and without a high likelihood PHT were examined: CILDemph  $p=0.0003$ ; VILDemph  $p=0.001$  (Figure 1; Cohort 2 results are shown in Supplementary Figure 1).

Binary logistic regression models were used to identify variables predictive of an increased likelihood of PHT in Cohort 1. Significant associations with an increased likelihood of PHT were identified for the combined morphologic scores: CILDemph and VILDemph following adjustment for patient age, gender or smoking history

(Table 2). Notably, the presence of emphysema (indicating the CPFE phenotype) was not independently associated with an increased likelihood of PHT after adjusting for baseline total lung disease extent on CT using either combined morphologic score. The results did not change when visual emphysema thresholds (>5% and >10%) were examined with adjustment made for patient age, gender or smoking history (Table 2). The results were also maintained when considering CT variables predictive of a high likelihood of PHT (Table 2). Results for equivalent analyses in patients in Cohort 2 are shown in Supplementary Table S6.

To avoid a potential confounding effect on emphysema presence scores following model adjustment using patient smoking history, all logistic regression analyses in Table 2 and Supplementary Table S6 were repeated with adjustment for patient age and gender alone. The results did not change in any of the analyses, when patient smoking history was not considered in logistic regression models.

#### Cohort-wide determinants of PHT likelihood in CPFE patients

When logistic regression models were applied to CPFE patients in both cohorts, both combined morphologic scores predicted an increased likelihood of PHT:

CILDemph=OR 1.04 CI=1.02-1.06,  $p<0.0001$ ; VILDemph=OR 1.03 CI=1.01-1.05,

$p=0.0004$ . Both combined morphologic scores also strongly predicted a high

likelihood of PHT in CPFE patients: CILDemph=OR 1.05 CI=1.03-1.07,  $p<0.0001$ ;

VILDemph=OR 1.05 CI=1.03-1.07,  $p<0.0001$ . When patients with severe disease

(characterized by a baseline DLco<35% predicted) across both cohorts were

examined together (n=204), CPFE did not independently predict an increased or high

likelihood of PHT after adjusting for baseline total lung disease extent on CT using either combined morphologic score (Supplementary Table S7).

When ILD extent (scored by either visual analysis or CALIPER) and visual emphysema extent were examined in CPFE patients in both Cohorts, ILD and emphysema scores had a similar impact on the likelihood of PHT (Table 3). The results were maintained when considering criteria representing an increased likelihood of PHT and a high likelihood of PHT (Table 3).

#### **Survival in patients with increased likelihood of PHT**

CPFE patients across both Cohorts with an increased echocardiographic likelihood of PHT, had a 60% survival at 12 months (Figure 2). No survival difference was identified between IPF or CPFE patients with an increased or high likelihood of PHT (Figures 2 and 3). Similarly, no survival difference was identified between IPF or CPFE patients without an increased or high likelihood of PHT (Figures 2 and 3).

## **DISCUSSION**

Our study has demonstrated that in patients with CPFE, once baseline disease extent had been considered (summed CT extents of ILD and emphysema), patients with CPFE are no more likely to develop PHT than IPF patients without emphysema. Our results were consistent across two separate IPF populations and were maintained using two separate definitions of PHT likelihood. Our findings indicate that CPFE patients do not express a unique phenotype that predisposes them to pulmonary hypertension beyond that expected from the extents of two disease processes, namely fibrosis and emphysema.

The CPFE patients with an increased likelihood of PHT in our study demonstrated similar baseline DLco characteristics to the studies by Cottin et al(2, 11). Both CPFE cohorts in the current study were similar in their CT extents of emphysema and prevalence of both increased and high PHT likelihood. Furthermore, both CPFE cohorts had an identical 60% 1-year survival when compared to the landmark CPFE study examining outcomes in patients with PHT(11). The CPFE population studied by Cottin et al(11) had all undergone right heart catheterization and the authors clearly acknowledged the potential for a selection bias towards patients at the more severe end of the PHT spectrum. The potential for a selection bias in our population-wide study of PHT likelihood in IPF patients, was limited by the high proportion of eligible patients that received transthoracic echocardiography and the small number of patients that therefore could not be analysed.



Our CPFE populations had a marginally lower prevalence of increased PHT likelihood (29% and 31%) compared to the study of Cottin et al(11) (20/43) 47% which is likely to partly reflect the higher threshold for PHT used in our paper (50mmHg versus 45mmHg) compared to the study of Cottin et al(11). The PHT prevalence in our study was markedly lower than that reported by Mejia et al(4) who found that 90% of CPFE patients had an RVSP>50mmHg. However the definition of CPFE in the Mejia et al(4) study required >10% of the lung to comprise emphysema, and unusually for CPFE cohorts, emphysema was positively associated with the extent of fibrosis in their study(4). Accordingly, it is probable that the population described by Mejia et al(4) represents an outlier subset of patients in whom extensive emphysema coexists with extensive fibrosis.

Our analyses have followed a similar strategy to the original description by Cottin et al(2). However, because of the accepted limitation of echocardiographic findings in an individual patient, instead of diagnosing PHT we have changed our approach to express a cohort-wide likelihood of PHT. To this end, we considered functional and structural echocardiographic data in 88/105 (84%) CPFE patients in Cohort 1 and 83/109 (76%) CPFE patients in Cohort 2 which was similar to the proportion of CPFE patients undergoing echocardiography in the study by Cottin et al: 43/61 (70%) CPFE patients(2).

We considered two definitions for PHT likelihood in our study as our population had undergone echocardiography before the release of the 2015 consensus guidelines(10). The first definition, namely that of an increased PHT likelihood,

enabled categorization of patients with regard to PHT likelihood even if they had not undergone measurements included in the new guidelines, but which were not always measured in our pre-2015 echocardiographs such as early pulmonary diastolic regurgitation velocity and pulmonary artery diameter. The second definition of a high PHT likelihood, whilst in line with the current guidelines(10), reduced the prevalence of PHT in both cohorts, yet did not change any of our cardinal study findings.

Our analyses allow us to interrogate arguments arguing for and against a microvascular phenotype in CPFE by examining whether the likelihood of PHT in CPFE is primarily linked to the summed extents of ILD and emphysema. As described in previous reports, survival in CPFE patients with PHT was curtailed(4, 11). However, once baseline extents of fibrosis and emphysema were accounted for, the likelihood of PHT did not differ between CPFE patients and IPF patients without emphysema suggesting that vasculopathic mechanisms may differ little between CPFE and IPF without emphysema.

The perceived limitations of our study may centre on our definition of an increased likelihood of PHT based on non-invasive data. In an ideal scenario, all patients would have undergone right heart catheterization. However, it is unlikely that such a study will ever be performed. We instead chose to evaluate PHT likelihood to avoid misleading PHT prevalence statements in our study population. We were obliged to rely on cohort wide expressions of PHT likelihood as indicated by the consensus European Cardiac Society and European Respiratory Society guidelines(10), and our

results remained unchanged across two CPFE cohorts both with the consensus criteria (high likelihood of PHT) and using more inclusive echocardiographic criteria (increased likelihood of PHT). The two PHT criteria appeared to be equivalent in identifying determinants of PHT as judged by extremely similar odds ratios for emphysema and fibrosis when CPFE patients in both cohorts were analysed in combination (Table 3).

In conclusion, the likelihood of having PHT in CPFE is linked to the summed extents of ILD and emphysema. There is no synergistic effect in CPFE increasing the likelihood of PHT. Accordingly, with regard to the likelihood of having PHT, CPFE is not greater than the sum of its parts (ILD and emphysema) and is not associated with a malignant microvascular phenotype.

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### **Disclosure statement**

JJ reports personal fees from Boehringer Ingelheim outside the current work. BJB, RK, SR report a grant from the Royal Brompton Hospital during the conduct of the study; another from Imbio, LLC, was outside the submitted work; and all have a patent '*Systems and methods for analyzing in vivo tissue volumes using medical imaging data*' licensed to Imbio, LLC.

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ER reports personal fees from Roche Boehringer Ingelheim and Takeda, outside the submitted work.

AUW reports personal fees from Intermune, Boehringer Ingelheim, Gilead, MSD, Roche, Bayer and Chiesi, outside the submitted work.

SLFW reports personal fees from Boehringer Ingelheim and Roche outside the submitted work.

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	ELEVATED PHT LIKELIHOOD			NO ELEVATED PHT LIKELIHOOD		
	CPFE	IPF	P value	CPFE	IPF	P value
Age (years)	67	68	0.60	66	66	0.57
Gender (M/F)	25/2	41/6	0.48	47/14	61/27	0.30
Mean FVC (% predicted)	70.3	55.0	0.001	78.7	66.6	0.0002
Mean DLco (% predicted)	28.0	28.8	0.81	37.5	38.3	0.68
CILDemph (%)	46.1	40.3	0.21	29.2	25.5	0.18
VILDemph (%)	66.2	58.4	0.11	52.2	46.6	0.08
Mean survival (months)	24.1±5.5	27.3±3.5	0.33	34.3±3.1	41.1±3.3	0.15
Increased likelihood PHT (%)	27/88 (31)	47/135 (35)	0.52			

**Table 1.** Characteristics of CPFE and IPF patients with (left column) and without (right column) an “Increased likelihood of PHT” in Cohort 1. The results were unchanged when patients with and without a “High likelihood of PHT” were examined. Differences were calculated using a Students T-test for continuous variables, the Chi-squared test for categorical variables and the Mann Whitney U test for medians. Survival differences were calculated using the Log Rank test. CILDemph=sum of CALIPER interstitial lung disease extent and visual emphysema extent, VILDemph=sum of visual interstitial lung disease extent and visual emphysema extent, FVC=forced vital capacity, DLco=diffusion capacity for carbon monoxide, PHT=pulmonary hypertension.

	Model	Variables	Odds ratio	95% Confidence Interval	P value
<b>Analysis 1</b> (Increased PHT Likelihood)	Model ia	CILDemph	1.05	1.03, 1.07	<0.0001
		Emphysema >0%	0.62	0.31, 1.26	0.19
	Model ib	VILDemph	1.04	1.02, 1.06	<0.0001
		Emphysema >0%	0.59	0.29, 1.17	0.13
<b>Analysis 2</b> (Increased PHT Likelihood)	Model iia	CILDemph	1.05	1.03, 1.07	<0.0001
		Emphysema >5%	0.63	0.27, 1.50	0.30
	Model iib	VILDemph	1.04	1.02, 1.06	<0.0001
		Emphysema >5%	0.59	0.25, 1.41	0.24
<b>Analysis 3</b> (Increased PHT Likelihood)	Model iiiia	CILDemph	1.05	1.03, 1.07	<0.0001
		Emphysema >10%	0.71	0.26, 1.90	0.49
	Model iiib	VILDemph	1.04	1.02, 1.06	<0.0001
		Emphysema >10%	0.72	0.26, 1.94	0.51
<b>Analysis 4</b> (High PHT Likelihood)	Model ia	CILDemph	1.06	1.04, 1.08	<0.0001
		Emphysema >0%	0.74	0.34, 1.62	0.45
	Model ib	VILDemph	1.05	1.03, 1.08	<0.0001
		Emphysema >0%	0.59	0.27, 1.29	0.19
<b>Analysis 5</b> (High PHT Likelihood)	Model iia	CILDemph	1.06	1.04, 1.08	<0.0001
		Emphysema >5%	0.76	0.30, 1.92	0.56
	Model iib	VILDemph	1.06	1.03, 1.08	<0.0001
		Emphysema >5%	0.53	0.20, 1.43	0.21
<b>Analysis 6</b> (High PHT Likelihood)	Model iiiia	CILDemph	1.06	1.04, 1.08	<0.0001
		Emphysema >10%	0.87	0.31, 2.48	0.79
	Model iiib	VILDemph	1.05	1.03, 1.08	<0.0001
		Emphysema >10%	0.68	0.22, 2.06	0.49

**Table 2.** Variables associated with an increased (Analysis 1-3) and high (Analysis 4-6) likelihood of PHT in patients undergoing echocardiography in Cohort 1. In each model, logistic regression was used to demonstrate visual and CALIPER determinants of an increased/high likelihood of PHT after correcting for the effects of age, gender and smoking status (never vs ever). Two morphological measures of baseline total disease severity were analysed. The first represented the combination of visual emphysema scores with CALIPER-derived ILD extent: CILDemph (Model a, white) and the second represented the combination of visual emphysema scores with visually-derived ILD extent: VILDemph (Model b, grey). Emphysema was not associated with PHT, regardless

of threshold (>0%=Model i, >5%=Model ii, >10%=Model iii), when adjusting for combined ILD and emphysema extents (a and b). The results were maintained when smoking history was excluded from all models to ensure the avoidance of any potential confounding with emphysema presence scores. PHT = pulmonary hypertension.



PHT Likelihood	Variables	Odds ratio	95% Confidence Interval	P value
Increased PHT Likelihood	Visual Emphysema extent	1.03	1.01, 1.06	0.01
	Visual ILD extent	1.03	1.01, 1.05	0.005
	CALIPER ILD extent	1.03	1.01, 1.05	0.002
High PHT Likelihood	Visual Emphysema extent	1.04	1.01, 1.07	0.003
	Visual ILD extent	1.05	1.03, 1.08	<0.0001
	CALIPER ILD extent	1.03	1.01, 1.06	0.002

**Table 3.** Logistic regression analyses identifying CT variables associated with an increased (white) or high (grey) likelihood of pulmonary hypertension in patients with combined fibrosis and emphysema (CPFE). CPFE patients undergoing echocardiography in both Cohort 1 and Cohort 2 were combined for the analysis (n=171).

## Figure legends

**Figure 1.** Scatterplots demonstrating the range of total CT disease extent (sum of visual emphysema and CALIPER ILD extent) in select patient populations in Cohort 1. The left graph (a) separates patients into those with or without an increased likelihood of PHT, whilst the right graph (b) separates patients into those with or without a high likelihood of PHT. Red bars represent group median values. Column 1 = IPF patients with an increased/high likelihood of PHT; Column 2 = CPFE patients with an increased/high likelihood of PHT; Column 3 = IPF patients without an increased/high likelihood of PHT; Column 4 = CPFE patients without an increased/high likelihood of PHT. No significant difference in total CT disease extent was seen between IPF and CPFE patients with an increased or high likelihood of PHT. However total CT disease extent was higher in CPFE patients with an increased or high likelihood of PHT compared to patients without an increased/high likelihood of PHT. PHT = pulmonary hypertension.

**Figure 2.** Kaplan Meier survival curves in for patients across both Cohorts with (a) and without (b) an **increased** likelihood of pulmonary hypertension: combined pulmonary fibrosis and emphysema (CPFE)[green], idiopathic pulmonary fibrosis (IPF)[blue]. Log rank test=0.99 for patients with an increased likelihood of pulmonary hypertension. Log rank test=0.18 for patients without an increased likelihood of pulmonary hypertension.

**Figure 3.** Kaplan Meier survival curves for patients across both Cohorts with (a) and without (b) a **high** likelihood of pulmonary hypertension: combined pulmonary fibrosis and emphysema (CPFE)[green], idiopathic pulmonary fibrosis (IPF)[blue]. Log rank test=0.72 for patients with a high likelihood of pulmonary hypertension. Log rank test=0.21 for patients without a high likelihood of pulmonary hypertension.