Early View

Original research article

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Computed tomography lung parenchymal descriptions in routine radiological reporting have diagnostic and prognostic utility in patients with idiopathic pulmonary arterial hypertension and pulmonary hypertension associated with lung disease

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Take home message / shareable abstract: Routine radiological reports describing extent of CT lung parenchymal disease can identify groups of patients IPAH and CLD-PH with significantly different prognoses.

Abstract

Background: Patients with pulmonary hypertension (PH) and lung disease may pose a diagnostic dilemma between idiopathic pulmonary arterial hypertension (IPAH) and PH associated with lung disease (PH-CLD). The prognostic impact of common CT parenchymal features is unknown.

Methods: 660 IPAH and PH-CLD patients assessed between 2001-19 were included. Reports for all CT scans one year prior to diagnosis were analysed for common lung parenchymal patterns. Cox regression and Kaplan-Meier analysis was performed.

Results: At univariate analysis of the whole cohort, centrilobular ground glass (CGG) changes (Hazard Ratio, HR 0.29) and ground glass opacification (GGO, HR 0.53) predicted improved survival while honeycombing (HR 2.79), emphysema (HR 2.09) and fibrosis (HR 2.38) predicted worse survival (p all <0.001). Fibrosis was an independent predictor after adjusting for baseline demographics, PH severity and DLco (HR 1.37, p<0.05). Patients with a clinical diagnosis of IPAH who had an absence of reported parenchymal lung disease (IPAH-noLD) demonstrated superior survival to patients diagnosed with either IPAH who had coexistent CT lung disease or PH-CLD (2-year survival of 85%, 60% and 46% respectively, p<0.05). CGG changes were present in 23.3% of IPAH-noLD and 5.8% of PH-CLD patients. There was no significant difference in survival between IPAH-noLD patients with or without CGG changes. PH-CLD patients with fibrosis had worse survival than those with emphysema.

Interpretation: Routine clinical reports of CT lung parenchymal disease identify groups of patients IPAH and CLD-PH with significantly different prognoses. Isolated CGG changes are not uncommon in IPAH but are not associated with worse survival.

Introduction

Pulmonary hypertension (PH) is a heterogenous, progressive and incurable condition associated with significant morbidity and mortality. Five classification groups with similar clinical and pathological characteristics are described including group 1 (Pulmonary Arterial Hypertension, PAH) and Group 3 (PH due to chronic lung disease and/or hypoxia, PH-CLD) [1]. PH-CLD most commonly complicates chronic obstructive pulmonary disease (COPD) and/or emphysema, interstitial lung disease (ILD) and alveolar hypoventilation [2–5]. Patients with PH-CLD typically present with mild to moderate PH, although a small proportion of patients have severe PH. In contrast patients with idiopathic PAH tend to have more severe PH at presentation. Accurate classification of the form of PH is important as it informs prognosis and impacts on treatment decisions. In PH-CLD the importance of haemodynamically characterising disease severity has also been highlighted [6–8].

In practice, distinguishing between IPAH and PH-CLD may be challenging [9]. Recommendations from the 6th World Symposium on PH recommended that patients with minor lung disease, who otherwise meet criteria for IPAH, may be considered to have IPAH [5]. More recently it has been suggested that those with mild lung disease who are haemdynamically similar to IPAH with a so-called "pulmonary vascular phenotype"[2, 10] are not part of the IPAH continuum but a different entity closer to PH-CLD[11]. We have recently demonstrated that the presence of a reduced diffusion capacity for carbon monoxide (DLco) percent predicted (<45%) is associated with poorer survival and response to PAH therapy in patients diagnosed with IPAH [12], in a carefully phenotyped population with minor lung disease were excluded. Hoeper *et al* subsequently identified a cluster amongst patients diagnosed with IPAH characterised by older age, frequent comorbidities, a higher proportion of males and a reduced DLco [13].

In addition to pulmonary function assessment, many patients undergoing assessment for suspected PH also undergo chest CT imaging. We therefore hypothesised that descriptions of lung parenchyma at routine radiological reporting could be used to predict outcomes in patients with IPAH and PH-CLD.

Methods

Patient cohort

Patients assigned a diagnosis of IPAH, familial PAH (FPAH), or PH-CLD between February 2001 and January 2019 were identified from the ASPIRE registry (a database of consecutive patients referred to the Sheffield Pulmonary Vascular Diseases Unit). All patients underwent comprehensive multimodality assessment including right heart catheterisation. Patients with PH-CLD associated with conditions other than COPD and/or emphysema or ILD were excluded. Patients with two or more radiological features of possible pulmonary veno-occlusive disease (centrilobular ground-glass opacities, significant mediastinal lymphadenopathy and interlobular septal lines) were also excluded [14].

CT analysis

All CT scans, including those performed externally, were reported by specialist cardiothoracic radiologists with expertise in pulmonary hypertension using a semi-quantitative assessment of the extent of parenchymal lung disease: none, mild, moderate or severe [15]. Patients had been assigned a diagnosis following a multidisciplinary meeting involving radiologists and pulmonary vascular clinicians. The clinical reports of CT scans performed in the year prior to diagnosis were retrieved. Reports were searched using a regular expression string-search function for mention of 6 specific lung parenchymal patterns - centrilobular ground glass (CGG) changes, ground glass opacification (GGO), honeycombing, consolidation, fibrosis, and emphysema. Representative images are shown in **figure 1**. Each result was manually validated to ensure they represented a true positive. Reports containing false positive phrases such as 'no evidence of emphysema' were not counted. The radiologist (KD) who reviewed the CT reports was blinded to the results of other investigations.

Clinical and morality data

Clinical data collected included age, sex, World Health Organization (WHO) functional class (FC), pulmonary haemodynamics obtained at right heart catheterisation and pulmonary function tests. Mortality data were obtained from systems linked to the National Health Service Personal Demographics Service (PDS), which is updated when a death is registered in the UK. Patients who emigrated (n=3) were excluded, as were patients without a record on

the PDS (n=2). Patients undergoing lung transplantation were censored at the time of surgery, and mortality data were collected using a census date of May 31, 2019.

IPAH sub-group analysis

Patients with an initial diagnosis of IPAH but with a radiological report of a degree of emphysema or fibrosis were reclassified as 'IPAH-Lung Disease' (IPAH-LD). The remainder of the patients were classified as IPAH-no Lung Disease (IPAH-noLD). Separate analysis also compared the effect of patients with initial diagnosis of IPAH and CGG changes. Patients with no significant lung disease and CGG were reclassified as 'IPAH-CGG'. Survival and group comparison was performed between IPAH-CGG, IPAH-LD and IPAH-noLD. Those with both CGG and significant lung disease (n=8) were excluded from this sub-group analysis.

Statistics

Analysis was performed using R statistical software package using version 4.0.3, using packages 'tidyverse' and 'survminer', and SPSS version 26.0 (IBM Corp). Continuous data is presented as mean±SD (compared using paired/unpaired t-tests) or median (interquartile range) for nonparametric data (compared using Wilcoxon signed-rank/Mann–Whitney U-tests). Frequencies are compared using the Chi-square test. Categorical variables are shown in magnitude and percentage.

Cox proportional hazard's regression was used to determine association between different CT parenchymal features and survival. Hazard ratios are presented with 95% confidence intervals. Three separate multivariate models were created. Model 1 adjusted for patient demographics: age, gender and WHO functional class. Model 2 adjusted for all demographics and additionally mPAP. Model 3 adjusted further for diffusing capacity for carbon monoxide (DLco). Kaplan–Meier survival curves were compared using the log-rank test, truncated at 5 years. Group comparisons were made with two-tailed ANOVA with post-hoc Bonferroni correction.

Ethics

Ethical approval was granted by Institutional Review Board and approved by the National Research Ethics Service (16/YH/0352). All research was conducted in agreement with the Declaration of Helsinki and the European General Data Protection Regulation.

Results

Patient characteristics

From 5643 patients diagnosed with all forms of pulmonary hypertension, 660 patients met the inclusion criteria and formed the main study cohort (**figure 2**). This included 335 patients diagnosed with IPAH and 325 with PH-CLD, who formed the sub-groups for analysis. Patients with PH-CLD were more frequently male (58% vs 39%, p<0.001), older (67 ±17 years vs 60 years ±17 years, p<0.001), had lower mPAP (42 ±10 mmHg vs 53 ±12mmHg, p<0.001) and DLco (28 ±14% vs 44 ± 20%, p<0.001) compared to those diagnosed with IPAH (**table 1**). Two hundred and eighty-three (43%) patients had imaging performed externally. RHC data was available in 100% and PFT data in 95% of patients.

Cox regression analysis

Univariate regression results for demographics, clinical parameters and CT features are shown in **Table 2**. Being older, male, and having a higher WHO Functional Class were significant univariate predictors of poor survival across all groups. **Table 3** shows the results for the different multivariate regression models performed on significant univariate variables.

Main Cohort

CGG changes (HR 0.29, 0.17-0.50) and GGO (HR 0.53, 0.38-0.74) were significant (p<0.001) predictors of improved survival at univariate analysis while honeycombing (HR 2.79, 1.57-4.99), emphysema (HR 2.09, 1.71-2.56) and fibrosis (HR 2.38, 1.94-2.91) were significant predictors of poor survival (p all <0.001). After adjusting for the impact of age, gender and WHO FC in multivariate model 1, CGG changes (HR 0.50, 0.28-0.89, p=0.01), emphysema (HR 1.48, 1.21-1.83, p<0.001) and fibrosis (HR 1.75, 1.42-2.15, p<0.001) remained significant

predictors of outcome. These parameters were also significant predictors of mortality in model 2 after additionally adjusting for the severity of PH. In model 3, fibrosis (HR 1.37, 1.09-1.73, p=0.008) remained an independent predictor after additionally adjusting for DLco.

IPAH

In patients assigned a diagnosis of IPAH, the presence of CGG changes (HR 0.44, 0.25-0.78, p=0.005) or GGO (HR 0.52, 0.32-0.86, p=0.01) predicted improved outcomes while the presence of any degree of emphysema (HR 2.74, 1.96-3.81, p<0.001), fibrosis (HR 2.48, 1.76-3.50, p<0.001) or honeycombing (HR 3.72, 1.37-10.1, p=0.01) were significant univariate predictors of increased mortality. Subgroup univariate analysis of IPAH patients with no degree of parenchymal lung disease demonstrated that CGG changes and GGO no longer significantly predicted survival (**table A1**). In multivariate model 1 of the overall IPAH group, only the presence of emphysema (HR 1.72, 1.22-2.42, p=0.002) remained a significant predictor. Emphysema was also a significant prognostic factor in model 2 (HR 1.76, 1.24-2.49, p=0.002) but not in model 3 (p=0.3).

PH-CLD

Fibrosis (HR 1.83, 1.04-4.30, p<0.001) and honeycombing (HR 2.11, 1.04-4.30, p=0.039) were significant predictors of mortality at univariate analysis while the presence of emphysema or GGO did not predict mortality. However, when sub-grouped by radiologically graded severity, severe emphysema was a significant prognostic factor at univariate (HR 1.81, p=0.02) but not multivariate analysis. Fibrosis was an independent predictor in all multivariate models, including after adjustment for DLco (Model 3, HR 1.46, 1.09-1.96, p<0.001). Honeycombing was not a significant predictor in any of the multivariate models.

Prognostic effect of extent of emphysema and fibrosis

Increasing extent of both emphysema and fibrosis derived from radiology reports was associated with increasing risk of mortality in the whole cohort at univariate analysis (Emphysema; mild: HR 1.78 (1.3-2.43), moderate: HR 2.18 (1.69-2.81), severe: HR 2.92 (2.15-3.97). Fibrosis; mild: HR 1.94 (1.46-2.58), moderate: 2.77 (1.99-3.85), severe: 3.19 (2.3-4.43), **table 2**). A similar pattern was observed in the IPAH group while in the PH-CLD group the presence of emphysema was not associated with significant increased mortality.

Kaplan-Meier survival analysis stratified by CT Features

The Kaplan-Meier survival curves for each cohort are presented in **figure 3**. In the full cohort, survival was significantly worse in patients with any form of parenchymal lung disease (p<0.001 in all). Survival was also significantly worse in patients with reported fibrosis compared to emphysema (p=0.023). There were 7 (of 33), 85 (of 213), 131 (of 189), 79 (of 100) and 63 (of 75) events in the CGG and no emphysema or fibrosis, no emphysema or fibrosis, emphysema, fibrosis and combined emphysema and fibrosis groups respectively.

In patients diagnosed with IPAH, the presence of any parenchymal lung disease was associated with significantly poorer survival (p all<0.001) with no significant difference in survival between patients with the different forms of lung disease. There was no significant difference in survival between patients with isolated CGG compared to those with no reported parenchymal abnormalities (p=0.57). There were 7 (of 33), 55 (of 164), 41 (of 64), 26 (of 34) and 18 (of 26) events in the CGG and no emphysema or fibrosis, no emphysema or fibrosis, emphysema, fibrosis and combined emphysema and fibrosis groups respectively.

In patients diagnosed with PH-CLD, survival in patients with emphysema was superior to survival in patients with fibrosis (p=0.02). Although some evidence of improved survival was observed between patients without parenchymal lung disease compared to those with emphysema, differences between groups did not meet conventional levels of statistical significance (p=0.09). There were 30 (of 49), 90 (of 125), 53 (of 66), and 45 (of 49) in the no emphysema or fibrosis, emphysema, fibrosis and combined emphysema and fibrosis groups respectively.

IPAH sub-group analysis

Impact of lung disease in IPAH compared to PH-CLD
Patients with an initial clinical diagnosis of IPAH (n=335) were firstly reclassified as either IPAH-lung disease (IPAH-LD, n=138) or IPAH-no lung disease (IPAH-noLD, n=197), based on the

presence or absence of emphysema and/or fibrosis. Survival in patients with IPAH-noLD was significantly superior to patients with IPAH-LD or PH-CLD (p<0.001, **figure** 4). There were 62 (of 197), 92 (of 138) and 247 (of 325) events in the IPAH, IPAH-LD and PH-CLD groups respectively. Patients with IPAH-LD were distinct from those diagnosed with PH-CLD with less severely impaired spirometry but more severely abnormal pulmonary haemodynamics (**table A2**). There was no statistically significant difference in survival (p=0.065) in patients with PH-CLD when compared to IPAH-LD. Two-year survival for patients with IPAH-noLD, IPAH-LD and PH-CLD was 85%, 60% and 46%, respectively (**table A3**).

Impact of CGG

The impact of CGG changes on characteristics and survival of patients with an initial clinical diagnosis of IPAH (n=335) was then assessed. CGG changes were uncommon in patients with co-existing lung disease (being present in 8/138 patients (5.8%) with IPAH-LD, **table A2**) compared with patients with no co-existing lung disease (being present in 46/197 patients (23.3%), **table 4**). Eight patients who had both CGG changes and parenchymal lung disease were excluded from this analysis. One hundred and thirty patients with emphysema or fibrosis were therefore reclassified as IPAH-LD, 46 patients with CGG changes as IPAH-CGG and 151 patients with no parenchymal abnormalities as IPAH-noLD. Patients with IPAH-CGG had more severe PH but a similar DLco when compared with patients with IPAH-noLD (**table 4**). Patients with IPAH-LD were older, with a greater proportion in WHO FC IV and less severe PH but a lower DLco than patients with IPAH-noLD. There was no significant difference in survival between patients with IPAH-noLD and IPAH-CGG while survival in patients with IPAH-LD was significantly worse (**figure 5**).

Discussion

We have demonstrated that parenchymal abnormalities noted at routine radiological reporting of CT scans performed in patients with suspected IPAH or PH-CLD have diagnostic and prognostic utility. We have also found that isolated CGG changes are not uncommon in patients with IPAH and are not associated with lower DLco or worse survival.

Routine radiological reports of the presence of emphysema or fibrosis have diagnostic and prognostic utility in patients diagnosed with IPAH

Differentiating PH-CLD from IPAH is an important part of the PH diagnostic algorithm and may be straightforward in the presence of severe lung function abnormalities or severe parenchymal lung disease, although in this study we still identified 5 patients (with mean mPAP of 55 mmHg) with severe emphysema who had been assigned a clinical diagnosis of IPAH. The presence of less severe degrees of lung disease provides more of a diagnostic challenge as has been highlighted by others [9, 11]. The 6th World Symposium on Pulmonary Hypertension (WSPH) task force suggested that patients with significant PH but only modest parenchymal abnormalities should be assigned a diagnosis of IPAH[5].

In the present study we found that radiological reports of emphysema or fibrosis in patients who had been clinically assigned a diagnosis of IPAH in keeping with the 6th WSPH recommendations was associated with significantly worse survival at Kaplan-Meier analysis. This supports the comments of Godinas *et al* who suggest that such patients represent a distinct group from those with IPAH being phenotypically closer to PH-CLD[11].

However, we also observed at Cox regression analysis that this prognostic importance of emphysema or fibrosis in patients diagnosed with IPAH was not independent of DLco. The prognostic importance of reduced DLco with or without co-existing parenchymal lung disease in patients assigned a diagnosis of IPAH has previously been reported[15–17]. We have previously demonstrated that response to PAH therapies in patients with IPAH-noLD and DLco

<45% is lower than in patients with IPAH-noLD and DLco ≥45%, while on average patients with IPAH-LD exhibit a lack of response to PAH therapies in terms of exercise capacity and quality of life[15]. Therefore, the identification of emphysema or fibrosis on CT provides clinically-relevant information in addition to that provided by DLco alone.

Routine radiological reports of the extent and nature of parenchymal lung disease have prognostic utility

In addition to the *presence* of parenchymal lung disease identified at routine reporting being associated with worse survival, we also observed that the *extent* and *nature* of lung disease described at routine reporting provided additional prognostic information. In patients originally assigned a diagnosis of IPAH, the extent of emphysema or fibrosis described qualitatively at reporting was strongly associated with prognosis. In patients with PH-CLD, the nature of parenchymal lung disease impacted on survival with the presence of fibrosis conveying a worse prognosis than emphysema, as previously described[18].

Centrilobular ground glass in IPAH

CGG changes in the absence of emphysema or fibrosis were not uncommon, being reported in 23.3% of those IPAH patients who had no emphysema or fibrosis but were only reported in only 5.8% of patients with co-existing emphysema or fibrosis. The nature of CGG changes in patients diagnosed with IPAH is not clear. It is possible they represent pulmonary veno-occlusive disease (PVOD), however we excluded patients with an additional radiological feature of PVOD (significant mediastinal lymphadenopathy or interlobular septal lines). Furthermore, there was no significant difference in DLco compared to IPAH-noLD patients without CGG changes. Nolan *et al* postulated that they represented cholesterol granulomas while Horton *et al* presented a case report of a patient with fenfluramine-induced PAH with diffuse micronodules on CT who had an extensive diffuse plexogenic arteriopathy at lung biopsy[19, 20]. In addition to IPAH, CGG changes have also been commonly described in other

forms of PAH including PAH associated with connective tissue disease and congenital heart disease [21]. In Eisenmenger syndrome and IPAH it has been postulated that this may be a feature of lung neovascularity [22] [23]. It is interesting to note that in our study there was no significant difference in survival compared with patients with IPAH-noLD at Kaplan-Meier analysis despite having significantly more severe pulmonary haemodynamics.

Limitations

This study has utilised clinical radiological reports involving semi-quantitative descriptions from the time of PH diagnosis rather than subsequent quantitative analysis. By using this approach, we have, however, been able to demonstrate that features described in routine "real-world" radiological reports have the ability to refine diagnostic and prognostic processes. It may well be that more in-depth quantitative analysis utilising artificial intelligence algorithms may provide superior diagnostic and prognostic information and further studies are therefore warranted[24]. Selection or recall bias is minimised by using a "real-world" clinical cohort of consecutive patients diagnosed over 18 years. Misclassification bias is minimised by including all consecutive patients with lung disease and pulmonary hypertension, not limiting to just an assigned diagnosis. An unavoidable limitation of a clinical cohort spanning 18 years is the variance in haemodynamic diagnostic criteria, treatment options and guidelines for patient management.

Conclusion

CT lung parenchymal descriptions in routine radiological reporting have diagnostic and prognostic utility in patients with idiopathic pulmonary arterial hypertension and pulmonary hypertension associated with chronic lung disease. Chest CT features should therefore be considered in patient assessment and risk-stratification. Patients diagnosed with IPAH who have modest lung disease demonstrate unique clinical and survival characteristics and are likely to represent a distinct phenotype separate from IPAH. Centrilobular ground glass changes are not uncommon in patients with IPAH and are associated with more severe pulmonary haemodynamics but non-inferior survival.

Conflicts of Interest

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Tables

Table 1: Baseline characteristics.

Characteristic	Full Cohort	Subgroups		
	N = 660	IPAH, N = 335	PH-CLD, N = 325	p-value
Age at diagnosis	64 (15)	60 (17)	67 (11)	<0.001
Male Gender	318 (48%)	131 (39%)	187 (58%)	<0.001
WHO Functional Class				0.020
II	78 (12%)	44 (13%)	34 (10%)	
III	398 (61%)	213 (64%)	185 (57%)	
IV	181 (28%)	76 (23%)	105 (32%)	
CT – Centrilobular Ground Glass (CGG)	54 (8.2%)	54 (16%)	0 (0%)	<0.001
CT – Ground Glass Opacification (GGO)	93 (14%)	62 (19%)	31 (9.5%)	<0.001
CT – Honeycombing	15 (2.3%)	5 (1.5%)	10 (3.1%)	0.2
CT – Consolidation	31 (4.7%)	9 (2.7%)	22 (6.8%)	0.013
CT – Fibrosis	213 (32%)	72 (21%)	141 (43%)	<0.001
CT – Fibrosis (by severity)				<0.001
None	447 (68%)	263 (79%)	184 (57%)	
Mild	82 (12%)	54 (16%)	28 (8.6%)	
Moderate	53 (8.0%)	9 (2.7%)	44 (14%)	
Severe	48 (7.3%)	0 (0%)	48 (15%)	
Unknown	30 (4.5%)	9 (2.7%)	21 (6.5%)	
CT – Emphysema	302 (46%)	98 (29%)	204 (63%)	<0.001
CT – Emphysema (by severity)				<0.001
None	358 (54%)	237 (71%)	121 (37%)	
Mild	77 (12%)	48 (14%)	29 (8.9%)	

Moderate	129 (20%)	38 (11%)	91 (28%)	
Severe	69 (10%)	5 (1.5%)	64 (20%)	
Unknown	27 (4.1%)	7 (2.1%)	20 (6.2%)	
CT – CPFE	101 (15%)	32 (9.6%)	69 (21%)	<0.001
mPAP (mmHg)	47 (13)	53 (12)	42 (10)	<0.001
mRAP (mmHg)	10.2 (5.6)	11.4 (5.8)	9.0 (5.1)	<0.001
PAWP (mmHg)	11.3 (3.8)	10.8 (3.3)	11.8 (4.2)	0.002
Cardiac output (L/min)	4.65 (1.66)	4.31 (1.62)	5.00 (1.64)	<0.001
Cardiac index (L/min/m²)	2.53 (0.87)	2.32 (0.81)	2.73 (0.87)	<0.001
PVR (Wood Units)	9.0 (5.1)	11.0 (5.2)	7.0 (4.1)	<0.001
SvO_2 %	63 (9)	61 (9)	65 (8)	<0.001
FEV_1 % predicted	72 (25)	83 (18)	60 (25)	<0.001
FEV_1 severity				<0.001
Normal (>80% predicted)	259 (41%)	187 (58%)	72 (24%)	
Mild (70-80% predicted)	87 (14%)	53 (17%)	34 (11%)	
Moderate (50-70% predicted)	139 (22%)	70 (22%)	69 (23%)	
Severe (<50% predicted)	140 (22%)	11 (3.4%)	129 (42%)	
FEV_1 / FVC (%)	66 (15)	71 (10)	61 (18)	<0.001
DLco % predicted	37 (19)	44 (20)	28 (14)	<0.001

Data are presented as number (percentage) or mean (standard deviation). Abbreviations: CT – Computed Tomography, WHO – World Health Organisation, CPFE – Combined Pulmonary Fibrosis and Emphysema, mPAP – mean pulmonary arterial pressure, mRAP – mean right atrial pressure, PAWP – pulmonary arterial wedge pressure, PVR – pulmonary vascular resistance, SvO_2 – mixed venous oxygen saturation. FEV_1 – forced expiratory volume in 1 second, FVC – forced vital capacity, DLco – diffusing capacity of carbon monoxide

Table 2: Univariate analysis of the overall study cohort.

Characteristic	Full cohort (n= 660)			IPAH (n= 335)			PH-CLD (n= 325)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
CT – Centrilobular Ground Glass (CGG)	0.29	0.17, 0.50	**<0.001**	0.44	0.25, 0.78	**0.005**			
CT – Ground Glass Opacification (GGO)	0.53	0.38, 0.74	**<0.001**	0.52	0.32, 0.86	**0.010**	0.72	0.46, 1.14	0.2
CT – Honeycombing	2.79	1.57, 4.99	**<0.001**	3.72	1.37, 10.1	**0.010**	2.11	1.04, 4.30	**0.039**
CT – Consolidation	0.84	0.50, 1.40	0.5	1.10	0.45, 2.68	0.8	0.60	0.32, 1.13	0.11
CT – Fibrosis	2.38	1.94, 2.91	**<0.001**	2.48	1.76, 3.50	**<0.001**	1.83	1.42, 2.35	**<0.001**
CT – Fibrosis (any present, ref: none)									
None	—	—		—	—		—	—	
Mild	1.94	1.46, 2.58	**<0.001**	2.51	1.72, 3.66	**<0.001**	1.73	1.11, 2.71	**0.016**
Moderate	2.77	1.99, 3.85	**<0.001**	4.53	2.07, 9.92	**<0.001**	1.71	1.18, 2.48	**0.005**
Severe	3.19	2.30, 4.43	**<0.001**				1.98	1.40, 2.80	**<0.001**
CT – Emphysema	2.09	1.71, 2.56	**<0.001**	2.74	1.96, 3.81	**<0.001**	1.13	0.87, 1.47	0.4
CT – Emphysema (any present, ref: none)									
None	—	—		—	—		—	—	
Mild	1.78	1.30, 2.43	**<0.001**	2.90	1.89, 4.46	**<0.001**	0.89	0.56, 1.42	0.6
Moderate	2.18	1.69, 2.81	**<0.001**	3.16	2.01, 4.97	**<0.001**	1.13	0.82, 1.55	0.5
Severe	2.92	2.15, 3.97	**<0.001**	11.1	3.92, 31.6	**<0.001**	1.37	0.97, 1.93	0.075

CT – CPFE	2.20	1.72, 2.80	**<0.001**	2.09	1.33, 3.29	**0.001**	1.82	1.36, 2.44	**<0.001**
Age at diagnosis	1.05	1.04, 1.05	**<0.001**	1.06	1.05, 1.08	**<0.001**	1.02	1.01, 1.04	**<0.001**
Male Gender	1.66	1.36, 2.03	**<0.001**	1.59	1.16, 2.18	**0.004**	1.42	1.10, 1.83	**0.007**
WHO Functional Class III & IV (ref: I & II)	1.78	1.45, 2.18	**<0.001**	1.88	1.34, 2.64	**<0.001**	1.74	1.35, 2.25	**<0.001**
WHO Functional Class									
II	—	—		—	—		—	—	
III	2.57	1.70, 3.89	**<0.001**	3.00	1.51, 5.96	**0.002**	2.45	1.46, 4.13	**<0.001**
IV	5.08	3.31, 7.79	**<0.001**	5.49	2.69, 11.2	**<0.001**	4.80	2.81, 8.21	**<0.001**
mPAP (mmHg)	0.99	0.98, 1.00	**0.028**	0.98	0.97, 0.99	**0.006**	1.04	1.03, 1.05	**<0.001**
mRAP (mmHg)	1.01	0.99, 1.03	0.4	1.03	1.00, 1.06	**0.023**	1.03	1.00, 1.05	0.057
PAWP (mmHg)	1.02	0.99, 1.04	0.3	1.03	0.98, 1.09	0.2	0.98	0.95, 1.01	0.2
Cardiac output (L/min)	0.92	0.86, 0.98	**0.009**	0.88	0.78, 0.99	**0.035**	0.79	0.72, 0.86	**<0.001**
Cardiac index (L/min.m^2)	0.87	0.76, 0.98	**0.028**	0.80	0.63, 1.01	**0.063**	0.61	0.51, 0.74	**<0.001**
PVR (Wood Units)	1.04	1.00, 1.08	**0.036**	0.98	0.91, 1.05	0.5	1.10	1.05, 1.16	**<0.001**
SvO2 %	0.98	0.97, 0.99	**0.001**	0.97	0.95, 0.98	**<0.001**	0.96	0.94, 0.97	**<0.001**
FEV$_1$ % predicted	1.00	0.99, 1.00	**0.032**	0.99	0.98, 1.00	0.11	1.01	1.01, 1.02	**<0.001**
FVC % predicted	1.00	0.99, 1.00	**0.028**	1.00	0.99, 1.01	0.9	1.00	1.00, 1.01	0.4
FEV$_1$/FVC Ratio	0.99	0.99, 1.00	**0.038**	0.97	0.95, 0.98	**<0.001**	1.02	1.01, 1.03	**<0.001**

Dlco % predicted	0.95	0.95, 0.96	**<0.001**	0.95	0.94, 0.96	**<0.001**	0.96	0.95, 0.97	**<0.001**

Abbreviations: HR - Hazard Ratio, CI - Confidence Interval , CT – Computed Tomography, WHO – World Health Organisation, CPFE – Combined Pulmonary Fibrosis and Emphysema, mPAP – mean pulmonary arterial pressure, mRAP – mean right atrial pressure, PAWP – pulmonary arterial wedge pressure, PVR – pulmonary vascular resistance, SvO2 – mixed venous oxygen saturation. FEV1 – forced expiratory volume in 1 second, FVC – forced vital capacity, Dlco – diffusing capacity of carbon monoxide.

Table 3: Multivariate analysis

	Univariate			Multivariate 1 (adjusted for demographics – age, gender, WHO FC)			Multivariate 2 (adjusted for demographics & mPAP)			Multivariate 3 (adjusted for demographics, mPAP & DLco)		
Full Cohort (n= 660)												
Characteristic	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
CT - Centrilobular Ground Glass (CGG)	0.29	0.17, 0.50	**<0.001**	0.50	0.28, 0.89	**0.010**	0.48	0.26, 0.86	**0.007**	0.76	0.39, 1.47	0.4
CT - Ground Glass Opacification (GGO)	0.53	0.38, 0.74	**<0.001**	0.82	0.58, 1.16	0.2	0.84	0.60, 1.19	0.3	0.80	0.54, 1.18	0.2
CT - Honeycombing	2.79	1.57, 4.99	**<0.001**	1.73	0.97, 3.11	**0.087**	1.74	0.97, 3.12	0.086	1.10	0.54, 2.24	0.8
CT - Emphysema	2.09	1.71, 2.56	**<0.001**	1.48	1.21, 1.83	**<0.001**	1.52	1.23, 1.88	**<0.001**	1.13	0.89, 1.44	0.3
CT - Fibrosis	2.38	1.94, 2.91	**<0.001**	1.75	1.42, 2.15	**<0.001**	1.77	1.43, 2.18	**<0.001**	1.37	1.09, 1.73	**0.008**

IPAH (n=335)												
CT - Centrilobular Ground Glass (CGG)	0.44	0.25, 0.78	**0.005**	0.79	0.43, 1.45	0.4	0.80	0.43, 1.48	0.5	0.92	0.47, 1.82	0.8
CT - Ground Glass Opacification (GGO)	0.52	0.32, 0.86	**0.010**	0.88	0.52, 1.47	0.6	0.91	0.54, 1.52	0.7	0.96	0.55, 1.69	0.9
CT - Honeycombing	3.72	1.37, 10.1	**0.010**	1.69	0.61, 4.65	0.3	1.68	0.61, 4.62	0.4	1.35	0.49, 3.74	0.6
CT - Emphysema	2.74	1.96, 3.81	**<0.001**	1.72	1.22, 2.42	**0.002**	1.76	1.24, 2.49	**0.002**	1.26	0.85, 1.86	0.2
CT - Fibrosis	2.48	1.76, 3.50	**<0.001**	1.42	0.99, 2.02	0.060	1.44	1.00, 2.07	0.056	1.23	0.84, 1.81	0.3
PH-CLD (n= 325)												
CT - Honeycombing	2.11	1.04, 4.30	**0.039**	1.80	0.88, 3.67	0.14	2.02	0.99, 4.14	0.081	1.06	0.39, 2.91	>0.9
CT - Fibrosis	1.83	1.42, 2.35	**<0.001**	1.73	1.34, 2.24	**<0.001**	1.63	1.26, 2.10	**<0.001**	1.46	1.09, 1.96	**0.011**

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; CT, computed tomography; IPA, idiopathic pulmonary arterial hypertension; PH-CLD, pulmonary hypertension associated with chronic lung disease.

**Table 4: Baseline characteristics of patients with initial diagnosis of IPAH**

Characteristic	IPAH-noLD, N = 151	IPAH-CGG, N = 46	IPAH-LD, N = 130	p-value
Age at diagnosis	56 (18) ‡	48 (19) ‡	70 (9) *†	<0.001
Male Gender	48 (32%)‡	11 (24%) ‡	69 (53%)*†	<0.001
WHO Functional Class	‡	‡	*†	0.011
II	25 (17%)	9 (20%)	9 (6.9%)	
III	98 (65%)	29 (64%)	81 (62%)	
IV	27 (18%)	7 (16%)	40 (31%)	
Smoker, ever	66 (49%) ‡	19 (42%) ‡	81 (86%) *†	<0.001
CT – Centrilobular Ground Glass	0 (0%) †	46 (100%) *‡	0 (0%) †	<0.001
CT – Ground Glass Opacification	9 (6.0%) †	39 (85%) *‡	8 (6.2%) †	<0.001
CT – Honeycombing	0 (0%) ‡	0 (0%) *‡	5 (3.8%) *	0.021
CT – Consolidation	5 (3.3%)	2 (4.3%)	2 (1.5%)	0.4
CT – Fibrosis	0 (0%) ‡	0 (0%) ‡	68 (52%) *†	<0.001
CT – Fibrosis (by severity)	‡	‡	*†	<0.001
None	151 (100%)	46 (100%)	62 (48%)	
Mild	0 (0%)	0 (0%)	52 (40%)	
Moderate	0 (0%)	0 (0%)	9 (6.9%)	
Unknown	0 (0%)	0 (0%)	7 (5.4%)	
CT – Emphysema	0 (0%) ‡	0 (0%) ‡	94 (72%) *†	<0.001
CT – Emphysema (by severity)	‡	‡	*†	
None	151 (100%)	46 (100%)	36 (28%)	
Mild	0 (0%)	0 (0%)	44 (34%)	
Moderate	0 (0%)	0 (0%)	38 (29%)	
Severe	0 (0%)	0 (0%)	5 (3.8%)	
Unknown	0 (0%)	0 (0%)	7 (5.4%)	
CT – CPFE	0 (0%) ‡	0 (0%) ‡	32 (25%) *†	<0.001
mPAP (mmHg)	54 (12) †‡	62 (13) *‡	49 (8) *†	<0.001
mRAP (mmHg)	12 (6)	10 (5)	11 (5)	0.3
PAWP (mmHg)	10.91 (3.10)	9.72 (2.77)	11.03 (3.21)	0.055
Cardiac output (L/min)	4.64 (1.87) †‡	3.85 (0.98) *	4.08 (1.44) *	0.014
Cardiac index (L/min/m^2)	2.47 (0.95) ‡	2.13 (0.52)	2.23 (0.73) *	0.031
PVR (Wood Units)	10.7 (5.2) †	14.6 (6.2) *‡	10.3 (4.4) †	<0.001
SvO$_2$ %	61 (10)	62 (7)	59 (8)	0.030
FEV$_1$ % predicted	82 (17)	88 (15)	83 (20)	0.124

|				
FEV$_1$ severity				0.056
Normal (>80% predicted)	83 (58%)	31 (70%)	67 (53%)	
Mild (70-80% predicted)	21 (15%)	8 (18%)	24 (19%)	
Moderate (50-70% predicted)	34 (24%)	5 (11%)	29 (23%)	
Severe (<50% predicted)	5 (3.5%)	0 (0%)	6 (4.8%)	
FVC % predicted	93 (20)	101 (18)	99 (21)	0.016
FEV$_1$/FVC (%)	74 (10) ‡	74 (8) ‡	67 (10) *†	<0.001
DLco % predicted	52 (20) ‡	56 (17) ‡	31 (14) *†	<0.001

Data are presented as number (percentage) or mean (standard deviation). Between-group comparisons performed using one-Way ANOVA with Bonferroni Post-Hoc Correction. Difference between groups noted: * significant difference to IPAH-noLD, † significant difference to IPAH-CGG, ‡ significant difference to IPAH-LD. 8 patients with both CGG and LD not included. Abbreviations: WHO, World Health Organisation; CT, computed tomography; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; DLco, diffusing capacity of carbon monoxide; IPAH, idiopathic pulmonary arterial hypertension; CGG, centrilobular ground glass; LD, lung disease; CPFE, combined pulmonary fibrosis and emphysema

Figures

Figure 1. CT lung parenchymal patterns assessed. A – emphysema, B – centrilobular ground glass change (windowed to emphasise subtle pattern), C – honeycombing, D – consolidation (with surrounding ground glass change), E – ground glass change, F – fibrosis.
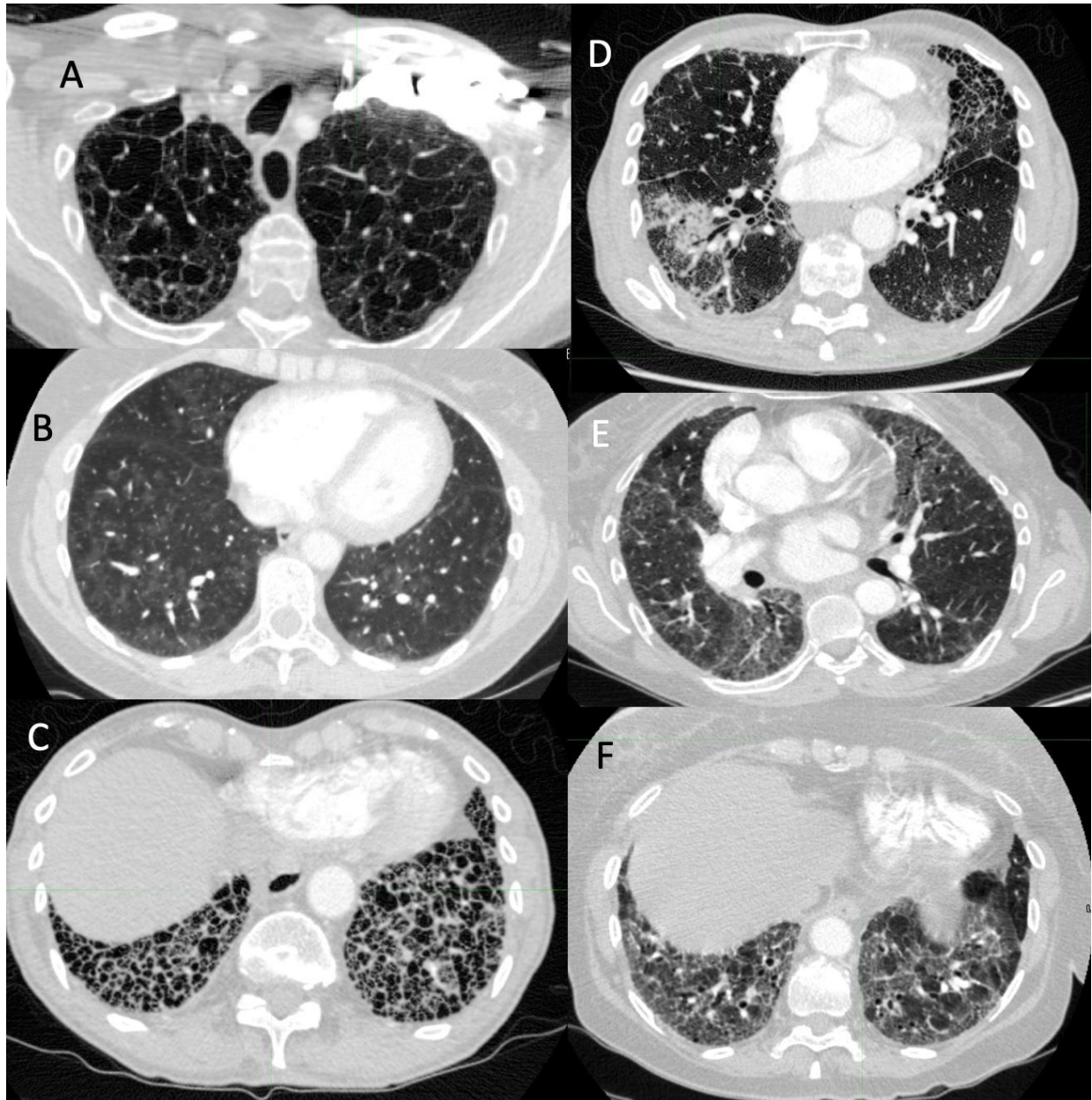
Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram showing selection of study cohort.
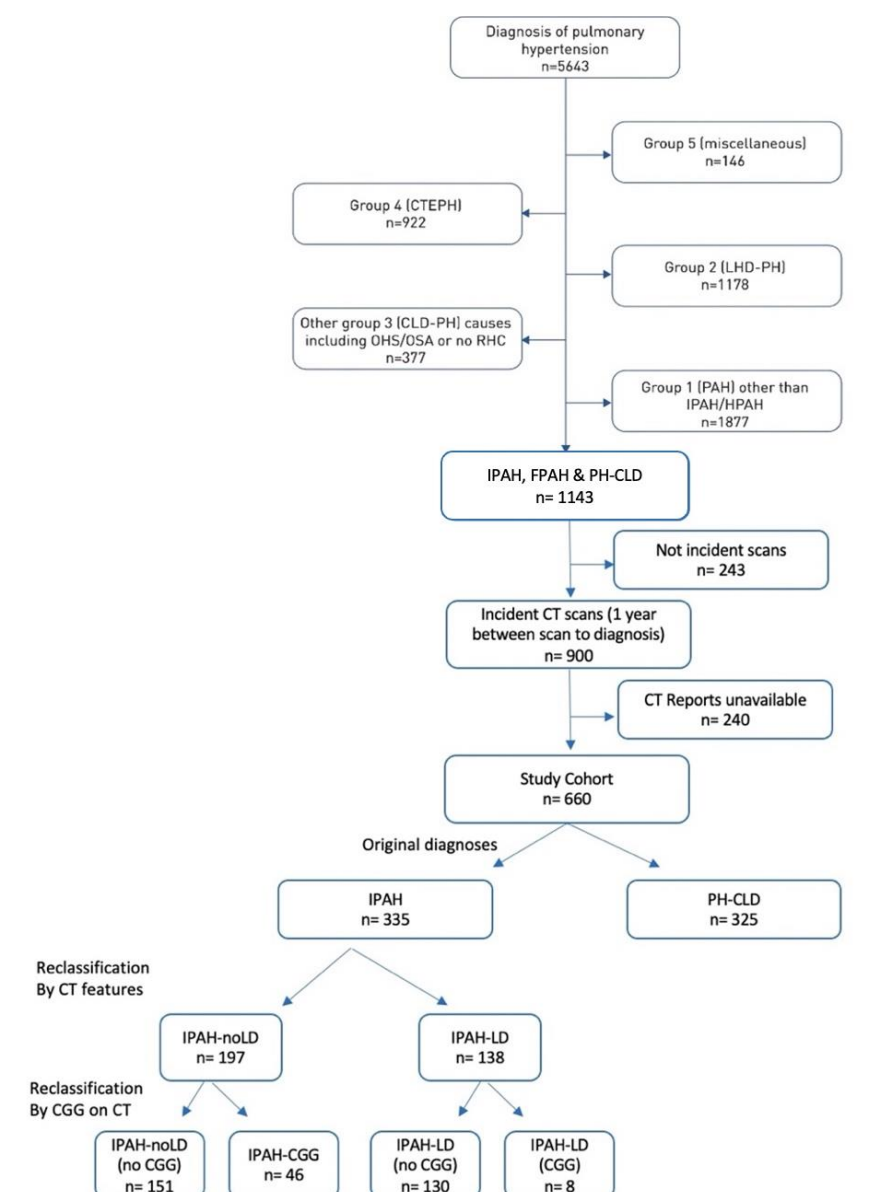

Abbreviations. CTEPH , Chronic ThromboEmbolic Pulmonary Hypertension; LHD-PH, Pulmonary Hypertension with Left Heart Disease; PH-CLD, PH due to chronic lung disease and/or hypoxia; IPAH, Idiopathic Pulmonary Arterial Hypertension; FPAH, Familial Pulmonary Arterial Hypertension; CT, Computed Tomography; IPAH-noLD, Idiopathic Pulmonary Arterial Hypertension with no lung disease; IPAH-LD, Idiopathic Pulmonary Arterial Hypertension with Lung Disease

Figure 3: Kaplan-Meier survival curves stratified by CT features of CGG, emphysema and fibrosis for: a. All patients, b. Patients initially diagnosed with IPAH and c., Patients initially diagnosed with PH-CLD.
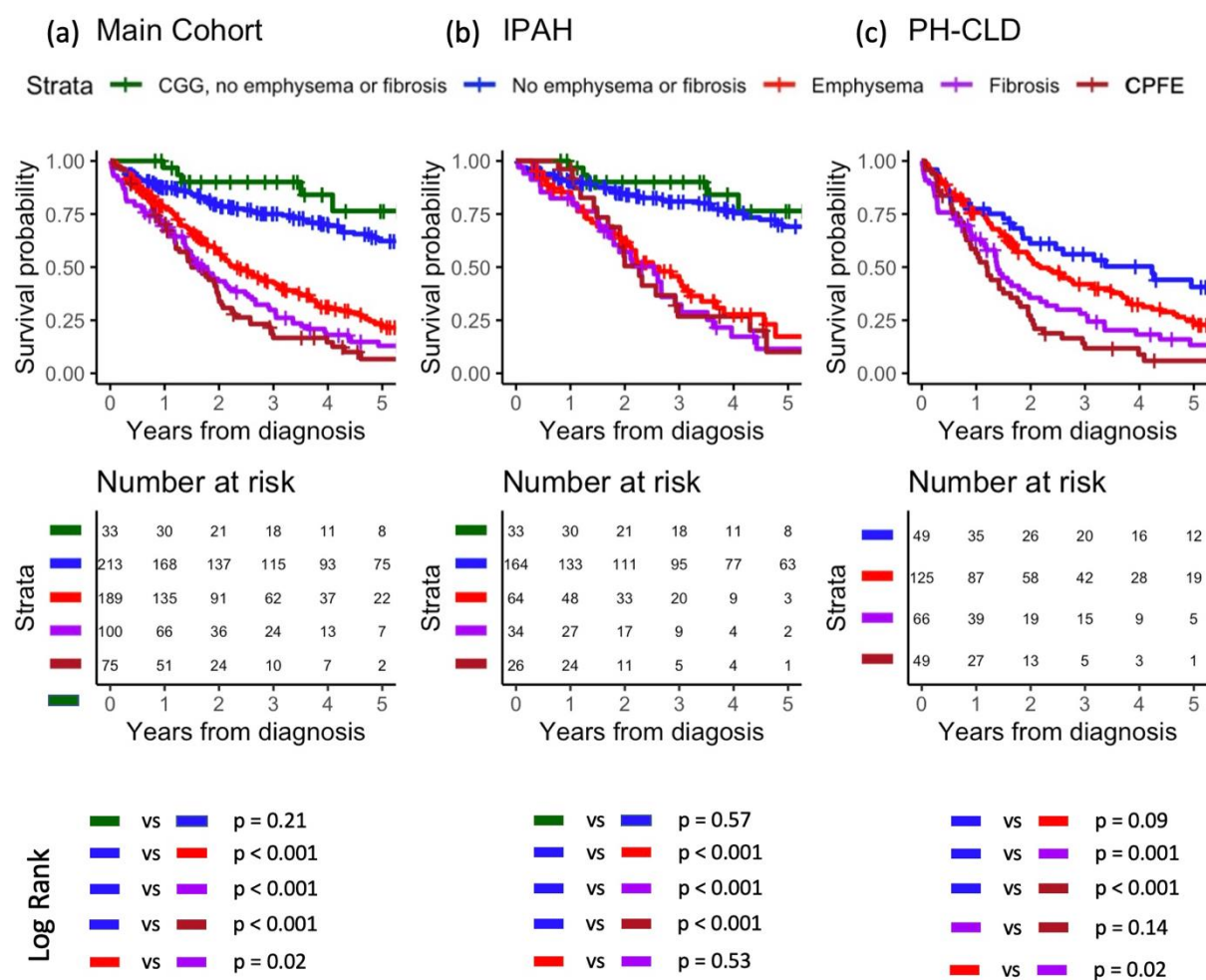
Abbreviations IPAH – Idiopathic Pulmonary Arterial Hypertension; PH-CLD – PH due to chronic lung disease and/or hypoxia.

Figure 4: Kaplan-Meier survival curves for patients classified as IPAH-LD, IPAH-noLD and PH-CLD.
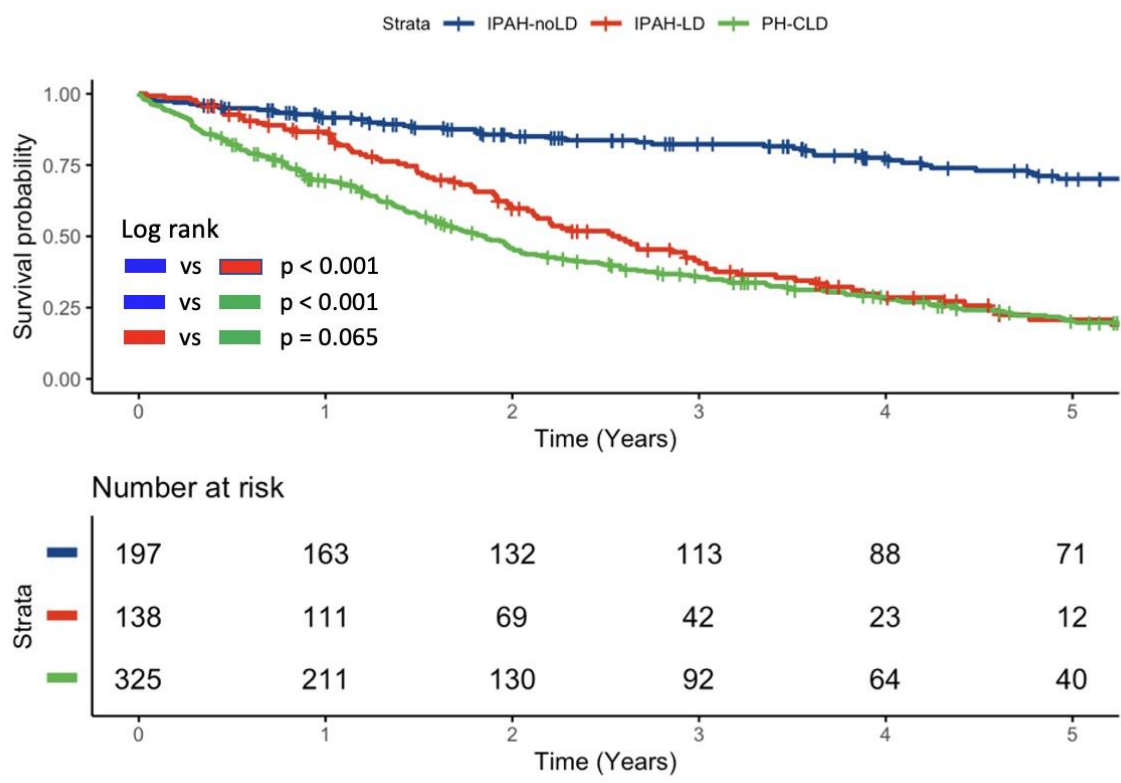
Abbreviations. IPAH-noLD, idiopathic pulmonary arterial hypertension with no CT features of lung disease; IPAH-LD, idiopathic pulmonary arterial hypertension with CT features of lung disease; PH-CLD, pulmonary hypertension associated with chronic lung disease.

Figure 5: Kaplan-Meier curve comparing survival in IPAH-noLD (IPAH with no CT features of lung disease), IPAH-LD (IPAH with CT features of lung disease) and IPAH-CGG (IPAH with centrilobular ground glass on CT).
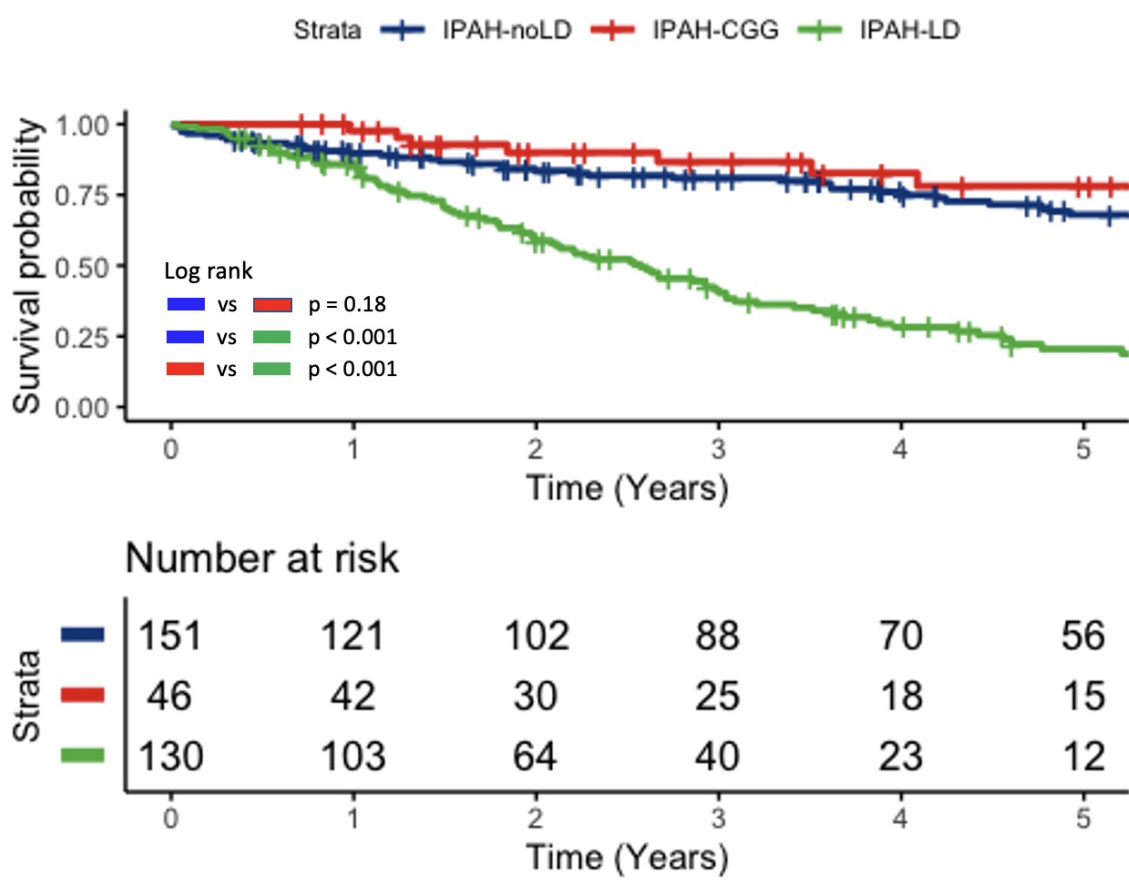
Abbreviations. IPAH-noLD, idiopathic pulmonary arterial hypertension with no CT features of lung disease; IPAH-LD, idiopathic pulmonary arterial hypertension with CT features of lung disease; IPAH-CGG, idiopathic pulmonary arterial hypertension with centrilobular ground glass changes.

Appendix

Table A1: Univariate analysis of patients with IPAH-noLD

Characteristic	HR[1]	95% CI[1]	p-value
CT - Centrilobular Ground Glass (CGG)	0.62	0.30, 1.26	0.2
CT - Ground Glass Opacification (GGO)	0.64	0.32, 1.26	0.2
CT - Honeycombing			
CT - Consolidation	1.55	0.48, 4.96	0.5
Age at diagnosis	1.05	1.03, 1.07	<0.001
Male Gender	1.50	0.90, 2.52	0.12
WHO Functional Class III & IV (ref: I & II)	1.78	1.12, 2.81	0.014
WHO Functional Class			
II	—	—	
III	2.61	1.02, 6.67	0.046
IV	5.62	2.07, 15.2	<0.001
mPAP (mmHg)	0.99	0.97, 1.01	0.3
mRAP (mmHg)	1.04	1.00, 1.08	0.085
PAWP (mmHg)	1.10	1.00, 1.20	0.040
Cardiac output (L/min)	1.00	0.84, 1.18	>0.9
Cardiac index (L/min/m^2)	0.98	0.70, 1.38	>0.9
PVR (Wood Units)	0.97	0.92, 1.02	0.2
SvO$_2$ %	0.96	0.94, 0.99	0.011
FEV$_1$ % predicted	0.98	0.97, 0.99	0.008
FVC % predicted	0.99	0.98, 1.00	0.11
FEV$_1$/FVC Ratio	0.96	0.94, 0.98	<0.001
DLco % predicted	0.95	0.93, 0.97	<0.001

Abbreviations: HR - Hazard Ratio, CI - Confidence Interval, IPAH-noLD, Idiopathic Pulmonary Arterial Hypertension with no lung disease, CT – Computed Tomography, WHO – World Health Organisation, CPFE – Combined Pulmonary Fibrosis and Emphysema, mPAP – mean pulmonary arterial pressure, mRAP – mean right atrial pressure, PAWP – pulmonary arterial wedge pressure, PVR – pulmonary vascular resistance, SvO2 – mixed venous oxygen saturation. FEV$_1$ – forced expiratory volume in 1 second, FVC – forced vital capacity, DLco – diffusing capacity of carbon monoxide.

Table A2: Baseline characteristics of IPAH-noLD vs IPAH-LD vs PH-CLD

Characteristic	IPAH-noLD, N = 197	IPAH-LD, N = 138	PH-CLD, N = 325	p-value
Age at diagnosis	54 (18) †‡	70 (10) *	67 (11) *	<0.001
Male Gender	59 (30%)†‡	72 (52%)*	187 (58%)*	<0.001
WHO Functional Class	†‡	*	*	<0.001
2	34 (17%)†‡	10 (7.2%)*	34 (10%)	
3	127 (65%)	86 (62%)	185 (57%)	
4	34 (17%)	42 (30%)	105 (32%)	
CT - Centrilobular Ground Glass (CGG)	46 (23%)†‡	8 (5.8%)*	0 (0%)*	<0.001
CT - Ground Glass Opacification (GGO)	48 (24%)†‡	14 (10%)*	31 (9.5%)*	<0.001
CT - Honeycombing	0 (0%)	5 (3.6%)	10 (3.1%)	0.013
CT - Consolidation	7 (3.6%)	2 (1.4%)‡	22 (6.8%)†	0.031
CT - Fibrosis	0 (0%)†‡	72 (52%)*	141 (43%)*	<0.001
CT - Fibrosis (by severity)	†‡	*‡	*†	<0.001
Mild	0 (0%)	54 (39%)	28 (8.6%)	
Moderate	0 (0%)	9 (6.5%)	44 (14%)	
None	197 (100%)	66 (48%)	184 (57%)	
Severe	0 (0%)	0 (0%)	48 (15%)	
Unknown	0 (0%)	9 (6.5%)	21 (6.5%)	
CT - Emphysema	0 (0%)†‡	98 (71%)*	204 (63%)*	<0.001
CT - Emphysema (by severity)	†‡	*‡	*†	<0.001
Mild	0 (0%)	48 (35%)	29 (8.9%)	
Moderate	0 (0%)	38 (28%)	91 (28%)	
None	197 (100%)	40 (29%)	121 (37%)	
Severe	0 (0%)	5 (3.6%)	64 (20%)	
Unknown	0 (0%)	7 (5.1%)	20 (6.2%)	
CT - CPFE	0 (0%)†‡	32 (23%)*	69 (21%)*	<0.001
mPAP (mmHg)	56 (13) †‡	49 (9)* ‡	42 (10)* †	<0.001
mRAP (mmHg)	11.4 (6.1) ‡	11.3 (5.3) ‡	9.0 (5.1)* †	<0.001
PAWP (mmHg)	10.6 (3.1) ‡	11.1 (3.6)	11.8 (4.2)*	0.004
Cardiac output (L/min)	4.46 (1.74) ‡	4.10 (1.41)	5.00 (1.64)	<0.001
Cardiac index (L/min x m^-2)	2.39 (0.87) ‡	2.23 (0.71) ‡	2.73 (0.87)* †	<0.001
PVR (Wood Units)	11.6 (5.7) †‡	10.2 (4.4)* ‡	7.0 (4.1)* †	<0.001
SvO2 %	62 (10) ‡	59 (8) ‡	65 (8)* †	<0.001

FEV$_1$ % predicted	83 (17)* ‡	83 (20) ‡	60 (25)* †	<0.001
FEV$_1$ severity	‡	‡	*†	<0.001
Normal (>80% predicted)	114 (61%)	73 (54%)	72 (24%)	
Mild (70-80% predicted)	29 (16%)	24 (18%)	34 (11%)	
Moderate (50-70% predicted)	39 (21%)	31 (23%)	69 (23%)	
Severe (<50% predicted)	5 (2.7%)	6 (4.5%)	129 (42%)	
FEV$_1$ / FVC (%)	74 (10) †‡	67 (10)* ‡	61 (18)* †	<0.001
DLco % predicted	53 (19) †‡	32 (15)* ‡	28 (14)* †	<0.001

Data are presented as number (percentage) or mean (standard deviation). Between-group comparisons performed using one-Way ANOVA with Bonferroni Post-Hoc Correction. Difference between groups noted: * significant difference to IPAH-noLD, † significant difference to IPAH-LD, ‡ significant difference to PH-CLD. Abbreviations: IPAH-LD, Idiopathic Pulmonary Arterial Hypertension with lung disease, PH-CLD, PH due to chronic lung disease and/or hypoxia, CT – Computed Tomography, WHO – World Health Organisation, CPFE – Combined Pulmonary Fibrosis and Emphysema, mPAP – mean pulmonary arterial pressure, mRAP – mean right atrial pressure, PAWP – pulmonary arterial wedge pressure, PVR – pulmonary vascular resistance, SvO$_2$ – mixed venous oxygen saturation. FEV$_1$ – forced expiratory volume in 1 second, FVC – forced vital capacity, DLco – diffusing capacity of carbon monoxide.

Table A3: Survival of patients with IPAH-noLD, IPAH-LD and PH-CLD

Characteristic	1 Year	2 Year	3 Year	4 Year	5 Year
IPAH-noLD	92%	85%	82%	78%	70%
IPAH-LD	87%	60%	41%	29%	21%
PH-CLD	69%	46%	36%	28%	20%

Abbreviations: IPAH-noLD, Idiopathic Pulmonary Arterial Hypertension with no lung disease; IPAH-LD, Idiopathic Pulmonary Arterial Hypertension with lung disease; PH-CLD, PH due to chronic lung disease and/or hypoxia.