Idiopathic pulmonary arterial hypertension and co-existing lung disease: is this a new phenotype?

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Abstract

Patients classified as idiopathic pulmonary arterial hypertension (defined as Group 1 on European Respiratory Society (ERS)/ European Cardiac Society (ESC) criteria) may have evidence of minor co-existing lung disease on thoracic computed tomography. We hypothesised that these idiopathic pulmonary arterial hypertension patients (IPAH $_{lung\ disease}$) are a separate subgroup of idiopathic pulmonary arterial hypertension with different phenotype and outcome compared with idiopathic pulmonary arterial hypertension patients without co-existing lung disease (IPAH $_{no\ lung\ disease}$). Patients with 'IPAH $_{lung\ disease}$' have been eligible for all clinical trials of Group 1 patients because they have normal clinical examination and normal spirometry but we wondered whether they responded to treatment and had similar survival to patients with 'IPAH $_{no\ lung\ disease}$'. We described the outcome of the cohort of patients with 'IPAH $_{no\ lung\ disease}$' in a previous paper. Here, we have compared incident 'IPAH $_{lung\ disease}$' patients with 'IPAH $_{no\ lung\ disease}$' patients diagnosed concurrently in all eight Pulmonary Hypertension centres in the UK and Ireland between 2001–2009. Compared with 'IPAH $_{no\ lung\ disease}$' (n = 355), 'IPAH $_{lung\ disease}$' patients (n = 137) were older, less obese, predominantly male, more likely to be current/ex-smokers and had lower six-minute walk distance, lower % predicted diffusion capacity for carbon monoxide, lower mean pulmonary arterial pressure and lower pulmonary vascular resistance index. After three months of pulmonary hypertension-targeted treatment, six-minute walk distance improved equally in 'IPAH $_{lung\ disease}$' and 'IPAH $_{no\ lung\ disease}$'. However, survival of 'IPAH $_{lung\ disease}$' was lower than 'IPAH $_{no\ lung\ disease}$' (one year survival: 72% compared with 93%). This survival was significantly worse in 'IPAH $_{lung\ disease}$' even after adjusting for age, gender, smoking history, comorbidities and haemodynamics. 'IPAH $_{lung\ disease}$' patients had similar short-term improvement in six-minute walk distance with anti-pulmonary arterial hypertension therapy but worse survival compared with 'IPAH $_{no\ lung\ disease}$' patients. This suggests that 'IPAH $_{lung\ disease}$' are a separate phenotype and should not be lumped with 'IPAH $_{no\ lung\ disease}$' in clinical trials of Group 1 pulmonary arterial hypertension.

Keywords

idiopathic pulmonary arterial hypertension (IPAH), lung disease, treatment response, survival

Introduction

The demographics of idiopathic pulmonary arterial hypertension (IPAH) has changed over the past decade compared with IPAH patients from the era of the NIH registry.[1,2]

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We have previously shown that younger subgroup of IPAH have different phenotype and survival compared with the older subgroup of IPAH.[1] Patients with evidence of lung disease on thoracic computed tomography (CT) were excluded from that study. Recently, Trip et al. identified a subgroup of IPAH characterised by severely reduced diffusion capacity and associated the poor survival of those patients with old age, male gender and co-existing coronary disease.[3] We hypothesised that IPAH patients with co-existing lung disease on thoracic CT (referred to as '*IPAH lung disease*' in this study) are a separate subgroup of IPAH. The objective of this study was to describe the phenotype of '*IPAH lung disease*' and compare them with IPAH patients without co-existing lung disease (referred to as '*IPAH no lung disease*' in this study) diagnosed and treated concurrently over the study period in all eight pulmonary hypertension (PH) centre in the UK and Ireland. We also aimed to determine whether the presence of co-existing lung disease on thoracic CT *without* clinical signs of lung disease or spirometric abnormalities has any impact on the response to PH-targeted treatment and survival of '*IPAH lung disease*'.

Methods

We identified all consecutive, treatment naïve, incident cases of IPAH diagnosed in all eight PH centres in the UK and Ireland between the 1 January 2001 and 31 December 2009. The diagnosis of IPAH was based on standard criteria used by all UK expert PH centres. All patients underwent multimodality assessment for their PH. This includes six-minute walk test, pulmonary function test, thoracic CT and right heart catheterisation (RHC). Patients were excluded if they had a family history or associated causes for their pulmonary arterial hypertension (PAH). We applied similar pulmonary function test exclusion criteria (defined in this study as forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) or total lung capacity <60% predicted) employed in randomised controlled trials of PAH to exclude Group 3 PH patients. Any patients who may also have had Group 2, Group 4 or Group 5 PH were also excluded. Patients were then divided into '*IPAH no lung disease*' or '*IPAH lung disease*' based on the presence or absence of minor co-existing lung disease on thoracic CT. Only emphysema and/or pulmonary fibrosis were included as co-existing lung disease in this study. These patients had no symptoms or signs of lung disease with the exception of breathlessness and had normal spirometry. Fig. 1 shows the flow chart of patients' selection as '*IPAH no lung disease*' or '*IPAH lung disease*'.

The date of diagnostic right heart catheter (RHC) was taken as the date of diagnosis. Four patients were too unwell to have RHC at the time of diagnosis and were started on empirical PH treatment. All four patients had follow-up RHC confirming pre-capillary PH.

We compared the baseline characteristics, treatments and outcomes of '*IPAH lung disease*' against '*IPAH no lung disease*' diagnosed and treated concurrently over the study period. Due to the nature of the study, ethical approval was deemed
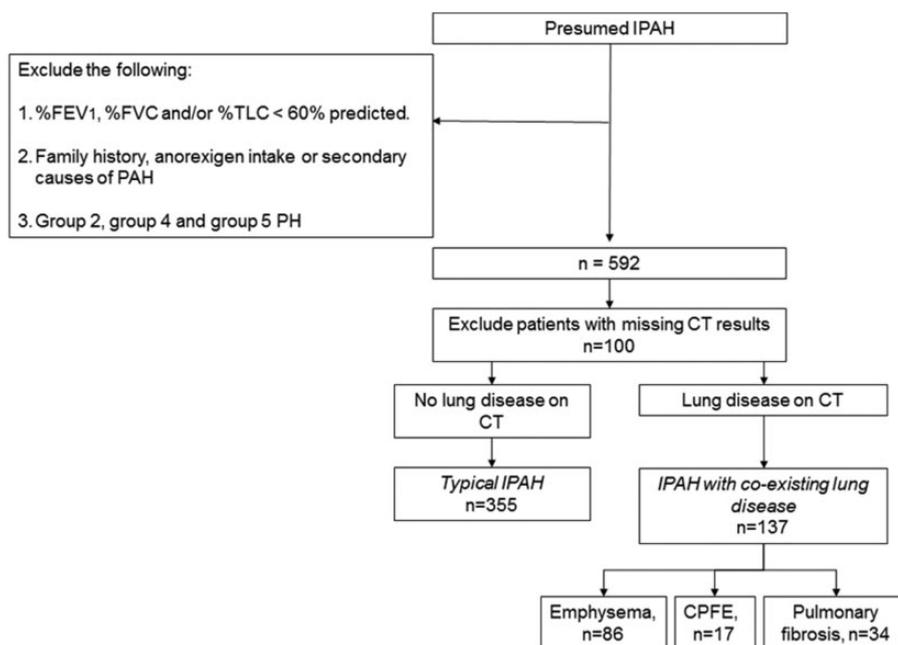

Fig. 1. Flow diagram showing patient selection for '*IPAH lung disease*' and '*IPAH no lung disease*'.
CPFE: combined pulmonary fibrosis and emphysema; CT: computed tomography; %FEV_1: % predicted forced expiratory volume in second; %FVC: % predicted forced vital capacity; IPAH: idiopathic pulmonary arterial hypertension; % TLC: % predicted total lung capacity; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension.

unnecessary by the West of Scotland Research Ethics Committee.

Statistical analysis

Analyses were performed using SPSS version 22 (SPSS, Chicago, IL). For quantitative variables, mean ± standard deviation was used to describe parametric data, whereas median and interquartile range were used for non-parametric data. Comparisons between two independent groups were performed using Student's t test or Mann–Whitney U test. Categorical variables were described by frequencies and percentages and comparisons between groups performed using χ^2 or Fisher's exact tests. Survival endpoint was taken as either date of death/transplant or censoring. Patients were censored if they were lost to follow up (date of last visit to PH centre was used as censor date) or if they were alive on the last day of the study (31 December 2009). Mortality was confirmed using PH centre records, general practitioner and NHS strategic tracing services. All-cause mortality was used in survival analyses. Survival from time of diagnosis was estimated using the Kaplan–Meier method. Multivariate Cox regression was used to compare the survival of '*IPAH lung disease*' against '*IPAH no lung disease*' after adjusting for potential confounders identified from univariate analyses. p-Values < 0.05 were considered to be significant.

Results

A total of 137 '*IPAH lung disease*' and 355 '*IPAH no lung disease*' patients were included in this study. Five patients were lost to follow up. The types of lung disease in patients with '*IPAH lung disease*' were as follows: emphysema only ($n = 86$), pulmonary fibrosis only ($n = 34$) and emphysema and pulmonary fibrosis ($n = 17$). All '*IPAH lung disease*' patients had FEV_1 and FVC > 60% predicted.

Demographics, pulmonary function and haemodynamics

Baseline characteristics of '*IPAH lung disease*' patients were compared with '*IPAH no lung disease*' patients diagnosed over the same period in the UK and Ireland (Table 1). Compared with '*IPAH no lung disease*', '*IPAH lung disease*' patients were older, had lower body mass index, were predominantly male and current or ex-smokers; 21% ($n = 28$) of '*IPAH lung disease*' patients had diabetes and 31% ($n = 41$) had ischaemic heart disease, compared with 13% ($n = 44$, $p < 0.001$) with diabetes and 12% ($n = 42$, $p < 0.001$) with ischaemic heart disease in '*IPAH no lung disease*'. However, left ventricular function was normal in all patients at Echo and RHC. Despite similar functional class distribution, '*IPAH lung disease*' patients had lower mean six-minute walk distances (6MWDs) at the time of diagnosis compared with '*IPAH no lung disease*'. Mean values of spirometry and lung volumes were within normal limits in both groups of patients, whereas % predicted diffusion capacity for carbon monoxide (%DL_{CO}) was impaired in '*IPAH lung disease*' patients. Mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance index were significantly lower in '*IPAH lung disease*' patients compared with '*IPAH no lung disease*' patients; 96% ($n = 129$) of patients with '*IPAH lung disease*' had severe PH (mPAP ≥ 35 mmHg or mPAP ≥ 25 mmHg with cardiac index < 2.0 L.min^{-1}.m^{-2}) as defined by Nice 2018 criteria.[4]

Treatment for '*IPAH lung disease*' and '*IPAH no lung disease*'

All patients were treatment-naive at the time of diagnosis of PH. First-line treatment data for '*IPAH lung disease*' and '*IPAH no lung disease*' patients are shown in Table 2; 27% ($n = 37$) of '*IPAH lung disease*' patients received combination therapy over the study period compared with 47% ($n = 167$) of '*IPAH no lung disease*' patients ($p < 0.001$); 21% ($n = 29$) of '*IPAH lung disease*' patients received prostanoids over the study period compared with 39% ($n = 139$) of '*IPAH no lung disease*' patients ($p < 0.001$).

Paired 6MWD at baseline and three months were available for 176 patients. 6MWD improved by 51 (95% CI: 22.6–78.7) metres after three months of disease-targeted therapies in '*IPAH lung disease*' patients compared with 46 (95% CI: 32.4–59.9) metres in '*IPAH no lung disease*' patients ($p = 0.753$). Absolute 6MWD at three months was 258 (± 144.4) metres in '*IPAH lung disease*' patients compared with 347 (± 108.7) metres in '*IPAH no lung disease*' patients ($p < 0.001$).

Functional class at three months was available for 299 patients. After three months of PH-targeted treatment, 17% ($n = 14$), 74% ($n = 61$) and 8.5% ($n = 7$) of '*IPAH lung disease*' patients remained in functional class I/II, III and IV, respectively. In '*IPAH no lung disease*' patients, after three months of PAH treatment, 32% ($n = 69$), 59.0% ($n = 128$) and 9.2% ($n = 20$) remained in functional class I/II, III and IV, respectively.

Survival

Eighty-nine '*IPAH no lung disease*' and 61 '*IPAH lung disease*' patients died over the study period. '*IPAH lung disease*' patients had overall worse survival compared with '*IPAH no lung disease*' patients. One-, two- and three-year survival of '*IPAH lung disease*' patients were 72%, 52% and 42%, respectively. This is less compared with one-, two- and three-year survival of 93%, 82% and 71%, respectively, in '*IPAH no lung disease*' patients ($p < 0.001$). Even after adjusting for age, gender, smoking history, co-morbidities and haemodynamics parameters, '*IPAH lung disease*' patients were more likely to have a shorter time to death or transplantation compared with '*IPAH no lung disease*' patients (Table 3).

Discussion

We report on the baseline characteristics and outcomes of a subgroup of IPAH patients characterised by severe

Table 1. Comparison of baseline demographics, pulmonary function tests and haemodynamics parameters between patients with 'IPAH _lung disease_' and 'IPAH _no lung disease_'.

Baseline characteristics	'IPAH _lung disease_' (n = 137)	'IPAH _no lung disease_' (n = 355)	p-Values
Age, years (n = 492)	68 (11.2)	50 (17.1)	<0.001
Gender, % female (n = 492)	41% (56)	71% (251)	<0.001
Ethnicity, % non-white (n = 436)	0% (0)	11% (35)	<0.001
Baseline functional class (n = 482)			
I and II	10% (14)	15% (51)	0.469
III	70% (93)	67% (233)	
IV	20% (27)	18% (64)	
Smoking history (n = 404)			
Current smoker	14% (17)	14% (39)	<0.001
Ex-smoker	75% (91)	40% (114)	
Never smoke	11% (13)	46% (130)	
Baseline 6MWD, metres (n = 262)	210 (117.1)	292 (119.5)	<0.001
Duration of symptoms, months, median (IQR) (n = 439)	18 (10.8–36.0)	18 (10.0–36.0)	0.880
Body mass index (n = 428)	26 (6.0)	29 (6.6)	<0.001
% obesity (n = 428)	17% (21)	34% (105)	<0.001
Haemoglobin, g/dL (n = 438)	15.3 (1.8)	15.1 (2.1)	0.347
% FEV_1 (n = 399)	88 (18.1)	85 (14.3)	0.070
% FVC (n = 396)	103 (20.0)	94 (16.3)	<0.001
FEV_1/FVC ratio (n = 412)	68 (9.6)	75 (8.7)	<0.001
% TLC (n = 232)	107 (99.5)	100 (64.1)	0.517
% DL_{CO} (n = 374)	38 (20.1)	61 (21.0)	<0.001
mRAP, mmHg (n = 467)	9.5 (5.2)	10 (5.8)	0.468
mPAP, mmHg (n = 479)	48 (9.0)	54 (14.1)	<0.001
PCWP, mmHg (n = 445)	9.4 (3.3)	9.0 (3.7)	0.386
CI, L.min^{-1}.m^{-2} (n = 404)	2.0 (0.6)	2.1 (0.7)	0.258
PVRI, WU.m^{-2} (n = 403)	21 (8.3)	23 (10.0)	0.019

6MWD: six-minute walk distance; CI: cardiac index; % DL_{CO}: % predicted diffusion capacity for carbon monoxide; % FEV_1: % predicted forced expiratory volume in 1 second; % FVC: % predicted forced vital capacity; IPAH; idiopathic pulmonary arterial hypertension; IQR: interquartile range; mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; PCWP: pulmonary capillary wedge pressure; PVRI: pulmonary vascular resistance index; % TLC: % predicted total lung capacity; WU: Woods unit.
Note: Results presented as mean ± SD or % (n) unless otherwise specified.

Table 2. Comparisons of treatment between 'IPAH _lung disease_' and 'IPAH _no lung disease_'.

	'IPAH _lung disease_' (n = 137)	'IPAH _no lung disease_' (n = 355)	p-Values
Lung transplantation (n = 492)	0% (0)	2.5% (9)	0.068
Atrial septostomy (n = 492)	0% (0)	1.1% (4)	0.580
First-line treatment (n = 491)			
No treatment	0.7% (1)	0.8% (3)	<0.001
PD5i	53% (73)	30% (106)	
ERA	32% (44)	44% (155)	
Prostanoids	7.4% (10)	19% (66)	
Calcium channel blockers	2.9% (4)	5.1% (18)	
Combination therapy	2.9% (4)	2.0% (7)	

ERA: endothelin receptor antagonist; IPAH: idiopathic pulmonary arterial hypertension; PD5i: phosphodiesterase type V inhibitor.

Table 3. Multivariate Cox regression models to determine whether 'IPAH $_{lung\ disease}$' and 'IPAH $_{no\ lung\ disease}$' patients differ after adjusting for confounders.

	p-Values	Hazard ratio	95% confidence interval
Model 1			
Diagnosis			
'IPAH $_{no\ lung\ disease}$'		1	
'IPAH $_{lung\ disease}$'	0.01	1.71	1.108–2.631
Age, years	<0.001	1.035	1.018–1.051
Male gender	0.94	1.02	0.688–1.498
Smoking history			
Never smoker		1	
Current/ex-smoker	0.04	1.56	1.023–2.445
Ischaemic heart disease	0.94	0.98	0.626–1.546
Hypertension	0.63	1.11	0.731–1.674
Diabetes	0.008	1.83	1.171–2.854
Model 2			
Diagnosis			
'IPAH $_{no\ lung\ disease}$'		1	
'IPAH $_{lung\ disease}$'	<0.001	2.72	1.863–3.980
mRAP, mmHg	0.60	1.01	0.973–1.049
SvO$_2$, %	0.1	0.98	0.955–1.004
CI, L.min^{-1}.m^{-2}	0.02	0.64	0.440–0.938

CI: cardiac index; IPAH: idiopathic pulmonary arterial hypertension; mRAP: mean right atrial pressure; SvO$_2$: mixed venous oxygen saturations.

pre-capillary PH, presence of minor co-existing lung disease on thoracic CT (IPAH $_{lung\ disease}$), absence of ventilatory impairment on pulmonary function testing and normal respiratory examination who were treated with PH-targeted therapies. These patients were managed as IPAH $_{no\ lung\ disease}$ patients in real life. They would not be excluded by pulmonary function criteria in PAH clinical trials. Hence, many of these patients were probably recruited as IPAH in pivotal PAH clinical trials that form the evidence base for our current practice. However, our results show that the phenotype and response to treatment of these 'IPAH $_{lung\ disease}$' patients are different compared with 'IPAH $_{no\ lung\ disease}$' patients. The short-term improvement in 6MWD in response to PH disease-targeted therapies in 'IPAH $_{lung\ disease}$' patients may have contributed to the positive results of PAH trials, many of which used change in 6MWD as the primary endpoint. However, functional class after three months of treatment and survival of 'IPAH $_{lung\ disease}$' patients appeared to be significantly worse than 'IPAH $_{no\ lung\ disease}$' patients and long-term survival for 'IPAH $_{lung\ disease}$' was worse than 'IPAH $_{no\ lung\ disease}$' despite similar haemodynamics at baseline.

'IPAH $_{lung\ disease}$' patients described in our study had normal clinical features, spirometry and lung volumes. The most common parenchymal abnormality in our study cohort was emphysema. Emphysema may be noted on CT

in otherwise asymptomatic healthy smokers and may not be associated with airflow obstruction on spirometry.[5] Interstitial changes are also frequently seen on the CT of asymptomatic elderly patients and would not normally be of any clinical relevance.[5] It is possible that this selective group of 'IPAH $_{lung\ disease}$' patients described in our study simply represents IPAH patients where the predominant disease is PAH and the parenchymal abnormality is an incidental insignificant finding noted on thoracic CT done as part of the standard assessment of PH. However, the differences in phenotypes and the worse survival of this group of patients compared with 'IPAH $_{no\ lung\ disease}$' suggest that 'IPAH $_{lung\ disease}$' patients are indeed a separate subgroup different to 'IPAH $_{no\ lung\ disease}$' patients.

Alternatively, some may argue that 'IPAH $_{lung\ disease}$' patients in our study are Group 3 PH patients with severe PH. However, most COPD patients with severe PH also have mild- to moderate airflow obstruction,[6,7] whereas spirometry was within normal limits in our 'IPAH $_{lung\ disease}$' patients and fulfilled the inclusion criteria of PAH clinical trials as Group 1 PH patients. Indeed, spirometry was better in 'IPAH $_{lung\ disease}$' than in 'IPAH $_{no\ lung\ disease}$'. A recent case report of three patients also described a similar phenotype to our study cohort: elderly male smokers with normal spirometry and lung volumes, emphysema on CT, severely reduced DL$_{CO}$ and severe precapillary PH.[8] With our larger patient number, our study not only confirmed the presence of this separate PH phenotype but also allowed comparison of this selective group of patients with 'IPAH $_{no\ lung\ disease}$' patients diagnosed and managed concurrently at the same PH centres.

Our study is multicentre and confirmed recent results from the Scottish Pulmonary Vascular Unit that showed different phenotype and poorer response to treatment of lung disease patients with severe PH compared with IPAH patients.[9] In that study, 88 patients had severe PH, of which 32 patients had mild lung disease and the rest had severe lung disease.[8] The ASPIRE registry also reported on the characteristics and outcomes of COPD patients with severe PH.[11] In that study, mean % FEV$_1$ was 65% in COPD patients with severe PH, whereas spirometry was normal in our 'IPAH$_{lung\ disease}$' cohort.

The higher prevalence of smokers amongst the 'IPAH $_{lung\ disease}$' patients may explain the lower DL$_{CO}$ observed in 'IPAH $_{lung\ disease}$' patients. Smoking is associated with subclinical interstitial lung abnormalities,[11,12] which in turn is associated with lower DL$_{CO}$ and 6MWD.[13,14] Furthermore, tobacco smoke may have a direct effect on the pulmonary vasculature. Cigarette smoking has been associated with smooth muscle cell proliferation and extracellular matrix-protein deposition in pulmonary artery wall of smokers who have not yet developed COPD.[15] Cigarette smoking was also associated with reduced expression of endothelial nitric oxide synthase in pulmonary arteries of smokers with airway disease.[16]

The short-term improvement in 6MWD observed in 'IPAH $_{lung\ disease}$' patients in our study cohort did not appear to translate into similar improvement in functional class or survival benefit to that observed in 'IPAH $_{no\ lung\ disease}$' patients. This is important because short-term improvement in 6MWD has been used as primary end point in many clinical trials of PH-targeted therapies. The poor long-term prognosis of 'IPAH $_{lung\ disease}$' patients may be explained by the lower absolute 6MWD achieved by 'IPAH $_{lung\ disease}$' patients at three months. Absolute 6MWD after three months of PAH treatment predicts survival in IPAH, whereas change in 6MWD does not.[17] PH-targeted therapies have vasodilatory and anti-proliferative properties and may help to unload the right ventricle to account for the short-term improvement in exercise capacity. However, other factors such as older age with associated co-morbidities and the effect of smoking may contribute to the worse survival of 'IPAH $_{lung\ disease}$' patients compared with 'IPAH $_{no\ lung\ disease}$' patients in our study. The male sex predominance amongst 'IPAH $_{lung\ disease}$' patients may also account for the survival difference. Male sex is associated with worse pulmonary haemodynamics, reduced right ventricle response to treatment and worse overall survival in PAH.[18–20] In addition, a higher proportion of 'IPAH $_{no\ lung\ disease}$' patients received combination therapy and prostanoids compared with 'IPAH $_{lung\ disease}$' patients in our study.

With the exception of the presence of incidental parenchymal lung abnormalities on thoracic CT, 'IPAH $_{lung\ disease}$' patients described in this study otherwise satisfied the haemodynamic and pulmonary function criteria of IPAH and would have been – and, in many cases were – classified as IPAH in real life or in clinical trials. Disproportionately reduced DL_{CO} as noted in our 'IPAH $_{lung\ disease}$' cohort should raise the suspicion of co-existing parenchymal lung disease even in the absence of ventilatory impairment on pulmonary function testing. Trip et al. similarly noted higher proportion of co-existing lung disease on thoracic CT in IPAH patients with severely reduced DL_{CO}.[3] 'IPAH $_{lung\ disease}$' patients need to be monitored closely because, despite similar short-term improvement in 6MWD compared with 'IPAH $_{no\ lung\ disease}$' patients, the survival of 'IPAH $_{lung\ disease}$' patients was relatively poor, and worse than 'IPAH $_{no\ lung\ disease}$' despite treatment with PH-targeted therapies. On the face of it, our patients fit with the classification of Pulmonary Vascular Phenotype in COPD.[21] They have severe precapillary PH and reduced DL_{CO} but crucially they do not have airflow limitation and would be (were) recruited into clinical trials of patients with Group 1 PAH. More randomised controlled studies are needed to inform whether the use of PH-targeted therapies is beneficial in 'IPAH $_{lung\ disease}$' patients. Better understanding of the phenotype of this subgroup of IPAH patients, as described in our study, may help to inform the selection of patients for future PAH trials. IPAH $_{lung\ disease}$ patients should be recognised and recruited as a separate subgroup to 'IPAH $_{no\ lung\ disease}$' patients in future PAH clinical trials.

Limitations of our study

Our study has several limitations. This was a retrospective observational study and we have not controlled for treatment. It is possible that the presence of co-existing subclinical radiographic lung disease may have biased the choice of PH treatment and contributed to the worse outcome of 'IPAH $_{lung\ disease}$' patients. Missing 6MWD data was unavoidable as not all centres used six-minute walk test to assess exercise capacity. Some patients were too unwell from their PH for their exercise capacity to be assessed. The small number of non-white subjects in our study may limit its generalisability. Our study population was comprised of a heterogeneous group of patients with different types and severity of parenchymal lung disease, although in all cases, the abnormalities were minor and associated with normal spirometry allowing classification by PH experts as Group 1 PAH. As CT images were not reviewed by an independent reviewer, potential misclassification bias cannot be excluded nor were the CT scans quantified. Chronic alveolar hypoxia may trigger pulmonary vascular remodelling. Although data were not collected for hypoxia or use of long-term oxygen therapy, there was no difference in haemoglobin level between 'IPAH $_{no\ lung\ disease}$' and 'IPAH $_{lung\ disease}$'. We do not have information on the cause of death. That will be useful to confirm that the increased risk of death of 'IPAH $_{lung\ disease}$' patients is not due to death unrelated to PH. Nevertheless, our results showed increased risk of death of 'IPAH $_{lung\ disease}$' patients after adjusting for age, gender, smoking status and co-morbidities.

Conclusion

'IPAH $_{lung\ disease}$' patients described in our study fulfilled current inclusion criteria for clinical trials of Group 1 PH patients and were treated as Group 1 PH patients in real life. However, they had different phenotype and outcomes compared with 'IPAH $_{no\ lung\ disease}$' patients. Thoracic CT and disproportionately reduced DL_{CO} help to differentiate 'IPAH $_{lung\ disease}$' from 'IPAH $_{no\ lung\ disease}$' patients. Despite similar baseline haemodynamic impairment and similar short-term response to PH-targeted therapies, survival of 'IPAH $_{lung\ disease}$' was worse than 'IPAH $_{no\ lung\ disease}$'. Age, the effect of smoking and the presence of co-morbidities may account for the difference in long-term outcome between these two subgroups of patients. More emphasis should be put on differentiating between subgroups of IPAH patients with or without co-existing lung disease when designing future PH clinical trials. Scoring the extent of parenchymal changes on thoracic

CT should be employed in addition to standard pulmonary function criteria when deciding whether a PH patient should be Group 1, a variant of Group 1 or Group 3 PH patient in future clinical trials and PH registries.

Author contributions

Andrew J Peacock and Yi Ling contributed equally. All other authors were involved in collecting data and read and approved the manuscript.

Conflict of interest

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