



# Severe pulmonary hypertension in lung disease: phenotypes and response to treatment

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**ABSTRACT** Pulmonary hypertension (PH) due to lung disease (World Health Organization (WHO) group 3) is common, but severe PH, arbitrarily defined as mean pulmonary artery pressure  $\geq 35$  mmHg is reported in only a small proportion. Whether these should be treated as patients in WHO group 1 (*i.e.* pulmonary arterial hypertension) with PH-targeted therapies is unknown.

We compared the phenotypic characteristics and outcomes of 118 incident patients with severe PH and lung disease with 74 idiopathic pulmonary arterial hypertension (IPAH) patients, all treated with pulmonary vasodilators.

Lung disease patients were older, more hypoxaemic, and had lower gas transfer, worse New York Heart Association functional class and lower 6-min walking distance (6MWD) than IPAH patients. Poorer survival in those with lung disease was driven by the interstitial lung disease (ILD) cohort.

In contrast to IPAH, where significant improvements in 6MWD and N-terminal pro-brain natriuretic peptide (NT-proBNP) occurred, PH therapy in severe PH lung disease did not lead to improvement in 6MWD or functional class, but neither was deterioration seen. NT-proBNP decreased from 2200 to 1596  $\text{pg}\cdot\text{mL}^{-1}$  ( $p=0.015$ ). Response varied by lung disease phenotype, with poorer outcomes in patients with ILD and emphysema with preserved forced expiratory volume in 1 s. Further study is required to investigate whether vasodilator therapy may delay disease progression in severe PH with lung disease.



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## Introduction

Mild-to-moderate pulmonary hypertension (PH) is a common complication of chronic lung disease. There is a reported prevalence of 30–70% in chronic obstructive pulmonary disease (COPD) [1–4], and 47–90% in patients with combined pulmonary fibrosis and emphysema (CPFE) syndrome [5, 6]. The presence of PH is associated with poorer survival [1, 7]. In contrast, severe PH (defined as mean pulmonary arterial pressure (mPAP)  $\geq 35$  mmHg) is rare (prevalence 5–13%), and is associated with less severe airflow obstruction but more marked hypoxaemia, impaired diffusing capacity of the lung for carbon monoxide (DLCO) and greater right ventricular dysfunction [2, 3]. The development of PH in COPD has been attributed to several mechanisms, including alveolar hypoxia with resultant vasoconstriction and vascular remodelling, destruction of the pulmonary vascular bed and compression of alveolar vessels in hyperinflated emphysematous lungs. Severe PH has been postulated to occur in susceptible individuals with more marked hypoxic vasoconstrictive response, such as serotonin transporter gene polymorphism [8, 9], or possible co-existent lung and idiopathic pulmonary vascular disease. The 5th World Symposium on Pulmonary Hypertension suggested criteria for discriminating between World Health Organization group 1 (pulmonary arterial hypertension (PAH)) and group 3 (PH due to lung disease) disease and a classification system for patients with severe PH and lung disease [10].

Long-term oxygen therapy (LTOT) has been demonstrated to stabilise or decrease mPAP in COPD with mild-to-moderate PH [11–13]. However, in those with severe PH results are less encouraging [12, 14]. The role of PH-specific medication in those with severe PH is uncertain. Studies to date have been of small sample sizes and included those with both mild and severe PH [15–18]. The ASPIRE (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre) registry reported no survival advantage in 43 COPD patients with severe PH treated with pulmonary vasodilators. However, this group did demonstrate a fall in pulmonary vascular resistance (PVR)  $>20\%$  in four out of seven patients with right heart catheterisation (RHC) data, but did not evaluate clinical response by commonly used outcome measures such as 6-min walking distance (6MWD) or N-terminal pro-brain natriuretic peptide (NT-proBNP) [19].

The aims of this study were to contrast and compare the survival and treatment response, defined by clinical variables such as 6MWD, NT-proBNP and New York Heart Association (NYHA) functional class in a large cohort of patients with severe PH associated with lung disease against a group with idiopathic PAH (IPAH), and secondly to analyse the influence of lung phenotype on outcome.

## Methods

We retrospectively studied 244 treatment-naïve incident cases of precapillary PH diagnosed between January 2000 and March 2014 at the Scottish Pulmonary Vascular Unit (Glasgow, UK). Patients were referred for investigation of unexplained PH, or PH felt disproportionate to the degree of lung disease and included after multidisciplinary evaluation based on RHC, echocardiography, pulmonary function testing and computed tomography (CT) of the thorax. Patients were excluded if there was incomplete RHC data, missing CT or lung function data, or an alternative aetiology for PH.

Patients were categorised by underlying lung disease into one of four phenotypes (fig. 1): 1) emphysema with preserved forced expiratory volume in 1 s (FEV<sub>1</sub>) (defined as FEV<sub>1</sub>  $>80\%$  predicted); 2) CPFE, characterised by co-existent emphysema and predominantly lower-lobe fibrosis on CT thorax, with reduced DLCO [20]; 3) interstitial lung disease (ILD); and 4) COPD, characterised by either FEV<sub>1</sub>  $<60\%$  pred or emphysema on CT with FEV<sub>1</sub>  $<80\%$  pred, in conjunction with an FEV<sub>1</sub>/forced vital capacity (FVC) ratio  $<0.7$ .

Only patients with severe pulmonary hypertension, defined as a mPAP  $\geq 35$  mmHg with a pulmonary artery wedge pressure (PAWP)  $\leq 15$  mmHg and normal or reduced cardiac output, were included. A “pure” IPAH group with neither parenchymal disease nor spirometric abnormalities was included for comparison. PH was defined in the IPAH group as mPAP  $\geq 25$  mmHg with a PAWP  $\leq 15$  mmHg and normal or reduced cardiac output. Patients were excluded if they had emphysema or interstitial abnormalities of any degree on CT, or were smokers with an FEV<sub>1</sub>/FVC ratio  $<0.7$  and FEV<sub>1</sub>  $<80\%$  pred.

In addition to the phenotypes described, the outcomes of patients meeting the criteria suggested by SEEGER *et al.* [10] were evaluated. Severe PH was defined as mPAP  $\geq 35$  mmHg or mPAP  $\geq 25$  mmHg with cardiac index  $<2.0$  L·min<sup>-1</sup>·m<sup>-2</sup>. Patients were classified into two groups: 1) severe PH/mild lung disease, defined as modest parenchymal abnormality on CT thorax, COPD with FEV<sub>1</sub>  $\geq 60\%$  pred or ILD with FVC  $\geq 70\%$  pred; and 2) severe PH/severe lung disease, defined as severe PH–CPFE (moderate–severe parenchymal abnormality), severe PH–COPD (defined by FEV<sub>1</sub>  $<60\%$  pred) or severe PH–idiopathic pulmonary fibrosis (defined by FVC  $<70\%$  pred).

All patients received a minimum of 3 months of disease-targeted therapy at the discretion of the prescribing PH physician. Patients with lung disease were treated with inhaled bronchodilators and LTOT in accordance

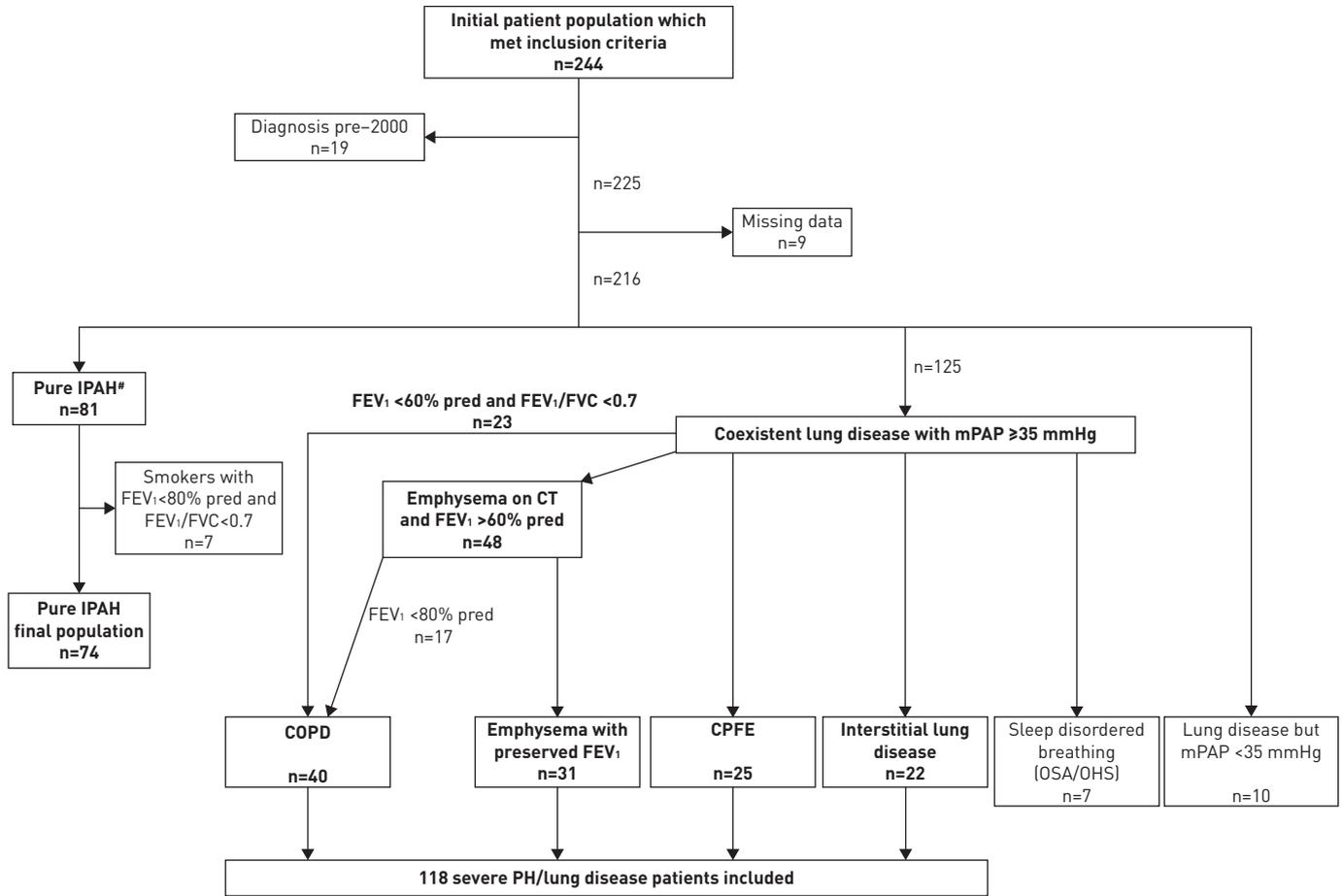


FIGURE 1 Population distribution. IPAH: idiopathic pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure; FEV<sub>1</sub>: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; CPFE: combined pulmonary fibrosis and emphysema syndrome; OSA: obstructive sleep apnoea; OHS: obesity hypoventilation syndrome. #: "pure" IPAH group had neither parenchymal disease nor spirometric abnormalities.

with UK guidelines [21, 22] and compassionate use of PH-targeted therapy. NYHA functional class, 6MWD and NT-proBNP were measured at diagnosis and reassessed at a time point >3 months. Cardiac magnetic resonance imaging (MRI) variables were indexed for body surface area and adjusted for age.

**Statistical analysis**

Statistical analysis was performed using SPSS 21 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5.00; GraphPad Software, La Jolla, CA, USA). Continuous variables were tested for normality using the D’Agostino–Pearson omnibus normality test. Normally distributed variables are shown as mean ±SD and non-normally distributed variables as median (interquartile range (IQR)). Categorical variables are described by percentages (n), unless otherwise stated. Comparison of baseline characteristics between phenotypes was made using unpaired t-tests or Mann–Whitney U-tests, depending on data distribution. Comparison of several groups was performed using ANOVA or Kruskal–Wallis tests with *post hoc* analysis using Tukey’s or Dunn’s multiple comparison test. Comparison between baseline and follow-up 6MWD and NT-proBNP was made by paired t-test or Wilcoxon signed rank test. Comparison between categorical variables was made using Chi-squared.

Survival was from date of diagnostic RHC and the study end-point was either date of death, lung transplant or censoring. Patients were censored if they were lost to follow-up or alive at last day of the study (August 5, 2014). All-cause mortality was used for survival analysis. Kaplan–Meier survival curves were performed to estimate 1- and 3-year survival with comparison of groups using log-rank testing. Survival predictors were determined using Cox proportional hazards regression analysis. Variables with p≤0.2 were considered for multivariate analysis. Indicator variable coding for missing data was used for multivariate analysis. At 3 months, 6MWD and NT-proBNP were dichotomised according to the median, and Kaplan–Meier survival curves compared using log-rank test. p<0.05 was considered statistically significant throughout.

## Results

### Baseline characteristics

118 patients had severe PH with coexistent lung disease and 74 patients had IPAH. Table 1 shows the characteristics of the two groups. IPAH patients were younger, more often female, had higher baseline NYHA functional class and 6MWD, and lower NT-proBNP despite worse haemodynamics. Phosphodiesterase-5 inhibitors were more commonly prescribed in those with lung disease. In those with COPD, FEV<sub>1</sub> correlated with 6MWD ( $r=0.458$ ,  $p=0.006$ ).

There were 31 patients with emphysema/preserved FEV<sub>1</sub>, 25 patients with CPFE, 22 patients with ILD (nonspecific interstitial pneumonia  $n=7$ , usual interstitial pneumonia  $n=8$ , cryptogenic organising pneumonitis  $n=1$  and indeterminate fibrosis  $n=6$ ) and 40 COPD patients. Of these 40 patients, 28 had emphysema, four had respiratory bronchiolitis and three patients were shown to have bronchiectasis on imaging. Five patients had isolated spirometric abnormalities. Table 2 shows the characteristics of the lung phenotype groups. 88 patients met the criteria suggested by SEEGER *et al.* [10]. 30 patients had marked

TABLE 1 Population characteristics

|                                                    | IPAH                           | All lung disease                | p-value    |
|----------------------------------------------------|--------------------------------|---------------------------------|------------|
| <b>Subjects</b>                                    | 74                             | 118                             |            |
| <b>Age years</b>                                   | 49±18                          | 67±9                            | <0.0001*** |
| <b>Female %</b>                                    | 72                             | 45                              | <0.0001*** |
| <b>Ever-smokers</b>                                | 32 (22)                        | 90 (105)                        |            |
| <b>Smoking pack-years</b>                          | 30±15                          | 42±24                           | 0.048*     |
| <b>Baseline haemodynamics</b>                      |                                |                                 |            |
| mPAP mmHg                                          | 54 (46–62)                     | 47 (42–51)                      | <0.0001*** |
| RAP mmHg                                           | 8±6                            | 9±5 <sup>#</sup>                | 0.873      |
| Cardiac index L·min <sup>-1</sup> ·m <sup>-2</sup> | 2.0±0.5 <sup>¶</sup>           | 1.9±0.5*                        | 0.159      |
| PVR Wood units                                     | 12.5 (9.2–17.9)                | 10.7 (8.3–14.7)                 | 0.034*     |
| PAWP mmHg                                          | 7±4                            | 8±3                             | 0.077      |
| SvO <sub>2</sub> %                                 | 63 (56–69) <sup>§</sup>        | 61 (53–67)                      | 0.315      |
| Peripheral oxygen saturations                      | 96 (94–98)                     | 94 (91–97) <sup>f</sup>         | 0.011      |
| Supplementary oxygen %                             | 22.7 (15)                      | 70.0 (77)                       |            |
| Flow rate L·min <sup>-1</sup>                      | 5 (2–10)                       | 4 (2–15)                        |            |
| <b>Initial PH therapy</b>                          |                                |                                 |            |
| CCB                                                | 9.5 (7)                        | 2.5 (3)                         | 0.005**    |
| PDE-5 inhibitor                                    | 44.6 (33)                      | 66.9 (79)                       |            |
| ERA                                                | 25.7 (19)                      | 22.9 (27)                       |            |
| Prostanoid                                         | 14.9 (11)                      | 4.2 (5)                         |            |
| Combination                                        | 5.4 (4)                        | 3.4 (4)                         |            |
| <b>Lung function</b>                               |                                |                                 |            |
| FEV <sub>1</sub> % pred                            | 91 (83–97)                     | 77 (60–94)                      | <0.0001*** |
| FVC % pred                                         | 101±13                         | 96±26                           | 0.085      |
| FEV <sub>1</sub> /FVC %                            | 76 (70–79)                     | 63 (55–71)                      | <0.0001*** |
| TLC %                                              | 93±10 <sup>##</sup>            | 92±17 <sup>¶¶</sup>             | 0.616      |
| DLco % pred                                        | 62 (39–76) <sup>++</sup>       | 24 (19–33) <sup>§§</sup>        | <0.0001*** |
| P <sub>a</sub> O <sub>2</sub> kPa                  | 9.6±2 <sup>ff</sup>            | 7.3±1.6 <sup>###</sup>          | <0.0001*** |
| P <sub>a</sub> CO <sub>2</sub> kPa                 | 4.1±0.7 <sup>ff</sup>          | 4.0±0.7 <sup>###</sup>          | 0.834      |
| <b>NYHA functional class</b>                       |                                |                                 |            |
| I/II                                               | 23.9 (17)                      | 11.4 (13)                       | 0.020*     |
| III                                                | 69.0 (49)                      | 71.1 (81)                       |            |
| IV                                                 | 7.0 (5)                        | 16.9 (20)                       |            |
| <b>6MWD m</b>                                      | 334±118 <sup>¶¶¶</sup>         | 202±108 <sup>§§§</sup>          | <0.0001*** |
| <b>NT-proBNP pg·mL<sup>-1</sup></b>                | 1128 (508–2890) <sup>+++</sup> | 2245 (943–4225) <sup>§§§§</sup> | 0.018*     |

Data are presented as n, mean±SD, % (n) or median (interquartile range), unless otherwise stated. IPAH: idiopathic pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure; RAP: right atrial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure; SvO<sub>2</sub>: mixed venous oxygen saturation; PH: pulmonary hypertension; CCB: calcium-channel blocker; PDE: phosphodiesterase; ERA: endothelin receptor antagonists; FEV<sub>1</sub>: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; DLco: diffusing capacity of the lung for carbon monoxide; P<sub>a</sub>O<sub>2</sub>: arterial oxygen tension; P<sub>a</sub>CO<sub>2</sub>: arterial carbon dioxide tension; NYHA: New York Heart Association; 6MWD: 6-min walking distance; NT-proBNP: N-terminal pro-brain natriuretic peptide. <sup>#</sup>: n=117; <sup>¶</sup>: n=73; <sup>\*</sup>: n=116; <sup>§</sup>: n=66; <sup>f</sup>: n=107; <sup>##</sup>: n=68; <sup>¶¶</sup>: n=97; <sup>++</sup>: n=71; <sup>§§</sup>: n=99; <sup>ff</sup>: n=43; <sup>###</sup>: n=79; <sup>¶¶¶</sup>: n=62; <sup>+++</sup>: n=46; <sup>§§§§</sup>: n=90. \*: p<0.05; \*\*: p<0.01; \*\*\*: p<0.001.

TABLE 2 Population characteristics of lung disease phenotypes

|                                                    | Emphysema                      | CPFE                            | COPD                         | ILD                             | p-value    |
|----------------------------------------------------|--------------------------------|---------------------------------|------------------------------|---------------------------------|------------|
| <b>Subjects n</b>                                  | 31                             | 25                              | 40                           | 22                              |            |
| <b>Age years</b>                                   | 70±10                          | 68±7                            | 64±10                        | 68±10                           | 0.040*     |
| <b>Female %</b>                                    | 52                             | 36                              | 45                           | 46                              |            |
| <b>Ever-smokers %</b>                              | 100                            | 100                             | 93                           | 52                              | 0.008*     |
| <b>Pack-years</b>                                  | 51±29                          | 47±23                           | 36±17                        | 25±16                           |            |
| <b>Current smokers</b>                             | 23 (7)                         | 16 (4)                          | 13 (5)                       | 0                               |            |
| <b>LTOT usage %</b>                                | 87.0                           | 91.3                            | 78.9                         | 64                              |            |
| <b>Baseline haemodynamics</b>                      |                                |                                 |                              |                                 |            |
| mPAP mmHg                                          | 46±7                           | 48±8                            | 49±10                        | 46±8                            | 0.488      |
| RAP mmHg                                           | 7±4                            | 9±5                             | 8±4                          | 10±6 <sup>#</sup>               | 0.098      |
| Cardiac index L·min <sup>-1</sup> ·m <sup>-2</sup> | 1.9±0.4                        | 1.8±0.4 <sup>¶</sup>            | 2.1±0.6 <sup>+</sup>         | 1.9±0.5 <sup>§</sup>            | 0.176      |
| PVR Wood units                                     | 12.2±4                         | 12.9±4                          | 11.8±5                       | 10.0±3                          | 0.143      |
| PAWP mmHg                                          | 8±3                            | 8±3                             | 9±3                          | 9±3                             | 0.373      |
| SvO <sub>2</sub>                                   | 60.9±11 <sup>f</sup>           | 58.8±11 <sup>¶</sup>            | 58.8±9 <sup>##</sup>         | 61.6±9 <sup>§</sup>             | 0.679      |
| <b>Initial PH therapy</b>                          |                                |                                 |                              |                                 |            |
| CCB                                                | 0                              | 0                               | 5.0 (2)                      | 4.5 (1)                         |            |
| PDE-5 inhibitor                                    | 71.0 (22)                      | 60 (15)                         | 65.0 (26)                    | 72.7 (16)                       |            |
| ERA                                                | 19.4 (6)                       | 24 (6)                          | 25.0 (10)                    | 22.7 (5)                        |            |
| Prostanoid                                         | 6.5 (2)                        | 4 (1)                           | 5.0 (2)                      | 0                               |            |
| Combination                                        | 3.2 (1)                        | 12 (3)                          | 0                            | 0                               |            |
| <b>Lung function</b>                               |                                |                                 |                              |                                 |            |
| FEV <sub>1</sub> % pred                            | 99±17                          | 81±22                           | 56±16                        | 78±19                           | <0.0001*** |
| FVC % pred                                         | 117 (105–139)                  | 101 (86–124)                    | 84 (76–97)                   | 74 (65–92)                      | <0.0001*** |
| FEV <sub>1</sub> /FVC %                            | 65±10                          | 62±9                            | 53±11                        | 79±12                           | <0.0001*** |
| TLC %                                              | 102±14 <sup>¶¶</sup>           | 89±15 <sup>++</sup>             | 95±15 <sup>§§</sup>          | 74±17 <sup>fff</sup>            | <0.0001*** |
| D <sub>LCO</sub> % pred                            | 26±9 <sup>###</sup>            | 21±7 <sup>¶¶¶</sup>             | 30±13 <sup>§§§</sup>         | 28±11                           | 0.029*     |
| P <sub>aO<sub>2</sub></sub> kPa                    | 7.0±2.1 <sup>¶¶¶</sup>         | 7.0±0.8 <sup>+++</sup>          | 7.6±1.4 <sup>###</sup>       | 7.6±1.7                         | 0.530      |
| P <sub>aCO<sub>2</sub></sub> kPa                   | 3.7±0.6 <sup>¶¶¶</sup>         | 3.9±0.4 <sup>+++</sup>          | 4.2 ± 0.6 <sup>###</sup>     | 4.3±0.7                         | 0.006**    |
| <b>NYHA functional class</b>                       |                                |                                 |                              |                                 |            |
| I/II                                               | 3.2 (1)                        | 0                               | 20.0 (8)                     | 19 (4)                          | 0.084      |
| III                                                | 80.6 (25)                      | 79.2 (19)                       | 62.5 (25)                    | 57.1 (12)                       |            |
| IV                                                 | 16.1 (5)                       | 20.8 (5)                        | 12.5 (5)                     | 23.8 (5)                        |            |
| <b>6MWD m</b>                                      | 224±99 <sup>++</sup>           | 174±78 <sup>§§§</sup>           | 216±110 <sup>##</sup>        | 184±132 <sup>#</sup>            | 0.325      |
| <b>NT-proBNP pg·mL<sup>-1</sup></b>                | 1447 (753–3881) <sup>¶¶¶</sup> | 2272 (1203–6384) <sup>¶¶¶</sup> | 2169 (769–3919) <sup>f</sup> | 2474 (1229–4115) <sup>fff</sup> | 0.638      |

Data are presented as n, mean±SD, % (n) or median (interquartile range), unless otherwise stated. p-values are Chi-squared, ANOVA or Kruskal-Wallis, depending on data distribution. CPFE: combined pulmonary fibrosis and emphysema; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; LTOT: long-term oxygen therapy; mPAP: mean pulmonary arterial pressure; RAP: right atrial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure; SvO<sub>2</sub>: mixed venous oxygen saturation; PH: pulmonary hypertension; CCB: calcium-channel blocker; PDE: phosphodiesterase; ERA: endothelin receptor antagonists; FEV<sub>1</sub>: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; D<sub>LCO</sub>: diffusing capacity of the lung for carbon monoxide; P<sub>aO<sub>2</sub></sub>: arterial oxygen tension; P<sub>aCO<sub>2</sub></sub>: arterial carbon dioxide tension; NYHA: New York Heart Association; 6MWD: 6-min walking distance; NT-proBNP: N-terminal pro-brain natriuretic peptide. #: n=21; ¶: n=24; +: n=39; §: n=19; f: n=29; ##: n=35; ¶¶: n=27; ++: n=23; §§: n=31; fff: n=16; ###: n=28; ¶¶¶: n=22; +++: n=15; §§§: n=20; fff: n=17. \*: p<0.05; \*\*: p<0.01; \*\*\*: p<0.001.

emphysema on CT, but preserved FEV<sub>1</sub> (>80% pred) and were excluded, as this group was not considered by this classification. 32 patients met the criteria for severe PH/mild lung disease and 56 patients were classified as having severe PH/severe lung disease (severe PH-CPFE n=22, severe PH-COPD n=24 and severe PH-ILD n=10).

**Prognostic indicators and survival**

28 patients (IPAH n=9, COPD n=3, CPFE n=5, ILD n=2 and emphysema n=9) were unable to perform 6MWD at diagnosis. 18 patients died prior to their first follow-up (IPAH n=4, emphysema n=4, CPFE n=1, ILD n=6, COPD n=3). Of these, nine were unable to walk at diagnosis. Median time to follow-up did not differ between IPAH and lung disease groups (111 (97–150) days versus 111 (96–148) days, p=0.888). In the IPAH group there were 25 deaths, and two patients underwent lung transplantation during the follow-up period, compared with 81 deaths in those with lung disease (CPFE n=19, ILD n=15, emphysema n=23 and COPD n=24). Survival was worse in those with lung disease. 1- and 3-year estimated survival rates in lung disease compared to IPAH were 76.3% versus 90.3% and 38.8% versus 72%, respectively (p<0.0001). The presence of lung disease remained an independent predictor when the

older age of this cohort in comparison to IPAH patients was considered using multivariate analysis ( $p=0.009$ ). Survival between lung phenotypes after age adjustment was not significantly different, with the exception of ILD patients, where survival was worse. There was no significant difference in survival between those meeting the criteria suggested by SEEGER *et al.* [10] for those with severe PH/mild lung disease *versus* those with severe PH/severe lung disease, with the exception of severe PH-ILD where survival was poorer. Kaplan–Meier survival curves are shown in online supplementary figures S1 and S2.

#### **Baseline predictors of survival**

When modelled with age, DLCO and PVR, right atrial pressure (RAP), cardiac index and sex were independent predictors of survival in the lung disease cohort. In IPAH, DLCO, male sex and 6MWD were found to be a predictors (table 3). The coding variable for missing 6MWD was also an independent predictor of survival in those with lung disease (hazard ratio (HR) 2.17, 95% CI 1.199–3.929;  $p=0.010$ ), suggesting that the inability to perform 6MWD is a prognostic variable.

Univariate analysis of the lung phenotypes is shown in online supplementary table S1. In a model with age, mPAP and cardiac index, RAP was an independent predictor of survival in the emphysema cohort (HR 1.423, 95% CI 1.063–1.742;  $p=0.001$ ). Comparative analysis of survivors and nonsurvivors at 3 years is presented in online supplementary table S2.

#### **Cardiac MRI**

Cardiac MRI data were available for 55 patients with lung disease (COPD  $n=14$ , ILD  $n=8$ , CPFE  $n=15$ , emphysema  $n=18$ ) and 35 IPAH patients. There were no significant differences between right and left ventricular function between the two groups (online supplementary table S3). Lung disease patients were older (66 *versus* 48 years,  $p<0.0001$ ) with a more significant smoking history (51 out of 55 previous smokers *versus* 11 out of 35).

In those with lung disease, right ventricular (RV) function was reduced (RV ejection fraction (RVEF)  $33 \pm 13\%$ ) with increased RV volumes and RV mass index (RVMI) ( $92 \pm 30 \text{ mL}\cdot\text{m}^{-2}$  and  $50 (39\text{--}59) \text{ g}\cdot\text{m}^{-2}$ , respectively). NT-proBNP moderately correlated with RVEF ( $r=-0.653$ ,  $p<0.0001$ ) and weakly with RV end-diastolic volume (RVEDV) ( $r=0.422$ ,  $p=0.003$ ). There were no significant correlations between lung function and RV or left ventricular function.

Univariate Cox regression of cardiac MRI indices with adjustment for age is shown in table 4. RVMI and stroke volume remained independent predictors of survival on multivariate analysis in a model with mPAP, RAP, age and sex (HR 1.026, 95% CI 1.002–1.051;  $p=0.033$  and HR 0.908, 95% CI 0.857–0.962;  $p=0.001$ , respectively). Excluding those with ILD, who were more commonly nonsmokers with less cardiovascular risk, left ventricular ejection fraction (LVEF) (HR 0.965, 95% CI 0.933–0.984;  $p=0.037$ ), stroke volume (HR 0.908, 95% CI 0.851–0.969;  $p=0.003$ ) and RVMI (HR 1.028, 95% CI 1.003–1.054;  $p=0.028$ ) were independent predictors of survival (online supplementary table S4).

#### **NT-proBNP and 6MWD at 3 months**

Kaplan–Meier survival curves were derived according to the median 6MWD and NT-proBNP at follow-up for patients with lung disease (online supplementary figure S3). Patients unable to perform a 6-min walk test (6MWT) despite treatment had significantly worse survival (1-year survival 97.2% *versus* 87.1% *versus* 58.3% and 3-year survival 56.7% *versus* 48.2% *versus* 20.8% in those with 6MWD  $>231 \text{ m}$ ,  $\leq 231 \text{ m}$  and unable to perform 6MWT, respectively;  $p=0.001$  and  $p=0.003$ ). A level of NT-proBNP  $<1449 \text{ pg}\cdot\text{mL}^{-1}$  in the lung disease group was associated with improved survival (1-year survival 95.0% *versus* 78.9% and 3-year survival 65.8% *versus* 23.6%;  $p<0.0001$ ).

#### **Treatment response**

There were significant improvements in 6MWD and NT-proBNP in the IPAH group. No improvements were observed in 6MWD or NYHA functional class for lung disease patients; however NT-proBNP decreased ( $2200 (850\text{--}4122) \text{ pg}\cdot\text{mL}^{-1}$  to  $1596 (614\text{--}3180) \text{ pg}\cdot\text{mL}^{-1}$ ;  $p=0.015$ ). Baseline and follow-up variables for each group are shown in table 5. Figure 2 shows the change in NT-proBNP and 6MWD with treatment for each cohort. In a model with age, sex, baseline RAP, cardiac index and mPAP, change in NT-proBNP but not 6MWD independently predicted survival in the lung disease group only (HR 1.508, 95% CI 1.062–2.142;  $p=0.022$ ).

Exercise oxygen saturation data were available for 47 patients with lung disease. No increase in desaturation upon exercise following PH therapy was observed ( $-8 (-30\text{--}-6)\%$  to  $-9 (-15\text{--}-6)\%$ ,  $p=0.834$ ).

TABLE 3 Cox regression survival analysis to identify predictors of survival in patients with severe pulmonary hypertension and lung disease in comparison to those with idiopathic pulmonary arterial hypertension (IPAH)

|                               | Univariate model           |                   |                            |                   | Multivariate model         |              |                            |              |
|-------------------------------|----------------------------|-------------------|----------------------------|-------------------|----------------------------|--------------|----------------------------|--------------|
|                               | IPAH                       | p-value           | Lung disease               | p-value           | IPAH                       | p-value      | Lung disease               | p-value      |
| <b>Age</b>                    | <b>1.047 (1.002–1.074)</b> | <b>0.001</b>      | <b>1.042 (1.016–1.069)</b> | <b>0.001</b>      | 1.012 (0.981–1.043)        | 0.460        | 1.020 (0.992–1.049)        | 0.161        |
| <b>Sex</b>                    | 0.911 (0.383–2.165)        | 0.833             | <b>0.682 (0.392–0.986)</b> | <b>0.043</b>      | <b>0.339 (0.120–0.952)</b> | <b>0.040</b> | <b>0.564 (0.340–0.934)</b> | <b>0.026</b> |
| <b>6MWD</b>                   | <b>0.994 (0.990–0.998)</b> | <b>0.003</b>      | <b>0.997 (0.994–0.999)</b> | <b>0.007</b>      | <b>0.994 (0.998–0.999)</b> | <b>0.020</b> |                            |              |
| <b>NT-proBNP</b>              | 1.066 (0.756–1.503)        | 0.717             | <b>1.349 (1.179–1.882)</b> | <b>0.001</b>      |                            |              |                            |              |
| <b>Haemodynamic variables</b> |                            |                   |                            |                   |                            |              |                            |              |
| mPAP                          | 1.005 (0.976–1.034)        | 0.744             | 0.830 (0.961–1.007)        | 0.166             |                            |              |                            |              |
| RAP                           | 1.006 (0.942–1.075)        | 0.855             | <b>1.091 (1.047–1.138)</b> | <b>&lt;0.0001</b> |                            |              | <b>1.084 (1.027–1.145)</b> | <b>0.004</b> |
| PVR                           | 1.009 (0.950–1.072)        | 0.767             | 1.030 (0.985–1.078)        | 0.194             | 1.036 (0.964–1.113)        | 0.335        | 0.971 (0.905–1.041)        | 0.404        |
| Cardiac index                 | 0.912 (0.436–1.905)        | 0.805             | <b>0.294 (0.171–0.507)</b> | <b>&lt;0.0001</b> |                            |              | <b>0.349 (0.169–0.724)</b> | <b>0.005</b> |
| PAWP                          | 0.964 (0.872–1.066)        | 0.477             | 0.997 (0.929–1.069)        | 0.926             |                            |              |                            |              |
| SvO <sub>2</sub>              | 0.989 (0.948–1.032)        | 0.605             | <b>0.974 (0.954–0.996)</b> | <b>0.023</b>      |                            |              |                            |              |
| <b>Lung function</b>          |                            |                   |                            |                   |                            |              |                            |              |
| D <sub>LCO</sub>              | <b>0.954 (0.934–0.975)</b> | <b>&lt;0.0001</b> | <b>0.974 (0.953–0.996)</b> | <b>0.021</b>      | <b>0.966 (0.941–0.992)</b> | <b>0.011</b> | 0.978 (0.954–1.003)        | 0.084        |
| P <sub>aO<sub>2</sub></sub>   | 0.808 (0.597–1.094)        | 0.168             | 0.808 (0.643–1.014)        | 0.065             |                            |              |                            |              |
| FEV <sub>1</sub>              | 1.003 (0.968–1.038)        | 0.879             | 1.004 (0.995–1.012)        | 0.368             |                            |              |                            |              |
| FEV <sub>1</sub> /FVC         | 0.923 (0.873–0.997)        | 0.006             | <b>1.022 (1.003–1.041)</b> | <b>0.022</b>      |                            |              |                            |              |

Data are presented as hazard ratio (95% CI), unless otherwise stated. Bold type represents statistically significant predictors of survival. 6MWD: 6-min walking distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; mPAP: mean pulmonary arterial pressure; RAP: right atrial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure; SvO<sub>2</sub>: mixed venous oxygen saturation; D<sub>LCO</sub>: diffusing capacity of the lung for carbon monoxide; P<sub>aO<sub>2</sub></sub>: arterial oxygen tension; FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity.

TABLE 4 Cox proportional hazard regression analysis of cardiac magnetic resonance imaging indices of right and left ventricular function in patients with severe pulmonary hypertension and lung disease

|                                        | Univariate model    | p-value | Multivariate model <sup>#</sup> | p-value |
|----------------------------------------|---------------------|---------|---------------------------------|---------|
| <b>RVEF %</b>                          | 0.925 (0.890–0.962) | <0.001  |                                 |         |
| <b>LVEF %</b>                          | 0.969 (0.944–0.994) | 0.017   |                                 |         |
| <b>Stroke volume mL·m<sup>-2</sup></b> | 0.920 (0.873–0.970) | 0.002   | 0.908 (0.857–0.962)             | 0.001   |
| <b>RVESV mL·m<sup>-2</sup></b>         | 1.022 (1.009–1.036) | 0.001   |                                 |         |
| <b>RVEDV mL·m<sup>-2</sup></b>         | 1.016 (1.004–1.029) | 0.009   |                                 |         |
| <b>LVEDV mL·m<sup>-2</sup></b>         | 0.992 (0.970–1.014) | 0.484   |                                 |         |
| <b>RVMI g·m<sup>-2</sup></b>           | 1.032 (1.011–1.054) | 0.003   | 1.026 (1.002–1.051)             | 0.033   |
| <b>LVMI g·m<sup>-2</sup></b>           | 1.004 (0.979–1.029) | 0.760   |                                 |         |

Data are presented as hazard ratio (95% CI), unless otherwise stated. RVEF: right ventricular ejection fraction; LVEF: left ventricular ejection fraction; RVESV: right ventricular end-systolic volume; RVEDV: right ventricular end-diastolic volume; LVEDV: left ventricular end-diastolic volume; RVMI: right ventricular mass index; LVMI: left ventricular mass index. <sup>#</sup>: with age, sex, right atrial pressure and mean pulmonary arterial pressure.

## Discussion

We report the characteristics, survival and response to pulmonary vasodilator therapy in four distinct lung disease phenotypes with severe PH and compare this with a group of patients with IPAH. During the 14-year study period, more patients with coexistent lung disease than pure IPAH were seen. This could possibly be explained by the large proportion of smokers (68%) and older age of the study population (mean age 60 years). The demographics of incident IPAH cases has shown a trend towards increasing age at diagnosis, and increasing presence of comorbid diseases in PH registries [23]. In the REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) study up to 17% of PAH diagnoses had coexistent COPD [24]. This highlights the importance of assessing the impact of coexistent lung disease on PH therapy in efforts to develop management strategies for “real-life” patients, many of which are excluded in drug trials. Severe PH in lung disease patients described by our study demonstrated severe hypoxaemia, grossly impaired DLCO, relatively mild airflow obstruction and more severe functional impairment measured by NYHA functional class and 6MWD than IPAH patients, despite similar haemodynamics. Similar characteristics have previously been reported in patients with COPD and severe PH [2, 19]. A recent case series of three male smokers described a severe PH and emphysema phenotype with preserved lung volumes and impaired DLCO [25]. NT-proBNP was higher in the lung disease group than IPAH despite similar haemodynamics. Furthermore, RVMI was higher in those with IPAH than lung disease patients. This could suggest a greater degree of right ventricular dysfunction and impaired adaptation to afterload in lung disease patients. There was no significant difference in renal function to account for the higher NT-proBNP (Modification of Diet in Renal Disease estimated glomerular filtration rate 63 (51–82) mL·min<sup>-1</sup>·1.73m<sup>-2</sup> versus 71 (53–82) mL·min<sup>-1</sup>·1.73m<sup>-2</sup>, p=0.340). Lung disease patients were significantly older (67 versus 49 years) and NT-proBNP has been shown to increase with age, by 36% in men and 15% in females per 8.4 years in one study [26]. PVR was higher (and therefore so was RV afterload) in the IPAH patients who underwent MRI, and therefore we would expect a greater degree of RV adaptation. Additionally, RVMI has been shown to fall with age: a 5% reduction per decade of age has been shown [27]. Differences in the demographics of the populations may therefore account for the apparent difference in NT-proBNP and RVMI. Our study describes the largest treated population of patients with severe PH in lung disease and further explores the impact of lung disease phenotype on outcome. Suggested mechanisms leading to the development of PH include vascular ablation, excessive hypoxic pulmonary vasoconstriction, pulmonary artery remodelling and endothelial dysfunction from inflammation and exposure to cigarette smoke [28]. One hypothesis may be that the emphysema phenotype described in this study demonstrated a poorer response to therapy because the pathophysiology may relate more to vascular loss than potentially treatment-responsive vascular dysfunction.

Survival in those with lung disease was worse, in comparison to IPAH, despite age adjustment. ILD patients displayed poorer survival in comparison to other lung phenotypes, with six out of 22 patients dying prior to the first follow-up assessment. We have identified sex, the inability to perform a 6MWT, cardiac index and RAP as independent predictors of survival in severe PH with lung disease. In the subset that underwent cardiac MRI, stroke volume and RVMI were independent predictors of survival.

Our results show that despite similar baseline haemodynamics, patients with severe PH and lung disease in comparison to IPAH do not respond to treatment with PH therapy when outcome measures such as

TABLE 5 Baseline and follow-up variables after a minimum of 3 months of pulmonary hypertension (PH) therapy for each group

|                                      | Subjects | Baseline         | Follow-up                    | p-value    |
|--------------------------------------|----------|------------------|------------------------------|------------|
| <b>IPAH</b>                          |          |                  |                              |            |
| 6MWD m                               | 58       | 337±114          | 376±97                       | <0.0001*** |
| NT-proBNP pg·mL <sup>-1</sup>        | 42       | 1085 (449–2545)  | 788 (289–1655)               | 0.001**    |
| NYHA functional class I+II/III/IV    |          | 17/4/1/4         | 30/29/3                      | 0.055      |
| <b>Lung disease (all)</b>            |          |                  |                              |            |
| 6MWD m                               | 75       | 226±101          | 242±103                      | 0.087      |
| NT-proBNP pg·mL <sup>-1</sup>        | 78       | 2200 (850–4122)  | 1596 (614–3180)              | 0.015*     |
| NYHA functional class I+II/III/IV    |          | 11/73/12         | 16/72/8                      | 0.421      |
| <b>COPD</b>                          |          |                  |                              |            |
| 6MWD m                               | 30       | 222±113          | 242±108                      | 0.113      |
| NT-proBNP pg·mL <sup>-1</sup>        | 26       | 2335 (562–4066)  | 1822 (411–3734)              | 0.094      |
| NYHA functional class I+II/III/IV    |          | 6/21/3           | 9/19/2                       | 0.638      |
| <b>CPFE</b>                          |          |                  |                              |            |
| 6MWD m                               | 16       | 191±70           | 230±94                       | 0.103      |
| NT-proBNP pg·mL <sup>-1</sup>        | 21       | 2258 (1153–5992) | 2471 (461–3325) <sup>#</sup> | 0.015*     |
| NYHA functional class I+II/III/IV    |          | 0/19/4           | 1/20/2                       | 0.429      |
| <b>Emphysema</b>                     |          |                  |                              |            |
| 6MWD m                               | 19       | 237±102          | 224±88                       | 0.575      |
| NT-proBNP pg·mL <sup>-1</sup>        | 19       | 1378 (440–3881)  | 1449 (663–3082)              | 0.365      |
| NYHA functional class I+II/III/IV    |          | 1/23/3           | 1/24/2                       | 0.895      |
| <b>ILD</b>                           |          |                  |                              |            |
| 6MWD m                               | 10       | 275±92           | 295±123                      | 0.324      |
| NT-proBNP pg·mL <sup>-1</sup>        | 12       | 2466 (1028–3991) | 1068 (710–2837)              | 0.021*     |
| NYHA functional class I+II/III/IV    |          | 4/10/2           | 5/9/2                        | 0.921      |
| <b>Severe PH/mild lung disease</b>   |          |                  |                              |            |
| 6MWD m                               | 22       | 255±109          | 259±118                      | 0.788      |
| NT-proBNP pg·mL <sup>-1</sup>        | 20       | 1852 (645–5594)  | 2073(599–3308)               | 0.110      |
| NYHA functional class I+II/III/IV    |          | 6/19/4           | 6/19/4                       | 0.943      |
| <b>Severe PH/severe lung disease</b> |          |                  |                              |            |
| 6MWD m                               | 56       | 185±85           | 216±100                      | 0.021*     |
| NT-proBNP pg·mL <sup>-1</sup>        | 35       | 2457 (1229–5992) | 1831 (580–3943)              | 0.005**    |
| NYHA functional class I+II/III/IV    | 41       | 2/36/8           | 7/36/3                       | 0.08       |

Data are presented as n, mean±SD or median (interquartile range), unless otherwise stated. IPAH: idiopathic pulmonary arterial hypertension; 6MWD: 6-min walking distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; CPFE: combined pulmonary fibrosis and emphysema syndrome; ILD: interstitial lung disease. <sup>#</sup>: in CPFE, while median NT-proBNP increased, a reduction in NT-proBNP was seen in 14 out of 21 cases, median change in NT-proBNP  $-596$  pg·mL<sup>-1</sup> and mean NT-proBNP decreased from  $4543\pm7426$  to  $3002\pm3850$  pg·mL<sup>-1</sup>. The increase in median values probably reflects nonparametric distribution. \*: p<0.05; \*\*: p<0.01; \*\*\*: p<0.001.

6MWD or NYHA functional class are considered; however, improvement in NT-proBNP was demonstrated. The response to therapy differs between lung phenotype groups. Those with emphysema and preserved FEV<sub>1</sub> showed no improvement in any outcome measure, and perhaps displayed evidence of deterioration in the 3-month observation period with a nonsignificant fall in 6MWD. ILD patients had the worst survival, although a reduction in NT-proBNP was demonstrated, albeit in a small population. Those with CPFE showed significant decreases in NT-proBNP. Survival analysis suggested that NT-proBNP may be a better outcome measure than 6MWD in those with lung disease where exercise capacity will be ventilatory-limited in addition to cardiovascular limitation. The negative correlation observed between FEV<sub>1</sub> and 6MWD in those with COPD could support this ventilatory limitation [29]. Surprisingly, using the classification suggested by SEEGER *et al.* [10], no difference in survival was suggested between those with severe PH/mild lung disease and severe PH/severe lung disease groups, with the exception of severe PH-ILD, which similarly to the overall ILD cohort showed poor survival. In addition, those with severe-PH/severe lung disease demonstrated improvements in both 6MWD and NT-proBNP with therapy whereas those who were classified as having co-existent mild lung disease did not.

NT-proBNP correlated with RVEF and RVEDV, so we can speculate that disease-targeted therapy may lead to improved outcome in those with improved RV function. Reduced LVEF as a prognostic variable in

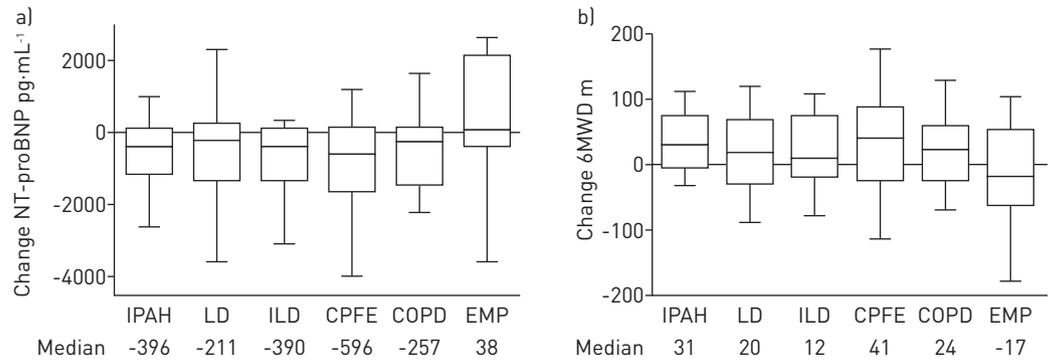


FIGURE 2 a) Change in N-terminal pro-brain natriuretic peptide (NT-proBNP) following 3 months of pulmonary hypertension (PH) therapy by group. No significant difference was observed between groups; b) change in 6-min walking distance (6MWD) following 3 months of PH therapy. There was no significant difference between lung disease (LD) and idiopathic pulmonary arterial hypertension (IPAH) or across lung phenotypes seen. Data are presented as median and Tukey hinges. ILD: interstitial lung disease; CPFE: combined pulmonary fibrosis and emphysema syndrome; COPD: chronic obstructive pulmonary disease; EMP: emphysema.

severe PH with lung disease occurred without clinical left ventricular dysfunction and normal PAWP. Evidence of subclinical left ventricular dysfunction on echocardiogram has been reported in COPD [30] alongside increased risk of cardiovascular abnormalities including increased arterial stiffness [31–33], ischaemic heart disease and heart failure. Left ventricular dysfunction has been shown to relate to fat-free mass and interleukin-6 linking to the catabolic-inflammatory COPD phenotype and increased arterial stiffness [30]. 51 out of 55 patients who underwent cardiac MRI were smokers with an average 40 pack-year history. Smoking has been shown to have acute effects on aortic pulse wave velocity (a measure of vascular stiffness) [34] and left ventricular function [35].

The ASPIRE registry reported similar 1-year but worse 3-year survival rates of 70% and 33%, respectively, compared to 79% and 47%, respectively, in our cohort (ILD excluded). 43 out of 59 patients received PH therapy and were of similar age to our cohort, but had a greater degree of pulmonary function impairment (FEV<sub>1</sub> 65% pred) and included patients with elevated PAWP. In addition they defined severe PH as mPAP  $\geq$ 40 mmHg. ASPIRE reported mixed venous oxygen saturation, age, NYHA functional class IV and DLCO as independent predictors of survival, but included patients with mild and moderate PH in survival analysis [19]. Direct comparison with our cohort is therefore not possible. COTTIN *et al.* [36] reported outcomes of 40 patients with PH in CPFE syndrome, of whom 24 (60%) received PH therapy. They reported no improvement in 6MWD, echocardiogram-derived pulmonary artery systolic pressure or NYHA functional class. Survival was significantly worse than reported here, with 1-year survival of only 60%. Similar to ASPIRE, they included patients with mild-to-moderate PH (mPAP 24–56 mmHg), but found that higher PVR, lower cardiac index and DLCO predicted worse survival.

There is no evidence in the literature to support the use of pulmonary vasodilators in severe PH with lung disease. Previous studies have been of small sample size, did not always include RHC-derived mPAP and included patients with mild or even no PH [16, 18, 37]. Bosentan treatment for 12 weeks in 30 patients with severe COPD (six of whom had PH on echocardiography) showed no functional benefit [18]. Similarly, a 12-week trial of sildenafil in 15 severe COPD patients (nine with PH) found no improvement in exercise capacity [16]. BLANCO *et al.* [38] demonstrated a fall in mPAP following acute administration of sildenafil in 20 COPD patients with mPAP >20 mmHg (or >30 mmHg on exercise) at RHC, but also demonstrated a fall in arterial oxygen tension ( $P_{aO_2}$ ) due to increased ventilation–perfusion mismatch. We did not demonstrate a deterioration in oxygen desaturation on 6MWT, although this should be interpreted with caution given the retrospective analysis of these data. The lack of demonstrated improvement in 6MWD in those with lung disease may suggest lack of efficacy of treatment. We did not demonstrate a survival benefit in those who improved 6MWD on treatment. This should be interpreted with caution as it may be that these patients were more ventilatory-limited so an alternative end-point should be used to determine efficacy. It is also possible that treatment led to a stabilisation of the clinical condition, as 6MWD did not fall at 3 months. A prospective trial with an untreated control arm could investigate this possibility further.

Improvement in NT-proBNP, a marker of RV dysfunction, is encouraging. Previous studies have not used this biomarker as outcome measure in PH associated with lung disease. In IPAH, NT-proBNP has been shown to correlate with RV function [39] and changes in serial NT-proBNP with treatment have been shown to predict survival [40]. In COPD, NT-proBNP has been shown to predict outcome following acute

exacerbations of airways disease [41–43], identify those with concurrent left ventricular dysfunction [42, 44] and function as a screening tool for PH in COPD [45]. Our study demonstrates that NT-proBNP reflects RV dysfunction in severe PH lung disease patients, predicts survival on univariate analysis and, in addition, change in NT-proBNP predicted survival. This may reflect improvement in RV function, and be a useful marker of therapy response in future studies.

Our study has several limitations. This was a single-centre retrospective observational study which allowed for variation in therapy used for each cohort, and the numbers of patients in each lung disease phenotype were small. In addition, there was no control arm with severe PH and lung disease that did not receive therapy to contrast outcomes. Additionally, the CT evidence of lung disease was based on the multidisciplinary report. It was not possible to score the severity of emphysema on CT.

### Conclusion

In comparison to IPAH patients, patients with severe PH associated with lung disease had poorer survival, which was driven by the ILD cohort and not abolished by adjusting for age. PH therapy did not lead to improvements in NYHA functional class or 6MWD; however, a reduction in NT-proBNP was seen. Survival and response to therapy may vary according to lung phenotype. Further studies with an untreated control group may establish if PH therapy has a role in delaying the progression of the pulmonary hypertension and improving survival.

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