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Phosphodiesterase 5 inhibitor treatment and survival in interstitial lung disease pulmonary hypertension: A Bayesian retrospective observational cohort study

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Abstract

Background and Objective: Pulmonary hypertension is a life-limiting complication of interstitial lung disease (ILD-PH). We investigated whether treatment with phosphodiesterase 5 inhibitors (PDE5i) in patients with ILD-PH was associated with improved survival.

Methods: Consecutive incident patients with ILD-PH and right heart catheterisation, echocardiography and spirometry data were followed from diagnosis to death, transplantation or censoring with all follow-up and survival data modelled by Bayesian methods.

Results: The diagnoses in 128 patients were idiopathic pulmonary fibrosis ($n = 74$, 58%), hypersensitivity pneumonitis ($n = 17$, 13%), non-specific interstitial pneumonia ($n = 12$, 9%), undifferentiated ILD ($n = 8$, 6%) and other lung diseases ($n = 17$, 13%). Final outcomes were death ($n = 106$, 83%), transplantation ($n = 9$, 7%) and censoring ($n = 13$, 10%). Patients treated with PDE5i ($n = 50$, 39%) had higher mean pulmonary artery pressure (median 38 mm Hg [interquartile range, IQR: 34, 43] vs. 35 mm Hg [IQR: 31, 38], $p = 0.07$) and percentage predicted forced vital capacity (FVC; median 57% [IQR: 51, 73] vs. 52% [IQR: 45, 66], p=0.08) though differences did not reach significance. Patients treated with PDE5i survived longer than untreated patients (median 2.18 years [95% CI: 1.43, 3.04] vs. 0.94 years [0.69, 1.51], $p = 0.003$) independent of all other prognostic markers by Bayesian joint-modelling (HR 0.39, 95% CI: 0.23, 0.59, $p < 0.001$) and propensity-matched analyses (HR 0.38, 95% CI: 0.22, 0.58, $p < 0.001$). Survival difference with treatment was significantly larger if right ventricular function was normal, rather than abnormal, at presentation (+2.55 years, 95% CI: −0.03, +3.97 vs. +0.98 years, 95% CI: +0.47, +2.00, $p = 0.04$).

Conclusion: PDE5i treatment in ILD-PH should be investigated by a prospective randomized trial.

KEYWORDS

Bayesian retrospective observational cohort study, interstitial lung disease, PDE5i, phosphodiesterase 5 inhibitor, pulmonary circulation and pulmonary hypertension

Stephen J. Wort and Laura C. Price contributed equally to this study.

This study was previously presented at the European Respiratory Society (ERS) International Congress 2021.

INTRODUCTION

In patients with interstitial lung disease, pulmonary hypertension (ILD-PH) is a common complication linked to exercise limitation and poor prognosis.[1] The success of pulmonary vasodilators in pulmonary arterial hypertension has encouraged therapeutic trials of pulmonary vasodilator treatment in ILD-PH,[2,3] with a successful recent trial of inhaled treprostinil.[4] However, the benefits of oral pulmonary vasodilators have been inconsistent preventing their widespread use.[3,5–8] Identifying which patients benefit from which treatments is difficult because haemodynamic phenotyping is inconsistent, and long-term follow-up data are rare.[9]

Electronic health records are a rich source of long-term follow-up data prospectively acquired in healthcare with the potential to streamline research efficiency and costs. However, data are often incomplete, asynchronous and of poor quality. Bayesian modelling can accommodate these real-world problems with the potential for new, data-driven, clinical insights.[10] We used contemporary Bayesian statistical approaches to investigate whether treatment with phosphodiesterase 5 inhibitors (PDE5i) is associated with improved survival in patients with ILD-PH.

SUMMARY AT A GLANCE

Retrospective cohort data from well phenotyped patients suggests that treatment with a phosphodiesterase 5 inhibitor (PDE5i) is associated with improved survival in patients with interstitial lung disease and severe pulmonary hypertension (ILD-PH), particularly in those with normal right ventricular function at presentation. A randomized controlled trial of pulmonary vasodilator therapy in ILD-PH is warranted.

METHODS

This is a retrospective cohort study of consecutive incident patients referred to the Royal Brompton Hospital National Pulmonary Hypertension Service (London, UK). All patients diagnosed between 1 January 2000 and 6 December 2021 with ILD-PH confirmed by multi-disciplinary review, pulmonary function testing, transthoracic echocardiography and right heart catheterisation (RHC) were included.[11] Presentations consistent with connective tissue disease, sarcoidosis, pulmonary thromboembolic disease or left heart disease were excluded. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and the Reporting Of Bayes Used in clinical STudies (ROBUST) guidelines.[12,13]

Pulmonary function testing

All patients underwent pulmonary function testing using published predicted values.[14] Spirometric, single-breath transfer factor and transfer coefficient for the lung for carbon monoxide adjusted for alveolar volume (DLco) were measured by standardized protocols.[15,16] The Composite Physiologic Index (CPI) was calculated from DLco, percentage predicted forced vital capacity (FVC%) and percentage predicted forced expiratory volume in 1 second (FEV_1%) to estimate morphologic severity while accounting for confounding by emphysema and pulmonary hypertension.[17]

Computed tomography

To clarify the contributions of emphysematous and fibrotic disease, high-resolution computed tomography was used with 1 mm axial sections reconstructed at 10 mm intervals. Images were acquired at full inspiration with contrast administered by automated intravenous injection equipment with bolus tracking.

Right heart catheterisation

Haemodynamic measurements at rest were obtained by RHC using a balloon-tipped, flow-directed Swan-Ganz catheter (Baxter Healthcare, Irvine, CA). Mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP) were averaged over the resting respiratory cycle. Cardiac output (CO) was calculated using the indirect Fick method with oxygen consumption estimated using the LaFarge equation. Pulmonary vascular resistance (PVR) was calculated as (mPAP–PCWP)/CO. Vasodilator and oxygen trials were not conducted.

Echocardiography

Images were acquired using a Philip's IE 33 or EPIQ 7 machine and S5-1 (1–5 MHz) PureWave transducer with interpretation by advanced echocardiography trained cardiologists.[18,19] Right ventricular (RV) dysfunction was quantified by tricuspid annular plane systolic excursion (TAPSE), tissue Doppler S′ wave and fractional area change using published definitions.[20]

Treatment and additional testing

All patients were discussed by a multi-disciplinary team who reviewed clinical and serological data, spirometry, computed tomography and, in rare cases, bronchoalveolar lavage and histology. Echocardiographic findings suggestive of significant ILD-PH were followed-up with RHC to confirm the diagnosis. Oxygen, sleep disorders and diuretic therapies were optimized. Patients with confirmed severe ILD-PH (mPAP ≥35 mm Hg or ≥25 mm Hg with low cardiac index) who had not been entered into concurrent randomized trials[21,22] were offered sildenafil as first-line treatment, or

tadalafil in the case of sildenafil intolerance. Doses were escalated after review in clinic.

Exercise tolerance, six-min walk distance (6MWD) and quality of life were assessed by World Health Organization functional class, American Thoracic Society guidelines and the emPHasis-10 questionnaire, respectively.[23,24]

Outcome measures

Patients were followed-up from initial diagnosis to death, with censoring at 1 March 2022 or cardiopulmonary transplantation. Outcomes were all-cause mortality (primary) and change in haemodynamic, echocardiographic and functional outcomes (secondary). Study size was determined by the cases available over the duration of the database.

Statistical analysis

Statistical methods are described in-depth in the Supplementary Statistical Analysis. Variables are reported as mean ± SD or median (inter-quartile range). To model the outcome of interest jointly with the missing data, a Bayesian joint-modelling approach was used.[25] To control for covariates, survival was modelled by a Bayesian Cox proportional hazards model including covariates with prognostic significance in ILD-PH (FVC,[26] diffusing capacity for carbon monoxide [DLco],[26,27] PVR[27,28]), pulmonary arterial hypertension (age,[29,30] gender[30]) or both (brain natriuretic peptide [BNP],[31–33] RV function,[34,35] 6MWD[27,36]) with an interaction term for treatment and RV function at presentation. To confirm the findings and to explore the benefits of integrating follow-up data into the analysis, Cox Proportional Hazards models using a propensity-matched cohort and using only baseline data were performed, respectively.

Baseline group characteristics were compared by two-way comparisons with a generalized linear model with link functions appropriate to the dependent variables' distributions. Follow-up data were modelled by Bayesian linear mixed models providing best estimates of physiological progression over time (fixed effect) and accommodating physiological variability at presentation (random intercept). The survival of patients with improvements in BNP, PVR, TAPSE or 6MWD after PDE5i treatment ("responders") was compared with patients in whom these markers were unchanged or deteriorated ("non-responders") at first follow-up and patients who were not treated with PDE5i.

RESULTS

Study population characteristics

In total, 932 consecutive incident patients with interstitial lung disease were referred for investigation to the Royal Brompton Hospital National Pulmonary Hypertension Service and evaluated for eligibility (Figure 1). Patients not deemed suitable for further investigation by RHC ($n = 473$), without echocardiography ($n = 397$) or spirometry ($n = 214$) data performed in the tertiary centre, or with connective tissue disease were excluded. After multi-disciplinary team confirmation of ILD-PH, data from 128 patients were

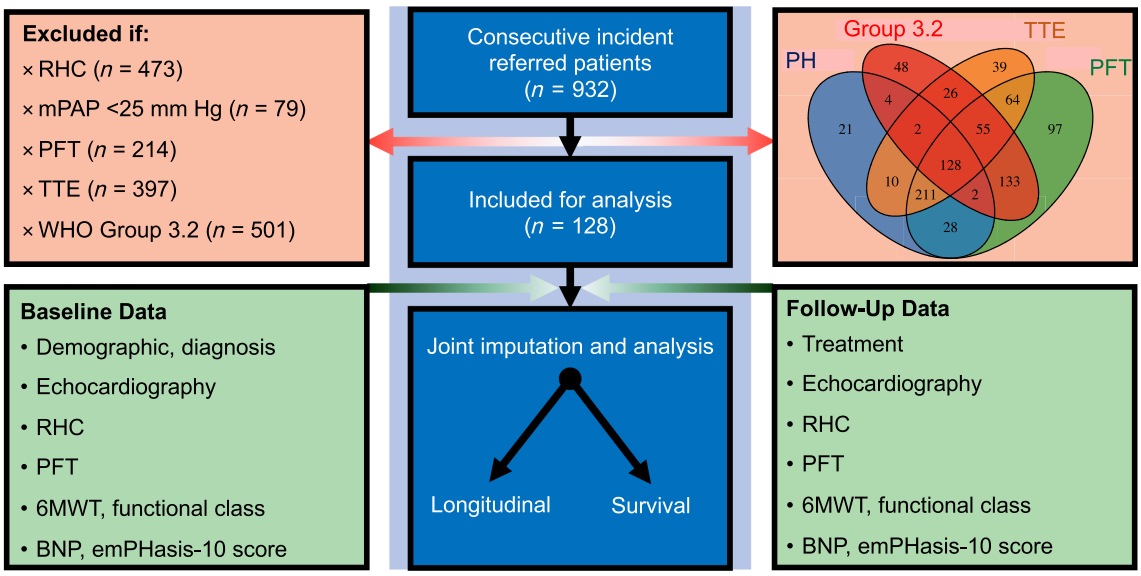

FIGURE 1 Flow diagram for inclusion of study subjects and data fields. Blue central column shows the workflow for identifying subjects and analysing data. Red boxes show the exclusion criteria (left) and Venn diagram of cases (right). Green boxes show the fields included for baseline (left) and follow-up (right) analysis. Imputation and analysis were jointly modelled for longitudinal and survival analyses. 6MWT, six-min walk test; BNP, brain natriuretic peptide; mPAP, mean pulmonary artery pressure; PFT, pulmonary function test; PH, pulmonary hypertension; RHC, right heart catheterisation; TTE, transthoracic echocardiogram; WHO, World Health Organization

TABLE 1 Baseline patient characteristics

Group/treatment	All		HP		IPF		NSIP		Other		Undifferentiated		p_{group}	$p_{treatment}$
Treated with PDE5i	+	−	+	−	+	−	+	−	+	−	+	−		
Number (%)	50 (47)	78 (53)	10 (8)	7 (5)	20 (16)	54 (42)	5 (4)	7 (5)	10 (8)	7 (5)	5 (4)	3 (2)	0.12	0.83
Demographics														
Age, years	64.8 ± 12.1	67.4 ± 10.3	63.5 ± 16.3	60.0 ± 10.8	67.7 ± 9.6	69.6 ± 8.1	58.3 ± 15.0	64.4 ± 8.4	64.7 ± 11.7	63.2 ± 15.1	62.9 ± 10.8	62.7 ± 25.4	0.40	0.83
Gender, F/M	29/21	58/20	3/7	4/3	16/4	43/11	2/3	3/4	5/5	6/1	3/2	2/1	0.93	0.06
BSA, m^2	1.95 ± 0.24	1.97 ± 0.26	1.90 ± 0.25	2.00 ± 0.18	2.02 ± 0.19	1.96 ± 0.24	1.96 ± 0.35	1.84 ± 0.25	1.97 ± 0.21	2.16 ± 0.39	1.69 ± 0.23	1.82 ± 0.30	0.02	0.38
Comorbidities 1	10/2/13	11/4/26	1/0/1	0/0/1	5/2/6	10/4/19	0/0/0	0/0/3	3/0/5	0/0/2	1/0/1	1/0/1	0.61/0.34/0.38	0.75/0.97/0.14
Comorbidities 2	7/5/11	6/4/20	0/0/3	1/0/0	5/2/3	5/3/16	0/0/2	0/0/1	2/3/3	0/1/2	0/0/0	0/0/1	0.52/0.18/0.97	0.82/0.77/0.76
Spirometry														
FEV_1, % predicted	59 (50–71)	55 (47–67)	57 (44–72)	51 (44–64)	64 (54–76)	58 (50–68)	47 (41–52)	55 (51–61)	58 (54–63)	42 (34–61)	58 (50–78)	46 (38–57)	0.43	0.10
FVC, % predicted	57 (51–73)	52 (45–66)	61 (49–74)	54 (47–71)	56 (52–76)	56 (46–66)	47 (41–48)	59 (53–67)	61 (55–69)	26 (25–49)	58 (60–73)	43 (37–50)	0.27	0.08
DLco, % predicted	25 (19–34)	26 (20–33)	24 (18–31)	27 (24–31)	28 (22–35)	25 (20–33)	22 (18–26)	27 (21–36)	28 (25–35)	24 (19–33)	17 (12–23)	23 (17–34)	0.24	0.38
CPI	62 ± 10	63 ± 10	61 ± 10	61 ± 7	60 ± 11	63 ± 9	67 ± 8	59 ± 9	59 ± 9	70 ± 15	67 ± 11	66 ± 11	0.59	0.64
Haemodynamics														
mPAP, mm Hg	38 (34–43)	35 (31–38)	38 (34–43)	34 (31–37)	38 (35–43)	35 (31–38)	37 (35–41)	35 (33–37)	38 (34–40)	37 (34–41)	41 (37–45)	37 (35–40)	0.63	0.07
PCWP, mm Hg	11 ± 5	10 ± 4	9 ± 3	9 ± 4	11 ± 4	10 ± 4	15 ± 10	10 ± 3	11 ± 3	11 ± 3	12 ± 4	10 ± 3	0.22	0.07
CO, L min^{-1}	4.1 (3.7–4.8)	4.3 (3.8–4.9)	4.0 (3.3–4.7)	4.5 (4.0–5.0)	4.2 (3.9–4.8)	4.3 (3.7–4.9)	4.3 (3.9–4.7)	4.1 (3.9–4.6)	4.1 (3.7–4.6)	4.4 (4.1–4.9)	3.9 (3.7–4.4)	4.2 (3.9–4.5)	0.97	0.37
PVR, WU	6.7 (5.7–8.5)	6.0 (4.8–7.8)	7.0 (6.1–8.8)	6.9 (5.9–8.1)	6.8 (5.8–8.3)	5.8 (4.6–7.6)	5.3 (4.9–7.1)	6.2 (5.4–7.4)	6.9 (5.7–8.1)	6.1 (5.2–7.5)	7.4 (6.4–9.0)	7.0 (6.3–8.0)	0.55	0.71
Echocardiography														
TAPSE, cm	1.7 ± 0.4	1.9 ± 0.4	1.6 ± 0.5	2.0 ± 0.7	1.7 ± 0.4	1.9 ± 0.4	1.6 ± 0.3	1.8 ± 0.3	1.8 ± 0.5	1.7 ± 0.3	1.7 ± 0.3	1.3 ± 0.4	0.27	0.53
Other														
WHO Functional Class, I/II/III/IV	0/8/33/9	0/10/45/23	0/1/6/3	0/1/5/1	0/4/12/4	0/7/34/13	0/1/3/1	0/1/3/3	0/2/8/0	0/1/3/3	0/0/4/1	0/0/1/2	0.82	0.66
6MWD, m	258 ± 92	222 ± 93	274 ± 99	248 ± 118	280 ± 97	220 ± 94	222 ± 85	222 ± 74	236 ± 79	226 ± 91	213 ± 82	196 ± 110	0.52	0.31
emPHasis-10	31 ± 7	31 ± 6	31 ± 7	27 ± 9	30 ± 7	31 ± 6	32 ± 6	30 ± 7	32 ± 7	34 ± 6	30 ± 6	35 ± 6	0.53	0.83
BNP, ng L^{-1}	135 (48–281)	72 (23–205)	120 (52–276)	36 (19–68)	211 (132–473)	72 (25–198)	35 (17–74)	45 (20–84)	63 (30–168)	107 (31–353)	491 (221–1230)	194 (77–336)	<0.001	0.09
Treatment														
LTOT/CPAP/NIV	38/4/6	53/2/13	8/0/0	5/0/1	16/1/1	37/2/10	3/1/1	5/0/0	7/2/4	5/0/1	4/0/0	1/0/1	0.50/0.33/0.24	0.64/0.97/0.50
Pirfenidone/Nintedanib	8/7	8/2	1/1	0/0	7/6	7/2	0/0	0/0	0/0	1/0	0/0	0/0	0.17/0.12	0.94/0.47
Prednisolone	32	64	9	4	11	47	4	5	6	6	2	2	0.14	0.76
Furos/Spiro/Bumet	24/25/9	34/17/2	5/4/0	1/1/0	10/11/4	25/13/2	2/2/0	3/1/0	6/7/5	3/1/0	1/1/0	2/1/0	0.74/0.65/0.12	0.21/0.38/0.71
ERA	7	9	1	0	4	5	0	4	2	0	0	0	0.93	0.13

Note: Data are presented as n, mean ± SD or median (interquartile range). Comorbidities 1: coronary artery disease/cerebrovascular disease/hypertension. Comorbidities 2: cancer/chronic kidney disease/diabetes. *p*-values show the significance of differences between diagnostic group membership (p_{group}) and PDE5i treatment ($p_{treatment}$).

Abbreviations: 6MWD, six-minute walk distance; BNP, brain natriuretic peptide; BSA, body surface area; CO, cardiac output; CPAP, continuous positive airway pressure; CPI, composite physiologic index; DLco, transfer factor for carbon monoxide; ERA, endothelin receptor antagonist; Furos/Spiro/Bumet, furosemide/spironolactone/bumetanide; HP, hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; LTOT, long-term oxygen therapy; mPAP, mean pulmonary artery pressure; NIV, non-invasive ventilation; NSIP, non-specific interstitial pneumonia; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization; WU, Wood units.

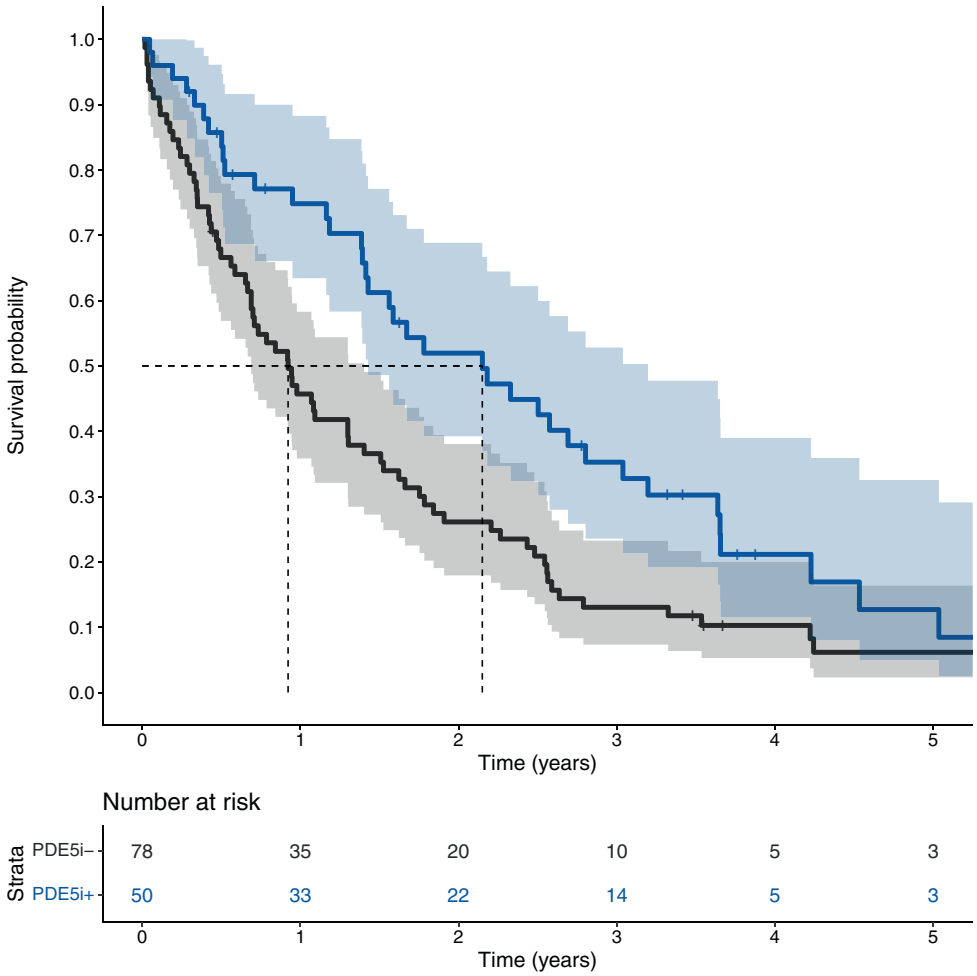

FIGURE 2 Kaplan–Meier plot showing the survival of patients treated with phosphodiesterase 5 inhibitors (PDE5i+, median survival 2.18 years [95% CI: 1.43, 3.04]) compared with patients not treated with phosphodiesterase 5 inhibitors (PDE5i−, median survival 0.94 years [95% CI: 0.69, 1.51], $p = 0.003$). Shaded regions and dotted lines denote 95% confidence intervals and median survival times, respectively. The included 'Number-at-risk' table shows group survival at 1-year intervals. CI, confidence interval; PDE5i±, treated/not-treated with phosphodiesterase 5 inhibitors

analysed, including 27 patients randomized in the B-PHIT study and one patient in the RISE-IIP study.[21,22]

All subjects had complete data describing survival, transplantation and treatment (Figure S1 in the Supporting Information). Haemodynamic, echocardiographic and functional data were complete in 90.9% (baseline) and 87.4% (follow-up) investigations. Imputation accuracy was acceptable in all variables included in the analysis (Figure S2 in the Supporting Information). Baseline data are described in Table 1. Patients were followed from diagnosis to death ($n = 106$, 83%), lung transplantation ($n = 9$, 7%) or censoring ($n = 13$, 10%) for a median of 1.17 years (interquartile range [IQR]: 0.44, 2.56).

After multi-disciplinary team review, the final diagnoses of idiopathic pulmonary fibrosis (IPF, $n = 74$, 58%), hypersensitivity pneumonitis ($n = 17$, 13%), non-specific interstitial pneumonia ($n = 12$, 9%), undifferentiated ($n = 8$, 6%) and other lung diseases ($n = 17$, 13%) were made. By Seeger's criteria (mPAP ≥ 35 mm Hg, or mPAP ≥ 25 mm Hg and cardiac index ≤2.0 L min^{-1} m^{-2}), 114 patients (89%) had severe pulmonary hypertension.[37] Eighty-four (66%) patients had echocardiographic RV dysfunction (Table S1 in the Supporting Information).

Sixty patients (46.9%) were trialled on pulmonary vasodilator treatment of whom 50 (39.1%) received PDE5i treatment. In 49 patients (38.2%), PDE5i was first-line treatment (sildenafil $n = 47$, 36.7%; tadalafil $n = 2$, 1.6%). One patient (0.5%) received PDE5i after initial treatment with an endothelin receptor antagonist. Ten patients (7.8%) received an endothelin receptor antagonist and one patient (0.8%) received a soluble guanylate receptor cyclase stimulator as part of the B-PHIT and RISE-IIP trials, respectively (Figure S3 in the Supporting Information).[21,22] Median treatment duration was 363 days (IQR: 130, 943). Sildenafil was up-titrated in 13 patients (10.2%) and down-titrated in one patient (0.8%) with a median final dose of 75 mg day^{-1} (IQR: 60, 150). In four patients, sildenafil was transitioned to another pulmonary vasodilator (tadalafil $n = 2$, 1.6%; bosentan $n = 2$, 1.6%) due to side effects. Four patients received dual therapy with a PDE5i and an endothelin receptor antagonist after clinical deterioration on monotherapy.

Patients treated with PDE5i had non-significantly higher mPAP (median 38 mm Hg, [IQR: 34, 43] vs. 35 mm Hg [IQR: 31, 38], $p = 0.07$) and FVC% (median 57%, [IQR: 51, 73] vs. 52%, [IQR: 45, 66], $p = 0.08$) than untreated patients and were no more likely to receive long-term oxygen therapy than untreated patients (odds ratio 1.93 [95% CI: 0.57, 2.69], $p = 0.61$, Table S2 in the Supporting Information).

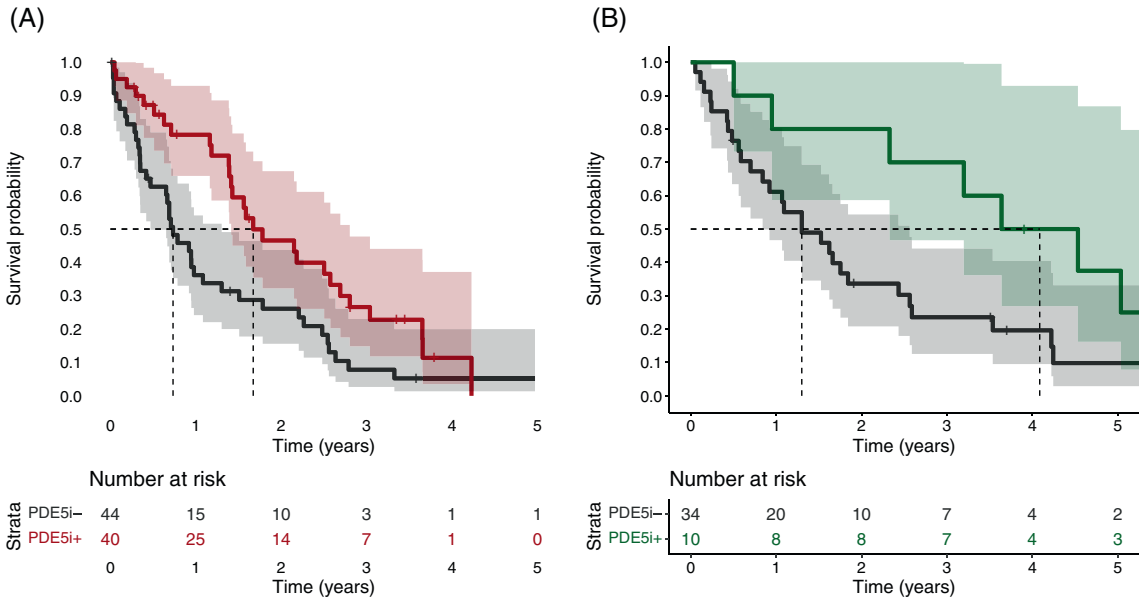

FIGURE 3 Kaplan–Meier plots for the survival of patients (A) with right ventricular (RV) dysfunction and (B) with normal RV function, at presentation. Shaded regions and dotted lines denote 95% confidence intervals and median survival, respectively. The included 'Number-at-risk' tables show group survival at 1-year intervals. (A) Patients with RV dysfunction taking PDE5i had a median survival of 1.67 years (95% CI: 1.39, 2.58) compared with 0.73 years (95% CI: 0.47, 1.08) in patients not taking PDE5i ($p = 0.007$). (B) Patients with normal RV function taking PDE5i had a median survival of 4.09 years (95% CI: 2.33, 5.04) compared with 1.30 years (95% CI: 0.84, 1.84) in patients not taking PDE5i ($p = 0.02$). CI, confidence interval; PDE5i±, treated/not treated with phosphodiesterase 5 inhibitor; RV, right ventricular

Thirty-seven patients (28.9%) had a follow-up RHC at a median of 4.2 months (IQR: 3.8, 10.1) after diagnosis (Figure S4 in the Supporting Information). Five patients (3.9%) had a second follow-up RHC at a median of 22.6 months (IQR: 7.7, 22.9) after diagnosis.

Survival

Survival at 1-, 3- and 5- years was 58.0%, 22.1% and 7.7%, respectively. Survival varied by diagnosis though these differences failed to reach significance ($p = 0.49$, Figure S5 in the Supporting Information).

Patients treated with PDE5i survived longer than patients not treated with PDE5i (median 2.18 years, [95% CI: 1.43, 3.04] vs. 0.94 years [95% CI: 0.69, 1.51], $p = 0.003$; Figure 2) and longer than patients not treated with any pulmonary vasodilator (median 0.92 years [95% CI: 0.67–1.30], $p = 0.001$). The association of PDE5i treatment with survival was consistent across all diagnostic subgroups (Figure S6 in the Supporting Information). In patients with normal RV function at presentation, median survival was 4.09 years on PDE5i treatment (95% CI: 2.33, 5.04) versus 1.30 years untreated (95% CI: 0.84, 1.84, $p = 0.02$, Figure 3). In patients with RV dysfunction at presentation, median survival was 1.67 years on PDE5i treatment (95% CI: 1.39, 2.58) vs. 0.73 years untreated (95% CI: 0.47, 1.08; $p = 0.007$). In bootstrapped samples, the difference in median survival with treatment was +2.55 years (95% CI: −0.03, +3.97) in patients with normal RV function and +0.98 years (95% CI: +0.47, +2.00) with treatment in patients with RV dysfunction at presentation ($p = 0.04$).

PDE5i treatment has a larger, independent effect on survival than all other prognostic markers (HR 0.39, 95% CI: 0.23, 0.59, $p < 0.001$, Figure 4A). Modelling confirmed a significant interaction between TAPSE and PDE5i treatment, further increasing the protective effect of PDE5i on survival at higher values of TAPSE (HR 0.65, 95% CI: 0.47, 0.91, $p = 0.01$, Figure 4B). This result was robust to sensitivity analysis with a range of priors (HR 0.39, 95% CI: 0.22, 0.63; $p < 0.001$, Figure S7 in the Supporting Information) and replicated by propensity-matched analysis (HR 0.38, 95% CI: 0.22, 0.58; $p < 0.001$; Table S4 in the Supporting Information). Analysis using baseline data demonstrated a non-significant association of PDE5i treatment with survival (HR 0.69, 95% CI: 0.36, 1.32, $p = 0.13$), confirming the benefit of methods which integrate follow-up data into the analysis (Table S5 in the Supporting Information).

Haemodynamics, functional capacity and quality of life

Change in physiological parameters over time were compared between patients treated with PDE5i and patients not treated with PDE5i. In patients treated with PDE5i, the periods before and after initiation of therapy were considered separately so that changes in physiological parameters before and after therapy could be compared (Figure 5). All groups showed negligible or non-significant changes in

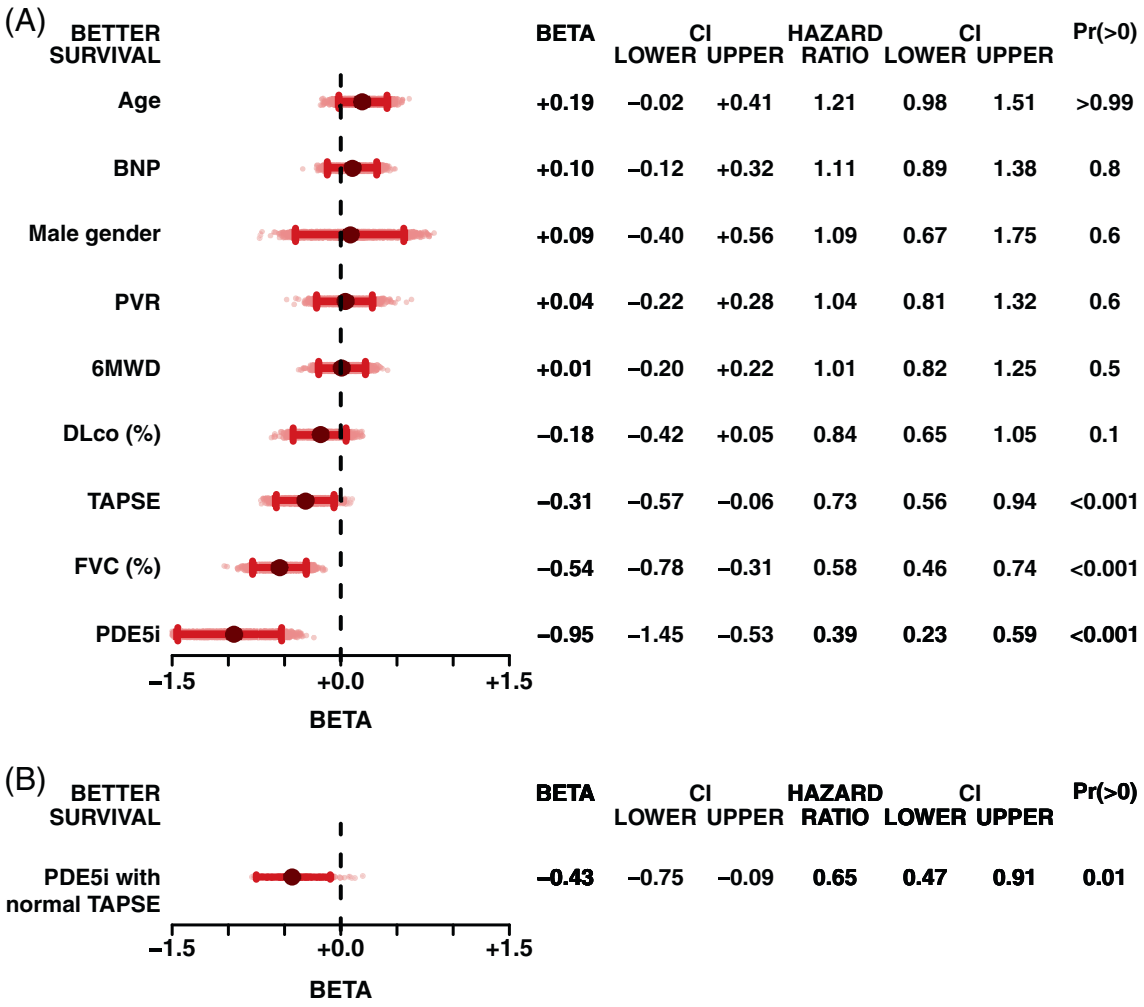

FIGURE 4 Dot-and-Whisker plot showing the association of prognostic markers with survival in a multivariate Bayesian Cox proportional hazards model. (A) The individual associations with survival. (B) The interaction between treatment with phosphodiesterase 5 inhibitors (PDE5i) and tricuspid annular plane systolic excursion (TAPSE), a marker of right ventricular function. For each prognostic marker (y-axis) the standardized beta coefficients, sampled from the posterior distribution, are shown as pink dots. Red dots and bars indicate the means and 95% credible intervals of the sampled data. Pr(>0) denotes the probability that the true beta coefficient exceeds zero, that is, in (A) that each marker is associated with worse survival, and in (B) that higher TAPSE is associated with a smaller treatment effect. Hazard ratios indicate the ratio of hazard rates for treated versus untreated patients. A hazard ratio below or above one indicates a reduction or an increase in the risk of death, respectively. 6MWD, six-minute walk distance; BNP, brain natriuretic peptide; CI, credible interval; DLco, percent transfer factor for carbon monoxide; FVC, forced vital capacity; PDE5i, phosphodiesterase 5 inhibitor; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic excursion

mPAP, CO and PVR. In patients not selected for PDE5i treatment, 6MWD (mean − 18 m year^{-1} [95% CI: −21, −14], $p < 0.001$) and TAPSE deteriorated (mean- − 0.02 cm year^{-1} [95% CI: −0.04, −0.01], $p < 0.001$). In patients treated with PDE5i, in the period between initial assessment and PDE5i treatment there was an increase in arterial oxygen saturations (mean + 1.14% year^{-1} [95% CI: +0.55, +1.72], $p > 0.99$), but also significant increases in heart rate (mean + 6.6 beats per min year^{-1} [95% CI: +2.1, +11.2], $p > 0.99$) and BNP (mean + 28 ng L^{-1} year^{-1} [95% CI: 11, 46], $p > 0.99$). After initiation of PDE5i, 6MWD deteriorated (mean − 16 m.yr^{-1} [95% CI: −25, −7], $p < 0.001$), TAPSE deteriorated (mean − 0.10 cm year^{-1} [95% CI: −0.18, −0.03], $p < 0.001$) and BNP continued to increase (mean + 36 ng L^{-1} year^{-1} [95% CI: 20, 54], $p > 0.99$). Arterial saturations showed no significant annual change after initiation of treatment (mean + 0.20% year^{-1} [95% CI: −0.70, 1.10], $p = 0.67$).

In patients treated with PDE5i, 18 patients (36.0%) responded to treatment, 28 patients (56.0%) showed no response and 4 patients had insufficient follow-up data to determine if a response had occurred. Responders survived significantly longer than non-responders and untreated patients with median survival 2.51 years (95% CI: 2.02, 3.40), 1.39 years (95% CI: 0.64, 2.45) and 0.94 years (95% CI: 0.69, 1.51, $p = 0.04$, Figure S8 in the Supporting Information), respectively. Comparing responders with non-responders, functional class was similar before and after treatment ($\beta = -0.08$, 95% CI: −0.27, 0.10, $p = 0.37$) and between treated and untreated groups ($\beta = -0.02$, 95% CI:

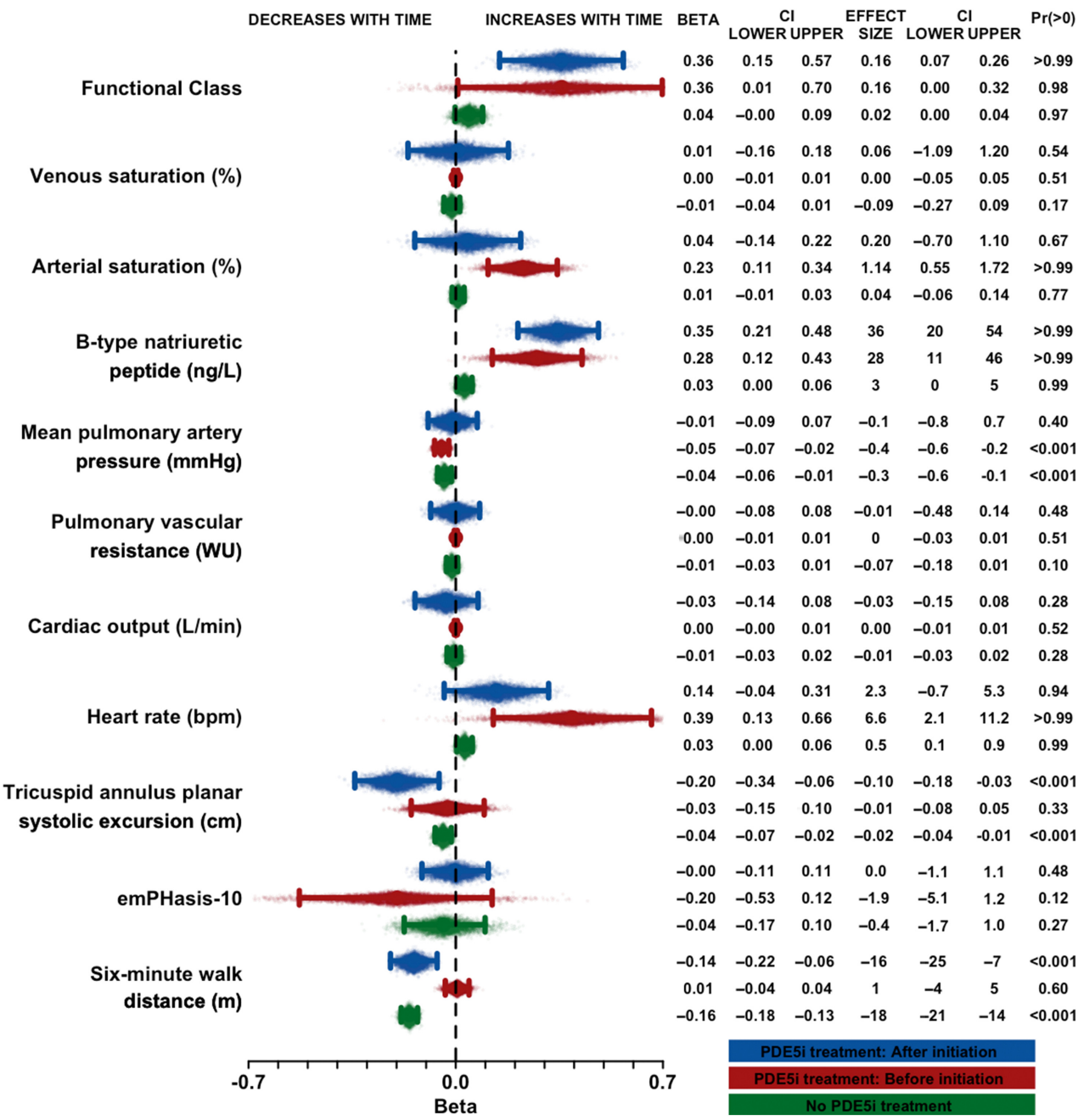

FIGURE 5 Dot-and-Whisker plot showing the annual changes in haemodynamic, echocardiographic and functional markers in patients not treated (green), before treatment (red) and after treatment (blue) with phosphodiesterase 5 inhibitors. For each coefficient (y-axis) the standardized beta coefficients from sampling the posterior distribution are shown as faint dots, with the means and 95% credible intervals shown as heavy dots and bars. Effect size indicates the change in each parameter per year. Pr(>0) denotes the probability of an effect size greater than zero. BPM, beats per min; CI, credible interval; PDE5i, phosphodiesterase 5 inhibitor; WU, wood units

−0.24, 0.20, $p = 0.88$, Figure S9 in the Supporting Information).

DISCUSSION

Our retrospective, observational study demonstrates that PDE5i treatment is independently associated with longer survival in patients with invasively confirmed ILD-PH. Survival difference is greatest in patients with normal baseline RV function.

Historically, ILD-PH was viewed as a late consequence of fibrotic parenchymal destruction, hypoxic pulmonary vasoconstriction and disruption of small vessel architecture.[38] Trials have therefore focused on patients with advanced ILD, without definitive consistent haemodynamic testing, though benefits to quality of life, BNP and exercise capacity have been seen.[3,5–7]

More recently, distinct histological and molecular signatures have been identified which suggests that a pulmonary vascular phenotype may exist within advanced ILD.[39] Our approach phenotypes patients by invasive catheterisation and echocardiography distinguishing a group with pulmonary vascular disease and normal RV function. These patients show greater survival difference between treated and untreated arms. It is unclear whether this effect represents an adaptive compensatory phenotype with prolonged survival or simply earlier disease. In the treatment cohort overall, TAPSE and BNP deteriorated after treatment initiation though improved survival in the treatment-responsive group supports the prognostic importance of these markers and the benefits of objective follow-up after a therapeutic treatment trial. Nonetheless, discordance between macroscopic haemodynamic investigations, circulating biomarkers and survival in our data support the need to improve RV phenotyping, understanding of cell signalling, target expression and cell transition to understand why clinical deterioration occurs, and in what phases treatment may be most efficacious.[5,40–44]

Concerns about worsening ventilation/perfusion mismatch have focused investigations on inhaled therapies.[4,45,46] Despite this, our data and that of others, support the view that oral pulmonary vasodilators including PDE5i may enhance normoxic vasodilatation without affecting ventilation/perfusion matching.[3,5,43]

Our work demonstrates how Bayesian joint modelling approaches can solve the problems of missing and asynchronous data, which challenge the use of real-world data for research. Rare-disease analysis is well-suited to Bayesian approaches, since cohorts are small and clinical approach is influenced by experience from similar clinical experience.

This is a retrospective analysis of a large, prospective, clinical database with in-house protocolisation of treatment. We have attempted to control for all relevant prognostic factors, but ILD severity, haemodynamic and quality of life markers are imperfect and the potential for selection bias remains. Emphysema may spuriously preserve FVC, pulmonary hypertension may reduce DLco and CPI has not been validated outside IPF.[17] The emPHasis-10 questionnaire is designed for patients with pulmonary arterial hypertension not ILD-PH,[24] and follow-up invasive catheterisation is used judiciously to minimize risk.

In conclusion, PDE5i may improve survival in patients with ILD-PH especially in patients with severe ILD-PH and normal baseline RV function. Randomized controlled trial confirmation is crucial before recommending widespread implementation.

AUTHOR CONTRIBUTION

Timothy Dawes: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); visualization (lead); writing – original draft (lead); writing – review and editing (equal). **Colm McCabe:** Investigation (equal); writing – review and editing (equal). **Konstantinos Dimopoulos:** Conceptualization (equal); investigation (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Iain Stewart:** Formal analysis (equal); methodology (equal); writing – review and editing (equal). **Simon Bax:** Data curation (equal); writing – review and editing (equal). **Carl Harries:** Data curation (equal); writing – review and editing (equal). **Chinthaka Samaranayake:** Data curation (equal); writing – review and editing (equal). **Aleksander Kempny:** Investigation (equal); writing – review and editing (equal). **Philip Molyneaux:** Data curation (equal); writing – review and editing (equal). **Samuel Seitler:** Data curation (equal); writing – review and editing (equal). **Thomas Semple:** Investigation (equal); writing – review and editing (equal). **Wei Li:** Investigation (equal); writing – review and editing (equal). **Peter M. George:** Data curation (equal); writing – review and editing (equal). **Vasileios Kouranos:** Investigation (equal); writing – review and editing (equal). **Felix Chua:** Investigation (equal); writing – review and editing (equal). **Elisabetta A. Renzoni:** Investigation (equal); writing – review and editing (equal). **Maria Kokosi:** Investigation (equal); writing – review and editing (equal). **Gisli Jenkins:** Methodology (equal); writing – review and editing (equal). **Athol U. Wells:** Funding acquisition (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Stephen J. Wort:** Conceptualization (equal); funding acquisition (equal); supervision (equal); writing – review and editing (equal). **Laura C. Price:** Conceptualization (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICTS OF INTEREST

Athol U. Wells: consulting fees and payments for educational events from Boehringer Ingelheim; Carl Harries: payments for lectures, attending meetings and travel from Janssen; Colm McCabe: educational and travel grants from Janssen; Chinthaka B. Samaranayake: honorarium for educational lectures from Pfizer, travel support for conference attendance from Janssen; Elisabetta A. Renzoni: payments for lectures and travel to the Institution; Felix Chua: lecture payments from Boehringer-Ingelheim and Roche; Gisli Jenkins: grants to institution from AstraZeneca, Biogen, Galecto, GlaxoSmithKline, RedX and Pliant; consulting fees from Bristol Myers Squibb, Daewoong, Veracyte, RedX, Resolution Therapeutics and Pliant; lecture payments from Chiesi, Roche, PatientMPower, AstraZeneca; participation in Data Safety Monitoring Board or Advisor Board for Boehringer Ingelheim, Galapagos, Roche, Vicore; leadership role in NuMedii; trustee of Action for Pulmonary Fibrosis; Laura C. Price: educational grants, payments for lectures and travel from Janssen, Ferrer, Altavant; Philip L. Molyneaux: grant funding to institution from AstraZeneca, advisory board fees from Hoffman-La Roche, Boehringer Ingelheim,

AstraZeneca; speaker fees from Boehringer Ingelheim and Hoffman-La Roche; Stephen J. Wort: honoraria from Acceleron and Bayer, grant funding from Janssen and Bayer, consulting fees for Adboards to institution, and for lectures, travel and Podcasts from Janssen; Vasileios Kouranos: Honoraria for educational events from Boehringer, Novartis and Roche.

The remaining authors had nothing to disclose.

Beyond the financial support granted, none of the funding sources provided any input or contribution to the development of this research or manuscript.

DATA AVAILABILITY STATEMENT

Code is publicly available on Github under a GNU General Public License (https://github.com/timdawes/Group-3-Pulmonary-Hypertension). Personal data are not available due to privacy restrictions.

HUMAN ETHICS APPROVAL DECLARATION

This study received institutional ethics review board approval with individual consent waived as the data were collected during routine clinical care (Royal Brompton and Harefield reference 2016PH002B).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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