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ASPIRE Registry: Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre

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ABSTRACT

Pulmonary hypertension (PH) is a heterogeneous condition. To date no registry data exists reflecting the spectrum of disease across the 5 diagnostic groups encountered in a specialist referral centre.

Data was retrieved for consecutive, treatment-naïve cases diagnosed during 2001-10 using a catheter-based approach. 1344 patients were enrolled, mean follow-up 2.9years. Three-year survival was 68% for pulmonary arterial hypertension (PAH), 73% for PH-Left heart disease, 44% for PH-Lung disease, 71% for chronic thromboembolic PH (CTEPH) and 59% for PH-Miscellaneous. Compared with PAH, survival was inferior in PH-Lung and superior in CTEPH ($p<0.05$). Multivariate analysis demonstrated that diagnostic group independently predicted survival. Within PAH, Eisenmenger's survival was superior to idiopathic PAH which was superior to PAH-systemic sclerosis ($p<0.005$). Within PH-Lung, 3-year survival in sleep disorders/alveolar hypoventilation (90%) was superior to PH-Lung with COPD (41%) and ILD (16%)($p<0.05$). In CTEPH, long-term survival was best in patients with surgically accessible disease undergoing pulmonary endarterectomy.

In this large registry of consecutive, treatment-naïve patients identified at a specialist PH centre outcomes and characteristics differ between and within PH groups. The current system of classification of PH has prognostic value even when adjusted for age and disease severity emphasizing the importance of systematic evaluation and precise classification.

Key Words: congenital heart disease

pulmonary hypertension

registry

survival

systemic sclerosis

thromboembolism

INTRODUCTION

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg at right heart catheterisation (RHC).[1] PH is a heterogeneous condition ranging from a rare, rapidly progressive vasculopathy (idiopathic pulmonary arterial hypertension (IPAH)) to more common and more minor elevations of pressure in the context of severe respiratory or cardiac disease. Greater understanding of underlying mechanisms resulted in the evolution of a classification system grouping diseases with shared pathophysiology with the intention of guiding treatment. The most recent classification identified 5 forms: Group 1-Pulmonary Arterial Hypertension (PAH), Group 2–PH associated with left heart disease (PH-LHD), Group 3–PH associated with lung disease (PH-Lung), Group 4–Chronic thromboembolic pulmonary hypertension (CTEPH), and a miscellaneous group 5 (PH-Misc).[1]

The majority of studies in PH have focused on PAH and CTEPH but there is limited data comparing outcome in the subgroups of these major pre-capillary forms of PH in a contemporaneous cohort. PAH can occur without known cause (IPAH) or in association with congenital heart disease (PAH-CHD) or a number of systemic diseases including connective tissue disease (PAH-CTD), particularly systemic sclerosis (PAH-SSc). In PAH, a pulmonary arteriopathy leads to progressively increasing pulmonary vascular resistance (PVR) resulting in right heart failure and early death. The emergence of targeted drug therapies since the late 1990's for PAH and pulmonary endarterectomy (PEA) as a definitive treatment for CTEPH revolutionised the previously limited options for patients.[2-4] Due to the rarity of these diseases, expense of therapies and required expertise, specialist PH centres

(n=7) which adhere to nationally agreed standards of care[5, 6] were first designated in the United Kingdom (UK) in 2001.

The Sheffield Pulmonary Vascular Disease Unit is a large, adult UK PH centre serving a referral population of approximately 15 million.[7] We assess patients across the whole clinical spectrum of PH seen in the developed world. This has provided an opportunity to compare characteristics of extensively phenotyped, treatment-naïve patients in the era of targeted drug therapies across the spectrum of PH identified at a specialist referral centre. Here we report the results of a large cohort study of all consecutive patients diagnosed with PH over a 9 year period.

METHODS

All consecutive patients undergoing assessment of suspected PH between February 2001-2010 were followed to 1st November 2010. All patients underwent a standard, systematic diagnostic evaluation including echocardiography, detailed blood testing, exercise testing, lung function testing, overnight oximetry, isotope perfusion scanning, high resolution CT (HRCT), CT pulmonary angiography (CTPA) and RHC. Cardiopulmonary MRI was routinely performed from 2004 while formal pulmonary angiography was performed when indicated. Diagnostic classification was by standard criteria following multidisciplinary assessment by experienced pulmonary vascular physicians and specialist radiologists.

In 2010, a detailed review of departmental databases and hospital records was performed. Data was captured in >95% of cases for the vast majority of parameters. Only 2 variables had <90% completeness (cardiac index in 87% and gas transfer (TL_{CO}) in 88%). Pulmonary function tests and World Health Organisation functional class obtained closest to date of RHC were recorded as baseline measures. Exercise capacity was assessed using the distance achieved during the incremental shuttle walking test (ISWD).[8] Patients were excluded if PH was attributable to multiple factors in unrelated diagnostic groups. Date of diagnosis was taken as date of first RHC showing PH, except in patients with Eisenmenger's Syndrome in whom RHC is not routinely required,[9] where date of diagnosis was taken as date first seen at our centre. A small number of patients (n=5) commenced targeted therapy on specialist advice prior to urgent transfer to our centre. In these cases, date of diagnosis was taken as the date therapy was started and their baseline haemodynamic data were not included in analyses.

Patients were excluded from group 1 (PAH) if the pulmonary capillary wedge pressure (PCWP) was >15mmHg. Patients with hereditable PAH or PAH in association with anorexigen or amphetamine use were considered to have idiopathic PAH (IPAH) as described elsewhere.[10-12] Patients with IPAH were excluded from the registry if FEV_1 and/or FVC were consistently <60% predicted. In the presence of significant parenchymal lung disease on HRCT patients were diagnosed with PH-Lung as described previously, regardless of spirometry.[13, 14] PAH-CHD was sub-classified in accordance with recent guidelines into 4 subgroups: Eisenmenger's Syndrome, PAH associated with systemic-to-pulmonary shunts, PAH with small defects and PAH after corrective cardiac surgery.[15] Patients with PH-LHD were sub-classified on the basis of echocardiographic and MR assessment of LV function, valvular sufficiency, left atrial size and presence of left ventricular hypertrophy as described elsewhere.[16, 17] Suitability for PEA in CTEPH was decided following assessment of clinical and radiological data at the UK national PEA centre. For subgroup analysis, patients who were awaiting PEA at census were excluded because many were treated medically prior to surgery and thus could not be clearly assigned to a treatment group.

Connective tissue disease associated PH (PH-CTD) may be present due to PAH, associated lung disease[18, 19] or left heart disease.[20, 21] Patients with CTD and significant lung or left heart disease were therefore sub-classified separately from groups 1, 2 and 3 to enable comparison of the full phenotypic range of PH-CTD. In PH-CTD, an FVC <60% predicted or the presence of moderate or severe fibrosis (more than 1/3 of the lung fields involved) on HRCT were used as criteria to define lung disease associated PH (PH-Lung-CTD) as previously described.[18, 19]

Treatment was in accordance with contemporaneous guidelines and national commissioning policies.[6, 22] Patients with a positive vasoreactivity test to nitric oxide, as defined by accepted practice at the date of RHC, were treated with calcium-channel blockers.[23, 24] Endothelin receptor antagonists, phosphodiesterase-5-inhibitors and prostanoids (nebulised or intravenous iloprost or subcutaneous treprostinil) were used as monotherapy or in combination as clinically indicated. All patients were anticoagulated where indicated[25] and referred for transplant assessment as appropriate. The underlying medical conditions were diagnosed and managed by specialists in each field in accordance with contemporary medical practice.

The census point was date of death or lung transplantation or 1st November 2010 in those with event-free survival. Mortality status was ascertained via the National Health Service enhanced reporting service death report. Patients who were untraceable at census (n=4) were deemed lost to follow up and excluded. Ethical approval for analysis of routinely collected clinical data was granted by the North Sheffield Research Ethics Committee.

Statistical Analysis

Continuous variables were described by mean (± standard deviation). Multiple comparisons between groups were performed using analysis of variance for parametric data. Categorical data were compared with the χ^2 test. Event (death or transplantation)-free survival from date of diagnosis was estimated using the Kaplan-Meier method with comparison between groups performed by the Log-Rank test. Cox regression analysis was used to assess individual predictors of survival. A p-value of

<0.05 was deemed statistically significant throughout. Statistical analysis was performed using PASW Statistics v18 (SPSS, Chicago, IL).

RESULTS

1737 consecutive patients were evaluated for suspected PH using a RHC-based approach and 1344 incident cases of PH were identified (figure 1). Three hundred and ninety-three patients underwent RHC but did not meet inclusion criteria, including 225 with mPAP <25 mmHg, 41 with PH-CTD on exercise only (mPAP ≥ 30mmHg on exercise) who did not fulfil current diagnostic guidelines[1] and 38 patients with multiple factors contributing to PH where no principle cause could be distinguished. Eighty-five patients did not meet the strict registry inclusion criteria and were excluded. For instance, 20 patients with a clear phenotype of PAH rather than PH-LHD had PCWP 16-18mmHg and so were excluded.

Overall, mean age at diagnosis was 59 (± 17) years with 44% aged >65 years and a female preponderance of 62%. Ethnic origin was caucasian in 92%, african-caribbean in 3% and asian in 5%. During follow-up, 521 (39%) patients died and 8 (1%) patients underwent lung transplantation. The number of incident cases increased throughout the study period from 25 in 2001 to 271 in 2009. Assuming a stable referral population of 15 million, between 2001-09 the incidence of patients diagnosed at our centre with PAH increased from 0.9 to 6.1, IPAH from 0.3 to 2.1, PAH-CTD from 0.3 to 2.4 and CTEPH from 0.3 to 3.7 cases/million/year respectively.

The maximal duration of follow up was 9.7 years with a mean follow-up of 2.9 (±2.1) years. Baseline characteristics, demographics and maximal therapy received for the 5 main groups are shown in table 1. One and three year survival was 88% and 68% for group 1 (PAH), 90% and 73% for group 2 (PH-LHD), 65% and 44% for group 3 (PH-Lung), 89% and 71% for group 4 (CTEPH) and 84%, and 59% for group 5 (PH-Misc) (figure 2a). Compared with group 1, survival in group 3 was

inferior and in group 4 was superior ($p<0.05$). To examine the prognostic value of PH group, data for patients in groups 2, 3 and 4 were in turn combined with data for patients in group 1. When age, WHO functional class and cardiac index were accounted for using multivariate Cox regression analysis the PH diagnostic group independently predicted survival for each comparison (table 2). Comparative survival of the 6 commonest forms of PH seen in clinical practice comprising 82% of cases is shown in figure 2b.

Therapeutic strategies changed over the study period as a result of an increase in available therapies and changing contemporaneous clinical guidelines and prescribing agreements. The intravenous prostanoid used during the registry period was iloprost which, although not licensed for the treatment of PH, in the UK is commonly used.[26] This was initially due to lower cost, its superior stability and half-life compared to epoprostenol. Selected patients outwith groups 1 and 4 were treated with agreement of funding bodies. Thirteen percent of patients were included in previously published registries.[3, 18]

Group 1: PAH

Baseline characteristics demonstrated differences between the subcategories within group 1. Noticeably, patients with PAH-SSc had less severe haemodynamics but lower TL_{CO} than patients with IPAH, while those with PAH-CHD were younger (table 3). Within the combined IPAH group, 6 patients (3%) had heritable PAH, 4 (2%) had a history of amphetamine or anorexigen exposure, while 6% had a positive vasodilator response to nitric oxide during RHC. Three-year survival in IPAH was 63%, poorer than in PAH-CHD (85%) but significantly better than PAH-SSc (52%) ($p<0.01$; figure 3a).

Group 2: PH-LHD

There was no significant difference in outcome between patients with diastolic or systolic left ventricular dysfunction although the numbers in the latter group were small. Survival in PH secondary to valvular heart disease (PH-LHD-Valvular), comprising 22 mitral, 4 aortic, 16 mixed mitral/aortic significant valvular abnormalities, was significantly worse than in PH secondary to diastolic dysfunction (PH-LHD-Diastolic) ($p=0.001$; figure 3b). Thirty-six percent of patients with PH-LHD-Valvular had undergone valve replacement. Patients with PH-LHD had relatively well maintained cardiac output and milder elevation of PVR but had higher right atrial pressures compared to IPAH (table 4).

Group 3: PH-Lung

Survival in patients with PH-Lung was dependent on subgroup. Three-year survival in PH associated with sleep disordered breathing/alveolar hypoventilation (90%) was markedly better than PH associated with COPD (PH-COPD: 41%, $p=0.001$) which in turn was better than PH associated with interstitial lung disease (PH-ILD: 16%, $p=0.011$; figure 3c). In PH-COPD, a moderate elevation in PVR but significant reduction in TL_{CO} was observed (table 5).

Group 4: CTEPH

Two hundred and forty-two patients were diagnosed with CTEPH. In 4 cases, confident delineation of disease distribution was impossible due to sub-optimal imaging which could not be repeated. At census date, 20 patients had not undergone planned PEA and were excluded from further analysis. Survival of the remaining 218

patients is illustrated in figure 3d. Three-year survival in patients undergoing PEA was 83%, significantly superior to surgically inaccessible CTEPH or unoperated surgically accessible CTEPH ($p<0.05$). There was no significant difference in hemodynamic severity between these groups (table 6). Survival in surgically inaccessible CTEPH did not differ significantly from IPAH (not shown on figure). Three-year survival in patients who were not candidates for PEA due to the presence of significant comorbidities (37%) was inferior to that in patients who declined PEA (69%) which was inferior to those with disease considered too mild to require intervention (100%, $p<0.05$; figure 3e). Eighty-nine (82%) of 108 patients who underwent PEA received bridging pulmonary vascular therapy (69 oral monotherapy and 20 prostanoid-based therapy).

Group 5: PH-miscellaneous

Thirty-two patients were diagnosed with PH in the subcategories of group 5. PH associated with sarcoidosis was most common (n=14) with 3-year survival 63%. Detailed interpretation of survival and baseline data for patients in group 5 was not performed due to limited numbers.

PH-CTD

In total 323 patients with PH-CTD met inclusion criteria; 188 with isolated PAH, 102 with PH-Lung-CTD and 33 with PH-CTD associated with LHD (PH-LHD-CTD). In isolated CTD-PAH, SSc was the most frequent underlying CTD, present in 156 (83%) patients. SSc was of the limited cutaneous form in 94% of these cases and there was no significant difference in survival between PAH associated with diffuse or limited SSc. Thirty-two patients without SSc were diagnosed with isolated PAH-CTD

including 9 patients with undifferentiated CTD, 7 SLE, 6 with overlap CTD, 5 with mixed CTD, 3 with rheumatoid arthritis, and 2 patients with Sjögren's syndrome. In patients with CTD other than SSc, the majority of PH was associated with parenchymal lung disease. Three-year survival in PH-LHD-CTD (73%) was significantly better than in PAH-CTD (54%) and PH-Lung-CTD (40%) ($p<0.05$; figure 3f).

DISCUSSION

This study reports the findings of a large cohort of consecutive cases of PH identified at a specialist centre. All patients were treatment-naïve at entry and diagnosis was made at RHC (with the exception of selected patients with CHD). Importantly, this study provides detailed phenotypic and prognostic information on consecutive, incident cases in the major subgroups of PAH and CTEPH and highly selected, consecutive patients with PH-LHD and PH-Lung referred for assessment of suspected severe PH. Our results demonstrate the differences between these distinct groups of patients with PH attending a specialist PH centre and highlight the need for precise characterisation.

There are several clinically important findings from our cohort regarding the previously well-described diagnostic groups 1 and 4. As expected, there was a marked difference in survival between the 3 commonest forms of Group 1 (Eisenmenger's, IPAH and CTD-PAH), likely related to differences in demographic characteristics such as age, the ability of the right ventricle to cope with increased afterload and severity of the underlying pulmonary vasculopathy.[27, 28] In the CTEPH group, patients with operable disease who underwent PEA had the best long-term outcome, confirming the importance of appropriate operative intervention. We have also shown that CTEPH patients with operable disease considered too mild to warrant PEA had an excellent survival. Patients with surgically accessible disease who did not proceed to PEA because of co-morbidities had poorer survival than those with operable disease who chose to be treated medically. Overall patients with unoperated surgically accessible CTEPH had similar outcomes to patients with disease of a surgically inaccessible distribution. This emphasises the importance of effective identification and counselling of patients with potentially operable CTEPH. In patients with a high

pre-test probability of PAH such as CTD, we have demonstrated the importance of identifying the type of PH as it influences prognosis. In CTD, those with PH-LHD-CTD have a significantly improved survival compared to PAH-CTD and PH-Lung-CTD.

Many additional findings regarding PAH and CTEPH concur with those previously described.[3, 18, 29-33] The proportion of patients with IPAH with a positive vasodilator response (6%) was of a similar order to that in previous registries.[29, 30] As observed elsewhere, survival in PAH-SSc was inferior to that of IPAH[18, 34, 35] and the number of cases of PAH-CTD associated with CTDs other than systemic sclerosis was small.[18, 36-41] In contrast to the French registry, limited cutaneous systemic sclerosis was far more common than the diffuse form (94% v 67% of PAH-CTD-SSc).[29] The proportion of patients with PH-CTD with LHD was also lower. These differences may reflect varying approaches to screening, referral criteria and diagnostic strategies. Survival in IPAH, PAH-SSc and CTEPH were superior to that described in historical series[42-45] and age at diagnosis in IPAH has increased from 34 years in the NIH registry to 55±16 years in our cohort, in keeping with other observations.[12, 29, 30, 42] Notably the proportion of patients with PAH associated with HIV was lower than observed elsewhere[29, 30] which may be related to a lower prevalence of HIV in UK[46] and differing epidemiological factors in HIV acquisition. The observed incidence of diagnosed PAH and CTEPH increased markedly during the study period in keeping with increased awareness of these conditions. The incidences at the end of the study period are comparable to those observed in other large registries and are indicative of the success of the UK PH network. [3, 29, 30, 33]

Several significant observations regarding patients identified at a specialist referral centre with Group 2, PH-LHD and Group 3, PH-Lung were made. Apart from significantly elevated right atrial pressures patients with PH-LHD had less severe pulmonary haemodynamic abnormalities compared to IPAH including only modest increases in PVR. This observation has recently been described elsewhere[47]; however we were also able to define long term survival in this patient group. In particular, in patients with PH-LHD-Diastolic survival is greatly superior to IPAH. In the PH-lung group, those patients with sleep disordered breathing or alveolar hypoventilation had significantly higher cardiac indices and superior outcomes compared to those with parenchymal or airways disease. This emphasizes the need for adequate investigation of patients with severe unexplained PH, particularly assessment with RHC, appropriate radiology and overnight oximetry, to ensure patients with PH-LHD or PH-Lung are not misdiagnosed as IPAH resulting in inappropriate management and prognostication. An important caveat is that this cohort comprises and thus reflects the population of patients referred to a supra-regional pulmonary vascular unit with unexplained PH or in whom the elevation in pulmonary artery pressure was thought to be out of proportion to the severity of the underlying cardiac or respiratory disease. Therefore, it is not representative of all patients with PH-LHD and PH-Lung. Although PH-LHD-Diastolic was the commonest form of PH-LHD in our registry, it is generally thought that PH-LHD-Systolic is more common in the population as a whole, but is referred infrequently to a specialist centre as a diagnosis of IPAH is less likely to be considered. Similarly, the PH-Lung patients within this registry represent a skewed sample since in the majority of patients with PH associated with respiratory disease the PH is mild (cor pulmonale) and is not referred for further assessment. Although the numbers of patients with PH-

LHD and PH-Lung were smaller than with PAH and CTEPH in our registry, in the population as a whole the numbers of patients with PH-LHD and PH-lung are clearly significantly higher. Importantly however, our findings provide prognostic information to inform clinicians counselling patients with more severe pulmonary hypertension in the context of left heart disease and lung disease.

A small number of previous studies have compared outcomes between selected different forms of PAH[30, 35] while national registries have either focused on a single PH group or PAH subtype.[3, 18, 32, 33, 42] A single study previously compared outcomes of groups 1, 3 and 4 but enrolled only 222 patients while the methodology was unclear.[48] A recognised criticism of several previous registries is the fact that the majority of patients included were prevalent cases (i.e. had been diagnosed prior to enrolment). [29-31, 49-51] It has recently been demonstrated that prevalent cases of PAH have more stable disease with superior outcomes compared with incident cases. Thus it is possible that registries which include prevalent patients give a less reliable picture of the true natural history. It must be acknowledged, however, that although incident registries likely provide the best representation of survival for the cohort as a whole, registries based on large numbers of prevalent cases may provide extremely useful prognostic information for a previously diagnosed individual.

The main limitation of this study is its single centre nature but this allowed exhaustive interrogation of patient records enabling excellent data completeness.

CONCLUSION

This registry describes baseline characteristics and survival for a large cohort of consecutive, treatment-naïve patients referred for evaluation of suspected PH at a

specialist PH centre. Outcomes in contemporaneous patients with PAH and CTEPH differed depending on diagnostic subgroup and within CTEPH, on surgical intervention. This study also demonstrates the poor outcome in increasingly recognised subgroups of PH-LHD and PH-Lung who are a focus of active research. Accurate classification of pulmonary vascular disease by systematic assessment not only informs management but also provides prognostic information.

Figure 1 Study cohort

RHC, right heart catheterisation; IPAH, idiopathic PAH; SSc, systemic sclerosis; CTD, connective tissue disease; CHD, congenital heart disease; PVOD, pulmonary veno-occlusive disease; LHD, left heart disease; ILD, interstitial lung disease; PEA, pulmonary endarterectomy

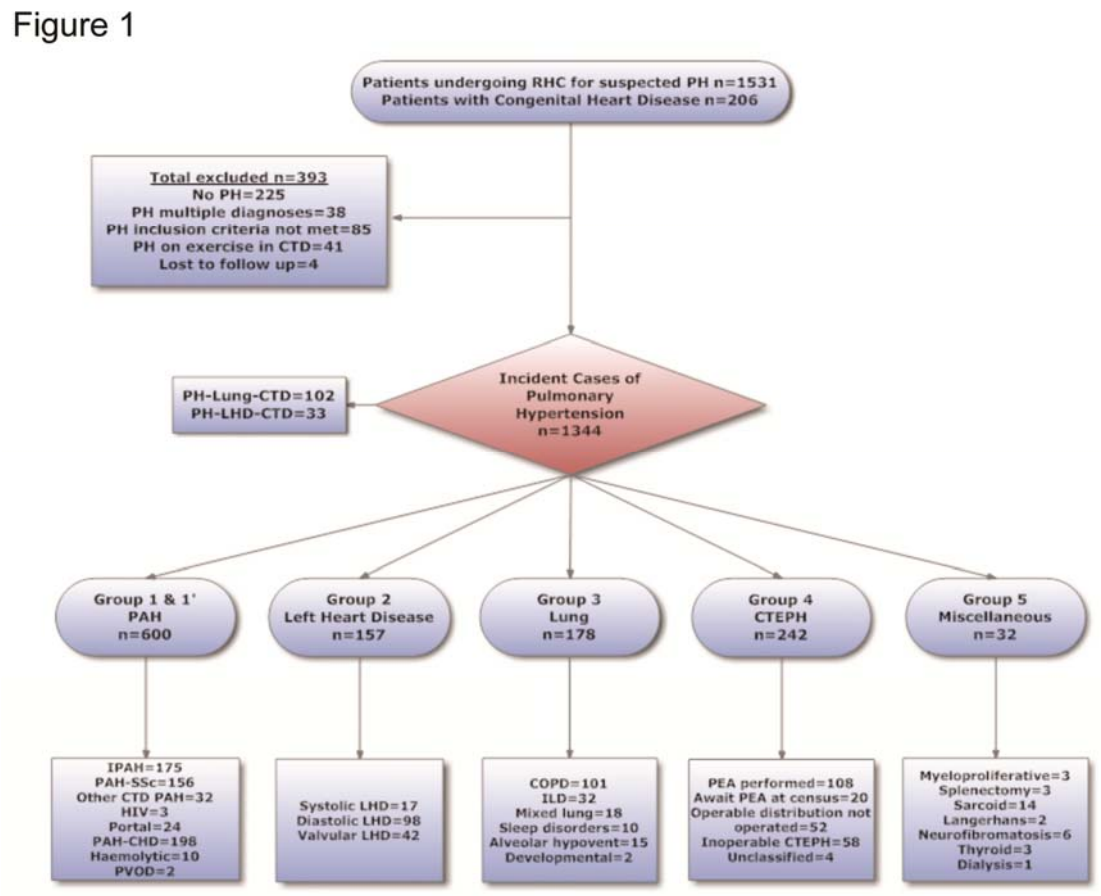

Figure 2 Cumulative survival from date of diagnosis a) in pulmonary hypertension by diagnostic group and b) in the 6 most common diagnostic sub-groups of pulmonary hypertension

Figure 2

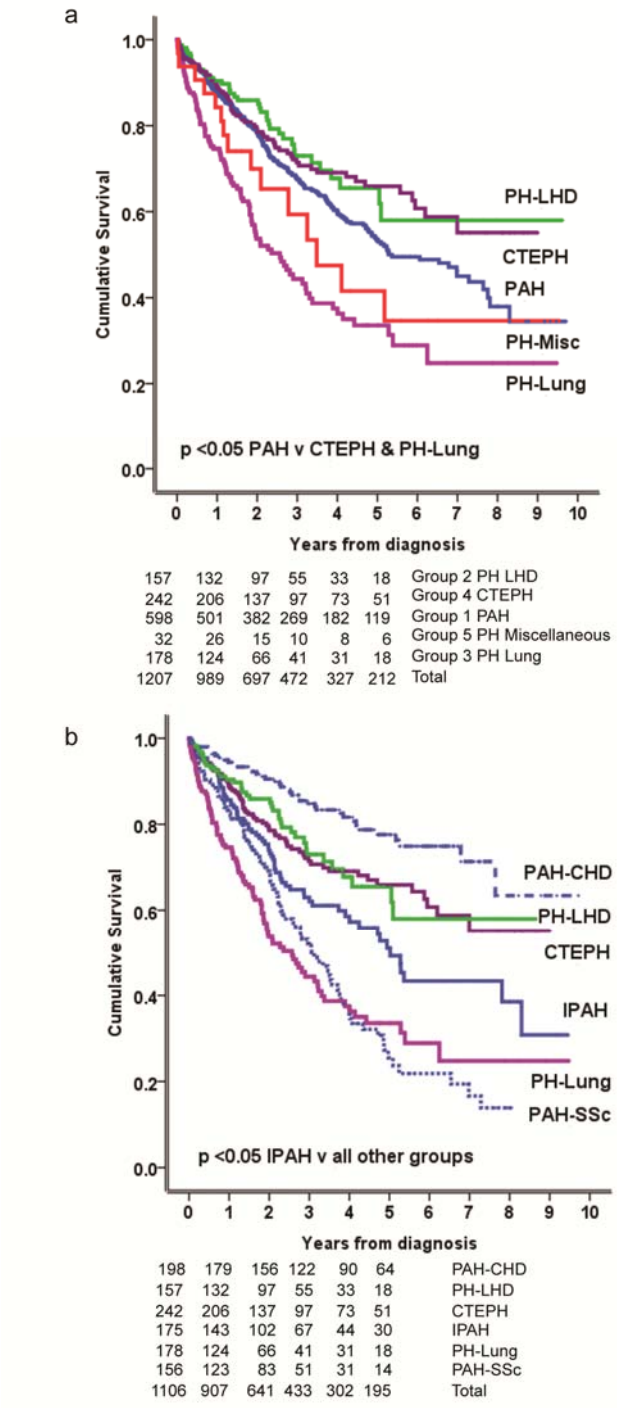

Figure 3 Cumulative survival from date of diagnosis a) in group 1 pulmonary arterial Hypertension; b) in group 2 pulmonary hypertension associated with left heart disease; c) in group 3; pulmonary hypertension associated with lung disease and d) in group 4; chronic thromboembolic pulmonary hypertension

patients operated (undergoing PEA), patients with surgically accessible CTEPH not operated and patients with surgically inaccessible disease. e) in patients with surgically accessible CTEPH not undergoing PEA by reason not operated. (* 2 patients were excluded because it was unclear whether PEA was not undertaken primarily due to comorbidities or patient choice)**; f) in PH-CTD by type of PH**

Figure 3

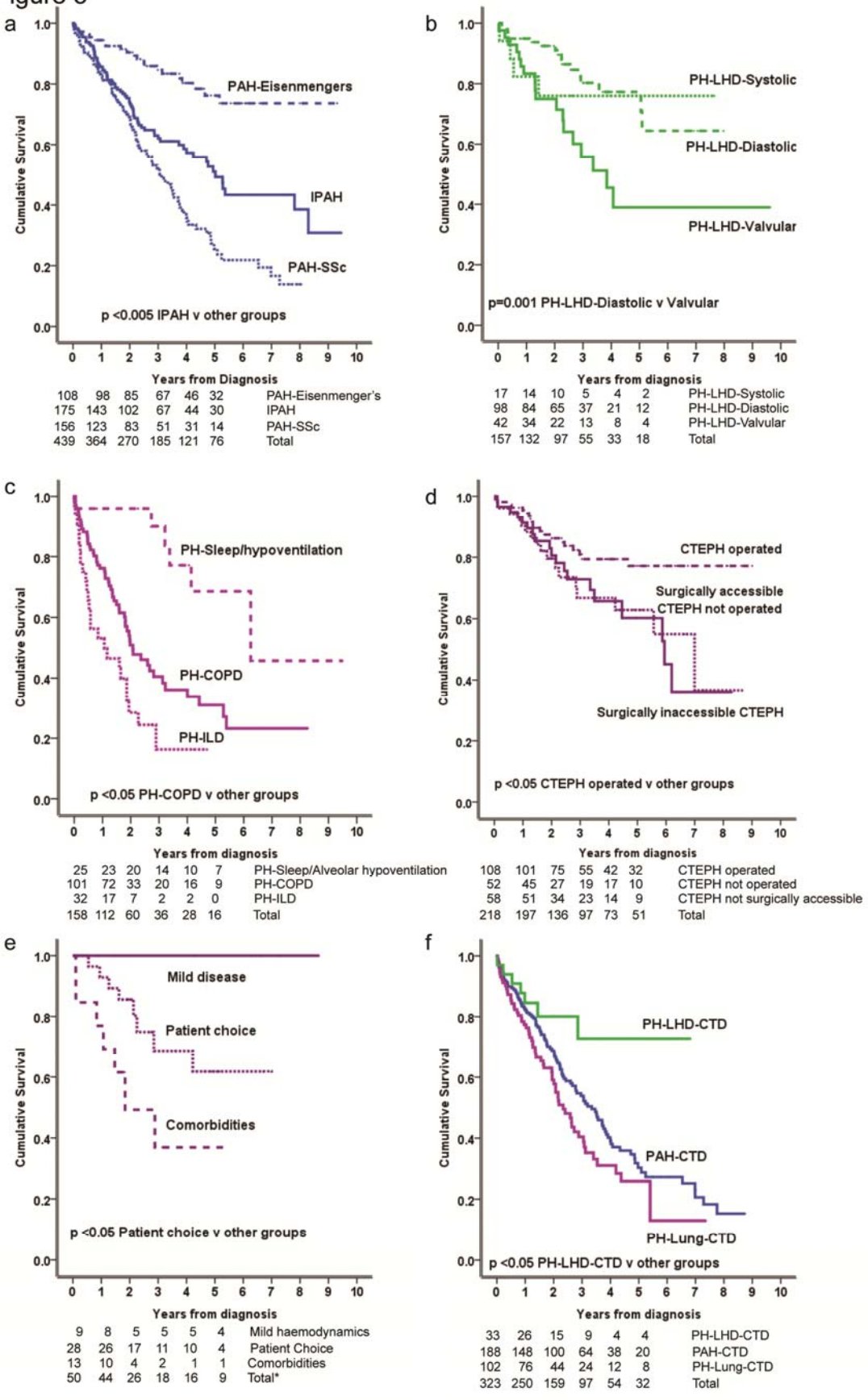
a
Cumulative Survival
PAH-Eisenmengers
IPAH
PAH-SSc
p <0.005 IPAH v other groups
Years from Diagnosis
108 98 85 67 46 32 PAH-Eisenmenger's
175 143 102 67 44 30 IPAH
156 123 83 51 31 14 PAH-SSc
439 364 270 185 121 76 Total
b
Cumulative Survival
PH-LHD-Systolic
PH-LHD-Diastolic
PH-LHD-Valvular
p=0.001 PH-LHD-Diastolic v Valvular
Years from diagnosis
17 14 10 5 4 2 PH-LHD-Systolic
98 84 65 37 21 12 PH-LHD-Diastolic
42 34 22 13 8 4 PH-LHD-Valvular
157 132 97 55 33 18 Total
c
Cumulative Survival
PH-Sleep/hypoventilation
PH-COPD
PH-ILD
p <0.05 PH-COPD v other groups
Years from diagnosis
25 23 20 14 10 7 PH-Sleep/Alveolar hypoventilation
101 72 33 20 16 9 PH-COPD
32 17 7 2 2 0 PH-ILD
158 112 60 36 28 16 Total
d
Cumulative Survival
CTEPH operated
Surgically accessible CTEPH not operated
Surgically inaccessible CTEPH
p <0.05 CTEPH operated v other groups
Years from diagnosis
108 101 75 55 42 32 CTEPH operated
52 45 27 19 17 10 CTEPH not operated
58 51 34 23 14 9 CTEPH not surgically accessible
218 197 136 97 73 51 Total
e
Cumulative Survival
Mild disease
Patient choice
Comorbidities
p <0.05 Patient choice v other groups
Years from diagnosis
9 8 5 5 5 4 Mild haemodynamics
28 26 17 11 10 4 Patient Choice
13 10 4 2 1 1 Comorbidities
50 44 26 18 16 9 Total*
f
Cumulative Survival
PH-LHD-CTD
PAH-CTD
PH-Lung-CTD
p <0.05 PH-LHD-CTD v other groups
Years from diagnosis
33 26 15 9 4 4 PH-LHD-CTD
188 148 100 64 38 20 PAH-CTD
102 76 44 24 12 8 PH-Lung-CTD
323 250 159 97 54 32 Total

Table 1 Baseline characteristics for the 5 diagnostic groups

	Overall	*Group1 PAH*	*Group 2 LHD*	*Group 3 Lung*	*Group 4 CTEPH*	*Group 5 Misc*
	n=1344	**n=598**	**n=157**	**n= 178**	**n=242**	**n=32**
Age (yrs)	59±17	54±18†‡§	69±10$^{*\S\|\|}$	66±11$^{*\S\|\|}$	61±15*†‡	57±12†‡
Female (%)	62	70	69	38	54	59
WHO III/IV (%)	65/16	64/14	66/6	62/27	70/17	66/19
ISWD (m)	169±149	189±156‡	154±144	111±104*§	178±156‡	140±114
mRAP (mmHg)	11±6	10±6†	15±6$^{*\ddagger\S\|\|}$	10±6†	11±6†	11±6†
mPAP (mmHg)	45±12	48±13†‡	41±11*§	41±11*§	48±11†‡	45±10
CI (L.min.m^{-2})	2.7±0.9	2.7±0.9†	2.9±0.7*§	2.8±0.9§	2.5±0.7$^{\dagger\ddagger\|\|}$	3.1±1.3§
PCWP (mmHg)	13±7	9±3†‡§	24±5 $^{*\ddagger\S\|\|}$	13±6*†§	11±5*†‡	11±5†
PVR (dyn.s.cm^{-5})	654±430	780±449†‡	289±225$^{*\ddagger\S\|\|}$	539±376*†§	735±389†‡	656±431†
MVO2 (%)	63±9	63±9§	64±8§	65±8§	60±9*†‡	60±11
FEV_1 (%)	73±22	77±20†‡§	67±20*‡§	57±25 $^{*\dagger\|\|}$	78±19†‡	69±24†‡
FVC (%)	85±24	88±22†‡	76±22*§	75±27*§	90±21†‡	82±19
TL_{CO} (%)	54±22	55±23†‡§	62±17$^{\ddagger\|\|}$	35±18*†§	63±16$^{*\ddagger\|\|}$	43±22*†§
Max Therapy (%)						
None	28	11	87	51	14	28
CCB	1	2	1	2	1	0
Oral monoRx	46	49	12	39	65	31
Oral comb	8	13	0	3	6	13
Prostanoid monoRx	8	10	0	2	12	22
Prostanoid comb	9	15	0	3	2	6

Abbreviations; WHO, World Health Organisation functional class; ISWD, incremental shuttle walking distance; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; CI, cardiac index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TL_{CO}, gas transfer; CCB, calcium-channel blocker; oral monoRx, oral monotherapy; oral comb, combination

phosphodiesterare-5-inhibitor and endothelin receptor antagonist; Prostanoid monoRx, prostanoid monotherapy; Prostanoid comb, prostanoid in combination with any other targeted therapy(s)

* $p<0.05$ in comparison to group 1, † $p<0.05$ in comparison to group 2, ‡ $p<0.05$ in comparison to group 3, § $p<0.05$ in comparison to group 4, || $p<0.05$ in comparison to group 5

Table 2: Survival analysis to assess prognostic value of PH group

	Univariate HR	*p-value*	*Multivariate HR*	*p-value*
Groups 1 & 2				
Age: per year	1.03 (1.03, 1.04)	<0.001	1.03 (1.02, 1.05)	<0.001
CI: per L/min/m^2	0.71 (0.59, 0.84)	<0.001	0.72 (0.60, 0.86)	<0.001
WHO: I/II	Reference		Reference	
III/IV	2.73 (1.89, 3.93)	<0.001	1.94 (1.23, 3.06)	<0.005
Group: 1	Reference		Reference	
2	0.74 (0.52, 1.03)	0.077	0.48 (0.33, 0.72)	<0.001
Groups 1 & 3				
Age: per year	1.04 (1.03, 1.05)	<0.001	1.03 (1.02, 1.04)	<0.001
CI: per L/min/m^2	0.67 (0.58, 0.78)	<0.001	0.66 (0.54, 0.78)	<0.001
WHO: I/II	Reference		Reference	
III/IV	2.78 (1.93, 4.00)	<0.001	1.77 (1.12, 2.80)	<0.05
Group: 1	Reference		Reference	
3	2.00 (1.57, 2.54)	<0.001	1.32 (1.01, 1.72)	<0.05
Groups 1 & 4				
Age: per year	1.03 (1.03, 1.04)	<0.001	1.03 (1.02, 1.04)	<0.001
CI: per L/min/m^2	0.71 (0.60, 0.84)	<0.001	0.66 (0.55, 0.79)	<0.001
WHO: I/II	Reference		Reference	
III/IV	2.32 (1.61, 3.34)	<0.001	1.62 (1.02, 2.57)	<0.05
Group: 1	Reference		Reference	
4	0.77 (0.59, 1.00)	<0.05	0.42 (0.32, 0.57)	<0.001

Abbreviations; HR, hazard ratio; CI, cardiac index. Data presented as HR (95% confidence interval).

Group1, PAH; Group 2, PH-LHD; Group 3, PH-Lung; Group 4, CTEPH

Table 3 Baseline characteristics for Group 1; Pulmonary Arterial Hypertension

	IPAH	*SSc*	*CTD not SSc*	*Porto-Pulmonary*	*Congenital Heart Disease*	
					All	**Eisenmenger's**
	n=175	**N= 156**	**n=32**	**n=24**	**n=198**	**n=108**
Age (yrs)	55±16$^{\dagger\|\|}$	66±9*$^{\ddagger\|\|}$	56±18$^{\dagger\|\|}$	58±13$^{\|\|}$	42±17*†‡§	37±15*†‡§
Female (%)	67†	87*$^{\S\|\|\#}$	81$^{\#}$	63†	62†	60†‡
WHO III/IV (%)	67/20	67/14	75/19	67/4	56/11	62/11
ISWD (m)	183±173	153±123$^{\|\|}$	162±135	211±145	218±163†	187±117
mRAP (mmHg)	11±6†‡	9±5*	7±6*	10±7	-	-
mPAP (mmHg)	53±13†‡	43±13*	45±11*	49±11	-	-
CI (L.min.m^{-2})	2.3±0.8†‡§	2.8±0.8*	3.0±0.9*	3.4±0.8*	-	-
PCWP (mmHg)	10±3	9±4	9±3	10±3	-	-
PVR (dyn.s.cm^{-5})	960±465†‡§	678±408*	649±323*	507±220*	-	-
MVO2 (%)	61±9†§	65±9*	63±10	69±9*	-	-
FEV_1 (%)	86±15$^{\ddagger\|\|}$	83±17$^{\|\|}$	74±17*	79±20$^{\|\|}$	64±20*†§	61±19*†‡§
FVC (%)	97±18$^{\|\|}$	97±17$^{\|\|}$	86±18 $^{\|\|}$	94±20$^{\|\|}$	73±23*†‡§	68±22*†‡§
TL_{CO} (%)	52±21$^{\dagger\|\|}$	40±11*$^{\S\|\|}$	45±12$^{\S\|\|}$	62±17†‡	73±24*†‡	72±20*†‡

Abbreviations see table 1

* p<0.05 in comparison to IPAH, † p<0.05 in comparison to SSc, ‡ p<0.05 in comparison to CTD not SSc, § p<0.05 in comparison to Porto-pulmonary, || p<0.05 in comparison to all CHD, # p<0.05 in comparison to Eisenmenger's

Table 4 Baseline characteristics for group 2; pulmonary hypertension due to left heart disease

	IPAH	***LV systolic dysfunction***	***LV diastolic dysfunction***	***Valvular Disease***
	n=175	**n =17**	**n =98**	**n =42**
Age (yrs)	55±16*†‡	69±8§	69±11§	67±10§
Female (%)	67*	41†‡§	69*	79*
WHO III/IV (%)	67/20†	59/12	67/3§	67/10
ISWD (m)	183±173	151±106	164±155	131±130
mRAP (mmHg)	11±6*†‡	17± 7§	15±6§	14±6§
mPAP (mmHg)	53±13*†	43±9§	37±9‡§	48±12†
CI ($L.min.m^{-2}$)	2.3±0.8†‡	2.7±0.8	3.0±0.8§	2.8±0.4§
PCWP (mmHg)	10±3*†‡	24±6§	22±4‡§	26±7†§
PVR ($dyn.s.cm^{-5}$)	960±465*†‡	283±155§	244±181§	406±301§
MVO2 (%)	61±9†	62±10	65±7§	62±11
FEV_1 (%)	86±15*†‡	60±19§	68±20§	67±22§
FVC (%)	97±18*†‡	67±23§	77±21§	77±23§
TL_{CO} (%)	52±21†	60±14	66±17‡§	55±17†

IPAH data shown for comparison. Abbreviations see table 1; LV, Left Ventricular

* p<0.05 in comparison to LV systolic dysfunction, † p<0.05 in comparison to LV diastolic dysfunction, ‡ p<0.05 in comparison to valvular disease, § p<0.05 in comparison to IPAH

Table 5 Baseline characteristics for group 3; pulmonary hypertension due to lung disease and/or hypoxia

	IPAH	***COPD***	***ILD***	***Sleep disorders & Alveolar hypoventilation***
	n=175	**n = 101**	**n = 32**	**n =25**
Age (yrs)	55±16*†	69±10§	68±11§	61±10
Female (%)	67*†‡	37§	22§	44§
WHO III/IV (%)	67/20†	67/25‡	53/44‡§	67/8*†
ISWD (m)	183±173*†	102±105§	97±97§	145±99
mRAP (mmHg)	11±6	10±5	8±7	11±7
mPAP (mmHg)	53±13*†‡	43±11§	39±9§	37±10§
CI (L.min.m^{-2})	2.3±0.8*‡	2.8±0.9§	2.5±0.6‡	3.2±0.7†§
PCWP (mmHg)	10±3*‡	13±5‡§	11±8‡	16±10*†§
PVR (dyn.s.cm^{-5})	960±465*†‡	568±382§	560±321§	375±284§
MVO2 (%)	61±9*‡	64±8§	63±10	69±8§
FEV_1 (%)	86±15*†‡	59±26§	66±25§	51±23§
FVC (%)	97±18*†‡	85±25†‡§	66±25*§	56±23*§
TL_{CO} (%)	52±21*†	32±16‡§	32±9‡§	57±19*†

IPAH data shown for comparison. Abbreviations see table 1

* p<0.05 in comparison to COPD, † p<0.05 in comparison to ILD, ‡ p<0.05 in comparison to sleep/alveolar hypoventilation, § p<0.05 in comparison to IPAH

Table 6 Baseline characteristics for group 4; chronic thromboembolic pulmonary hypertension

	IPAH	*CTEPH operated*	*CTEPH not operated*	*CTEPH not surgially accessible*
	n=175	**n = 108**	**n = 52**	**n = 58**
Age (yrs)	55±16†‡	57±15†	70±12*§	63±16§
Female (%)	67*	44†‡§	67*	60*
WHO III/IV (%)	67/20	72/14	65/24	74/14
ISWD (m)	183±173	203±174	129±122	177±141
mRAP (mmHg)	11±6	10±5	10±6	11±5
mPAP (mmHg)	53±13†‡	49±10	45±11§	46±13§
CI (L.min.m^{-2})	2.3±0.8	2.3±0.6	2.5±0.9	2.6±0.8
PCWP (mmHg)	10±3‡	10±4	10±5	11±6§
PVR (dyn.s.cm^{-5})	960±465*†‡	780±389§	740±373§	689±424§
MVO2 (%)	61±9	60±8	60±9	61±10
FEV_1 (%)	86±15*†‡	80±16§	74±23§	79±21§
FVC (%)	97±18	92±17	89±25	89±23
TL_{CO} (%)	52±21*†‡	66±15§	61±18§	62±15§

IPAH data shown for comparison. Abbreviations see table 1

* $p<0.05$ in comparison to Proximal operated, † $p<0.05$ in comparison to proximal not operated, ‡ $p<0.05$ in comparison to distal, § $p<0.05$ in comparison to IPAH

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