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The Giessen Pulmonary Hypertension Registry: Survival in pulmonary hypertension subgroups

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BACKGROUND: Pulmonary hypertension (PH) is a severe, progressive disease. Although 5 PH subgroups are recognized, reports on survival have focused mainly on pulmonary arterial hypertension (PAH).

METHODS: Long-term transplant-free survival and its determinants were investigated in patients with PH (diagnosed by right heart catheterization) within a prospective registry at a single referral center in Giessen, Germany.

RESULTS: In total, 2,067 patients were enrolled (PAH, 685 patients [33.1%]; pulmonary venous hypertension, 307 patients [14.9%]; PH due to lung diseases (LD-PH), 546 patients [26.4%; mainly interstitial lung disease and chronic obstructive pulmonary disease]; chronic thromboembolic PH, 459 patients [22.2%]; PH owing to miscellaneous/unknown causes, 70 patients [3.4%]). Median follow-up was 37 months. Differences in transplant-free survival between etiologic groups were highly significant ($p < 0.001$), with 1-, 3- and 5-year survival rates of 88.2%, 72.2% and 59.4%, respectively, for those with PAH compared with 79.5%, 52.7% and 38.1%, respectively, for patients with LD-PH. Patients' age, gender and 6-minute walk distance (6MWD), but not New York Heart Association (NYHA) functional class, associated significantly with survival across all PH subtypes in multivariate Cox regression analyses.

CONCLUSIONS: This is the largest single-center PH cohort described so far. Some parameters used in clinical practice do not independently predict survival. Age, gender and 6MWD outperformed NYHA functional class in predicting survival across all etiologic groups.

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Pulmonary hypertension (PH) is a progressive pulmonary vascular disease defined by an elevated mean pulmonary artery pressure (PAP) of ≥25 mm Hg. PH is associated with increased pulmonary vascular resistance (PVR) that can lead

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to right heart failure and subsequent death.[1] PH has 5 main subtypes,[2] but most PH survival studies concern only 1 subtype (pulmonary arterial hypertension [PAH], particularly idiopathic PAH [IPAH]).

In an early registry investigation, 68%, 48% and 34% of patients with IPAH survived 1, 3 and 5 years, respectively.[3,4] Survival has since improved: 1-year survival was 83% to 91% in more recent French-based and United States–based PAH registries.[5–7] Several clinical factors predict PAH course and outcome, including exercise tolerance and New York Heart Association (NYHA) functional class.[8–11] Hemodynamic parameters, such as mean right atrial pressure (RAP) and cardiac index, are also associated with survival.[3,12] However, equivalent information is lacking for other PH etiologies.

This report presents, for the first time, comprehensive long-term transplant-free survival data from >2,000 patients with different PH subtypes from a single referral center (the Giessen Pulmonary Hypertension Registry [Gi-PH-Reg]).

Methods

Data collection

The single-center Gi-PH-Reg started in March 1993 at the University Hospital Giessen. Eligible patients were recruited by October 13, 2011, with PH defined as mean PAP ≥25 mm Hg at rest by right heart catheterization. Patients with isolated exercise-induced PH (mean PAP <25 mm Hg at rest and >30 mm Hg at exercise)[13,14] were excluded. From 2008 onward, patients had to have their diagnostic right heart catheterization at Giessen to be included in the Gi-PH-Reg. All patients with suspicion of left heart involvement received right heart catheterization with a fluid challenge. Cases were discussed by our expert PH team and the PH subgroup was assigned based on the team's judgment rather than by using strict cut-offs (except for pulmonary venous hypertension [PVH], which was defined as pulmonary capillary wedge pressure [PCWP] >15 mm Hg). Patients were assigned to a PH subgroup based on the main cause of their PH. The Dana Point classification[2] and STROBE guidelines[15] were applied. Prevalent cases had been diagnosed with PH and started PH-targeted therapy before the first visit to our center; incident cases were those diagnosed initially at our center or referred after diagnosis without targeted therapy. Survival status was determined by contacting the patient or their local physician. Dates and causes of death were obtained from medical records; if no information was available, then the patient was classified as lost to follow-up and censored at the date of the last visit. Patients undergoing lung transplantation were considered to have had an event at the transplantation date. Baseline demographics, PH etiology, medication use, echocardiographic parameters, and data from exercise testing, lung function testing, and right heart catheterization were entered into an electronic database. Date of first visit was taken as the start date, and patients were classified into modified NYHA functional Classes I to IV.[16] The study was approved by the University of Giessen institutional review board (#266/11). All patients gave written informed consent.

Right heart catheterization

At their baseline visit, 1,422 patients underwent right heart catheterization, usually via the internal jugular vein with a 7F Swan–Ganz catheter. Other patients were diagnosed invasively before referral; heart catheterization data from these patients were excluded unless the catheterization was repeated at Giessen. Cardiac output (CO) was measured by thermodilution. PCWP was registered and PVR calculated as: (mean PAP − PCWP) × 80 / CO.[17] Arterial partial oxygen pressure (PaO_2) was determined from a capillary blood test, whereas mixed venous oxygen saturation ($venSO_2$) was measured from blood sampled from the Swan–Ganz catheter.

The 6-minute walk distance test

The 6-minute walk distance (6MWD) was assessed in 1,290 patients at baseline according to American Thoracic Society guidelines.[18] Other patients received spiroergometry as a baseline cardiopulmonary exercise test, or were not able to walk for different reasons, so data were not available.

Statistical methods

Data were collected, checked and entered by independent research assistants. Two PH specialists checked medical information independently. Kaplan–Meier curves were constructed and log-rank tests performed to compare survival distributions. For overall survival analysis in the CTEPH group, patients who underwent a pulmonary endarterectomy (PEA) were considered as withdrawn alive at the date of the PEA. Association of parameters with survival was tested using uni- and multivariate Cox regression. Regression analysis parameters were selected based on clinical grounds, own previous analyses and literature review. Comparisons between groups were performed using the *t*-test or chi-square test, as appropriate, with $p < 0.05$ considered statistically significant. Bonferroni correction for multiple testing was performed for multivariate Cox regression (cut-off for significance = 0.0029). Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY).

Results

Study population

Virtually all patients with PH who visited our center were included in the Gi-PH-Reg; <1% were excluded because they did not provide written informed consent. Isolated exercise-induced PH was found in 368 patients, who were excluded from the current analyses. Of 689 incident cases visiting our center during the period 2008 to 2011, 140 (20.3%) had PH excluded by right heart catheterization. In total, 2,067 patients were enrolled and analyzed (1,856 were enrolled from the year 2000 onward); 33.1% had PAH, 14.9% had PVH, 26.4% had LD-PH (mainly interstitial lung disease [ILD] and chronic obstructive pulmonary disease [COPD]) and 22.2% had CTEPH (Table 1). Seventy patients (3.4%) had PH due to miscellaneous or unknown causes; no separate analyses were performed in this group owing to its small size and heterogeneity. Mean age overall was 59.6 years, with a female-to-male ratio of 1.24:1. Incident cases accounted for 90% (1,861 patients) of the overall study population, and 76.9%, 94.8%, 95.9%, 93.6% and 93.0% of the patients with IPAH, PVH, ILD-associated PH, COPD-associated PH and CTEPH, respectively.

Table 1 Baseline Characteristics[a]

	PAH ($n = 685$)	PVH ($n = 307$)	LD-PH ($n = 546$)	CTEPH ($n = 459$)
Female gender, *n* (%) [female:male ratio]	447 (65) [1.9:1]	184 (60) [1.5:1]	218 (40) [0.66:1]	258 (56) [1.28:1]
Age, mean (SD), years	51 (16)	67 (11)	64 (11)	62 (13)
NYHA FC, *n* (%)				
II	106 (19)	41 (18)	39 (12)	52 (15)
III	338 (59)	149 (64)	182 (54)	206 (60)
IV	126 (22)	43 (19)	119 (35)	84 (25)
6MWD, mean (SD), m	325 (126)	302 (110)	263 (115)	308 (116)
RAP, mean (SD), mm Hg	8 (6)	10 (6)	5 (4)	8 (5)
mPAP, mean (SD), mm Hg	51 (16)	34 (12)	34 (11)	44 (13)
PCWP, mean (SD), mm Hg	8 (4)	18 (7)	8 (4)	9 (4)
CI, mean (SD), liters/min/m^2	2.3 (0.8)	2.3 (0.6)	2.5 (0.7)	2.2 (0.6)
PVR, median (IQR), dyne.s/cm^5	846 (720)	253 (214)	407 (329)	720 (558)
$venSO_2$, mean (SD), %	61 (10)	63 (8)	65 (8)	60 (9)
PaO_2, mean (SD), mm Hg	68 (14)	71 (12)	67 (16)	65 (12)

CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; IQR, interquartile range; LD-PH, pulmonary hypertension due to lung disease; mPAP, mean pulmonary artery pressure; NYHA FC, New York Heart Association functional class; PAH, pulmonary arterial hypertension; PaO_2, arterial oxygen partial pressure; PCWP, pulmonary capillary wedge pressure; PVH, pulmonary hypertension due to left heart disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; $venSO_2$, mixed venous oxygen saturation; 6MWD, 6-minute walk distance.

[a]A total of 70 patients (with PH due to miscellaneous or unknown causes) were not included in this table but formed the remainder of the 2,067 patients enrolled and included in the analysis.

Survival analysis

By the end of the observation period (median follow-up: 37 months), 924 patients (44.7%) had died or had undergone lung or heart and lung transplantation ($n = 52$), and 162 patients (7.8%) were lost to follow-up. Overall 1-, 3- and 5-year survival was 85.5%, 66.7% and 53.6%, respectively. Survival differed significantly between the etiologic groups (Figure 1A).

More deaths occurred among men (483 of 922; 52.4%) than women (441 of 1,145; 38.5%) ($p < 0.001$). Baseline NYHA data were available for 1,533 patients, and Classes I and II were pooled because only 16 patients were Class I. Five-year survival was 78.3%, 58.2% and 39.4% for patients in NYHA Classes I/II, III and IV, respectively (overall $p < 0.001$). Survival showed no significant difference between incident and prevalent patients across all etiologies (refer to Figure S1 in Supplementary Material, available at www.jhltonline.org/).

PAH

The subtype distribution among the 685 patients with PAH was: IPAH, 42.9%; connective tissue disease (CTD), 21.2%; congenital heart disease (CHD), 13.3%; porto-PH, 7.4%; pulmonary veno-occlusive disease (PVOD), 4.1%; human immunodeficiency virus (HIV), 3.9%; and PAH from other causes, 7.2% (see Table S1 online). Women predominated (Table 1).

Overall, 295 patients with PAH (43.1%) died within the observation period, including 180 (40.3%) of the female patients and 115 (48.3%) of the male patients (5-year survival: 63.4% vs 51.9%, respectively; $p = 0.032$). Of the patients with PAH, those with CHD had the highest survival, whereas patients with PVOD had the worst prognosis (Table 2). Survival differed significantly between the largest PAH subgroups (IPAH, CTD and CHD; Figure 1B).

Survival differed significantly between incident and prevalent cases of associated PAH but not IPAH (Table 3, and Figures S2 and S3 online); however, numbers at risk were low in the prevalent groups (associated PAH: $n = 49$ at first visit, $n = 8$ after 5 years; IPAH: $n = 68$ at first visit, $n = 24$ after 5 years).

PVH

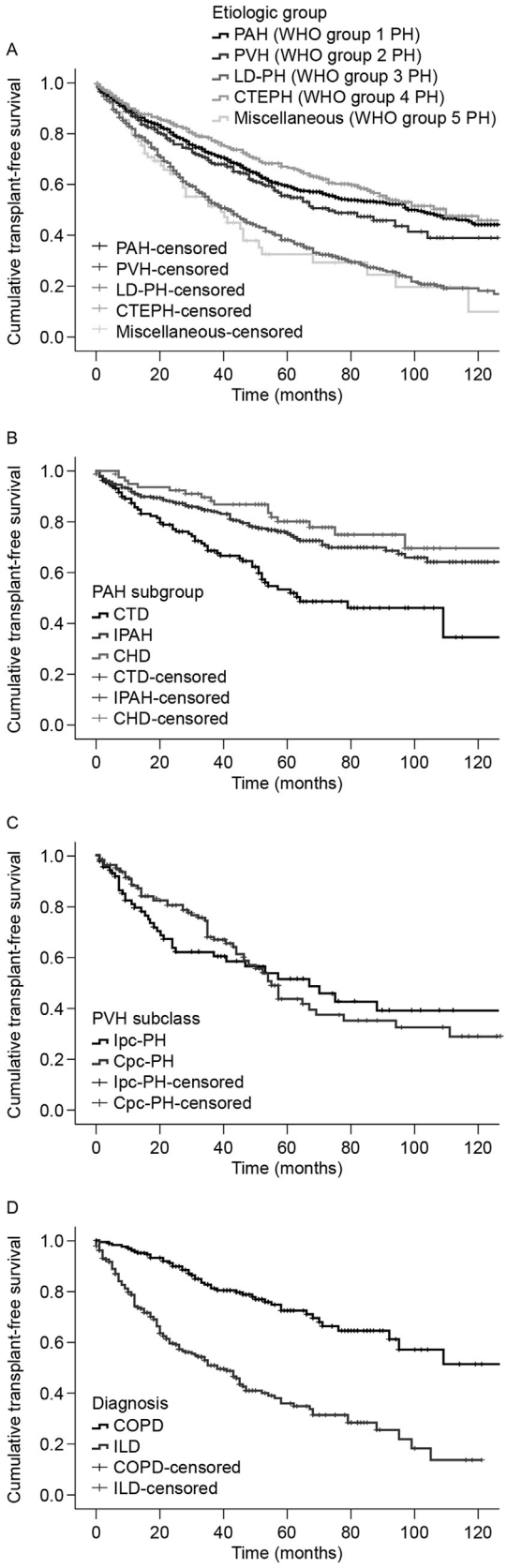
Of 307 patients with PVH, 111 (36.2%) died within the follow-up period; 1-, 3- and 5-year survival was 86.7%, 68.6% and 55.6%, respectively. Women predominated (Table 1), and 5-year survival was 61.8% for women and 47.1% for men ($p = 0.004$); 5-year survival was also worse for patients in NYHA Classes III (59.3%) and IV (32.5%) than for those in NYHA Class I/II (85.9%; $p < 0.001$ overall).

Based on PVR, 129 patients (43%) had isolated post-capillary PH (Ipc-PH; PVR ≤ 3 Wood units) and 172 (57%) had combined pre- and post-capillary PH (Cpc-PH; PVR >3 Wood units; see Table S2 online). These groups differed with regard to mean PAP and PVR ($p < 0.001$) but not cardiac index, PCWP or RAP ($p > 0.18$). NYHA functional class also showed no significant difference ($p = 0.619$), although exercise capacity was better in the group with Ipc-PH rather than Cpc-PH ($p = 0.019$). Both groups had comparable 1-, 3- and 5-year survival (Ipc-PH: 79.5%, 62.2% and 51.6%, respectively; Cpc-PH: 88.0%, 67.9% and 43.7%, respectively) (Figure 1C). More patients with Cpc-PH than Ipc-PH were treated with PAH-specific medications (46% vs 26%, respectively).

LD-PH

Most of the 546 patients with LD-PH had COPD ($n = 218$; 39.9%) or ILD ($n = 283$; 51.8%; see Table S3 online). All patients with LD-PH were treated with optimized therapy

for their lung disorder and received PAH-specific medications if necessary (Table 4). Patients with COPD had significantly better 1-, 3- and 5-year survival than those with ILD (87.7%, 66.3%, and 54.0% vs 71.9%, 40.3% and 22.5%, respectively) (Figure 1D). Men predominated (Table 1), and 5-year survival was 44.0% for women and 34.3% for men ($p = 0.001$). Survival after 1, 3 and 5 years was 90.9%, 74.2% and 52.4%, respectively, for patients in NYHA Class I/II; 83.2%, 56.2% and 37.7%, respectively, for patients in NYHA Class III; and 76.6%, 42.5% and 33.2%, respectively, for patients in NYHA Class IV ($p = 0.011$).



CTEPH

Of 459 patients with CTEPH, 138 (30.1%) died and 91 (19.8%) underwent PEA; 1-, 3- and 5-year survival was 89.2%, 77.4% and 66.7%, respectively (PEA: 96.1%, 87.1% and 76.7%, respectively; non-PEA: 84.5%, 72.5%, and 61.8%, respectively). Survival over 5 years was 71.6% for women and 60.1% for men ($p = 0.012$). Survival at 1, 3 and 5 years was 97.8%, 92.2% and 87.8% for patients in NYHA Class I/II; 93.6%, 85.6% and 73.5%, respectively, for those in NYHA Class III; and 83.4%, 62.9% and 45.6%, respectively, for those in NYHA Class IV (overall $p < 0.001$).

Causes of death

The cause of death was known in 592 of the 924 patients who died. Main causes of death were right heart failure related to PH (23.8%), respiratory insufficiency (21.8%), combined left and right heart failure (9.5%), malignancy (9.0%), sepsis (7.6%), pulmonary infection (5.4%) and sudden cardiac death (4.4%). Causes of death are shown by PH subgroup in Table S4 (online).

Factors associated with survival

The relationship between survival and prognostic factors (NYHA, age, gender and 6MWD) was assessed in a univariate model (Table 5). All factors were prognostic in the PAH group. NYHA was predictive in all etiologic groups, except LD-PH. Age <50 years predicted survival in all etiologic groups (vs >71 years), in PAH, PVH and LD-PH groups (vs 63 to 71 years), and in PAH and PVH groups (vs 50 to 63 years). Female gender predicted survival

Figure 1 Kaplan–Meier transplant-free survival estimates for: (A) all PH etiologic groups (significant difference between groups, log rank $p < 0.001$); (B) the main PAH subgroups (significant difference between groups, log rank $p < 0.001$); (C) patients with PVH categorized by PVR (≤ 3 WU vs >3 WU; no significant difference between groups, log rank $p = 0.896$); and (D) the main LD-PH subgroups (COPD and ILD; significant difference between groups, log rank $p < 0.001$). CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; CTD, connective tissue disease; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension; LD-PH, pulmonary hypertension due to lung disease; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVH, pulmonary venous hypertension; PVR, pulmonary vascular resistance; WHO, World Health Organization; WU, Wood units.

Table 2 Survival in Patients With Pulmonary Arterial Hypertension or Pulmonary Venous Occlusive Disease

	PAH	IPAH	CTD	CHD	PVOD
Patients, *n*	685	294	145	91	28
Survival (%)					
At 1 year	88.2	89.7	85.3	95.4	78.6
At 3 years	72.2	76.2	65.6	84.2	41.2
At 5 years	59.4	65.3	50.9	74.5	18.7

CHD, pulmonary arterial hypertension associated with congenital heart disease; CTD, pulmonary arterial hypertension associated with connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PVOD, pulmonary venous occlusive disease.

in all etiologic groups. A 6MWD >390 meters predicted survival in all etiologic groups (vs <216 meters and 216 to 311 meters) and in PAH and CTEPH groups (vs 311 to 390 meters). When placed in one multivariate model per etiologic group, the NYHA class lost its predictive value, but 6MWD (all etiologic groups), age (PAH) and gender (PAH and CTEPH) still predicted survival (see Table S5 online).

Comparison with other key registries

A systematic literature search (see Appendix online) identified 15 key registries, which are summarized alongside the Gi-PH-Reg in Tables 6 (PAH) and 7 (CTEPH).

Discussion

This study encompasses the largest single-center PH cohort reported to date. The single-center approach has inherent advantages, namely homogeneity of data quality and consistency of standards and procedures. Only 4 other large, single-center registries have been reported, 2 based in the UK, including 1,344 incident PH cases[19] and 880 patients with CTEPH,[20] and 2 based in the USA, encompassing 578 and 697 patients with PAH, respectively.[21,22] During the long time span covered by the Gi-PH-Reg, the number of available PAH therapies in Germany increased dramatically; inhaled prostanoids were available in the 1990s and were joined by parenteral prostanoids in the late 1990s and oral therapies (phosphodiesterase type-5 inhibitors and endothelin-receptor antagonists) in the early 2000s. The overall survival rates reported herein are similar to results from other registries covering a similar era. We found significant variation in survival between PH subtypes; these subgroup survival rates were similar to those reported in the literature for PAH and CTEPH, similar or slightly better for LD-PH[19,23] and slightly worse for PVH[19] (owing at least partly to baseline differences). Causes of death showed patterns consistent with etiology; death due to right heart failure was most common in PAH and CTEPH, death due to combined left and right heart failure was most common in PVH, and death due to respiratory failure was most common in LD-PH. Malignancy accounted for a substantial proportion of deaths in each PH group (3.7% to 6.0%).

Table 3 Survival in Subgroups With Incident or Prevalent Pulmonary Arterial Hypertension

	IPAH		APAH	
	Incident	Prevalent	Incident	Prevalent
Patients, *n*	226	68	325	38
Survival (%)				
At 1 year	90.6	86.8	88.2	79.2
At 3 years	77.8	71.3	70.5	61.1
At 5 years	67.1	58.9	56.8	39.2
At 10 years	54.9	47.3	37.2	19.6

APAH, associated pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension.

Patients with PAH in the Gi-PH-Reg were comparable with those in other national registries in terms of mean age, 6MWD, NYHA distribution, female-to-male ratio and main hemodynamic parameters (Table 6). This concordance underlines the appropriate allocation of patients to the PAH subgroup. We found that patients with IPAH were younger, on average, than patients with other PAH subtypes, and had more severely impaired hemodynamics. Nevertheless, the NYHA distribution and 6MWD were more favorable in patients with IPAH than in those with CTD-PAH. Patients with CHD had the best survival in the PAH group; this coincides with previous publications, showing good long-term survival in patients with CHD/Eisenmenger syndrome.[19,24,25,26] The survival of patients with IPAH (Table 2) compares favorably with outcomes from registries in France (83% and 58% at 1 and 3 years, respectively) and the UK/Ireland (93%, 73% and 61%, respectively, at 1, 3 and 5 years),[25,27] and is broadly consistent with recent reports from the USA (68% to 69% at 5 years) and Spain (91%, 78%, and 69%, respectively, at 1, 3 and 5 years).[26,28] However, when comparing patients with incident and prevalent IPAH, no significant difference was observed within our registry. This is in contrast to the French PAH registry, which showed greater survival in prevalent vs incident cohorts, suggesting "immortal time bias" in the prevalent cohort.[25] The discrepancy may be at least partly due to differences in definitions: in the French registry, prevalent cases were patients diagnosed before the start of the study, whereas prevalent cases in the Gi-PH-Reg were patients who were diagnosed and had started PH therapy elsewhere before referral to our center. Environmental and/or socioeconomic differences between regions may also affect the "immortal time bias." Corroborating our findings, recent data from the Study with an Endothelin Receptor Antagonist in PAH to Improve Clinical Outcome (SERAPHIN), investigating the long-term effects of macitentan in patients with PAH, also showed no difference in survival between incident and prevalent patients in the setting of a well-conducted randomized, controlled clinical trial.[29]

Patients with CTEPH were the third largest group in our database, and had slightly better hemodynamics and survival than the PAH group. Age appeared to be a weaker

Table 4 Initial Therapy[a]

	PAH	PVH	LD-PH[b]	CTEPH
Complete data, *n*	510	83	357	310
Initial monotherapy, *n* (%)				
PDE5i	170 (33)	29 (35)	209 (59)	200 (65)
ERA	102 (20)	1 (1)	36 (10)	12 (4)
IP	86 (17)	—	11 (3)	17 (6)
Other	8 (2)	—	1 (0)	2 (1)
Initial combination therapy, *n* (%)				
PDE5i + ERA	37 (7)	2 (2)	15 (4)	16 (5)
PDE5i + IP	21 (4)	1 (1)	4 (1)	7 (2)
Other	16 (3)	—	1 (0)	—
Triple therapy, *n* (%)	12 (2)	—	—	2 (1)
No specific therapy, *n* (%)	58 (11)	50 (60)	80 (22)	54 (17)

CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin-receptor antagonist; LD-PH, pulmonary hypertension due to lung disease; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type-5 inhibitor; IP, inhalative prostacyclins; PVH, pulmonary hypertension due to left heart disease.

[a]Data are presented as absolute numbers and percent of patients with complete data on drug use. During right heart catheterization, the patients were offered a PAH drug challenge to assess the acute effect of the drug on pulmonary and systemic hemodynamics and gas exchange.

[b]Treatment decisions were made on a patient-by-patient basis, referring to the criteria listed in the 2011 Cologne Consensus Conference[41] for the presence of severe pulmonary hypertension in patients with chronic lung disease (at least 2 of the following: mean pulmonary arterial pressure >35 mm Hg; mean pulmonary arterial pressure ≥ 25 mm Hg with cardiac index <2.0 liters/min/m^2; and pulmonary vascular resistance >480 dyne.s/cm^5).

prognostic indicator in CTEPH compared with other PH subtypes in the univariate analysis, although this pattern was lost in the multivariate analysis. The phenotype and survival of our CTEPH group were similar to results from other CTEPH registries (Table 7), yet a smaller proportion of patients underwent PEA in our cohort. This may be because our registry extends further back in time than other registries comparing operated and non-operated CTEPH. Operability assessment is based predominantly on surgical experience.[30] As experience with PEA has grown over time, the proportion of patients considered operable has also increased. Reasons for not undergoing PEA were not recorded in the Gi-PH-Reg, and may have included patient choice as well as inoperability.

Table 5 Risk Factors for Survival (All-cause Mortality) Using Univariate Cox Regression Analysis

	PAH, $n = 685$ [HR (95% CI; *p*-value)]	PVH, $n = 307$ [HR (95% CI; *p*-value)]	LD-PH, $n = 546$ [HR (95% CI; *p*-value)]	CTEPH, $n = 459$ [HR (95% CI; *p*-value)]
NYHA				
Class II	Reference	Reference	Reference	Reference
Class III	1.80 (1.18 to 2.77; 0.007)	3.04 (1.10 to 8.40; 0.032)	1.69 (0.99 to 2.87; 0.054)	3.51 (1.27 to 9.71; 0.015)
Class IV	3.60 (2.29 to 5.65; <0.001)	6.35 (2.18 to 18.52; 0.001)	2.18 (1.27 to 3.75; 0.005)	7.84 (2.80 to 21.95; <0.001)
Age (years)[a]				
<50	Reference	Reference	Reference	Reference
50 to 63	1.41 (1.06 to 1.88; 0.20)	6.23 (1.45 to 26.68; 0.014)	1.38 (0.93 to 2.03; 0.109)	0.88 (0.50 to 1.55; 0.654)
63 to 71	2.11 (1.55 to 2.86; <0.001)	12.11 (2.92 to 50.31; 0.001)	1.83 (1.24 to 2.71; 0.002)	1.30 (0.76 to 2.24; 0.343)
>71	1.97 (1.34 to 2.88; 0.001)	12.94 (3.13 to 53.59; <0.001)	2.47 (1.65 to 3.70; <0.001)	2.43 (1.46 to 4.02; 0.001)
Gender				
Male (female as reference)	1.29 (1.02 to 1.63; 0.033)	1.70 (1.17 to 2.47; 0.005)	1.43 (1.15 to 1.80; 0.002)	1.53 (1.10 to 2.14; 0.013)
6MWD (meters)[b]				
>390	Reference	Reference	Reference	Reference
311 to 390	1.99 (1.31 to 3.02; 0.001)	2.65 (0.56 to 12.51; 0.217)	1.50 (0.87 to 2.61; 0.147)	3.98 (1.69 to 9.40; 0.002)
216 to 311	2.82 (1.84 to 4.33; <0.001)	7.94 (1.83 to 34.52; 0.006)	2.00 (1.18 to 3.37; 0.010)	3.82 (1.67 to 8.75; 0.002)
<216	5.78 (3.87 to 8.63; <0.001)	12.91 (2.96 to 56.31; 0.001)	2.95 (1.75 to 4.96; <0.001)	6.56 (2.82 to 15.26; <0.001)

CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; HR, hazard ratio; LD-PH, pulmonary hypertension due to lung disease; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PVH, pulmonary hypertension due to left heart disease; 6MWD, 6-minute walk distance.

[a]Age groups represent quartiles.

[b]6MWD groups represent quartiles of the full population.

Table 6 Comparison of Patients with Pulmonary Arterial Hypertension in the Giessen Pulmonary Hypertension Registry and Other Key Registries

	Gi-PH-Reg	ASPIRE[19]	French[7]	Swiss[23]	NIH-PPH[3]	REHAP[42]	REVEAL[5]	PAH-QuERI[43]	PHC[44]	Cleveland Clinic[22]	SMR[45]	UK and Ireland[27]	KORPAH[24]
Recruitment period, years	1993 to 2011	2001 to 2010	2002 to 2003	1998 to 2012	1981 to 1985	1998 to 2008	2006–	2005 to 2007	1982 to 2006	1990 to 2013	1986 to 2001	2001 to 2009	2008 to 2011
PAH population, *n*	685	600	674	549	194 (PPH)	866	2,716	791	578	697	374	482	625
Type of PAH, %													
Idiopathic	43	29	39	60	—	36	47	35	48[a]	41	47	93	23
CTD	21	31	15	18	—	18	24	29	30	30	30	0	50
CHD	13	33	11	8	—	19	12	7	11	15	24	0	25
Porto-PH	7	4	10	5	—	7	5	4	7	11	0	0	—
HIV	4	1	6	7	—	6	2	4	1	—	0	0	—
PVOD	4	<1[b]	—	2	—	2	—	<1	—	—	0	0	—
Female gender, %	65	70	65	60	—	71	79	77	77	73	70	70	80
Mean age, years	51	54	50	57	—	45	50	55[c]	48	54	50 to 52	50	48
NYHA FC, %													
II	19	—	—	24	—	31 (I to II)	38	39	—	30	—	16 (I to II)	35
III	59	64	75 (III and IV)	57	—	58	48	48	80 (III and IV)	49	—	67	38
IV	22	14		17	—	11	5	5		19	—	18	5
Mean 6MWD, m	325	—	329	362	—	363	370	—		313	—	292	376
Mean RAP, mm Hg	8	10	8	9	—	9	9	—	11	—	—	10	9
Mean mPAP, mm Hg	51	48	55	48	—	54	50	—	52	—	—	54	55
Mean PCWP, mm Hg	8	9	8	12	—	—	10	—	10	—	—	9	8
Mean CI, liters/min/m^2	2.3	2.7	2.5	2.5	—	2.6	2.6	—	2.3	—	—	2.1	2.4
Mean PVR, dyne.s/cm^5 (or WU where specified)	846[c]	780	—	753	—	12 WU	11 WU	—	13 WU	—	—	13 WU	—
Treatment, %													
Monotherapy	72	59	—	59	—	—	—	—	—	—	—	97	49
DC	15	—	—	10	—	—	40 (DC + TC)	—	—	—	—	2 (DC + TC)	12 (DC + TC)
TC	2	—	—	3	—	—		—	—	—	—		
No PAH therapy	11	11	—	28	100	—	—	—	—	—	—	1	39
Survival, %													
At 1 year	88	88	88	87	68	86	91	—	84	82	—[d]	93	91
At 3 years	72	68	—	69	48	75	—	71	67	66	—[d]	73	84
At 5 years	59	—	—	—	34	—	—	—	58	—	—[d]	61	—

ASPIRE, Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Center; CHD, congenital heart disease; CI, cardiac index; DC, dual combination; CTD, connective tissue disease; Gi-PH-Reg, Giessen Pulmonary Hypertension Registry; HIV, human immunodeficiency virus; KORPAH, Korean Registry of Pulmonary Arterial Hypertension; mPAP, mean pulmonary artery pressure; NIH-PPH, National Institutes of Health Patient Registry for the Characterization of Primary Pulmonary Hypertension; NYHA FC, New York Heart Association functional class; PAH, pulmonary arterial hypertension; PAH-QuERI, Pulmonary Arterial Hypertension–Quality Enhancement Research Initiative; PCWP, pulmonary capillary wedge pressure; porto-PH, porto-pulmonary hypertension; PHC, Pulmonary Hypertension Connection; PPH, primary pulmonary hypertension; PVOD, pulmonary venous occlusive disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REHAP, Spanish Registry of Pulmonary Arterial Hypertension; REVEAL, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; SMR, Scottish Morbidity Record; TC, triple combination; WU, Wood units; 6MWD, 6-minute walk distance.

[a]Idiopathic/familial PAH.

[b]Patients with PVOD ($n = 2$) were not included in the analysis of patient characteristics and outcomes in the ASPIRE PAH group.

[c]Data expressed as median.

[d]Median survival was 3.8 and 5.6 years, respectively, for women and men with idiopathic PAH.

Table 7 Comparison of Patients with Chronic Thromboembolic Pulmonary Hypertension in the Giessen Pulmonary Hypertension Registry and Other Key Registries

	Gi-PH-Reg			International CTEPH[46]		REHAP[47]		Swiss[23]	UK PH Service[48]		UK national cohort[20]
	PEA	Non-PEA	ASPIRE[19]	Operated CTEPH	Non-operated CTEPH	PEA	Non-PEA	Non-operated CTEPH	Surgically accessible CTEPH	Non-surgical CTEPH	PEA
Recruitment period, years	1993 to 2011	1993 to 2011	2001 to 2010	2007 to 2009	2007 to 2009	2006 to 2013	2006 to 2013	1998 to 2012	2001 to 2006	2001 to 2006	1997 to 2012
CTEPH population, *n*	123	336	242	404	275	122	269	249	321	148	880
Female gender, %	51	59	54	45	57	44	64	52	47	56	47
Mean age, years	58	63	61	60[a]	67[a]	50[a]	69[a]	63	58	60	57
NYHA FC, %											
II	18	13	—	19 (I or II)	18 (I or II)	28 (I or II)	30 (I to II)	—	12	16	9
III	63	59	70	69	69	68	62	–	73	68	68
IV	19	28	17	12	13	4	9	—	15	16	23
Mean 6MWD, m	316	301	—	340[a]	315[a]	400[a]	320[a]	365	243	239	260
Mean RAP, mm Hg	10	7	11	9[a]	8[a]	—	—	9	9[a]	10[a]	—
Mean mPAP, mm Hg	49	40	48	48[a]	45[a]	48	45	45	48	49	47
Mean PCWP, mm Hg	8	9	11	10[a]	10[a]	—	—	12	—	—	—
Mean CI, liters/min/m^2	2.0	2.3	2.5	2.2[a]	2.3[a]	—	—	2.3	2.1	2.1	—
Mean PVR, dyne.s/cm^5 (or WU where specified)	868[a]	594[a]	735	728[a]	676[a]	9 WU[a]	8 WU[a]	767	1,091	1,098	830
Treatment, %											
Monotherapy	78	74	77	29	43	—	71	65	—	—	—
SC	7	7	—	0	18	—	—	8	—	—	—
TC	1	1	—	0	0	—	—	0.4	—	—	—
No PAH therapy	14	18	14	71	39	57	18	27	35—71	10—30	36
Survival, %											
At 1 year	96.1	84.5	89	93	88	97	93	91	88[b]	82	86
At 3 years	87.1	72.5	71	89	70	91	81	77	76[b]	70	84
At 5 years	76.7	61.8	—	—	—	86	65	—	—	—	79

ASPIRE, Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Center; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; DC, dual combination; Gi-PH-Reg, Giessen Pulmonary Hypertension Registry; mPAP, mean pulmonary artery pressure; NYHA FC, New York Heart Association functional class; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REHAP, Spanish Registry of Pulmonary Arterial Hypertension; TC, triple combination; WU, Wood units; 6MWD, 6-minute walk distance.

[a]Data expressed as median.

[b]Survival was reported for 236 patients who underwent pulmonary endarterectomy.

Our patients with PVH had worse survival than those with PAH, despite having less compromised hemodynamics. Our PVH group also had poorer survival than the PVH group in the UK-based ASPIRE registry, despite having a higher rate of treatment with PAH therapies (40% vs 13%).[19] This could be interpreted as a lack of benefit of PAH therapies in PVH, consistent with the disappointing clinical trial results in this group,[31] but other factors are also likely to have contributed to the difference in survival. For example, the Gi-PH-Reg PVH group showed classical features of an elderly population with more severely impaired exercise ability than the younger PAH group; it also had a greater proportion of patients in NYHA Class IV than the ASPIRE PVH group (19% vs 6%).[19]

The diastolic pulmonary gradient (DPG) has been suggested as a measure to distinguish Ipc-PH and Cpc-PH,[32,33] but studies of its prognostic value have shown inconsistent results, and recent European PH guidelines recommend using a combination of DPG and/or PVR (Ipc-PH: DPG <7 mm Hg and/or PVR ≤ 3 Wood units; Cpc-PH: DPG ≥ 7 mm Hg and/or PVR >3 Wood units).[34] Eighty-four patients in our PVH group had a negative (uninterpretable) DPG. Furthermore, many of our patients were not classified when we applied both DPG and PVR criteria, whereas classification based on either DPG or PVR resulted in many patients being classified as having both Ipc-PH and Cpc-PH. Therefore, we classified our patients based on PVR and found that long-term survival was similar in the Ipc-PH and Cpc-PH subgroups. Further clarification of the new definition of Ipc-PH vs Cpc-PH would help to ensure its appropriate implementation in clinical practice.

The LD-PH group was the only subgroup in which men outnumbered women. The outcome of this group overall was worse than for patients with PAH or CTEPH. Comparing COPD and ILD subgroups, the latter had a considerably worse outcome, consistent with epidemiologic data for these populations.[19] In ASPIRE, the LD-PH subgroup had 1- and 3-year survival of 65% and 44%, respectively[19]; our patients lived slightly longer, but this may have been due to the differing proportions of COPD and ILD or differences in severity of PH.[35]

Known prognostic indicators in PAH (particularly IPAH) were examined thoroughly in other PH subtypes in our study: the 6MWD remains the strongest predictor across all groups of PH, although the results are most robust in PAH. Following current guidelines, patients are classified according to PH etiology. This specific diagnosis should be considered when judging which prognostic factor is relevant.

NYHA functional class has been previously highlighted as a major prognostic factor in PAH.[14,36] However, in our PAH subgroup, NYHA was identified as a predictor of mortality only by univariate and not multivariate analysis. This is consistent with the findings of several other studies,[37] although a large study of 2,716 patients with PAH did identify functional class as an independent prognostic factor.[5] Prognosis is better assessed by considering a combination of factors rather than a single factor in isolation; recent European PH guidelines recommend determining functional class, at least 1 measurement of exercise capacity and right ventricular function.[34]

Limitations

We studied a single-center cohort, but our reference center is one of the largest worldwide and therefore survival data may be representative of the PH population—although milder cases may not be referred to us. Referral bias may also partly explain the relatively small size and poor outcome of the PVH group. According to the current guidelines, referral to an expert PH center is recommended for patients with PVH if a severe pre-capillary component is found.[34,38] This may only be the case in a small number of patients with advanced heart failure: although PH is common in patients with left heart disease,[34] the prevalence of Cpc-PH in chronic heart failure is low (12% in a recent database study),[39] and results from a community-based study suggest that right ventricular dysfunction is associated with advanced stages of heart failure.[40] Thus, our PVH group may represent patients with severe disease.

We did not have complete data on right heart catheterization at baseline: some patients came with clinically acceptable right heart catheterization values from secondary centers, but these data were not entered in the database. Baseline 6MWD data were also not available for all patients, but this is unlikely to have introduced selection bias; the choice of baseline exercise test (6MWD vs spiroergometry) was based on availability of functional units rather than patients' characteristics, and patients who underwent spiroergometry at baseline had 6MWD assessed at the following visit.

Finally, PAH therapies were used off-label in a substantial proportion of patients with other PH subtypes, highlighting the need for further research to develop treatments for these patient groups. It should be emphasized that this off-label use reflects the current conditions at a tertiary care center only and must not be generalized. Off-label use of PAH therapies is not the standard of care for patients with PVH, LD-PH or PH due to miscellaneous or unknown causes, and current guidelines advise against the initiation of such vasoactive therapies in a primary care setting.[34] The initiation of specific therapies should only be considered in a tertiary care center after thorough evaluation of the patient by an expert PH team, and for patients in whom pre-capillary PH and subsequent right heart insufficiency are the main drivers of symptoms and disease progression. Close re-evaluation is mandatory to assess effectiveness and side effects to decide whether the treatment is beneficial for the individual patient. The transferability of our results may vary depending on regional healthcare system practice regarding the use of off-label therapies.

Conclusions

This is the largest single-center PH cohort reported to date. Overall 1-, 3- and 5-year survival was 85.5%, 66.7% and

53.6%, respectively, and survival differed significantly between PH subtypes. Although NYHA functional class is used commonly to predict the likelihood of survival, it was a less powerful predictor across all etiologic groups when compared with patients' age, gender and 6MWD.

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Supplementary materials

Supplementary materials associated with this article can be found in the online version at www.jhltonline.org/.

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