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Pediatric Cardiology

Survival Differences in Pediatric Pulmonary Arterial Hypertension

Clues to a Better Understanding of Outcome and Optimal Treatment Strategies

Willemijn M. H. Zijlstra, BSc,* Johannes M. Douwes, MD,* Erika B. Rosenzweig, MD,† Sandor Schokker, BSc,* Usha Krishnan, MD,† Marcus T. R. Roofthooft, MD, PhD,* Kathleen Miller-Reed, RN,‡ Hans L. Hillege, MD, PhD,§ D. Dunbar Ivy, MD,‡ Rolf M. F. Berger, MD, PhD*

Groningen, the Netherlands; New York, New York; and Aurora, Colorado

Objectives In order to describe survival and treatment strategies in pediatric pulmonary arterial hypertension (PAH) in the current era of PAH-targeted drugs and to identify predictors of outcome, we studied uniformly defined contemporary patient cohorts at 3 major referral centers for pediatric PAH (New York [NY], Denver, and the Netherlands [NL]).

Background In pediatric PAH, discrepancies exist in reported survival rates between North American and European patient cohorts, and robust data for long-term treatment effects are lacking.

Methods According to uniform inclusion criteria, 275 recently diagnosed consecutive pediatric PAH patients who visited the 3 referral centers between 2000 and 2010 were included.

Results Unadjusted survival rates differed between the center cohorts (1-, 3-, and 5-year transplantation-free survival rates: 100%, 96%, and 90% for NY; 95%, 87%, and 78% for Denver; and 84%, 71%, and 62% for NL, respectively; $p < 0.001$). Based on World Health Organization (WHO) functional class and hemodynamic parameters, disease severity at diagnosis differed between the center cohorts. Adjustment for diagnosis, WHO functional class, indexed pulmonary vascular resistance, and pulmonary-to-systemic arterial pressure ratio resolved the observed survival differences. Treatment with PAH-targeted dual and triple therapy during the study period was associated with better survival than treatment with PAH-targeted monotherapy.

Conclusions Survival rates of pediatric PAH patients differed between 3 major referral centers. This could be explained by differences between the center cohorts in patients' diagnoses and measures of disease severity, which were identified as important predictors of outcome. In this study, treatment with PAH-targeted combination therapy during the study period was independently associated with improved survival. (J Am Coll Cardiol 2014;63:2159–69)
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Pulmonary arterial hypertension (PAH) is a rare, progressive pulmonary vascular disease that has a poor prognosis with a median survival of <3 years if untreated (1). It can present at any age, including childhood, during which survival is believed to be even worse (2,3). Substantial progress has been made in treatment strategies for adult PAH, resulting in improved quality of life and survival (4,5). Adult studies alone do not provide a basis for optimal care for children. However, due to the virtual absence of pediatric efficacy and outcome data, these adult treatment strategies have been extrapolated to children with PAH.

Recently, survival data for pediatric PAH in the current treatment era of PAH-targeted drugs have been reported from different patient cohorts. These include 2 reports of national cohorts of children with PAH from Europe (United Kingdom and the Netherlands) and 2 reports from the United

From the *Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; †Columbia University College of Physicians and Surgeons, New York, New York; ‡Children's Hospital Colorado, Aurora, Colorado; and the §Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands. Dr. Rosenzweig has received honoraria from Actelion and the United Therapeutics for Scientific Advisory Board, and research support through Columbia University College of Physicians and Surgeons from Actelion, Gilead, and United Therapeutics. The University of Colorado has received consulting fees for Dr. Ivy from Actelion, Bayer, Gilead, Lilly, Pfizer, and United Therapeutics. The University Medical Center Groningen has received consulting fees for Dr. Berger from Actelion, Bayer, Glaxo-SmithKline, Lilly, Novartis, and Pfizer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

APAH = associated pulmonary arterial hypertension
BNP = brain natriuretic peptide
CCB = calcium channel blocker
CHD = congenital heart disease
HPAH = hereditary pulmonary arterial hypertension
IPAH = idiopathic pulmonary arterial hypertension
IV = intravenous
mPAP/mSAP = mean pulmonary-to-systemic arterial pressure ratio
NT-proBNP = N-terminal pro-brain natriuretic peptide
PAH = pulmonary arterial hypertension
PH = pulmonary hypertension
PVRi = pulmonary vascular resistance index
SC = subcutaneous
WHO = World Health Organization

States, including 1 study of a cohort of children followed in 2 major US referral centers and 1 of a subgroup of patients with childhood-onset PAH included in a U.S.-based multicenter PAH registry (REVEAL [Registry to Evaluate Early and Long-Term PAH Disease Management]) (6–10). In all cohorts, the reported survival seemed to be improved compared to historical reports. However, intriguingly, the reported survival rates appeared to differ significantly between the European and U.S. reports.

No direct comparisons can be made between these reported survival rates due to differences in inclusion criteria, patient characteristics, and data collection. Nevertheless, these discrepancies in survival are of interest, because they might be a consequence of varying patient characteristics or different treatment strategies adopted by the reporting centers. Therefore, they may reveal information on the importance of clinical predictors of survival and on the optimal treatment strategy.

We directly compared patient characteristics, treatment strategies, and outcomes and identified predictors of outcome in pediatric PAH patients seen on both sides of the Atlantic Ocean, specifically those seen in 2 major referral centers in the United States (New York, New York, and Denver, Colorado) and those seen in a national referral center for pediatric PAH based in Europe (the Netherlands) using similar standardized inclusion criteria.

Methods

Patient data were retrospectively collected from 3 major referral centers for pediatric PAH: 2 U.S.-based centers, the Children's Hospital Colorado, Denver, Colorado (Denver cohort) and Columbia University Medical Center, New York, New York (NY cohort) and 1 Europe-based center, the University Medical Center Groningen/Beatrix Children's Hospital, Groningen (Dutch cohort). The Europe-based center serves as the national referral center for pulmonary hypertension (PH) in childhood in the Netherlands. All Dutch children with (suspected) PAH are referred to this center for diagnostic workup, treatment, and follow-up. It therefore follows a national cohort of children with PAH.

Patients. To define patient cohorts in a way that allowed for direct comparison, we used uniform inclusion criteria: all pediatric PAH (group 1 PH, Dana Point classification [11]) patients who visited the 3 referral centers between 2000 through 2010, diagnosed by cardiac catheterization at <18 years of age, were included. Diagnosis of PAH was defined as mean pulmonary arterial pressure ≥25 mm Hg, mean pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance index (PVRi) ≥3 Woods units·m^2. To ensure similar PAH-targeted drug availability for all studied patients, only patients who visited the referral centers between 2000 and 2010 were included. To study a contemporary cohort, only patients diagnosed after 1997 were included. In patients with a corrected heart defect, diagnosis of PAH was confirmed at least 1 year after corrective surgery (12). Patients who had pulmonary arterial pressures normalized while therapy was discontinued were considered not to have PAH because of the progressive character of the disease, and were not included. To avoid double inclusion, 1 patient who switched from one to the other U.S. center was included in the cohort of the latter center. All patient data were uniformly collected in a database specifically designed for this study.

Patients with PH secondary to left heart disease, lung disease, thromboembolic disease, or PH with unclear multifactorial mechanisms (group 2 to 5 PH, Dana Point classification [11]) were not included in this study.

Study assessments. Patients were diagnosed according to the Clinical Classification of Pulmonary Hypertension (Dana Point update) (11). For this study, diagnosis was classified as idiopathic or hereditary PAH (IPAH/HPAH), PAH associated with congenital heart disease (PAH-CHD), or associated PAH-non-CHD (APAH-non-CHD) (12). In case of CHD, type of shunt was defined as pre-tricuspid (e.g., atrial septal defect), post-tricuspid (e.g., ventricular septal defect), repaired pre- or repaired post-tricuspid shunt, or as no previous shunt (e.g., coarctation of the aorta). Furthermore, Eisenmenger syndrome was defined as the presence of a post-tricuspid shunt with right-to-left shunting and systemic arterial, or if not available, transcutaneous, oxygen saturation of less than 90%.

Baseline parameters included clinical and hemodynamic characteristics at diagnosis. Age-normalized scores (z-scores) for height and body mass index were calculated using World Health Organization (WHO) child growth standards (13,14). Mean pulmonary-to-systemic arterial pressure ratios (mPAP/mSAP), pulmonary-to-systemic vascular resistance ratios and pulmonary-to-systemic blood flow ratios were calculated. Acute responder status was determined according to criteria defined by the REVEAL study for childhood-onset PAH (10), Barst et al. (15), and Sitbon et al. (16).

Specific PAH therapy was classified as either calcium channel blocker (CCB) therapy without the need for additional PAH-targeted therapy (CCB monotherapy) or as PAH-targeted therapy, including prostanoids, endothelin receptor antagonists, and type 5-phosphodiesterase inhibitors. PAH-targeted therapy was further classified as monotherapy or as combination therapy with a combination

of 2 (dual therapy) or 3 (triple therapy) PAH-targeted drugs administered for at least 3 months or until end of follow-up. Real-time therapy was cumulatively plotted per center cohort for visual comparison. Furthermore, treatment strategy was defined as either CCB monotherapy when a CCB was the only specific PAH drug used during the patient's disease course or the maximum number of simultaneously used PAH-targeted drugs (mono-, dual, or triple therapy). Also, it was determined whether therapy included an intravenously (IV) or subcutaneously (SC) administered prostanoid. Two Dutch patients and 1 Denver patient were excluded from this latter comparison because their death within 7 days after diagnosis did not allow for start of specific PAH therapy.

Statistical analysis. Data are presented as mean ± SD, median (interquartile range), and number (percentage) of patients, as appropriate. Patient characteristics, baseline parameters, and treatment strategy were compared between the 3 center cohorts, using one-way analysis of variance (ANOVA) for continuous normally distributed variables, and Kruskal-Wallis test and Mann Whitney *U* test for ordinal and not normally distributed continuous variables. Multiple chi-square tests and Fisher exact tests were used for categorical variables. Post-hoc Bonferroni was used to correct for multiple comparisons, as appropriate.

Survival analyses were based on transplantation-free survival. Patients who did not die or undergo (heart-)lung transplantation were censored at the last recorded visit. For this study, patients who had had their last recorded visit more than 2 years before the end of the study period were considered lost to follow-up.

Survival rates were compared between the 3 center cohorts by using Kaplan-Meier curves with log rank testing. Kaplan-Meier curves were also used to illustrate the survival of the patient groups who underwent different treatment strategies. To determine predictors of survival in the total cohort, univariate Cox regression analysis was performed. Multivariate backward stepwise Cox regression analysis was used to identify the strongest independent predictors of survival. P values <0.05 were considered significant.

To assess potential overfitting, we conducted secondary sensitivity analyses using bootstrap model selection to assess independent predictors of survival. This method has been used previously in the context of a population of coronary stent thromboses to avoid an overfit model (17). Among the variables, bootstrap selection with 500 models was performed in the full dataset only without natriuretic peptides due to the substantial number of missing cases, the full dataset without natriuretic peptides, and blood pressure and, finally, the full dataset without natriuretic peptides, blood pressure, and center (see Table 3).

Results

In total, 275 pediatric patients were included in this study: 135 patients from NY, 93 patients from Denver, and 47 patients from the Netherlands. Patient characteristics and clinical and hemodynamic parameters at time of diagnosis are shown in Table 1.

Patients were comparable regarding age at diagnosis and sex. Time between first symptoms and diagnosis was significantly longer in the NY cohort than in the Dutch and Denver cohorts ($p < 0.001$). In all 3 cohorts, most patients had diagnoses of IPAH/HPAH or PAH-CHD, although its distribution differed between the center cohorts. In the Dutch and NY cohorts, most patients had diagnoses of IPAH/HPAH versus PAH-CHD in the Denver cohort. The occurrence of APAH-non-CHD (including PAH associated with connective tissue disease, human immunodeficiency virus antibodies, hemolytic anemia, portal hypertension, drugs/toxins, pulmonary capillary hemangiomatosis, or pulmonary veno-occlusive disease) was higher in the Dutch cohort than in the NY cohort ($p = 0.025$).

At time of diagnosis, patients in the Dutch cohort had higher WHO functional class, shorter 6-min walk distance, higher PVRi and pulmonary-to-systemic vascular resistance ratio, and lower systemic blood flow index and mean systemic arterial pressure than the NY and Denver cohorts. Prevalence of acute responders depended on the criteria used, ranging from 14% to 19% of the NY patients, 15% to 31% of the Denver patients, and 8% to 25% of the Dutch patients, and did not differ between the center cohorts.

Treatment. The 7-year cumulative treatment follow-up of the 3 center cohorts is plotted in Figure 1. The figure shows that in all 3 center cohorts, there was a similar, stable percentage of patients receiving CCB monotherapy. Considering PAH-targeted therapy, in all 3 cohorts, most patients started on monotherapy, with high percentages of patients on monotherapy within the first 3 years after diagnosis. In time, patients were switched from monotherapy to dual or triple therapy. In all 3 center cohorts a small number of patients received no specific PAH therapy within this 7-year period. These patients either died shortly after diagnosis before therapy could be started, received therapy after 7 years of follow-up, or received no therapy because their low WHO functional classification at that time did not warrant therapy according to evolving treatment strategies. Furthermore, the figure illustrates a higher mortality rate in the Dutch cohort and a higher percentage of patients lost to follow-up in the Denver and NY cohorts. The distribution of treatment strategy did not differ among the center cohorts (Table 2).

Transplantation-free survival and predictors of prognosis. Follow-up time ranged from 0.01 to 13.7 years (median, 4.0 years). During the study period, 7 NY patients (5%), 18 Denver patients (19%), and 15 Dutch patients (32%) died. Furthermore, 6 NY patients (4%) and 1 Dutch patient (2%) underwent lung transplantation. Overall, 1-, 3-, 5-, and 7-year transplantation-free survival rates were 96%, 89%, 81%, and 79%, respectively (Fig. 2A). Unadjusted survival of children in the NY cohort was significantly more favorable than survival of patients in the other 2 cohorts (Fig. 2B).

Table 1 Patient Characteristics and Clinical and Hemodynamic Parameters at Diagnosis Stratified by Center Cohort

	All Patients		New York Cohort		Denver Cohort		Dutch Cohort		
	N	Value	n	Value	n	Value	n	Value	p Value
Age at diagnosis, yrs	275	6.4 (2.5–11.8)	135	7.2 (2.6–12.1)	93	5.0 (2.5–9.7)	47	7.9 (2.5–13.7)	0.283
Age at first symptoms, yrs	225	5.0 (1.1–10.1)	124	4.5 (0.6–9.7)	55	5.1 (2.5–10.1)	46	6.1 (0.7–11.4)	0.260
Time from first symptoms to diagnosis, months	225	7.6 (2.2–22.9)	124	11.7 (4.2–29.7)	55	3.4 (0.7–12.2)	46	4.1 (2.0–15.1)	<0.001*†
Incident patients	275	244 (89)	135	114 (84)	93	87 (94)	47	43 (92)	0.087
Female	275	162 (59)	135	81 (60)	93	55 (59)	47	26 (55)	0.869
Ethnicity	275		135		93		47		0.004†
Caucasian		187 (68)		78 (58)		68 (73)		41 (87)	
Black		13 (5)		8 (6)		3 (3)		2 (4)	
Asian		23 (8)		17 (13)		4 (4)		2 (4)	
Hispanic		33 (12)		17 (13)		14 (15)		2 (4)	
Other or unknown		19 (7)		15 (11)		4 (4)		0	
Down syndrome	275	35 (13)	135	12 (9)	93	18 (19)	47	5 (11)	0.059
Diagnosis	275		135		93		47		0.023
IPAH/HPAH		144 (52)		76 (56)		40 (43)		28 (60)	
PAH-CHD		114 (42)		54 (40)		47 (51)		13 (28)	
No shunt		6 (5)		1 (2)		5 (11)		0	0.011‡
Pre-tricuspid shunt		13 (11)		4 (7)		8 (17)		1 (8)	
Post-tricuspid shunt		54 (47)		30 (56)		13 (28)		11 (85)	
Repaired pre-tricuspid shunt		6 (5)		2 (4)		4 (9)		0	
Repaired post-tricuspid shunt		35 (31)		17 (32)		17 (36)		1 (8)	
Eisenmenger syndrome§		14 (12)		7 (13)		3 (6)		4 (31)	0.067
APAH-non-CHD		17 (6)		5 (4)		6 (7)		6 (13)	
Symptoms at diagnosis	215		109		59		47		
Dyspnea in rest		27 (13)		13 (12)		0		14 (30)	<0.001*†‡
Dyspnea on exertion		124 (58)		63 (58)		25 (42)		36 (77)	0.002‡
Chest discomfort		29 (13)		22 (20)		5 (9)		2 (4)	0.012†
Fatigue		52 (24)		26 (24)		19 (32)		7 (15)	0.117
Syncope		36 (17)		23 (21)		4 (7)		9 (19)	0.053
WHO functional class	236		123		67		46		0.011†‡
I		14 (6)		13 (11)		0		1 (2)	
II		107 (45)		56 (46)		40 (60)		11 (24)	
III		78 (33)		33 (27)		18 (27)		27 (59)	
IV		37 (16)		21 (17)		9 (13)		7 (15)	
Height, cm	193	119.3 ± 34.1	88	123.4 ± 32.4	63	112.3 ± 34.1	42	121.4 ± 36.7	0.131
Weight, kg	198	29.0 ± 21.1	90	31.3 ± 22.3	63	25.5 ± 19.0	45	29.2 ± 21.1	0.242
BMI, kg/m^2	192	17.8 ± 5.0	87	18.5 ± 5.6	63	17.2 ± 4.3	42	17.3 ± 4.4	0.262
Z-score height	193	−0.87 ± 1.5	88	−0.78 ± 1.27	63	−1.11 ± 1.68	42	−0.72 ± 1.61	0.295
Z-score BMI	190	−0.12 ± 1.6	87	0.07 ± 1.63	62	−0.22 ± 1.45	41	−0.36 ± 1.58	0.299
$TcSO_2$, %	166	94 ± 7	70	95 ± 4	59	92 ± 8	37	92 ± 8	0.020
6MWD, m	72	428 ± 100	34	471 ± 71	20	444 ± 103	18	329 ± 75	<0.001†‡
Log value of NT-proBNP	41	2.85 ± 0.77		—	15	2.85 ± 0.82	26	2.85 ± 0.76	0.991
Log value of BNP	51	1.91 ± 0.63	20	2.03 ± 0.46	26	1.96 ± 0.67	5	1.33 ± 0.86	0.079
Systolic blood pressure, mm Hg	190	96 ± 16	91	99 ± 12	66	87 ± 17	33	104 ± 16	<0.001*‡
Diastolic blood pressure, mm Hg	181	58 ± 12	82	63 ± 10	66	51 ± 12	33	62 ± 12	<0.001*‡
mPAP, mm Hg	275	55 ± 18	135	57 ± 19	93	52 ± 19	47	53 ± 16	0.094
mSAP, mm Hg	273	66 ± 14	134	68 ± 14	92	66 ± 14	47	59 ± 13	<0.001†‡
mRAP, mm Hg	269	6 ± 3	131	6 ± 3	92	7 ± 3	46	7 ± 4	0.241
mPCWP, mm Hg	275	9 ± 3	135	8 ± 3	93	9 ± 3	47	9 ± 3	0.666
Qsi, l/min/m^2	270	3.60 ± 1.73	131	3.73 ± 1.91	93	3.67 ± 1.34	46	3.10 ± 1.85	0.089
Qpi, l/min/m^2	275	3.65 ± 1.74	135	3.86 ± 1.98	93	3.77 ± 1.53	47	2.78 ± 1.03	0.001†‡
PVRi, WU·m^2	275	15.81 ± 10.79	135	15.93 ± 10.62	93	14.01 ± 10.20	47	19.04 ± 11.83	0.032‡
SVRi, WU·m^2	252	19.78 ± 10.69	117	20.96 ± 11.80	90	18.27 ± 10.01	45	19.75 ± 8.62	0.200
mPAP/mSAP	273	0.86 ± 0.30	134	0.87 ± 0.30	92	0.81 ± 0.29	47	0.92 ± 0.30	0.095
PVR/SVR	252	0.87 ± 0.78	117	0.82 ± 0.54	90	0.79 ± 0.46	45	1.16 ± 1.47	0.021†‡

Continued on the next page

Table 1 Continued

	All Patients		New York Cohort		Denver Cohort		Dutch Cohort		
	N	Value	n	Value	n	Value	n	Value	p Value
Qp/Qs	270	1.05 ± 0.31	131	1.08 ± 0.35	93	1.04 ± 0.24	46	1.00 ± 0.34	0.336
Acute vasodilator response									
Sitbon criteria	217	29 (13)	98	14 (14)	79	12 (15)	40	3 (8)	0.475
Barst criteria	203	37 (18)	88	12 (14)	75	18 (24)	40	7 (18)	0.230
REVEAL childhood criteria	203	50 (25)	88	17 (19)	75	23 (31)	40	10 (25)	0.245

Values are mean ± SD, median (interquartile range), or n (%). *Post-hoc test with Bonferroni correction shows a p value <0.05 between the Denver and NY cohorts. †Post-hoc test with Bonferroni correction shows a p value <0.05 between the Dutch and NY cohorts. ‡Post-hoc test with Bonferroni correction shows a p value <0.05 between the Dutch and Denver cohorts. §Of all PAH-CHD patients, separate from shunt types.

6MWD = 6-min walk distance; APAH-non-CHD = associated pulmonary arterial hypertension non-congenital heart disease; BMI = body mass index; BNP = brain natriuretic peptide; IPAH/HPAH = idiopathic/hereditary PAH; mPAP = mean pulmonary arterial pressure; mPAP/mSAP = pulmonary-to-systemic arterial pressure ratio; mPCWP = mean pulmonary capillary wedge pressure; mRAP = mean right atrial pressure; mSAP = mean systemic arterial pressure; NT-proBNP = N-terminal pro brain natriuretic peptide; PAH-CHD = PAH associated with congenital heart disease; PVRi = pulmonary vascular resistance index; PVR/SVR = pulmonary-to-systemic vascular resistance ratio; Qpi = pulmonary blood flow index; Qp/Qs = pulmonary-to-systemic blood flow ratio; Qsi = systemic blood flow index; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; SVRi = systemic vascular resistance index; $TcSO_2$ = transcutaneous oxygen saturation; WU = Woods units.

Within the Dutch cohort, 33% of the deceased patients died within 3 months after diagnosis versus 6% and 0% of the deceased Denver and NY patients, respectively. Exclusion of these patients did diminish but not completely abolish the survival differences among the center cohorts (Fig. 3A). Thirty-three NY patients (24%), 6 Denver patients (7%), and 2 Dutch patients (4%) were considered lost to follow-up according to the study methodology ($p < 0.001$). In theory, such patients could favorably bias survival estimates because their potential death during the study period would not be taken into account. To illustrate the maximal effect, we estimated survival rates, hypothesizing that all such patients had died, regardless of any knowledge of these patients' health status after the end of the study period. In this worst-case scenario, no survival difference between the center cohorts was observed (Fig. 3B).

Acute responders according to the Sitbon criteria had better survival than those who did not meet the Sitbon criteria ($p = 0.029$). The Barst criteria and the REVEAL for childhood-onset PAH criteria did not differentiate between patients with better and worse survival in this population.

Univariate Cox regression analysis (Table 3) showed that compared to children with IPAH/HPAH, those with PAH-CHD had better transplantation-free survival, whereas those with APAH-non-CHD had worse survival. Furthermore, younger age at first symptoms, lower WHO functional class, lower systemic blood pressure, lower plasma N-terminal pro brain natriuretic peptide (NT-proBNP), lower mean right atrial pressure, higher systemic blood flow index, lower PVRi, and lower mPAP/mSAP were associated with better outcome. Sex, ethnicity, Down syndrome, age at diagnosis, syncope, 6-min walk distance, z-scores for height and body mass index, plasma brain natriuretic peptide (BNP), and mean pulmonary arterial pressure were not associated with transplantation-free survival.

NT-proBNP and systolic and diastolic blood pressure were excluded from multivariate analysis because of >20% missing cases. Multivariate backward stepwise Cox regression analysis with the remaining variables that emerged from univariate analysis showed that diagnosis, WHO functional class, PVRi, mPAP/mSAP, and treatment strategy were the strongest independent predictors of transplantation-free survival (Table 4). To eliminate a potential effect of PAH-CHD patients with an open shunt for the value of these predictors, we repeated these analyses after exclusion of these 67 patients, which did not change these findings. Also, the findings did not change when accounting for referral center.

Table 2 Treatment Strategy Stratified by Center Cohort

Treatment Strategy	All patients (N = 272)	New York Cohort (n = 135)	Denver Cohort (n = 92)	Dutch Cohort (n = 45)	p Value
No specific PAH therapy	13 (5)	3 (2)	5 (5)	5 (11)	0.088
CCB monotherapy	24 (9)	11 (8)	10 (11)	3 (7)	
PAH-targeted monotherapy	96 (35)	44 (33)	34 (37)	18 (40)	
Without IV/SC prostanoids	76 (28)	31 (23)	32 (35)	13 (29)	
With IV/SC prostanoids	20 (7)	13 (10)	2 (2)	5 (11)	
PAH-targeted dual therapy	92 (34)	48 (36)	28 (30)	16 (36)	
Without IV/SC prostanoids	51 (19)	28 (21)	13 (14)	10 (22)	
With IV/SC prostanoids	41 (15)	20 (15)	15 (16)	6 (13)	
PAH-targeted triple therapy	47 (17)	29 (21)	15 (16)	3 (7)	
Without IV/SC prostanoids	14 (5)	10 (7)	3 (3)	1 (2)	
With IV/SC prostanoids	33 (12)	19 (14)	12 (13)	2 (4)	

Values are n (%).

CCB = calcium channel blocker; IV = intravenous; PAH = pulmonary arterial hypertension; SC = subcutaneous.

Table 3 Patient, Baseline Clinical, and Hemodynamic Characteristics Associated With Survival

	Univariate Cox Regression Analysis	
	Hazard Ratio (95% CI)	p Value
Cohort		
New York	1.00	
Denver	2.356 (1.153–4.814)	0.019
Dutch	4.612 (2.215–9.602)	<0.001
Diagnosis		
IPAH/HPAH	1.00	
PAH-CHD	0.470 (0.228–0.966)	0.040
APAH-non-CHD	3.986 (1.798–8.836)	0.001
Age at first symptoms	1.080 (1.012–1.153)	0.020
WHO functional class III–IV versus I–II	2.231 (1.087–4.579)	0.029
Systolic blood pressure	1.030 (1.005–1.057)	0.020
Diastolic blood pressure	1.039 (1.005–1.075)	0.026
Log value of NT-proBNP	4.042 (1.173–13.926)	0.027
mRAP	1.107 (1.035–1.183)	0.003
Systemic blood flow index	0.734 (0.576–0.935)	0.012
PVRi	1.034 (1.011–1.057)	0.003
mPAP/mSAP*	1.133 (1.033–1.243)	0.008
Treatment strategy		
PAH-targeted monotherapy	1.00	
No specific PAH therapy	2.057 (0.828–5.108)	0.120
CCB monotherapy	0.121 (0.016–0.904)	0.040
PAH-targeted dual therapy	0.421 (0.203–0.874)	0.020
PAH-targeted triple therapy	0.401 (0.175–0.923)	0.032

*Hazard ratio per 0.1 change of mPAP/mSAP.

APAH-non-CHD = associated pulmonary arterial hypertension non-congenital heart disease; CCB = calcium channel blocker; CI = confidence interval; IPAH/HPAH = idiopathic/hereditary PAH; mPAP/mSAP = pulmonary-to-systemic arterial pressure ratio; mRAP = mean right atrial pressure; NT-proBNP = N-terminal pro brain natriuretic peptide; PAH-CHD = PAH associated with congenital heart disease; PVRi = pulmonary vascular resistance index; WHO = World Health Organization.

In the total population, during the study period, 5% of patients did not receive any specific PAH therapy, 9% of patients continued CCB monotherapy, 35% of patients were treated with PAH-targeted monotherapy, and 34% and 17% were treated with dual and triple therapy, respectively (Table 2). Figure 4 shows survival rates stratified by treatment strategy. Patients' disease severity at diagnosis (defined by the identified predictors of survival) is shown in Tables 5 and 6. Patients receiving CCB monotherapy had significantly better hemodynamics than patients taking PAH-targeted therapy. Patients treated with dual and triple therapy during the study period had a diagnosis of PAH-CHD less frequently, higher mPAP/mSAP, and tended to have higher WHO functional class and PVRi at diagnosis than patients who were treated with monotherapy. Patients who received IV/SC prostanoids had significantly higher WHO functional class and worse hemodynamics than patients who did not receive IV/SC prostanoids. Cox regression analysis indicated that dual and triple therapy treatments during the study period were associated with better survival than treatment with monotherapy. Although the non-use of PAH drugs was associated with worse survival compared to monotherapy in multivariate analysis,

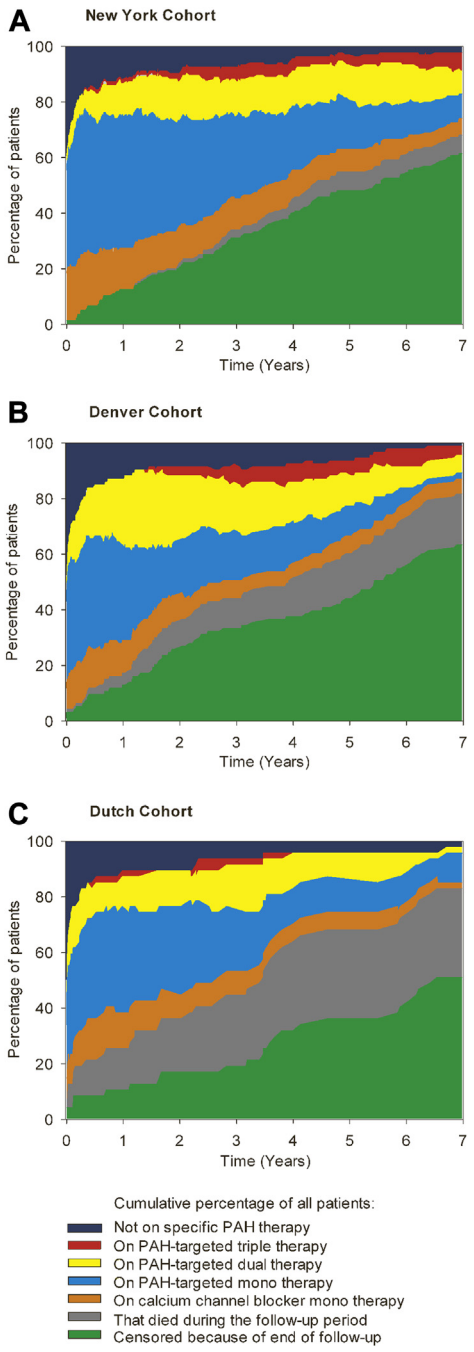

Figure 1 Real-Time Therapy Per Center Cohort During a 7-Year Follow-Up Period

Real-time cumulative percentages of all patients per therapy group were plotted for the NY cohort **(A)**, the Denver cohort **(B)**, and the Dutch cohort **(C)**. This plot shows the actual percent of patients in a specific therapy group, patients who died, and patients who were censored per follow-up time point. For example, 40% of the NY cohort at diagnosis (time point 0) did not receive any specific PAH therapy; after 1 year, 10% of this cohort received no specific PAH therapy; and after 5 years, 2% received no specific PAH therapy. The legend key is shown in the same descending order as in the figure. PAH = pulmonary arterial hypertension.

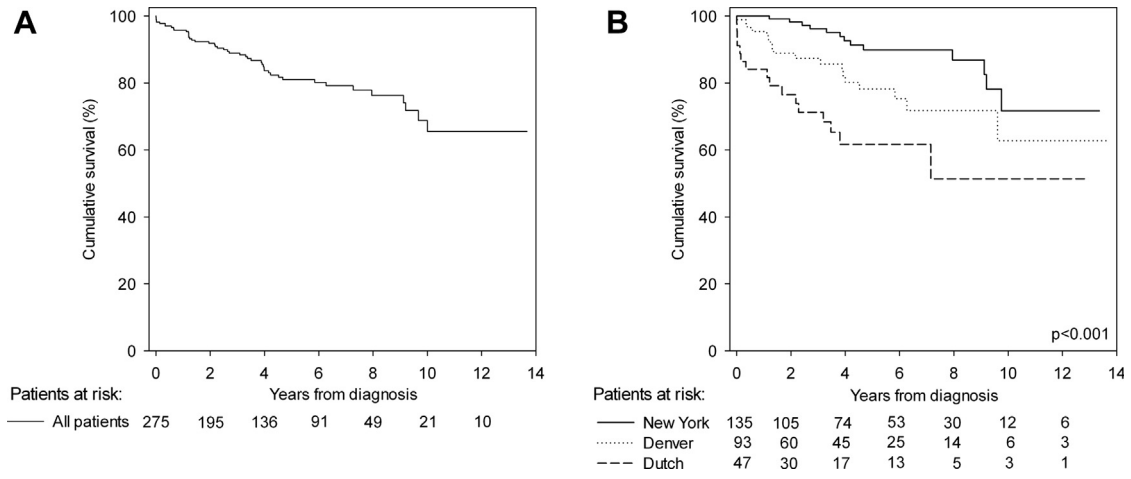

Figure 2 **Survival of All Included Pediatric PAH Patients and Stratified by Center Cohort**

Kaplan-Meier curves showing the survival **(A)** for all included pediatric PAH patients: 1-, 3-, 5-, and 7-year transplantation-free survival rates were 96%, 89%, 81%, and 79%, respectively. **(B)** For all patients stratified by center cohort: 1-, 3-, 5-, and 7-year survival rates were 100%, 96%, 90%, and 90% for NY; 95%, 87%, 78%, and 72% for Denver; and 84%, 71%, 62%, and 62% for NL, respectively ($p < 0.001$). Significant survival differences existed between all 3 center cohorts. PAH = pulmonary arterial hypertension.

we consider the "no-therapy group" not to be a meaningful control group for patients taking therapy, due to the composition of this group, including both patients with low WHO functional classes doing well without therapy and patients who died shortly after diagnosis.

In secondary sensitivity analyses, in which the robustness of the multivariate models was assessed in 3 different datasets, the variables mPAP/mSAP (78% to 89%), diagnosis (63% to 97%), and treatment strategy (50% to 95%) were selected in more than 50% of the models, whereas WHO functional class and PVRi were not.

Discussion

By direct comparison of contemporary patient cohorts from 3 major pediatric PAH referral centers, using standardized inclusion criteria, differences in unadjusted, transplantation-free survival rates were observed. However, adjustment for clinical and hemodynamic patient characteristics, which were identified as predictors of survival in the total cohort, resolved the survival differences among the center cohorts. Independent of these patient-related predictors, treatment with combination therapy with PAH-targeted drugs

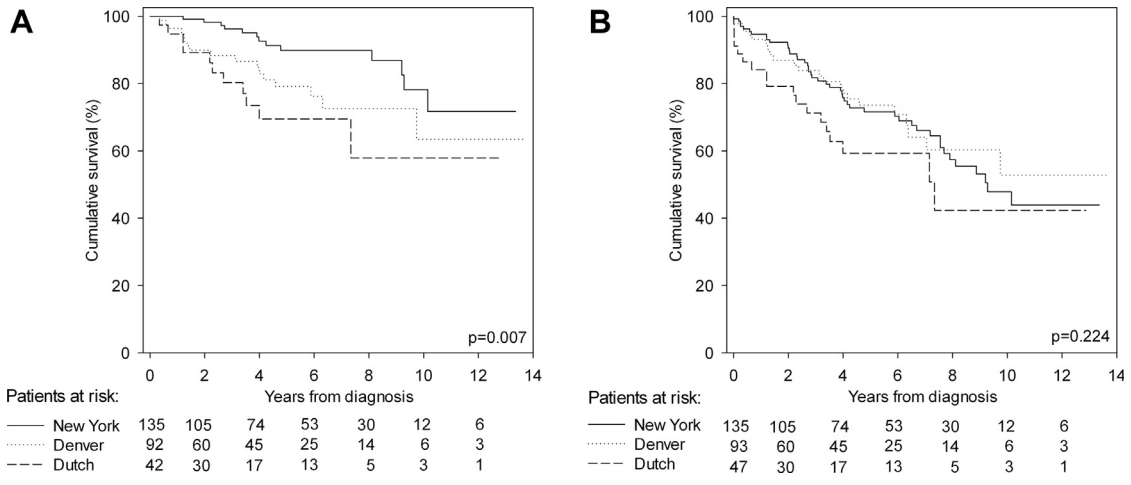

Figure 3 **Survival of Pediatric PAH Patients Adjusted for Early Death and Patients Lost to Follow-Up**

Kaplan-Meier curves show survival stratified by center cohort **(A)** after exclusion of all patients who died within 3 months after diagnosis. Significant survival differences between the NY cohort and the other 2 cohorts persist. **(B)** Assuming all patients lost to follow-up died. Now, no significant survival difference could be observed between the center cohorts.

Table 4 Multivariate Backward Stepwise Cox Regression Analysis of Parameters Associated With Survival (N = 196)

	Backward Stepwise Cox Regression Analysis	
	Hazard Ratio (95% CI)	p Value
Diagnosis		
IPAH/HPAH	1.00	
PAH-CHD	0.103 (0.027–0.396)	0.001
APAH-non-CHD	15.974 (4.402–57.960)	<0.001
WHO functional class III–IV versus I–II	3.251 (1.316–8.028)	0.011
PVRi	1.053 (1.017–1.090)	0.003
mPAP/mSAP*	1.282 (1.104–1.489)	0.001
Treatment strategy		
PAH-targeted monotherapy	1.00	
No specific PAH therapy†	19.311 (3.682–101.274)	<0.001
CCB monotherapy	0.385 (0.047–3.191)	0.377
PAH-targeted dual therapy	0.156 (0.057–0.422)	<0.001
PAH-targeted triple therapy	0.094 (0.029–0.302)	<0.001

*Hazard ratio per 0.1 change of mPAP/mSAP. †This "non-treated" group consisted of patients who were clinically very well without therapy or who died rapidly after diagnosis before therapy could be started. In this statistical analysis, the hazard ratio seems determined predominantly by the rapidly dying patients, not doing justice to the patients doing very well without treatment. Therefore this is regarded as not a meaningful hazard ratio.

APAH-non-CHD = associated pulmonary arterial hypertension non-congenital heart disease; CCB = calcium channel blocker; CI = confidence interval; IPAH/HPAH = idiopathic/hereditary PAH; mPAP/mSAP = pulmonary-to-systemic arterial pressure ratio; PAH-CHD = PAH associated with congenital heart disease; PVRi = pulmonary vascular resistance index; WHO = World Health Organization.

during the study period was associated with better survival than treatment with monotherapy with a PAH-targeted drug.

Parameters associated with survival. Children with APAH-non-CHD had significantly worse survival, whereas those with PAH-CHD showed favorable survival compared to IPAH/HPAH patients. This is congruent with several previous reports, although discrepant data also have been reported that show similar survival rates for pediatric PAH-CHD and IPAH/HPAH patients (6,7,9,18). These reported discrepancies may be due to the heterogeneity of the heart defects that underlie PAH-CHD (e.g., closed versus open shunts, simple versus complex defects) for which survival rates may differ (18). Further studies of this issue are needed.

WHO functional class is a non-invasive but subjective assessment of clinical condition that is widely used to predict outcome and guide therapy in adult PAH (1,19). Its applicability in pediatric PAH has been debated as WHO functional class may be difficult to assess in infants and young children. However, various major referral centers for pediatric PAH have independently shown WHO functional class to be an important predictor of outcome, which was confirmed in the primary analysis in this study (7–9,20). Secondary sensitivity analyses in the current study could not confirm the robustness of WHO functional class as an independent predictor. This indicates that further studies, in addition to the current study, are needed to confirm the robustness of WHO functional class as independent predictor of outcome in pediatric PAH. A functional

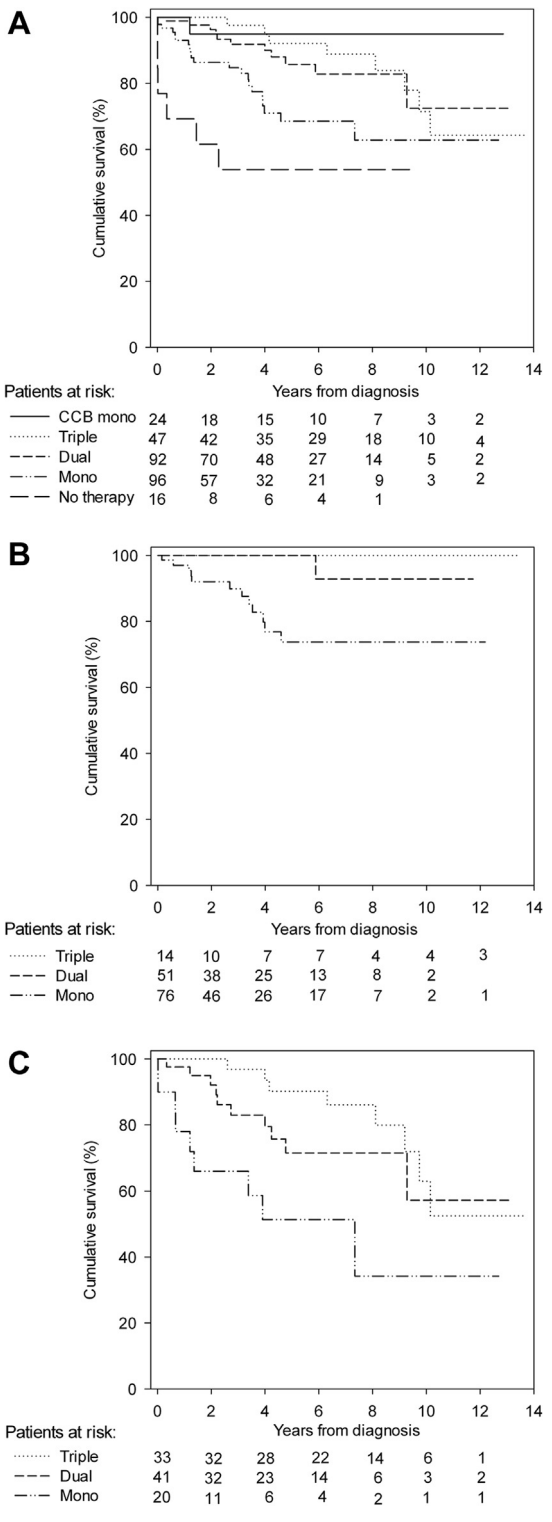

Figure 4 Survival of Pediatric PAH Patients Stratified by Treatment Strategy

Kaplan-Meier curves show survival stratified by treatment strategy **(A)** for all patients; **(B)** for patients who did not receive intravenous/subcutaneous prostanoids; and **(C)** for patients who did receive intravenous/subcutaneous prostanoids. PAH = pulmonary arterial hypertension.

Table 5 Predictors of Outcome Stratified by Treatment Strategy

			PAH-Targeted Therapy							
	CCB Monotherapy		Monotherapy		Dual Therapy		Triple Therapy			
Predictor	N	Value	N	Value	N	Value	N	Value	p Value*	p Value†
Diagnosis	24		96		92		47		<0.001	0.164
IPAH/HPAH		17 (71)		31 (32)		52 (57)		37 (79)		
PAH-CHD		7 (29)		56 (58)		33 (36)		9 (19)		
APAH-non-CHD		0		9 (9)		7 (8)		1 (2)		
WHO functional class	21		74		89		40		0.078	0.271
I–II		13 (62)		44 (60)		40 (45)		16 (40)		
III–IV		8 (38)		30 (41)		49 (55)		24 (60)		
PVRi	24	8.73 ± 5.63	96	15.09 ± 10.99	92	16.84 ± 11.08	47	19.51 ± 9.27	0.068	<0.001
mPAP/mSAP	24	0.58 ± 0.21	94	0.80 ± 0.26	92	0.94 ± 0.27	47	0.95 ± 0.32	0.001	<0.001

Values are mean ± SD or n (%). *p Values for PAH-targeted mono- versus dual versus triple therapy. †p Values for CCB monotherapy versus PAH-targeted therapy.

APAH-non-CHD = associated pulmonary arterial hypertension non-congenital heart disease; CCB = calcium channel blocker; IPAH/HPAH = idiopathic/hereditary PAH; mPAP/mSAP = pulmonary-to-systemic arterial pressure ratio; PAH-CHD = PAH associated with congenital heart disease; PVRi = pulmonary vascular resistance index; WHO = World Health Organization.

classification system customized for young children has been proposed but has yet to be validated (21).

The hemodynamic parameters independently associated with survival in this study have previously been identified as predictors of outcome in other, mostly single-center studies (7,10,22). Hemodynamic parameters have the advantages of objectivity and obtainability at any age. However, an important disadvantage is the need for a cardiac catheterization procedure, which often requires anesthesia or sedation in infants and young children with associated risks. In contrast to the Barst and REVEAL for childhood-onset PAH criteria, acute responders according to the Sitbon criteria had better survival than non-responders in this study, confirming previous reports (22). Therefore, the Sitbon criteria seem to be applicable also in children and may better predict long-term survival in pediatric PAH.

In the current study, the natriuretic peptides BNP and NT-proBNP were available at diagnosis only for a small number of patients. We could not demonstrate an association between BNP and survival. However, despite low numbers, NT-proBNP was associated with survival, confirming previous reports (9,23,24). Due to these low numbers, NT-proBNP could not be included in multivariate analysis, limiting its evaluation as an independent predictor. However, on the basis of the currently available data, the authors feel that NT-proBNP should be part of the standardized follow-up for children with PAH and be included in future studies in order to adequately assess its value as an independent predictor of survival in pediatric PAH.

Other parameters, which have been previously reported to be associated with survival in pediatric PAH, such as age at diagnosis and z-score for height, were not associated with survival in the current study (10,20).

Survival differences among the center cohorts. There were relatively more IPAH/HPAH and APAH-non-CHD patients in the Dutch cohort than in the U.S. cohorts, which attributed to the observed survival differences.

Based on WHO functional class and hemodynamics, children in the Dutch cohort appeared to have more severe disease than children in the U.S. cohorts. Differences in the organization of care and referral patterns, in traveling distances and in accessibility to referral centers, may be factors

Table 6 Predictors of Outcome Stratified by Use of IV/SC Prostanoids and PAH-Targeted Mono-, Dual, and Triple Therapy

	No IV/SC Prostanoids Used				IV/SC Prostanoids Used				
Predictor	Monotherapy (N = 76)	Dual (N = 51)	Triple (N = 14)	p Value*	Monotherapy (N = 20)	Dual (N = 41)	Triple (N = 33)	p Value*	p Value†
Diagnosis				<0.001				0.529	<0.001
IPAH/HPAH	18 (24)	20 (39)	12 (86)		13 (65)	32 (78)	25 (76)		
PAH-CHD	52 (68)	27 (53)	2 (14)		4 (20)	6 (15)	7 (21)		
APAH-non-CHD	6 (8)	4 (8)	0		3 (15)	3 (7)	1 (3)		
WHO functional class	(N = 56)	(N = 50)	(N = 14)	0.134	(N = 18)	(N = 39)	(N = 26)	0.251	<0.001
I–II	40 (71)	32 (64)	6 (43)		4 (22)	8 (21)	10 (39)		
III–IV	16 (29)	18 (36)	8 (57)		14 (79)	31 (80)	16 (62)		
PVRi	13.63 ± 10.66	15.38 ± 10.65	17.09 ± 7.79	0.421	20.64 ± 10.68	18.66 ± 11.47	20.54 ± 9.75	0.692	<0.001
mPAP/mSAP	0.75 ± 0.24	0.89 ± 0.23	0.94 ± 0.40	0.003	0.98 ± 0.23	0.99 ± 0.30	0.96 ± 0.30	0.843	<0.001

Values are mean ± SD or n (%). *p Values for PAH-targeted monotherapy versus dual versus triple therapy within the no-IV/SC prostanoids used and the IV/SC prostanoids used groups. †p Values for no IV/SC prostanoids used versus IV/SC prostanoids used.

Abbreviations as in Table 5.

that contribute to the Dutch cohort having an over-representation of the most severely ill patients. Such patients may not always reach the referral centers in the United States. Such factors could explain the observed difference in disease severity between the center cohorts.

Also, the proportion of patients lost to follow-up, which differed among the center cohorts, may attribute to the observed survival differences. In a hypothetical worst-case scenario, where all patients lost to follow-up are assumed dead (obviously representing an over-estimate of the number of deaths), a survival difference between the center cohorts could not be demonstrated.

Treatment patterns, as defined for this study (CCB monotherapy or PAH-targeted monotherapy, or dual or triple therapy), did not differ among the center cohorts and, thus, did not contribute to the survival differences between the center cohorts.

Treatment. Our findings confirm that, as in adult PAH, in pediatric PAH a small select subgroup of patients (with favorable hemodynamics) has a favorable, long-term survival with CCB monotherapy without the need for additional PAH-targeted therapy (25).

In this study, treatments with PAH-targeted dual and triple therapy during the study period were associated with better survival than treatment with PAH-targeted monotherapy, whether or not treatment strategy included IV/SC prostanoids. Differences in disease severity at diagnosis could not explain the observed survival differences among patients taking monotherapy or dual and triple therapy. Patients who received IV/SC prostanoid therapy had more severe disease at diagnosis. These data also illustrate that IV/SC prostanoids as monotherapy may not suffice in children with severe disease and is associated with poor outcome. Therefore, this study provides additional support for the notion of a more aggressive treatment approach in pediatric PAH, with the use of combination therapy. Given the relatively large proportion of patients receiving monotherapy found in all 3 center cohorts, there may be room for improvement in this respect. Whether an initial or an add-on treatment strategy would be most beneficial to improve outcome in pediatric PAH patients should be further evaluated.

A goal-oriented treatment strategy aiming at predefined improvement of the clinical condition instead of reacting to deterioration of the patient's clinical condition and leading to intensification of treatment has been suggested to improve outcome in adult PAH (26,27). Such a strategy is likely to be beneficial also in pediatric PAH. However, in contrast to adult PAH, treatment goals to guide goal-oriented treatment are neither well defined nor validated in pediatric PAH (12). The parameters identified to predict survival in this study may qualify for such treatment goals in the future. However, further research is essential to establish and validate treatment goals and to determine the effects of a goal-oriented treatment strategy on survival in this vulnerable patient population.

Study limitations. Retrospective studies come with certain limitations. However, the 3 center cohorts that were brought together come from 3 PAH-dedicated centers with standardized diagnostic and treatment protocols, minimizing these limitations. Multivariate analysis was limited by missing values within specific parameters that may be caused by either different diagnostic and follow-up strategies among centers or by the inherent impossibility of obtaining certain data in certain age or patient groups. In the analyses regarding treatment strategy, individual variations in doses and time relationships were not taken into account, precluding definitive conclusions on a causal relationship between treatment strategy and outcome. To address the risk of overfitting in this relatively small study, we performed secondary sensitivity analyses, in which the variables diagnosis, mPAP/mSAP, and treatment strategy were confirmed to be independent predictors of outcome, whereas WHO functional class and PVRi could not be confirmed in these secondary analyses, indicating that their robustness as independent predictors of outcome should be further studied. Diagnostic cardiac catheterizations were performed under both general anesthesia and conscious sedation. A potential effect of the mode of anesthesia on hemodynamics was not investigated in this study. Furthermore, the moderately high altitude of Denver was not taken into account in this study and may have negatively biased the outcome of the Denver cohort. Bringing together the complete consecutive patient cohorts of 3 major referral centers for pediatric PAH provided a unique opportunity to validate clinical patient characteristics that appeared to be responsible for observed survival differences and to find clues to optimize and guide therapy.

Conclusions

Unadjusted survival rates of pediatric PAH patients differed among 3 major referral centers. This study identified diagnosis, WHO functional class, mPAP/mSAP, and PVRi as independent predictors of outcome that could explain the observed survival differences among the center cohorts. Moreover, we found that treatment with PAH-targeted combination therapy during the study period was independently associated with improved transplantation-free survival. Secondary sensitivity analyses indicated that the robustness of WHO functional class and PVRi as predictors of outcome in pediatric PAH deserves further evaluation.

Reprint requests and correspondence: Prof. Dr. Rolf M. F. Berger, Pediatric and Congenital Cardiology, Beatrix Children's Hospital, University Medical Center Groningen, Center for Congenital Heart Diseases, P.O. Box 30.001, 9700 RB Groningen, the Netherlands. E-mail: r.m.f.berger@umcg.nl.

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Key Words: pediatrics ■ pulmonary hypertension ■ survival.