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ORIGINAL ARTICLE

Long-term outcome of children with newly diagnosed pulmonary arterial hypertension: results from the global TOPP registry

Mark-Jan Ploegstra[1], David Dunbar Ivy[2], Maurice Beghetti[3], Damien Bonnet[4], Dursun Alehan[5], Laszlo Ablonczy[6], Sandra Mattos[7], David Bowers[8], Tilman Humpl[9] and Rolf M.F. Berger[1,*], TOPP Investigators

[1]Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Hanzeplein 1, PO Box 30.001, 9700 RB Groningen, The Netherlands; [2]Department of Pediatrics, Section of Pediatric Cardiology, University of Colorado School of Medicine, Children's Hospital Colorado Heart Institute, Aurora, CO, USA; [3]Pediatric Cardiology Unit, Department of the Child and Adolescent, Children's University Hospital Geneva, Geneva, Switzerland; [4]M3C-Necker, Hôpital Universitaire Necker-Enfants Malades, Université de Paris Cité, Paris, France; [5]Hacettepe University Faculty of Medicine, Ankara, Turkey; [6]Gottsegen National Cardiovascular Center, Budapest, Hungary; [7]Maternal–Fetal Cardiac Unit, Royal Portuguese Hospital, Recife, Brazil; [8]School of Engineering, Arts, Science & Technology, University of Suffolk, Ipswich, UK; and [9]The Hospital for Sick Children, Critical Care and Cardiology, University of Toronto, Toronto, Canada

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Background and aims The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry is a global network established to gain insights into the disease course and long-term outcomes of paediatric pulmonary arterial hypertension (PAH). Previously published cohorts in paediatric PAH are obscured by survival bias due to the inclusion of both prevalent (previously diagnosed) and incident (newly diagnosed) patients. The current study aims to describe long-term outcome and its predictors in paediatric PAH, exclusively of newly diagnosed patients.

Methods and results Five hundred thirty-one children with confirmed pulmonary hypertension, aged ≥3 months and <18 years, were enrolled in the real-world TOPP registry at 33 centres in 20 countries, from 2008 to 2015. Of these, 242 children with newly diagnosed PAH with at least one follow-up visit were included in the current outcome analyses. During long-term follow-up, 42 (17.4%) children died, 9 (3.7%) underwent lung transplantation, 3 (1.2%) atrial septostomy, and 9 (3.7%) Potts shunt palliation (event rates: 6.2, 1.3, 0.4, and 1.4 events per 100 person-years, respectively). One-, three-, and five-year survival free from adverse outcome was 83.9%, 75.2%, and 71.8%, respectively.

Overall, children with open (unrepaired or residual) cardiac shunts had the best survival rates. Younger age, worse World Health Organization functional class, and higher pulmonary vascular resistance index were identified as independent predictors of long-term adverse outcome. Younger age, higher mean right atrial pressure, and lower systemic venous oxygen saturation were specifically identified as independent predictors of early adverse outcome (within 12 months after enrolment).

Conclusion This comprehensive analysis of survival from time of diagnosis in a large exclusive cohort of children newly diagnosed with PAH describes current-era outcome and its predictors.

Keywords Outcome • Survival • Paediatric pulmonary arterial hypertension • Prognosis

Introduction

Pulmonary arterial hypertension (PAH) is a progressive incurable disease of the pulmonary vasculature with substantial morbidity and mortality, especially in children.[1] Considerable progress has been made in the management of paediatric PAH over the last few decades.[2] This has coincided with advancements in the diagnosis and management of the disease in adults, including the use of paediatric treatment algorithms modified from those used in adults with PAH.[3–5]

Retrospective evaluations have suggested that the outcome of paediatric PAH has improved since the availability of PAH-targeted drugs.[6–10] However, the survival rates of previously published cohorts in paediatric PAH are obscured by survival bias due to the inclusion of both prevalent (previously diagnosed) and incident (newly diagnosed)

* Corresponding author. Tel: +31-50-3612800, Fax: +31-50-3614235, Email: r.m.f.berger@umcg.nl

patients. Prospectively collected outcome data from incident cohorts are essential to obtain a representative view of the clinical course and current outcome in paediatric PAH.

Previous reports have also identified valuable candidate predictors of adverse outcome in paediatric PAH,[6–9,11–16] very welcome for risk stratification of children with PAH at the time of diagnosis and for guiding treatment decisions throughout the disease course.[17] The currently proposed predictors, however, were often identified in relatively small patient series. Consequently, a systematic review demonstrated a high degree of heterogeneity regarding the prognostic value of the reported predictors.[13] Adequate risk stratification, being the cornerstone of current treatment strategies in PAH, requires the identification of independent predictors of outcome, preferably identified from a well-defined prospectively followed cohort of newly diagnosed patients.[4] The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry is a global network that was established in 2007 to provide real-world epidemiological, diagnostic, clinical, and outcome data on children with PAH confirmed by heart catheterization and prospectively enrolled newly diagnosed (incident) patients and previously diagnosed (prevalent) patients.[18] The current study aims to describe the current outcome and its predictors in this large worldwide cohort of paediatric patients, exclusively newly diagnosed with PAH.

Methods

Study design and population

The TOPP registry is a real-world multicentre, prospective observational registry; the design and baseline characteristics have been detailed previously.[18] In short, children with pulmonary hypertension (PH) aged ≥3 months and <18 years from 33 centres in 20 countries were enrolled between January 2008 and July 2015 if they were diagnosed with PAH (World Symposium on Pulmonary Hypertension, PH Group 1), PH associated with respiratory disorders (PH Group 3), chronic thrombo-embolic PH (PH Group 4), or PH due to miscellaneous causes (PH Group 5).[4] PH caused by left-heart disease with increased left-sided filling pressures (PH Group 2) forms a distinct clinical and haemodynamic entity; hence, these patients were not enrolled. The diagnosis of PH required right-heart catheterization (RHC) with mean pulmonary artery pressure (mPAP) of at least 25 mmHg at rest, a pulmonary vascular resistance index (PVRi) of at least 3 WU·m^2, and mean pulmonary capillary wedge pressure below or equal to 12 mmHg. Both newly diagnosed patients (incident; diagnostic RHC within 3 months of enrolment) and previously diagnosed patients (prevalent; diagnostic RHC >3 months before enrolment) were enrolled in TOPP. In July 2015, the first phase of the registry (TOPP-1) closed after enrolling 531 children with confirmed PH. For the current study, only newly diagnosed (incident) patients with PAH (PH Group 1) with at least one follow-up visit at any time after enrolment were included.

The TOPP registry was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice as outlined in the International Conference of Harmonization. Ethical approval was obtained from the relevant Institutional Review Board or Independent Ethics Committee for each participating centre. Written informed consent was obtained from all patients or their legal guardians. All authors had full access to the study data and take responsibility for the integrity of the data and the accuracy of the data analyses. All authors were involved in the development and review of the manuscript.

Patient follow-up and data collection

Patient characteristics specifically collected for the current study included demographics, PAH aetiology, comorbid conditions, weight, occurrence of syncope, World Health Organization functional class (WHO-FC), 6 min walk distance (6MWD), and haemodynamics assessed by RHC at the time of diagnosis. To guarantee the accuracy of haemodynamic calculations, RHC data of all included patients were manually reviewed by the TOPP registry executive board members. 6MWD was not analysed in patients under 7 years of age and in children with trisomy 21 as the test was regarded not reliable in these children. Aetiology of PAH was defined according to the following subgroups that are in congruence with the WSPH classification system: idiopathic/heritable PAH (IPAH/HPAH), PAH associated with congenital heart disease (APAH-CHD), and PAH associated with other conditions (APAH-other). Because of the different clinical and haemodynamic profiles within the APAH-CHD subgroup with potential prognostic consequences, a further distinction was made between patients *with* open shunts (unrepaired or residual shunt defects) and patients *without* open shunts (fully repaired shunt defects or patients who never had shunts).

During follow-up, adverse outcomes, including all-cause death, heart and/or lung transplantation, atrial septostomy, and Potts shunt palliation, were prospectively registered. Causes of death were also captured in the registry.

Statistical analysis

For subgroup comparisons, descriptive statistics are provided, including counts and percentages for categorical data and medians [interquartile range (IQR)] for continuous data. No imputation methods were used for missing data. *P*-values <0.05 were considered statistically significant. In the analyses, outcome was defined in two ways: (1) *long-term adverse outcome*, defined as the occurrence of either death, heart and/or lung transplantation, atrial septostomy, or Potts shunt palliation; and (2) *early adverse outcome*, defined as death, heart- and/or lung-transplantation, atrial septostomy, or Potts shunt palliation within 12 months from diagnosis.

Kaplan–Meier estimates were conducted for the time to the first occurrence of either Potts shunt palliation, atrial septostomy, transplantation, or death. The prognostic value of candidate predictors of both long-term and early adverse outcomes was evaluated using Cox proportional hazards models. The proportional hazards assumption was checked by observing reasonable parallelism in the log(−log) plots for categorical variables and by inspecting the pattern of Schoenfeld residuals for continuous variables. Individual candidate predictors of outcome found to be significant ($P < 0.05$) in the univariable models were considered as covariates in adjustment models to provide adjusted hazard ratios. In addition, age and sex were forced in the adjustment models, and stepwise multivariable modelling was used to identify any additional predictors. Univariable predictors with >20% missing values were not used as adjustment covariates to prevent omission of patients and power reduction in the adjustment models. The final choice of covariates for the adjustment models was guided by the principle of ensuring around 10 events per predictor variable.[19] In the long-term outcome models, all adverse outcome events during the full follow-up period were considered: Patients who did not undergo an adverse outcome event were censored at the last recorded visit. In the early adverse outcome models, right-truncation was applied from 12 months so that only adverse outcome events and follow-up durations up to 12 months were considered; patients who did not undergo an adverse outcome event within 12 months were censored at 12 months. In all models, PAH aetiology was handled as a multi-level categorical variable existing of the following four subgroups: (1) IPAH/HPAH (reference category), (2) APAH-CHD with open shunts, (3) APAH-CHD without open shunts, and (4) APAH-other.

Results

Patient characteristics

Of 531 PH-confirmed patients enrolled in TOPP-1, 456 patients were diagnosed with PAH and had at least one follow-up visit. For the current analysis, 214 prevalent patients were excluded, leaving a final study cohort of 242 incident patients with newly diagnosed PAH (see flowchart *Figure 1*). The median year of diagnosis was 2010 (IQR 2009–11, range 2008–15).

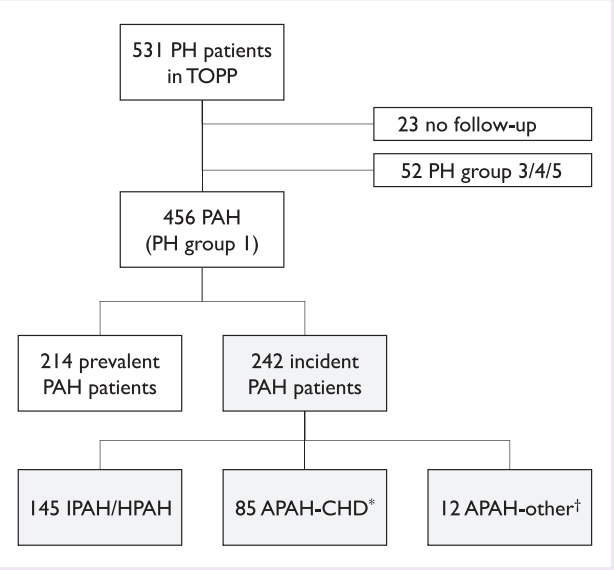

Figure 1 Flow chart of patient inclusion. A total of 531 patients with PH were enrolled in TOPP between 2008 and 2015. Of these, 242 incident patients with pulmonary arterial hypertension (PAH, PH Group 1 according to the World Symposium on Pulmonary Hypertension classification) were included in the current evaluation. One hundred forty-five had idiopathic or heritable PAH, 85 had PAH associated with congenital heart disease [*53 with open shunts (unrepaired or residual shunts) and 32 without open shunts (either fully repaired or never shunt)], and 12 had PAH associated with other conditions (†3 chronic liver disease, 3 connective tissue disease, 3 pulmonary veno-occlusive disease, 2 hereditary haemorrhagic telangiectasia, and 1 other). TOPP indicates Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension Registry; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; HPAH, heritable PAH; APAH-CHD, PAH associated with congenital heart disease; APAH-other, PAH associated with other conditions.

Of the 242 incident patients that comprise the current study cohort, median (IQR) time between diagnostic RHC and enrolment was 0.3 (0.0–1.1) months. Median (IQR) age was 7 (2–12) years, and most patients were female (59%). Of the included patients, 145 (60%) had IPAH/HPAH, 85 (35%) had APAH-CHD, and 12 (5%) had APAH-other. Clinical and haemodynamic baseline characteristics are provided in *Table 1*. Compared to patients with APAH-CHD, patients with IPAH/HPAH had worse WHO-FC, higher levels of brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), higher incidence of syncope, higher systemic arterial oxygen saturation (SA-SO_2), and lower pulmonary pulse pressure. The proportion of patients with trisomy 21 was the highest in the APAH-CHD group. Treatment characteristics of the cohort at baseline are enumerated in Supplementary material online, *Table S1*.

Of the patients with APAH-CHD, 53 (62%) patients had open (unrepaired or residual) shunts, 29 (34%) had repaired shunts, and 3 (4%) never had shunts. An overview of the types of cardiac shunts and repair status of the patients with APAH-CHD is available in Supplementary material online, *Table S2*. An overview of baseline characteristics stratified by shunt repair status is available in Supplementary material online, *Table S3*.

The subgroup of APAH-other consisted of patients with PAH associated with chronic liver disease ($n = 3$), connective tissue disease ($n = 3$), pulmonary veno-occlusive disease ($n = 3$), hereditary haemorrhagic telangiectasia ($n = 2$), and other ($n = 1$).

Outcome

The median (IQR) time between diagnosis and the last registered follow-up visit before study closure was 2.6 (0.9–4.5) years ranging to 6.8 years for the full study cohort, and was 3.2 (1.2–5.0) years ranging to 6.8 years for the patients who survived without adverse events. The median (IQR) time between diagnosis and end of observation was 4.1 (1.7–5.8) years ranging to 7.4 years for the full study cohort, and was 5.0 (3.4–6.2) years ranging to 7.4 years for the patients who survived without adverse events. During follow-up, 42 (17.4%) patients died, of whom 29 (69.0%) died within 1 year after diagnosis. Nine (3.7%) patients underwent lung transplantation, three (1.2%) atrial septostomy, and nine (3.7%) Potts shunt palliation. Potts shunt palliation, atrial septostomy, lung transplantation, and death occurred with event rates of 1.4, 0.4, 1.3, and 6.2 events per 100 person-years, respectively. The top three causes of death were PH crisis ($n = 9$), progressive right heart failure ($n = 9$), and sudden death ($n = 8$) (*Figure 2*).

Figures 3 and *4* depict absolute survival and survival free from Potts shunt palliation, atrial septostomy, or lung transplantation. One-, three-, and five-year adverse outcome free survival from time of diagnosis was 83.9%, 75.2%, and 71.8%, respectively. Panels B of *Figures 3* and *4* show stratification by aetiology subgroups and demonstrate the best adverse outcome free survival for children with APAH-CHD with open shunts.

Predictors of outcome

Table 2 shows the results of Cox regression analysis taking the full long-term follow-up into account, and with time to adverse outcome (death, lung transplantation, atrial septostomy, or Potts palliation) defined as analysis endpoint. The following candidate predictors were significantly associated with long-term adverse outcome in the univariable model: younger age, lower body weight, worse WHO-FC, higher PVRi, higher pulmonary to systemic vascular resistance ratio, higher PAP/SAP-ratio, and lower systemic venous oxygen saturation (SV-SO_2). Aetiology correlated with outcome as well, with lower risk of adverse outcome for patients with APAH-CHD with open shunts. In the adjustment model, age, aetiology, WHO-FC, and PVRi were identified as independent predictors of long-term adverse outcome ($P = 0.013$, $P = 0.031$, $P = 0.004$, and $P = 0.012$, respectively).

Table 3 shows the results of Cox regression analysis after applying 12-month right-truncation, with time to early adverse outcome (death, lung transplantation, atrial septostomy, or Potts palliation within 12 months) defined as analysis endpoint. The following candidate predictors were significantly associated with early adverse outcome in the univariable model: younger age, worse WHO-FC, higher mRAP, and lower SV-SO_2. In the adjustment model, age, aetiology, mRAP, and SV-SO_2 were identified as independent predictors of early adverse outcome ($P = 0.006$, $P = 0.024$, $P = 0.032$, and $P = 0.024$, respectively).

Stepwise multivariable modelling did not identify any further independent predictors of outcome across the models. An exploratory subgroup analysis of the group of children with IPAH/HPAH only is shown in Supplementary material online, *Table S4*. In this subgroup, younger age and worse WHO-FC were identified as independent predictors of long-term adverse outcome ($P = 0.028$ and $P = 0.010$, respectively).

For a subset of the patients, levels of BNP or NT-proBNP were available at baseline. Due to substantial missing data (>50%), these

Table 1 Clinical and haemodynamic baseline characteristics

	n	Full cohort (*N* = 242)	*n*	IPAH/HPAH (*N* = 145)	*n*	APAH-CHD (*N* = 85)	*P*-value[a]
Patient characteristics							
Age at diagnosis (years)	242	7 (2, 12)	145	7 (3, 12)	85	5 (2, 12)	0.395
Sex (female)	242	142 (58.7)	145	89 (61.4)	85	45 (52.9)	0.210
Weight (kg)	240	22.8 (12.0, 42.9)	144	23.2 (13.3, 41.9)	85	18.7 (9.5, 41.5)	0.112
Trisomy 21	242	29 (12.0)	145	4 (2.8)	85	25 (29.4)	<0.001*
Clinical characteristics							
WHO functional class	241		144		85		0.004*
I		34 (14.1)		18 (12.5)		14 (16.5)	
II		105 (43.6)		53 (36.8)		47 (55.3)	
III		76 (31.5)		52 (36.1)		21 (24.7)	
IV		26 (10.8)		21 (14.6)		3 (3.5)	
6 min walk distance (m)	80	445 (369, 489)	50	432 (366, 489)	24	450 (380, 509)	0.390
BNP (log units)	88	4.61 (3.37, 6.18)	60	5.05 (3.86, 6.35)	24	4.12 (2.80, 5.20)	0.039*
NT-pro BNP (log units)	78	5.77 (4.37, 7.77)	50	6.75 (4.75, 8.07)	25	4.74 (4.11, 6.13)	0.006*
Syncope	241		144		85		<0.001*
Never		184 (76.3)		96 (66.7)		78 (91.8)	
Once		25 (10.4)		19 (13.2)		5 (5.9)	
Several times		28 (11.6)		25 (17.4)		2 (2.4)	
Regularly		4 (1.7)		4 (2.8)		0 (0.0)	
Haemodynamics							
Mean RAP (mmHg)	232	7 (5, 9)	139	6 (5, 9)	82	7 (5, 9)	0.332
Mean PAP (mmHg)	236	57 (41, 71)	141	59 (42, 73)	84	58 (44, 71)	0.986
Cardiac Index (L/min/m^2)	224	3.32 (2.51, 4.11)	137	3.34 (2.55, 4.42)	76	3.21 (2.51, 3.84)	0.391
PVRi (WU·m^2)	236	13.6 (8.0, 22.1)	141	14.4 (8.3, 22.4)	84	11.7 (7.9, 21.9)	0.259
PVR/SVR ratio (log units)	216	−0.25 (−0.65, 0.08)	132	−0.21 (−0.55, 0.08)	73	−0.38 (−0.73, 0.10)	0.239
SV-SO_2 (%)	186	68 (61, 73)	104	68 (61, 73)	74	67 (61, 73)	0.710
SA-SO_2 (%)	226	95 (91, 98)	134	96 (93, 98)	81	94 (88, 97)	<0.001*
Systolic SAP (mmHg)	231	90 (79, 104)	138	90 (79, 104)	82	90 (79, 103)	0.767
Diastolic SAP (mmHg)	231	52 (44, 62)	138	53 (46, 62)	82	51 (43, 60)	0.348
Mean SAP (mmHg)	230	66 (58, 78)	138	66 (59, 78)	81	65 (55, 78)	0.692
PAP/SAP ratio (log units)	230	−0.17 (−0.42, 0.04)	138	−0.15 (−0.43, 0.06)	81	−0.15 (−0.35, 0.01)	0.938
Pulmonary pulse pressure (mmHg)	233	39 (31, 50)	139	39 (30, 48)	83	42 (34, 54)	0.017*
Systemic pulse pressure (mmHg)	231	37 (30, 46)	138	36 (30, 45)	82	39 (30, 47)	0.309
Positive response to vasodilator testing	221	82 (37.1)	133	49 (36.8)	77	29 (37.7)	0.892

Values are *n* (%) or median (interquartile range). PAH indicates pulmonary arterial hypertension; IPAH/HPAH, idiopathic or hereditary PAH; APAH, associated PAH; CHD, congenital heart disease; WHO-FC, World Health Organization functional class; RAP, right atrial pressure; PAP, pulmonary arterial pressure; PVRi, pulmonary vascular resistance index; PVR/SVR, pulmonary to systemic vascular resistance ratio; SV-SO_2, systemic venous oxygen saturation; SA-SO_2, systemic arterial oxygen saturation; SAP, systemic arterial pressure; PAP/SAP, pulmonary to systemic arterial pressure; BNP, brain natriuretic peptide; NT-pro BNP, N-terminal Pro-B-type natriuretic peptide. *$P < 0.05$.
[a]Comparison of IPAH/HPAH with APAH-CHD: uncorrected χ^2 test for categorical variables, Mann–Whitney *U* test for continuous variables (12 patients with APAH-other not included in this comparison).

markers could not be included in the main models and could not be analysed in a multivariable fashion. In a subset of 88 patients with available BNP at baseline, unadjusted hazard ratios of 1.33 [confidence interval (CI) 0.95–1.86] and 1.81 (CI 1.09–3.03) per log-unit increase were calculated for the association with long-term and early adverse outcomes, respectively ($P = 0.099$ and $P = 0.023$, respectively). In a subset of 78 patients with available NT-proBNP at baseline, these respective unadjusted hazard ratios were 1.46 (CI 1.14–1.87, $P = 0.003$) and 1.55 (CI 1.13–2.13, $P = 0.007$).

Discussion

The results of this study in children with newly diagnosed PAH from the global TOPP registry show that outcome in paediatric PAH in the current management era is still poor, although survival rates are now slightly improved when compared to historical cohorts. Especially early mortality remains substantially high and needs further improvement. Adequate risk stratification is the cornerstone of modern treatment strategies in PAH and is required for optimal

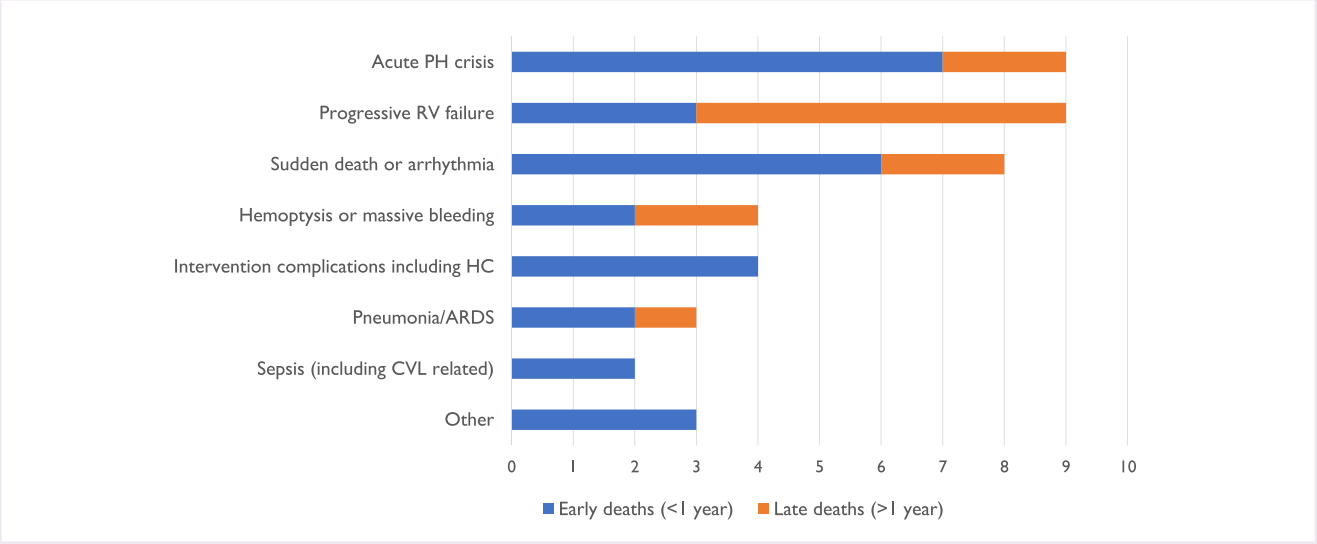

Figure 2 Causes of death stratified by early [<1 year from diagnostic right-heart catheterization (RHC)] and late (>1 year from diagnostic RHC) deaths. PH indicates pulmonary hypertension; RV, right ventricular; HC, heart catheterization; ARDS, acute respiratory distress syndrome; CVL, central venous line.

tailoring of personalized treatments for children with PAH. This entails reliable independent predictors of adverse outcome, from a well-defined prospectively followed cohort. The key predictors of adverse outcome identified in this study include young age, aetiology, WHO-FC, and a set of haemodynamic predictors.

An important finding is that *younger* age independently predicts adverse outcome in newly diagnosed children with PAH. Previous paediatric studies that consisted of a mix of both prevalent and incident patients with PAH have yielded contradictory findings: In some cohorts, younger age tended to correlate with outcome,[20,21] whereas others demonstrated older age to be prognostically unfavourable.[8,9,12,17,22] These contradictions might be explained by the varying proportions of prevalent patients in previous cohorts, illustrating one of the biases that may be introduced when analysing incident and prevalent patients together. Our prospective study in a pure incident cohort may put an end to the discussion regarding the prognostic value of age by demonstrating *younger* age to be a strong, consistent, and robust predictor of adverse outcome in newly diagnosed children with PAH.

The aetiological subgroup APAH-CHD has repeatedly been reported to carry a better prognosis than other forms of PAH.[9,23] However, within this patient group, the pace of disease progression is known to depend on the presence, anatomical location (pre-tricuspid or post-tricuspid), and size of a cardiac shunt.[23,24] We subdivided the APAH-CHD group in patients with and without open shunts, and our results confirmed a better long-term prognosis for children with open shunts. In these children, the shunt defect may contribute to preservation of cardiac output despite PAH progression and to off-loading of the right-sided heart structures in the end-stage of the disease. This underlines the clinical importance of the currently proposed shunt-based World Symposium on Pulmonary Hypertension sub-classification of APAH-CHD.[4,25,26]

WHO-FC has historically been considered a robust indicator of disease severity in paediatric PH.[17] In this study, a worse WHO-FC at the time of diagnosis was associated with a 2.4-fold increase in the risk of long-term adverse outcome. This finding is in line with previous studies in paediatric PAH and supports its role in currently proposed risk stratification guidelines.[4,5,27,28] The applicability of WHO-FC in the youngest children has previously been questioned,[29] but also in the current cohort, consisting of a large proportion of very young children, worse WHO-FC does indeed predict worse long-term adverse outcome.

Syncope occurs more frequently in children compared to adults,[18] and has been considered an important prognostic element in history taking in PH. Details of syncope events have been carefully registered in TOPP at each follow-up visit, with the aim to reliably explore whether syncope could be of prognostic significance in children in the same way as in adults. However, the current results do not support this hypothesis. Syncope is more common in IPAH, but in the IPAH subgroup analyses, its occurrence did not correlate with outcome. This negative finding is consistent with previous studies in paediatric PAH that specifically evaluated the prognostic importance of syncope and failed to show a relevant correlation.[7,9,30]

The value of 6MWD might be regarded controversial in paediatric PAH, as its use is restricted to those old enough to comply with the test protocol. In addition, developmental capabilities and motivational issues may affect the test results. Previous studies on the 6MWD and its association with outcome have yielded contradictory findings.[13,31] Paediatric cohorts consisting of more patients sufficiently able and old enough to perform a reliable test (e.g. >7 years) were more likely to demonstrate significant associations with outcome.[31,32] Although we excluded patients <7 years for this particular analysis, our study could not demonstrate a correlation between 6MWD and outcome in the TOPP-1 paediatric population. Limitations to consider are the fact that TOPP-1 did not prospectively collect 6MWD at specific time points and that 6MWD data could only be analysed for one-third of the current cohort after excluding children <7 years of age for this analysis.

Multiple haemodynamic measurements were identified as outcome predictors in the current cohort. PVRi and mRAP are established predictors of outcome, both in paediatric and adult PH.[13,33] The prognostic value of these parameters is confirmed in this study, albeit with an important nuance: mRAP carries independent prognostic value at the short term (early adverse outcome), while PVRi is specifically prognostic regarding long-term adverse outcome. This distinctive prediction pattern might be explained by the fact that increased mRAP represents failure of right ventricular adaptation to right-sided heart overload, whereas high PVRi indicates high RV afterload, independent

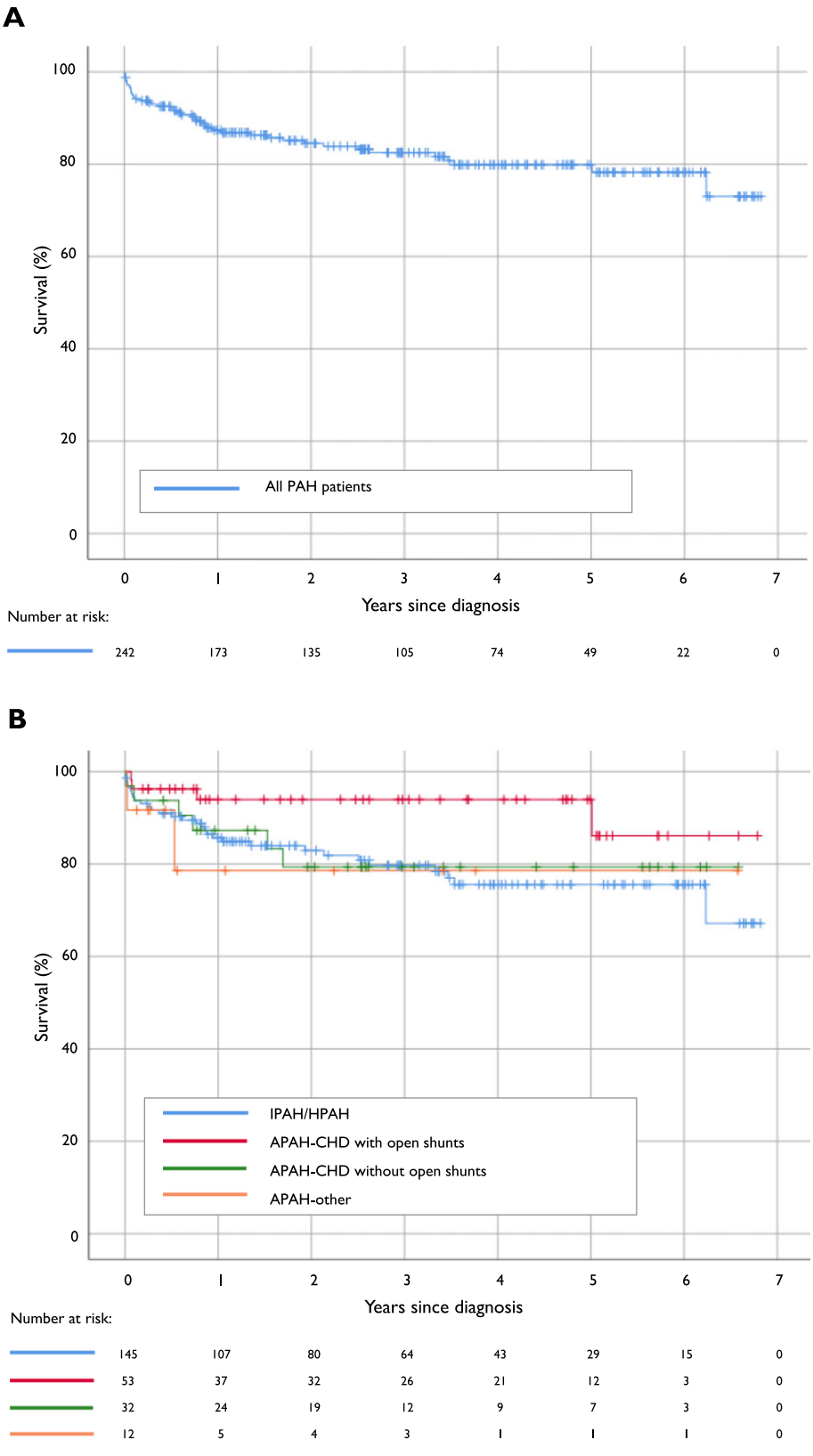

Figure 3 Survival displayed as Kaplan–Meier survival curves. Data are shown for (*A*) the total cohort of incident PAH patients and (*B*) stratified by aetiology subgroups. PAH indicates pulmonary arterial hypertension; IPAH, idiopathic PAH; HPAH, heritable PAH; APAH-CHD, PAH associated with congenital heart disease; APAH-other, PAH associated with other conditions.

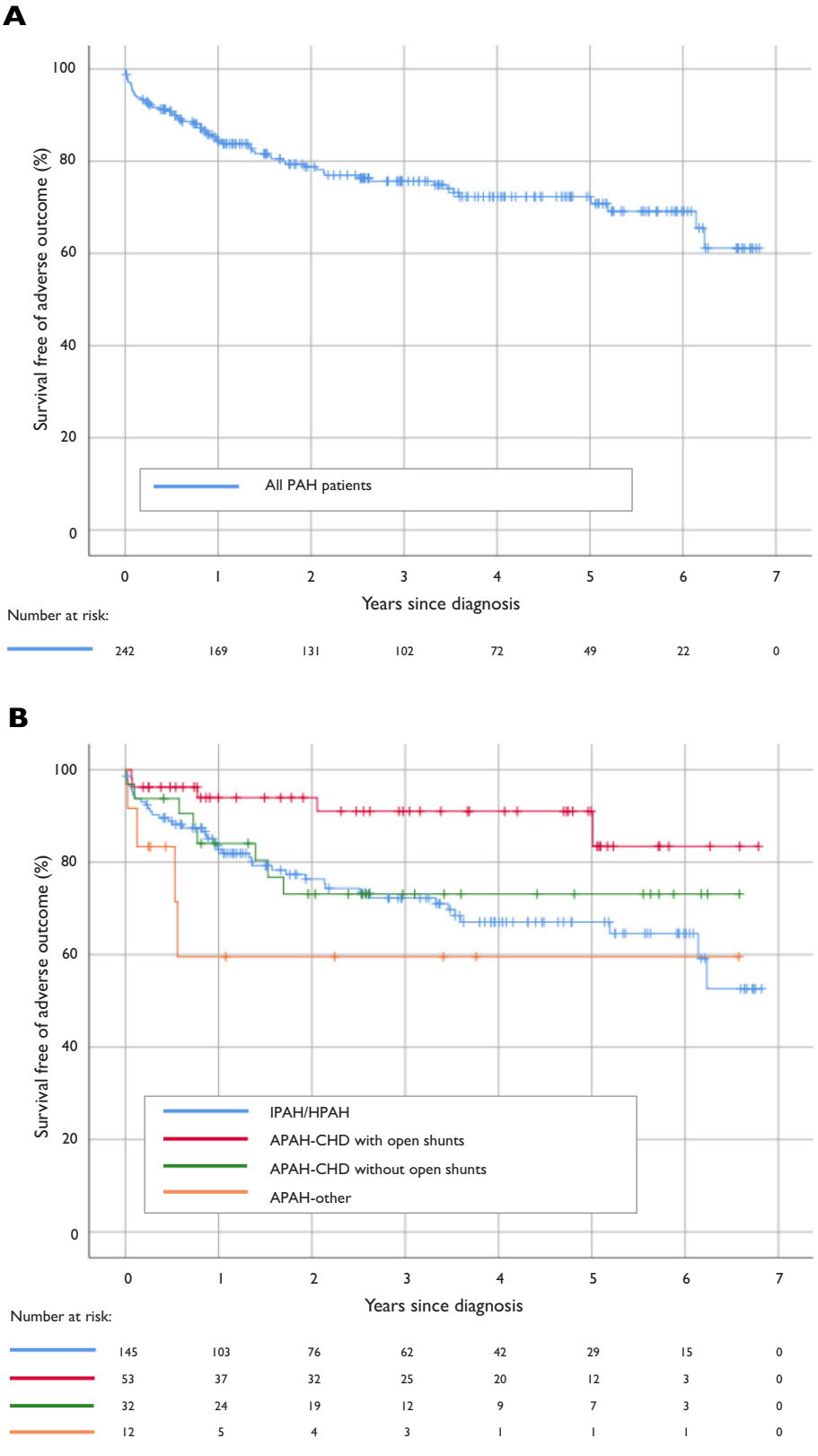

Figure 4 Survival free of adverse outcomes (death, lung transplantation, atrial septostomy, or Potts shunt palliation). Data are shown for (*A*) the total cohort of incident PAH patients and (*B*) stratified by aetiology subgroups. PAH indicates pulmonary arterial hypertension; IPAH, idiopathic PAH; HPAH, heritable PAH; APAH-CHD, PAH associated with congenital heart disease; APAH-other, PAH associated with other conditions.

Table 2 Predictors of long-term adverse outcome (59 events)

	Univariable			Adjusted[a]		
	n	HR (95% CI)	*P*-value	*n*	HR (95% CI)	*P*-value
Age at diagnosis (per year increase)	242	0.941 (0.894–0.990)	0.020*	229	0.932 (0.882–0.985)	0.013*
Sex (female compared to male)	242	0.758 (0.454–1.266)	0.289	229	0.867 (0.493–1.526)	0.621
Weight (per kg increase)	240	0.983 (0.968–0.999)	0.037*	228	1.001 (0.972–1.032)	0.935
Aetiology group	242		0.060	229		0.031*
IPAH/HPAH	145	1.000 (reference)	N.A.	137	1.000 (reference)	N.A.
APAH-CHD with open shunts	53	0.315 (0.125–0.796)	0.015*	50	0.344 (0.132–0.895)	0.029*
APAH-CHD without open shunts	32	0.828 (0.389–1.765)	0.626	31	1.070 (0.456–2.511)	0.876
APAH-other	12	1.620 (0.579–4.531)	0.358	11	3.238 (0.935–11.213)	0.064
Trisomy 21	242	0.550 (0.199–1.519)	0.249	229	0.793 (0.278–2.262)	0.664
WHO-FC (III/IV compared to I/II)	241	2.864 (1.671–4.911)	<0.001*	229	2.356 (1.314–4.224)	0.004*
6 min walk distance (per m increase)	80	0.995 (0.990–1.000)	0.066	77	1.001 (0.992–1.009)	0.891
Presence of syncope	241		0.447	229		0.602
Never	184	1.000 (reference)	N.A.	172	1.000 (reference)	N.A.
Once	25	1.730 (0.873–3.575)	0.139	25	1.593 (0.744–3.412)	0.231
Several times	28	1.405 (0.679–2.906)	0.360	28	1.396 (0.632–3.082)	0.410
Regularly	4	0.941 (0.129–6.862)	0.952	4	0.827 (0.110–6.220)	0.853
Haemodynamics						
Mean RAP (per mmHg increase)	232	1.056 (0.991–1.125)	0.091	226	1.055 (0.970–1.147)	0.213
Mean PAP (per mmHg increase)	236	1.009 (0.996–1.022)	0.161	229	0.973 (0.944–1.002)	0.072
Cardiac index (per L/min/m^2 increase)	224	0.962 (0.779–1.189)	0.723	218	1.033 (0.803–1.330)	0.799
PVRi (per WU·m^2 increase)	236	1.026 (1.006–1.045)	0.009*	229	1.029 (1.006–1.053)	0.012*
PVR/SVR ratio (per log-unit increase)	216	2.374 (1.325–4.252)	0.004*	215	3.292 (0.904–11.981)	0.071
SV-SO_2 (per % increase)	186	0.953 (0.926–0.981)	0.001*	180	0.983 (0.948–1.020)	0.363
SA-SO_2 (per % increase)	226	0.996 (0.952–1.043)	0.864	221	1.026 (0.981–1.072)	0.265
Mean SAP (per mmHg increase)	230	0.989 (0.969–1.009)	0.266	228	0.977 (0.950–1.004)	0.092
PAP/SAP ratio (per log-unit increase)	230	2.620 (1.165–5.892)	0.020*	229	1.033 (0.394–2.705)	0.948
Positive response to vasodilator testing	221	0.764 (0.411–1.420)	0.395	215	0.840 (0.438–1.609)	0.599

Long-term adverse outcome is defined as the occurrence of either death, heart and/or lung transplantation, atrial septostomy, or Potts shunt palliation during the full follow-up duration. During long-term follow-up, 59 events occurred. *$P < 0.05$.

[a]Adjustment variables are age, sex, WHO-FC, PVRi, and PAP/SAP ratio (5 adjustment variables, 11.8 events per adjustment variable). PAH indicates pulmonary arterial hypertension; HR, hazard ratio; CI, confidence interval; IPAH/HPAH, idiopathic or heritable PAH; APAH-CHD, PAH associated with congenital heart disease; APAH-other: PAH associated with conditions other than congenital heart disease; WHO-FC, World Health Organization functional class; RAP, right atrial pressure; PAP, pulmonary arterial pressure; PVRi, pulmonary vascular resistance index; PVR/SVR, pulmonary to systemic vascular resistance ratio; SV-SO2, systemic venous oxygen saturation; SA-SO2, systemic arterial oxygen saturation; SAP, systemic arterial pressure; PAP/SAP, pulmonary to systemic arterial pressure.

of RV adaptation, or compensation state. A systematic review of prognostic factors in paediatric PH has identified PVRi as the most frequently identified haemodynamic predictor of adverse outcome.[8,9,13]

In the current analyses, lower SV-SO_2 correlated with higher risk of (especially early) adverse outcome, even in the cohort including children with open shunts and Eisenmenger physiology with lower SV-SO_2 due to right–left shunting. This might seem somewhat in contrast to our finding of a better prognosis for children with open shunts. However, it is important to note—in line with previous findings in paediatric PH—that SV-SO_2 did not remain an independent predictor of long-term adverse outcome when adjusted for other clinical characteristics.[7] In the current cohort, also in the subgroup analysis of children with IPAH without shunts, SV-SO_2 did not remain a significant predictor of long-term outcome.

Cardiac index is considered an important predictor of outcome in adults with PAH but was not identified as predictor of outcome in the current paediatric cohort, neither regarding early nor long-term adverse outcome. Earlier reports on the prognostic value of the cardiac index in paediatric PAH are marked by a high degree of inconsistency: Although some paediatric studies did identify cardiac index as predictor of outcome at least in an unadjusted fashion,[7–9,12] the majority of previous reports could not demonstrate its prognostic value in children.[11,20–22,34,35]

The prognostic value of a positive response to acute vasodilator testing during RHC could not be confirmed in the current study. This might be due to the obscuring effects of many different vasodilator agents and different responder criteria that were applied by the centres participating in this observational registry. Previous studies have shown a more favourable outcome for children who responded to acute vasodilator testing and were treated with calcium channel blockers.[9,12,36–38] Also, a previous study from the TOPP registry, devoted to a far more detailed level evaluation of used agents and criteria in performed acute vasodilator response tests in TOPP, described the clinical usefulness of the Sitbon response criteria and its prognostic significance in children with PAH.[37]

Table 3 Predictors of early adverse outcome (36 events)

	Univariable			Adjusted[a]		
	n	HR (95% CI)	*P*-value	*n*	HR (95% CI)	*P*-value
Age at diagnosis (per year increase)	242	0.910 (0.850–0.975)	0.007*	231	0.896 (0.828–0.970)	0.006*
Sex (female compared to male)	242	0.596 (0.310–1.146)	0.121	231	0.922 (0.432–1.996)	0.834
Weight (per kg increase)	240	0.979 (0.958–1.000)	0.052	230	1.020 (0.982–1.060)	0.302
Aetiology group	242		0.067	231		0.024*
IPAH/HPAH	145	1.000 (reference)	N.A.	138	1.000 (reference)	N.A.
APAH-CHD with open shunts	53	0.337 (0.102–1.120)	0.076	51	0.438 (0.127–1.514)	0.192
APAH-CHD without open shunts	32	0.916 (0.349–2.401)	0.858	31	0.963 (0.307–3.020)	0.948
APAH-other	12	2.580 (0.892–7.459)	0.080	11	5.441 (1.465–20.210)	0.011*
Trisomy 21	242	0.885 (0.313–2.503)	0.818	231	1.027 (0.339–3.118)	0.962
WHO-FC (III/IV compared to I/II)	241	2.482 (1.250–4.927)	0.009*	231	1.777 (0.841–3.756)	0.132
6 min walk distance (per m increase)	80	0.996 (0.987–1.006)	0.461	79	0.999 (0.986–1.013)	0.929
Presence of syncope	241		0.850	231		0.547
Never	184	1.000 (reference)	N.A.	174	1.000 (reference)	N.A.
Once	25	1.454 (0.556–3.797)	0.445	25	1.703 (0.603–4.810)	0.315
Several times	28	1.331 (0.510–3.477)	0.559	28	1.960 (0.688–5.581)	0.207
Regularly	4	no event	N.A.		no event	N.A.
Haemodynamics						
Mean RAP (per mmHg increase)	232	1.112 (1.030–1.201)	0.007*	231	1.116 (1.009–1.233)	0.032*
Mean PAP (per mmHg increase)	236	0.997 (0.979–1.015)	0.725	231	0.988 (0.967–1.010)	0.284
Cardiac Index (per L/min/m^2 increase)	224	1.044 (0.821–1.327)	0.725	219	0.994 (0.767–1.286)	0.961
PVRi (per WU·m^2 increase)	236	1.009 (0.981–1.039)	0.534	231	1.014 (0.982–1.047)	0.399
PVR/SVR ratio (per log-unit increase)	216	2.046 (0.977–4.284)	0.058	215	1.373 (0.634–2.971)	0.421
SV-SO_2 (per % increase)	186	0.943 (0.911–0.975)	0.001*	182	0.958 (0.924–0.995)	0.024*
SA-SO_2 (per % increase)	226	0.980 (0.928–1.034)	0.459	221	0.985 (0.932–1.040)	0.582
Mean SAP (per mmHg increase)	230	0.979 (0.952–1.006)	0.124	225	0.983 (0.952–1.015)	0.288
PAP/SAP ratio (per log-unit increase)	230	1.617 (0.579–4.520)	0.359	226	0.905 (0.302–2.715)	0.859
Positive response to vasodilator testing	221	0.966 (0.431–2.169)	0.934	217	1.020 (0.447–2.324)	0.963

Early adverse outcome is defined as death, heart and/or lung transplantation, atrial septostomy, or Potts shunt palliation within 12 months from diagnosis. During the first 12 months, 36 events occurred. *$P < 0.05$.

[a]Adjustment variables are age, sex, WHO-FC, and mean RAP (four adjustment variables, nine events per adjustment variable). PAH indicates pulmonary arterial hypertension; HR, hazard ratio; CI, confidence interval; IPAH/HPAH, idiopathic or heritable PAH; APAH-CHD, PAH associated with congenital heart disease; APAH-other: PAH associated with conditions other than congenital heart disease; WHO-FC, World Health Organization functional class; RAP, right atrial pressure; PAP, pulmonary arterial pressure; CI, cardiac index; PVRi, pulmonary vascular resistance index; PVR/SVR, pulmonary to systemic vascular resistance ratio; SV-SO2, systemic venous oxygen saturation; SA-SO2, systemic arterial oxygen saturation; SAP, systemic arterial pressure; PAP/SAP, pulmonary to systemic arterial pressure.

The long-term follow-up data from our study show RV failure to be the main cause of death in paediatric PAH, highlighting the importance of RV function assessment throughout the disease course. Echocardiography is the most commonly used clinical tool for this, but its measurements are difficult to standardize and severely suffer from operator dependency, hampering its evaluation in a decentralized global registry setting.[39] Cardiac magnetic resonance imaging has emerged as the most accurate method for evaluating RV function and has proved useful for risk stratification in paediatric PAH, but the required infrastructure and expertise are not globally available and therefore not captured in the current evaluation.[40,41]

Both BNP and NT-proBNP are established prognostic biomarkers reflecting RV dysfunction in patients with PAH.[42,43] Inconsistencies between centres regarding biomarker collection in TOPP-1 have hampered extensive multivariable evaluations of BNP and NT-proBNP in the current study. Our results from preliminary univariable explorations in subgroups confirm associations with both early and long-term adverse outcomes, but the independent prognostic value in the context of other outcome predictors deserves further evaluation.

Strengths and limitations

The TOPP registry is the first global prospective registry designed to describe the disease course and outcome of newly diagnosed paediatric PH. Important strengths include the sample size, well-defined enrolment criteria, manually reviewed haemodynamic evaluation, the broad patient representation, and the high-quality longitudinal registration without significant loss to follow-up.

Limitations of the study are inherent to the observational design of the registry: no randomization was applied, and enrolment criteria might have introduced selection bias. RHC requirement for confirmation of diagnosis is a major strength of the study, but this could have led to under enrolment of patients with PH. Although many centres from many countries have participated, TOPP is not population-based and its coverage is not fully global. Not all clinical data were collected; for instance, imaging modalities, genetic testing, serial evaluation of

serum biomarkers, and changing treatment strategies were not part of TOPP-1 and could not be analysed regarding their prognostic value. TOPP-2, the successive registry of TOPP-1, addresses some of these limitations and is specifically designed to evaluate treatment goals and compare treatment strategies (NCT02610660). It was considered inappropriate to evaluate treatment in the context of the current survival analyses, as its effects on outcome should preferably be analysed in a randomized controlled setting.

Since the conception of TOPP, international diagnostic criteria to define PAH have slightly evolved over time. A cut-off of mPAP $>$ 20 mmHg has recently been proposed to identify abnormal elevation of mPAP based on healthy controls.[27] In TOPP, the diagnosis of PAH required RHC with mPAP $\geq$ 25 mmHg, PVRI $\geq$ 3 WU·m^2, and PCWP $\leq$ 12 mmHg, ensuring a representative cohort of children with PAH.

We used a composite endpoint of all-cause death, lung transplantation, atrial septostomy, and Potts shunt palliation. A general caveat of composite endpoints in prognostic studies is reduced interpretability compared to single endpoints, especially when the incorporated components have different clinical meaning.[44] The indications for and availability of lung transplantation, atrial septostomy, and Potts shunt palliation might slightly differ between subgroups and study centres. However, all four endpoint components are unignorable adverse outcome events in PH, and their occurrences clearly indicate progression of irreversible, often end-stage disease, justifying their use as composite endpoint components.

Clinical implications

The currently reported adverse event-free survival rates of children with PAH are still unsatisfactory and underline the need for further optimization of management strategies in these children. Adequate risk stratification is essential for the optimization of tailored treatment strategies. The currently identified key predictors of both early and long-term adverse outcomes provide an important basis for further development and refinement of treatment strategies and practice guidelines in paediatric PAH and for the tailoring of treatment of the individual child with PAH.

Conclusions

This study describes current-era, real-world outcome of children with newly diagnosed PAH in a large, representative global cohort. Especially early mortality is substantially high and needs urgent improvement. The current study identifies key predictors of adverse outcome to be used for risk stratification and tailoring of PAH-targeted treatment.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Conflict of interest: The co-authors who have received grants, fees, and/or travel meeting support or who serve on advisory boards/steering committees have detailed this using the ICMJE Disclosure Form.

Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request, within the restrictions imposed by the consent given by participants and/or their caregivers and by applicable privacy legislation.

Appendix

TOPP Investigators:

- Robert G. Weintraub, Royal Children's Hospital and Murdoch Children's Research Institute, Melbourne, Australia
- Ralf Geiger, Innsbruck Medical University, Innsbruck, Austria
- Manfred Marx, Universitätsklinik für Kinder- und Jugendheilkunde Wien, Wien, Austria
- Bjorn Cools, Universitair Ziekenhuis Leuven, Leuven, Belgium
- Sandra Mattos, Maternal–Fetal Cardiac Unit, Royal Portuguese Hospital, Recife, Brazil
- Tilman Humpl, The Hospital for Sick Children, Toronto, Canada
- Zhi-Cheng Jing, State Key Lab of Cardiovascular Disease, FuWai Hospital, National Center for Cardiovascular Disease, PUMC & CAMS, Beijing, China
- Lars Sondergaard, Rigshospitalet, Copenhagen, Denmark
- Damien Bonnet, Marilyne Lévy, Hôpital Necker Enfants Malades, Paris, France
- Christian Apitz, Universitätsklinikum Gießen, Gießen, Germany
- Alfred Hager, Deutsches Herzzentrum, München, Germany
- Laszlo Ablonczy, Gottsegen National Cardiovascular Center, Budapest, Hungary
- Ornella Milanesi, University of Padua, Padua, Italy
- Ben T. Saji†, Toho University Medical Center Omori Hospital, Tokyo, Japan
- Tomás Pulido, National Heart Institute, Mexico City, Mexico
- Rolf Berger and Menno Douwes, Beatrix Children's Hospital, University Medical Center Groningen, Groningen, The Netherlands
- Henrik Brun, Rikshospitalet, Oslo, Norway
- Jadwiga Moll and Krzysztof W. Michalak, Polish Mothers Memorial Hospital Research Institute, Lodz, Poland
- Wanda Kawalec and Małgorzata Żuk Children's Memorial Health Institute, Warszawa, Poland
- Maurice Beghetti, Hospital des Enfants, Geneva, Switzerland
- Margrit Fasnacht Boillat, Kantonsspital Winterthur, Switzerland
- Rana Olguntürk and Serdar Kula, Faculty of Medicine, Gazi University, Ankara, Türkiye
- Dursun Alehan, Hacettepe University Faculty of Medicine, Ankara, Türkiye
- Ingram Schulze-Neick†, Great Ormond Street Hospital for Children, London, UK
- Robyn Barst†, Columbia Presbyterian Medical Center, New York, NY, USA
- Andrew M. Atz, Medical University of South Carolina, Charleston, SC, USA
- D. Dunbar Ivy, Children's Hospital Colorado, Aurora, Denver, CO, USA
- Ronald W. Day, University of Utah, Salt Lake City, UT, USA
- Eric D. Austin and J. Donald Moore, Vanderbilt Monroe Carell Jr Children's Hospital at Vanderbilt, Nashville, TN, USA
- Jeffrey A. Feinstein, Stanford University Medical Center, Palo Alto, CA, USA

- Delphine Yung, Seattle Children's Hospital and University of Washington School of Medicine, Seattle, WA, USA
- John T. Berger, Children's National Medical Center, Washington, WA, USA
- George B. Mallory, Texas Children's Hospital, Houston, TX, USA

References

1. Ivy D. Pulmonary hypertension in children. *Cardiol Clin* 2016;**34**:451–472.
2. Latus H, Delhaas T, Schranz D, Apitz C. Treatment of pulmonary arterial hypertension in children. *Nat Rev Cardiol* 2015;**12**:244–254.
3. Galiè N, Channick RN, Frantz RP, Grünig E, Jing ZC, Moiseeva O *et al.* Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J* 2019;**53**:1801889.
4. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S *et al.* Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. *Eur Respir J* 2019;**53**:1801916.
5. Hansmann G, Koestenberger M, Alastalo T-P, Apitz C, Austin ED, Bonnet D *et al.* 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. *J Heart Lung Transplant* 2019;**38**:879–901.
6. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001–2006. *Heart* 2009;**95**:312–317.
7. van Loon RLE, Roofthooft MTR, Delhaas T, van Osch-Gevers M, ten Harkel ADJ, Strengers JLM *et al.* Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. *Am J Cardiol* 2010;**106**:117–124.
8. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. *Circulation* 2012;**125**:113–122.
9. Zijlstra WMH, Douwes JM, Rosenzweig EB, Schokker S, Krishnan U, Roofthooft MTR *et al.* Survival differences in pediatric pulmonary arterial hypertension: clues to a better understanding of outcome and optimal treatment strategies. *J Am Coll Cardiol* 2014;**63**:2159–2169.
10. Constantine A, Dimopoulos K, Haworth SG, Muthurangu V, Moledina S. Twenty-year experience and outcomes in a National Pediatric Pulmonary Hypertension Service. *Am J Respir Crit Care Med* 2022;**206**:758–766.
11. Clabby ML, Canter CE, Moller JH, Bridges ND. Hemodynamic data and survival in children with pulmonary hypertension. *J Am Coll Cardiol* 1997;**30**:554–560.
12. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. *Circulation* 1999;**99**:1197–1208.
13. Ploegstra M, Zijlstra WMH, Douwes JM, Hillege HL, Berger RMF. Prognostic factors in pediatric pulmonary arterial hypertension: a systematic review and meta-analysis. *Int J Cardiol* 2015;**184**:198–207.
14. O'Byrne ML, Glatz AC, Hanna BD, Shinohara RT, Gillespie MJ, Dori Y *et al.* Predictors of catastrophic adverse outcomes in children with pulmonary hypertension undergoing cardiac catheterization. *J Am Coll Cardiol* 2015;**66**:1261–1269.
15. O'Byrne ML, Kennedy KF, Kanter JP, Berger JT, Glatz AC. Risk factors for major early adverse events related to cardiac catheterization in children and young adults with pulmonary hypertension: an analysis of data from the IMPACT (Improving Adult and Congenital Treatment) registry. *J Am Heart Assoc* 2018;**7**:e008142.
16. Gu L, Li YY, Gu L, Xie L, Liu HM. Idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease in Chinese children: similarities, differences, and prognostic factors. *Front Pediatr* 2020;**8**:106.
17. Ploegstra M-J, Berger RMF. Prognostic biomarkers in pediatric pulmonary arterial hypertension. *Cardiovasc Diagn Ther* 2021;**11**:1089–1101.
18. Berger RMF, Beghetti M, Humpl T, Raskob GE, Ivy DD, Jing Z-C *et al.* Clinical features of paediatric pulmonary hypertension: a registry study. *Lancet* 2012;**379**:537–546.
19. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007;**165**:710–718.
20. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. *Heart* 2010;**96**:1401–1406.
21. Douwes JM, Roofthooft MTR, Bartelds B, Talsma MD, Hillege HL, Berger RMF. Pulsatile haemodynamic parameters are predictors of survival in paediatric pulmonary arterial hypertension. *Int J Cardiol* 2013;**168**:1370–1377.
22. Wagner BD, Takatsuki S, Accurso FJ, Ivy DD. Evaluation of circulating proteins and hemodynamics towards predicting mortality in children with pulmonary arterial hypertension. *PLoS One* 2013;**8**:e80235.
23. van Loon RLE, Roofthooft MTR, Hillege HL, ten Harkel ADJ, van Osch-Gevers M, Delhaas T *et al.* Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. *Circulation* 2011;**124**:1755–1764.
24. Zijlstra WMH, Douwes JM, Ploegstra M-J, Krishnan U, Roofthooft MTR, Hillege HL *et al.* Clinical classification in pediatric pulmonary arterial hypertension associated with congenital heart disease. *Pulm Circ* 2016;**6**:302–312.
25. Ivy DD, Abman SH, Barst RJ, Berger RMF, Bonnet D, Fleming TR *et al.* Pediatric pulmonary hypertension. *J Am Coll Cardiol* 2013;**62**:D117–D126.
26. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;**62**:D34–D41.
27. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M *et al.* 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2022;**43**:3618–3731.
28. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK *et al.* Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation* 2015;**132**:2037–2099.
29. Lammers AE, Adatia I, del Cerro, MJ, Diaz G, Freudenthal AH, Freudenthal F *et al.* Functional classification of pulmonary hypertension in children: report from the PVRI pediatric taskforce, Panama 2011. *Pulm Circ* 2011;**1**:280–285.
30. Takatsuki S, Yanai S, Ikehara S, Nakayama T, Matsuura H. Clinical effects of syncope on disease severity and adverse outcomes in children with idiopathic and heritable pulmonary arterial hypertension. *Pediatr Cardiol* 2019;**40**:209–214.
31. Douwes JM, Hegeman AK, van der Krieke-van der Horst M, Roofthooft MTR, Hillege HL, Berger RRMF *et al.* Six-minute walk-test in childhood pulmonary arterial hypertension: walking distance and decrease in oxygen saturation provide additional prognostic information. *Eur Heart J* 2014;**35**:174–175.
32. Lammers AE, Munnery E, Hislop AA, Haworth SG. Heart rate variability predicts outcome in children with pulmonary arterial hypertension. *Int J Cardiol* 2010;**142**:159–165.
33. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS *et al.* Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010;**122**:164–172.
34. Sandoval J, Bauerle O, Gomez A, Palomar A, Martínez Guerra ML, Furuya ME. Primary pulmonary hypertension in children: clinical characterization and survival. *J Am Coll Cardiol* 1995;**25**:466–474.
35. Ivy DD, Rosenzweig EB, Lemarié J-C, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. *Am J Cardiol* 2010;**106**:1332–1338.
36. Apitz C, Zimmermann R, Kreuder J, Jux C, Latus H, Pons-Kühnemann J *et al.* Assessment of pulmonary endothelial function during invasive testing in children and adolescents with idiopathic pulmonary arterial hypertension. *J Am Coll Cardiol* 2012;**60**:157–164.
37. Douwes JM, Humpl T, Bonnet D, Beghetti M, Ivy DD, Berger RMF, TOPP Investigators. Acute vasodilator response in pediatric pulmonary arterial hypertension: current clinical practice from the TOPP registry. *J Am Coll Cardiol* 2016;**67**:1312–1323.
38. Apitz C, Berger RMF, Ivy DD, Humpl T, Bonnet D, Beghetti M *et al.* Hemodynamic and prognostic impact of the diastolic pulmonary arterial pressure in children with pulmonary arterial hypertension-a registry-based analysis. *Cardiovasc Diagn Ther* 2021;**11**:1037–1047.
39. Beghetti M, Berger RMF, Bonnet D, Grill S, Lesage C, Lemarie J-C *et al.* Echocardiographic changes and long-term clinical outcomes in pediatric patients with pulmonary arterial hypertension treated with bosentan for 72 weeks: a post-hoc analysis from the FUTURE 3 study. *Front Pediatr* 2021;**9**:681538.
40. Moledina S, Pandya B, Bartsota M, Mortensen KH, McMillan M, Quyam S *et al.* Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. *Circ Cardiovasc Imaging* 2013;**6**:407–414.
41. Latus H, Kuehne T, Beerbaum P, Apitz C, Hansmann G, Muthurangu V *et al.* Cardiac MR and CT imaging in children with suspected or confirmed pulmonary hypertension/pulmonary hypertensive vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;**102 Suppl**:ii30–ii35.
42. Said F, Haarman MG, Roofthooft MTR, Hillege HL, Ploegstra M-J, Berger RMF. Serial measurements of N-terminal pro-B-type natriuretic peptide serum level for monitoring pulmonary arterial hypertension in children. *J Pediatr* 2020;**220**:139–145.
43. Bernus A, Wagner BD, Accurso F, Doran A, Kaess H, Ivy DD. Brain natriuretic peptide levels in managing pediatric patients with pulmonary arterial hypertension. *Chest* 2009;**135**:745–751.
44. Fleming TR, Powers JH. Biomarkers and surrogate endpoints in clinical trials. *Stat Med* 2012;**31**:2973–2984.