Pediatric pulmonary arterial hypertension
Zijlstra, Willemijn

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Prognostic factors in pediatric pulmonary arterial hypertension: a systematic review and meta-analysis

Mark-Jan Ploegstra, Willemijn M.H. Zijlstra, Johannes M. Douwes, Hans L. Hildege, Rolf M.F. Berger

Groningen, the Netherlands
ABSTRACT

Background—Despite the introduction of targeted therapies in pediatric pulmonary arterial hypertension (PAH), prognosis remains poor. For the definition of treatment strategies and guidelines, there is a high need for an evidence-based recapitulation of prognostic factors. The aim of this study was to identify and evaluate prognostic factors in pediatric PAH by a systematic review of the literature and to summarize the prognostic value of currently reported prognostic factors using meta-analysis.

Methods and Results—Medline, EMBASE and Cochrane Library were searched on April 1st 2014 to identify original studies that described predictors of mortality or lung transplantation exclusively in children with PAH. 1053 citations were identified, of which 25 were included for further analysis. Hazard ratios (HR) and 95% confidence intervals were extracted from the papers. For variables studied in at least three non-overlapping cohorts, a combined HR was calculated using random-effects meta-analysis. WHO functional class (WHO-FC, HR 2.7), (N-terminal pro) brain natriuretic peptide ([NT-pro]BNP, HR 3.2), mean right atrial pressure (mRAP, HR 1.1), cardiac index (HR 0.7), indexed pulmonary vascular resistance (PVRi, HR 1.3) and acute vasodilator response (HR 0.3) were identified as significant prognostic factors (p≤0.001).

Conclusions—This systematic review combined with separate meta-analyses shows that WHO-FC, (NT-pro)BNP, mRAP, PVRi, cardiac index and acute vasodilator response are consistently reported prognostic factors for outcome in pediatric PAH. These variables are useful clinical tools to assess prognosis and should be incorporated in treatment strategies and guidelines for children with PAH.
INTRODUCTION

Pulmonary arterial hypertension (PAH) is a severe progressive disease of the pulmonary vasculature, leading to increased pulmonary vascular resistance (PVR), right ventricular (RV) failure and death. Since the recent introduction of specific PAH-targeted drugs, quality of life and survival in both children and adults have improved, but remain unsatisfactory.

For clinical decision-making in the treatment of these patients, it is important to be able to predict survival using prognostic factors. In adults with idiopathic PAH, various prognostic factors have been identified and reviewed. Although data in children are limited, several pediatric studies have recently reported on survival and prognostic factors. These data, however, are mostly derived from relatively small patient series and contradictory findings have been reported. It is unclear whether contradictions that have emerged from recent pediatric studies can be explained by differences in study populations, different treatment strategies or by insufficient power of the individual studies due to small sample sizes.

There is a high clinical need to improve treatment strategies and to define guidelines for the management of children with PAH. Therefore, it is of great importance to identify, appraise, synthesize and combine the currently available data on prognostic factors in pediatric PAH. This will help in defining current evidence and in developing supportive guidelines for the management of infants and children with PAH. Hence, the aim of this study was to identify and evaluate prognostic factors in pediatric PAH, by a systematic review of the literature and to subsequently summarize the prognostic value of currently reported prognostic factors in children with PAH using meta-analysis.

METHODS

Literature search
Medline, EMBASE and Cochrane Library were searched on April 1st 2014. The initial literature search focused on the overlapping part of three elements: (1) PAH, (2) children and (3) survival. To achieve this, a search string was composed and adapted to the three literature databases (supplementary file, Table A.1). The keyword ‘primary pulmonary hypertension’ was also included, as this term was previously used for idiopathic PAH (IPAH). In contrast, the formerly used term ‘secondary pulmonary hypertension’ for PH other than IPAH was not included because this group also comprised forms of PH with different etiologies and disease mechanisms than PAH. The search was limited to human studies and English language. The reference lists of all primary identified articles were hand searched for additional relevant publications.
Chapter 6

Study selection
Titles and abstracts were screened by two independent reviewers (M.J.P and W.M.H.Z., investigators) to identify studies that described predictors of mortality in children with PAH. Eligible studies were required to report at least (1) data on mortality in pediatric PAH and (2) variables studied in relation to mortality. Studies were considered ineligible if they were animal studies or review articles, were not limited to children or when no survival analysis (Cox regression analysis or Kaplan-Meier survival analysis) was performed. All remaining studies underwent full-text review, with a targeted focus on the study population and survival analysis details. Studies were excluded when >20% of the study population did not meet the current PAH definition according to the updated Nice classification. Studies using endpoints other than death or death + lung transplantation were also excluded. Any disagreements between the reviewers were resolved by discussion leading to consensus or by consulting a third-party arbitrator (H.L.H., epidemiologist/statistical consultant).

Data extraction
Of all studied variables, hazard ratios (HR) and 95% confidence intervals (CI) derived from univariable Cox regression analysis were extracted from the papers. When the CI was not reported, the P-value was used to estimate the CI. When only Kaplan-Meier analysis was performed to assess a variable’s relation with survival, HR and CI were estimated using Parmar’s survival curve method, on the condition that picture quality and description of patient numbers were sufficient. When individual patient data were provided in the paper in the absence of a reported HR, the HR and CI were calculated using Cox regression analysis rather than estimated from the survival curve. When the HR was described for death and death + lung transplantation, the HR for death was extracted. When analyses were performed for characteristics at different baseline moments (e.g. both time of diagnosis and study enrollment), the baseline with least missing values was used.

Data synthesis
Multiple separate random-effects meta-analyses were conducted to calculate combined HRs for sufficiently studied candidate prognostic factors. The following methodological considerations were taken into account: (1) patient-overlap between studies, (2) sufficiency of number of combinable studies, (3) differences in how the HR was calculated and (4) potential between-study heterogeneity.

Patient-overlap between studies is likely to exist, since most studies on pediatric PAH are performed in a limited number of centers. When a variable was studied and reported more than once by the same center with overlapping inclusion periods, only the HR from the largest study was included in the meta-analysis. In case of exactly matching patient numbers, the most recent study was included. HRs from studies that combined previously published cohorts in a new individual patient data level analysis were excluded,
unless a HR was not available from the original cohort studies. The HRs of all excluded studies were still displayed in the meta-analysis forest plots in a different color to retain overview of the entirety and consistency of the available data.

Meta-analysis was only considered appropriate when a candidate prognostic factor was studied in at least three non-overlapping cohorts. When meta-analysis was not appropriate, results were summarized in tabular form.

Differences in how the HR was calculated, such as variation in the number of units change used for HR calculation (e.g. when one study reported the HR per 1 mmHg pressure change while another reported the HR per 5 mmHg change), were addressed by recalculating the HRs using a uniform clinically applicable number of units change. HRs of dichotomized continuous variables (i.e. when patients with high values were compared to patients with low values), could not be recalculated and were left unadjusted. HRs based on dichotomized variables were not combined with HRs based on continuous variables, but were displayed separately. The choice of including HRs based on dichotomized or continuous variables in meta-analyses depended on how often the methods were applied: studies with the least applied method were excluded from the meta-analysis but were still displayed in the forest plot in a different color to retain overview of the entirety and consistency of the available data.

Heterogeneity was assessed using both Cochran’s Q-test and the $I^2$ quantity. In view of the small number of studies to be compared, a Q-test p-value <0.10 or an $I^2$ quantity >50% were considered indicative of substantial heterogeneity. In the case of a statistically significant combined weighted HR in combination with substantial evidence for heterogeneity, the methodological characteristics and study populations were compared and exploratory subgroup analysis and meta-regression were conducted to identify potential causes of heterogeneity. Analyses were performed using STATA 11.0 (STATA corp., College Station, Texas, USA).

RESULTS

Identified studies
In total, 1053 citations were identified (Figure 1). With screening titles and abstracts, 989 citations were excluded, leaving 64 articles for full-text review (references are listed in the supplementary file). Screening full articles identified 27 articles that described prognostic factors for survival exclusively in pediatric PAH (supplementary file, Table A.2). Exclusion reasons per publication are shown in Table A.3. Additionally, two primarily identified studies were excluded from further data analysis because of inconsistency in data reporting within the paper, and because of demonstrable 100% patient-overlap with a previously published report. The main characteristics of the remaining 25 studies are outlined in Table 1.
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Data presented as percentage or mean, unless stated otherwise. PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; IPAH = idiopathic PAH; APAH = associated PAH; CHD = congenital heart disease; WHO-FC = WHO functional class; NT-proBNP = N-terminal-pro brain natriuretic peptide; BNP = brain natriuretic peptide; mRAP = mean right atrial pressure; mPAP = mean pulmonary artery pressure; PVRI = indexed pulmonary vascular resistance; D = diagnosis; T = treatment start; P = presentation; E = enrollment; O = other; Cox = Cox regression analysis; KM = Kaplan-Meier analysis; Dt = death; Dt/Ltx = death or lung-transplantation.

* Also individual patient data available in paper, allowing for hazard ratio calculation. † The diagnosis of 18% of the patients in this study was described as ‘miscellaneous causes of PH’, which could be interpreted as either APAH-non-CHD or other types of PH. ‡ Median (mean not reported in paper). § Calculated within a subgroup of the cohort. †† Vasodilators and definitions of a favorable response differed throughout the studies.
Table 2 summarizes a total of 40 variables that have been shown to be significantly related to survival in one or more studies. The availability of HRs (either directly reported or indirectly calculable) is also shown in Table 2. For 10 of the 40 identified variables, there were HRs available from at least three non-overlapping cohorts. For these 10 candidate prognostic factors, a combined HR and accompanying P-value could be calculated using meta-analysis (Table 3). The corresponding forest plots are displayed in Figures 2-4. The meta-analysis results of the 10 candidate prognostic factors are detailed below.

**Age** was investigated in 10 studies, with HRs available from 6/10 studies (Table 2). One of these 6 was omitted from meta-analysis to prevent duplicate patient inclusion (Figure 2). Combining the remaining 5 non-overlapping cohorts representing 426 patients yielded a HR (CI) of 1.01 (0.92-1.10) per year increase (Figure 2, p=0.866), indicating no significant association with survival. North-American studies (Sandoval, Barst 1999, ...
Table 2. Variables associated with survival per study

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N times studied: Number of times the variable was studied in the respective study. N times significant: Number of times the variable was significant in the respective study. N times extractable HRs: Number of times the variable was extractable for HRs in the respective study. N HRs from non-overlapping cohorts: Number of HRs from non-overlapping cohorts.
Table 2. Variables associated with survival, per study (continued)

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✔ = significant association with survival; X = no significant association with survival; grey indicates that sufficient survival analysis results were provided in the paper to be included in meta-analysis; HR = hazard ratio; WHO-FC = WHO functional class; 6MWT = 6-minute walk test; RR = blood pressure; BSA = body surface area; VO2 = oxygen consumption; VE/VCO2 = ventilatory-efficiency slope; BMPR2 = bone morphogenetic protein receptor type I; (NT-pro)BNP = (N-terminal pro) brain natriuretic peptide; Hb = hemoglobin; Apo A1 = apolipoprotein A-1; TIMP-1 = metalloproteinase-inhibitor-1; sST2 = soluble ST2; mRAP = mean right atrial pressure; mPAP = mean pulmonary artery pressure; mPAP/mSAP = pulmonary-to-systemic arterial pressure ratio; PVRi = indexed pulmonary vascular resistance; Qp(i) = pulmonary blood flow (index); SvO2 = mixed venous oxygen saturation; PAC(i) = pulmonary arterial capacitance (index); PVR/SVR = pulmonary-to-systemic vascular resistance ratio; VRT = vasoreactivity testing; PFR = pulmonary flow reserve; PSVi = pulmonary stroke volume index; CMR = cardiac magnetic resonance imaging; CT = computed tomography.

a HR was only extractable when sufficient survival analysis results were provided in the paper.

b Echocardiographic variables once shown to be associated with survival include: semi-quantitatively assessed RV-hypertrophy, RV-dilatation and RV-function (score 1-4), systolic to diastolic duration ratio, maximum tricuspid regurgitation velocity, RV-fractional area change, Z-score of tricuspid annular plane systolic excursion, Z-score of RV end-diastolic area, RV end systolic area index and right to left ventricular dimension ratio.

c CMR variables once shown to be associated with survival include: RV end-diastolic volume index, RV end-systolic volume index, RV ejection fraction, RV mass index, LV stroke volume index, tricuspid regurgitation fraction, right atrial area index, and mid right ventricle diameter index.
Barst 2012 and Wagner\textsuperscript{13-16} and European studies (Moledina and Douwes\textsuperscript{17,18}) reported contradictory findings.

Sex was investigated in 10 studies, with HRs available from 5/10 studies (Table 2). Combining these 5 non-overlapping cohorts representing 428 patients yielded a HR (CI) of 1.38 (0.55-3.43) for male compared to female (Figure 2, p=0.495), indicating no significant association with survival.

Diagnosis was investigated in 9 studies, with HRs available from 2 studies and survival curves available from 5 studies (Table 2). Four of these 7 were omitted from meta-analysis to prevent duplicate patient inclusion (Figure 3).\textsuperscript{3,4,18,19} Combining the remaining 3 non-overlapping cohorts representing 585 patients yielded a HR (CI) of 0.70 (0.41-1.19) for associated PAH (APAH) compared to IPAH (Figure 3, p=0.191), indicating no significant association with survival.
**Systematic review of prognostic factors in pediatric PAH**

**Diagnosis**

HR of APAH compared to IPAH

- Haworth 2009, n=216
- Van Loon 2010, n=52
- Hislop 2011, n=101
- Van Loon 2011, n=154
- Barst 2012, n=215
- Douwes 2013, n=52
- Zijlstra 2014, n=236

**WHO-FC**

HR of high compared to low WHO-FC or per FC increase

- Sandovol 1995, n=18 (III/IV vs. I/II)
- Van Loon 2010, n=52 (per FC)
- Lammers 2010, n=47 (III/IV vs. I/II)
- Moledina 2010, n=64 (per FC)
- Ivy 2010, n=81 (III/IV vs. I/II)
- Moledina 2011, n=31 (per FC)
- Barst 2012, n=190 (III/IV vs. I/II)
- Douwes 2013, n=52 (IV vs. I/II/III)
- Wagner 2013, n=83 (III/IV vs. I/II)
- Zijlstra 2014, n=236 (III/IV vs. I/II)

**(NT-pro)BNP**

HR of high compared to low (NT-pro)-BNP or per unit increase

- Nakayama 2007, n=27 (400 pg/mL)a,d
- Van Albada 2008, n=24 (per ng/mL)b,e
- Bemus 2009, n=78 (180 pg/mL)c
- Lammers 2009, n=50 (130 pg/mL)c
- Van Loon 2010, n=52 (per 10-Log value)e
- Barst 2012, n=215 (50/300) pg/mLf
- Chida 2014, n=59 (537 pg/mL)e
- Zijlstra 2014, n=41 (per 10-Log value)e

**APAH**

HR of APAH compared to IPAH

- Haworth 2009, n=216
- Van Loon 2010, n=52
- Hislop 2011, n=101
- Van Loon 2011, n=154
- Barst 2012, n=215
- Douwes 2013, n=52
- Zijlstra 2014, n=275

**Heterogeneity**

- p=0.452, I2=0.0%
- p=0.664, I2=0.0%
- p=0.191, p=0.0%
- p=0.108, I2=55.1%
- p=0.001, p=0.0%
- p=0.191, p=0.0%

**Figure 3.** Forest plots showing clinical and biochemical candidate prognostic factors

HRs displayed as diamonds ♦ are based on dichotomized variables, HRs displayed as dots • are based on continuous variables. Area of each diamond/dot is proportional to the sample size of the studied cohort. Only HRs in blue are non-overlapping and included in meta-analysis. * HR estimated from survival curve. b HR calculated from reported individual patient data. c Between brackets are the cut-off values used in dichotomization or the number of units increase at which the HR calculation was based. d Studied biomarker was BNP. e Studied biomarker was NT-proBNP. f Both BNP and NT-proBNP were studied. HR = hazard ratio; CI = confidence interval; APAH = associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; FC = functional class; (NT-pro)BNP = (N-terminal-pro) brain natriuretic peptide.
World Health Organization functional class (WHO-FC) was investigated in 11 studies, with HRs available from 10/11 studies (Table 2). Since WHO-FC was mostly studied as a dichotomized variable, 3 studies that reported HRs based on WHO-FC as a continuous variable were omitted from meta-analysis (Figure 3). An additional 3 studies were omitted to prevent duplicate patient inclusion. Combining the remaining 4 non-overlapping cohorts representing 307 patients yielded a HR (CI) of 2.67 (1.49-4.80), for high compared to low WHO-FC (Figure 3, p=0.001), without substantial heterogeneity-evidence (p=0.452, \( I^2 = 0.0\% \)).

\((N\text{-Terminal-pro}) \ \text{brain natriuretic peptide ((NT-pro)BNP)}\) was investigated in 9 studies (Table 2, 4x BNP, 3x NT-proBNP, 2x both) and the results of these studies were combined. HRs, survival curves and individual patient data were available from 4, 3 and 1 studies, respectively (Figure 3). Since (NT-pro)BNP was mostly studied as a dichotomized variable, 3 studies that reported HRs based on (NT-pro)BNP as a continuous variable were omitted from meta-analysis. One additional study was omitted to prevent duplicate patient inclusion. Combining the 4 remaining non-overlapping cohorts representing 351 patients yielded a HR (CI) of 3.24 (1.76-6.02) for high levels compared to low (Figure 3, p<0.001), without substantial heterogeneity-evidence (p=0.664, \( I^2 = 0.0\% \)).

To be able to selectively analyze BNP instead of analyzing BNP and NT-proBNP together, we performed a sensitivity analysis. In the studies of Nakayama et al., Bernus et al., and Lammers et al., BNP was studied exclusively. Combining these 3 non-overlapping cohorts representing 155 patients yielded a HR (CI) of 4.24 (1.80-9.96) for high levels compared to low (Supplemental file, Figure A.1, p=0.001), without substantial heterogeneity-evidence (p=0.284, \( I^2 = 20.5\% \)). A similar separate analysis for NT-proBNP was hampered by the low number of non-overlapping cohorts in which NT-proBNP was studied exclusively (n=2).

Mean right atrial pressure (mRAP) was investigated in 9 studies, with HRs available from 6/9 studies (Table 2). Since mRAP was mostly studied as a continuous variable, 1 study that reported a HR based on dichotomized mRAP was omitted from meta-analysis (Figure 4). An additional 2 studies were omitted to prevent duplicate patient inclusion. Combining the remaining 3 non-overlapping cohorts representing 404 patients yielded a HR (CI) of 1.12 (1.05-1.20) per mmHg increase (Figure 4, p=0.001), without substantial heterogeneity-evidence (p=0.289, \( I^2 = 19.3\% \)).

Mean pulmonary artery pressure (mPAP) was investigated in 11 studies, with HRs available from 7/11 studies (Table 2). Since mPAP was mostly studied as a continuous variable, 1 study that reported a HR based dichotomized mPAP was omitted from meta-analysis (Figure 4). An additional 2 studies were omitted to prevent duplicate patient inclusion. Combining the remaining 4 non-overlapping cohorts representing 254 patients yielded a HR (CI) of 1.18 (0.99-1.40) per mmHg increase (Figure 4, p=0.056), without substantial heterogeneity-evidence (p=0.289, \( I^2 = 19.3\% \)).
An additional 2 studies were omitted to prevent duplicate patient inclusion. Combining the remaining 4 non-overlapping cohorts representing 360 patients yielded a HR
(CI) of 0.66 (0.52-0.84) per L/min/m² increase (Figure 4, p=0.001), without substantial heterogeneity-evidence (p=0.685, I²=0.0%).

Indexed pulmonary vascular resistance (PVRI) was investigated in 12 studies, with HRs available in 10/12 studies (Table 2). Since PVRI was mostly studied as a continuous variable, 2 studies that reported a HR based on dichotomized PVRI were omitted from meta-analysis (Figure 4). An additional 4 studies were omitted to prevent duplicate patient inclusion. Combining the remaining 4 non-overlapping cohorts representing 353 patients yielded a HR (CI) of 1.32 (1.17-1.48) per 10 Wood units.m² increase (Figure 4, p<0.001), without substantial heterogeneity-evidence (p=0.731, I²=0.0%).

Acute vasodilator response was investigated in 7 studies, with HRs and survival curves available from 3 and 1 studies, respectively (Table 2). It must be noted that the used vasodilators and definitions of a favorable response differed in these studies (Figure 4). Still, combining these 4 non-overlapping cohorts representing 312 patients yielded a HR (CI) of 0.27 (0.14-0.45) for responders compared to non-responders (Figure 4, p<0.001), without substantial heterogeneity-evidence (p=0.801, I²=0.0%).

Other variables. Table 2 shows that imaging modalities have also been studied more than once (5x echocardiography, 1x cardiac magnetic resonance imaging [CMR]). None of the investigated echo-variables has been studied more than once in the same way, hampering further comparison or meta-analysis.

### Table 3. Combined prognostic value of candidate prognostic factors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>N</th>
<th>HR (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per year</td>
<td>426</td>
<td>1.01 (0.92-1.10)</td>
<td>0.866</td>
</tr>
<tr>
<td>Sex, male compared to female</td>
<td>428</td>
<td>1.38 (0.55-3.43)</td>
<td>0.495</td>
</tr>
<tr>
<td><strong>Clinical/biochemical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis, APAH compared to IPAH</td>
<td>585</td>
<td>0.70 (0.41-1.19)</td>
<td>0.191</td>
</tr>
<tr>
<td>WHO-FC (high compared to low)</td>
<td>307</td>
<td>2.67 (1.49-4.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(NT-pro)BNP</td>
<td>351</td>
<td>3.24 (1.76-6.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hemodynamic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRAP, per mmHg</td>
<td>404</td>
<td>1.12 (1.05-1.20)</td>
<td>0.001</td>
</tr>
<tr>
<td>mPAP, per 10 mmHg</td>
<td>254</td>
<td>1.18 (0.99-1.40)</td>
<td>0.056</td>
</tr>
<tr>
<td>Cardiac index, per 1 L/min/m²</td>
<td>360</td>
<td>0.66 (0.52-0.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>PVRI, per 10 WU.m²</td>
<td>353</td>
<td>1.32 (1.17-1.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute vasodilator response</td>
<td>312</td>
<td>0.27 (0.14-0.54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data presented as hazard ratio (95% confidence interval). HR = hazard ratio; CI = 95% confidence interval; APAH = associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; WHO-FC = WHO functional class; (NT-pro)BNP = (N-terminal-pro) brain natriuretic peptide; mRAP = mean right atrial pressure; mPAP = mean pulmonary arterial pressure; PVRI = (indexed) pulmonary vascular resistance; WU = wood units.
DISCUSSION

To our knowledge, this is the first study systematically reviewing and meta-analyzing all currently available prognostic factors in pediatric PAH. Separate meta-analyses for candidate prognostic factors showed convincing evidence for the prognostic value of the following six variables: WHO-FC, (NT-pro)BNP, mRAP, PVRi, cardiac index and acute vasodilator response.

Systematic reviews combined with meta-analyses are powerful methods for summarizing and synthesizing data and are the building blocks of evidence-based practice. The highest level of evidence is reached when only randomized studies are included in a systematic review, but the available systematic reviews in adults show that this is not possible in a rare disease like PAH. As stated by the Cochrane Collaboration, a systematic review of non-randomized observational studies is justified when the question of interest cannot be answered by a review of randomized trials. As only one randomized trial has been performed in children with PAH, this justification especially applies to the field of pediatric PAH.

Prognostic factors have also been systematically reviewed in adult PAH. Well-established predictors of mortality in adults include: WHO-FC, heart rate, 6-minute walk distance (6MWD), (NT-pro)BNP, pericardial effusion, tricuspid annular plane systolic excursion, mPAP, mRAP, cardiac index, stroke volume index, PVR, acute vasodilator response and mixed venous oxygen saturation. The six prognostic factors identified in the current study are highly in line with adult evidence. However, an important difference between adult and pediatric PAH is the available evidence for 6MWD as a prognostic factor. Whereas 6MWD has repeatedly and consistently been shown to predict survival in adults, the prognostic value of 6MWD in children has been questioned because of its limited feasibility at young age and the lack of available data (Table 2). More pediatric research is needed on this topic and might focus on the prognostic value of 6MWD in older children (e.g. ≥7 years).

Several recommendations regarding the clinical assessment of prognosis have been made in current adult treatment guidelines. Since the results from the current systematic review provide an overview of evidence for prognostic factors specifically in pediatric PAH, such recommendations are now also possible for children.

Prognostic factors with moderate to high level of evidence

WHO-FC. The applicability of WHO-FC in young children has been questioned in the past, because it is mainly based on the observation and impression of caregivers. Despite this apparent limitation, the current study shows WHO-FC to be one of the strongest prognostic factors in pediatric PAH, also in the relatively younger pediatric cohorts. Not all studies on WHO-FC could be included in meta-analysis because of potential
patient-overlap, but combining 4 non-overlapping cohorts showed a strong association with survival which was consistent with the results of the 6 excluded studies. The results support the recent consensus statement from the Pediatric Task Force of the 5th World Symposium on Pulmonary Hypertension (WSPH) held in Nice, France, 2013, which proposes to strive for WHO-FC I or II as a treatment goal in pediatric PAH. Treatment-induced changes in WHO-FC carry prognostic value in both adults and children, which further underscores its usefulness and validity as a pediatric treatment goal.

(NT-pro)BNP. Pediatric studies that evaluated the prognostic value of (NT-pro)BNP differed regarding the biomarker under study (BNP, NT-proBNP or both), the used cut-off values and the analysis techniques. Nevertheless, there was a high degree of consistency and a strong association with survival in the combined meta-analysis. A sensitivity analysis with solely inclusion of studies that studied BNP, also showed a significant association with survival. It has recently been shown that children who stay on NT-proBNP levels below 1200 ng/L during treatment have significantly better survival rates, which is in line with adult findings regarding this topic. This suggests that a low NT-proBNP level is not only a strong predictor of survival, but is also a valid treatment goal to be used in pediatric goal-oriented treatment strategies.

Hemodynamic variables. Cardiac catheterization in childhood often requires sedation or general anesthesia and has been reported to be accompanied by a complication rate of 4-6%. However, the fact that 4 of the 6 identified prognostic factors in this study are hemodynamic measures underlines the importance of cardiac catheterization, at least to assess disease severity and prognosis at time of diagnosis.

Prognostic factors with low level of evidence

Although not statistically significant, APAH appeared to have a slightly more favorable prognosis compared to IPAH. Importantly, it must be noted that the meta-analysis concerning diagnosis was based upon HRs that were predominantly estimated from survival curves using Parmar’s survival curve method. This method is known to lead to underestimations of the HRs in smaller sample sizes, which subsequently could have led to an underestimation of the combined HR. In addition, all subtypes of APAH were analyzed together, while differences in prognostic value might exist within this group.

Other biomarkers than (NT-pro)BNP have also been shown to correlate with survival in pediatric PAH. The current systematic literature search showed that uric acid was a significant prognostic factor in 3 separate studies based on 2 non-overlapping cohorts (Table 2). Although uric acid was not frequently enough studied to be combined in meta-analysis, this indicates at least a low level of evidence for this prognostic factor.

Although meta-analysis could not be performed for echocardiography, this imaging modality has repeatedly been shown to yield important measures for prognosis (Table 2). Echocardiography is a generally accessible follow-up tool without the need
for sedation or anesthesia and its role in assessing prognosis is already well established in adults.\textsuperscript{40} Five pediatric studies showed echocardiographic variables to be associated with survival (Table 2), which makes this modality a promising tool in managing pediatric PAH. Further research is needed to enhance the body of evidence regarding these prognostic factors with low level of evidence.

**Potential prognostic factors requiring further study**

Other variables that were reported not sufficiently frequent to be meta-analyzed but may be potential prognostic factors include heart rate, blood pressure, height and weight, body surface area, heart rate variability, peak oxygen consumption, ventilatory-eficiency slope, genetic mutations, hemoglobin, norepinephrine, Apolipoprotein-A-1, metallopeptidase-inhibitor-1 and soluble ST2 (Table 2). Future research should reveal which role these variables could play in assessing prognosis in pediatric PAH.

The prognostic value of CMR has only been studied incidentally in children and the accessibility to required infrastructure and expertise may not be widely available.\textsuperscript{41} However, the well established role of CMR in adults makes this a promising future imaging modality in addition to echocardiography also in pediatric PAH.\textsuperscript{42}

Of special future interest in relation to survival are measures of pulmonary artery capacitance, pulmonary artery distensibility, RV stroke work, and ventricular-vascular coupling, which to date have only been studied incidentally and anecdotally in relatively small cohorts.\textsuperscript{11,18,43-45} The feasibility and potential prognostic value of combining imaging modalities and cardiac catheterization are also under study and are expected to yield valuable insights in pulmonary arterial wall dynamics.\textsuperscript{44}

**Strengths and limitations**

This recapitulation of published evidence for prognostic factors in pediatric PAH provides a unique clinical overview. Combining only randomized controlled trials would have been the most ideal way to identify prognostic factors. However, such trials reporting on prognostic factors are unavailable in this field. This could have led to a certain degree of heterogeneity, which was addressed in the current study by combining only studies with similar methodologies and providing a detailed description of the study characteristics (Table 1). Heterogeneity was tested for every meta-analyzed candidate prognostic factor, and revealed no substantial heterogeneity-evidence for the six identified statistically significant prognostic factors.

When HRs were not available, these were estimated using Parmar’s survival curve method, which is known to lead to underestimations of the hazard ratios in smaller sample sizes.\textsuperscript{39} HRs of statistically insignificant associations were sometimes not reported and could in those cases not be included in meta-analysis. Since this could potentially have led to an overrepresentation of significant results in the combined HR,
these excluded studies are shown in tabular form to avoid bias within the current paper (Table 2).

We aimed to prevent duplicate patient representation in the meta-analyses. This was accomplished by restricting study inclusion to non-overlapping cohorts. Overlap was suspected in case of overlapping inclusion periods in studies performed at the same center. Although conservative and accompanied by the risk of also excluding non-overlapping patients, this method ensured a pure and unbiased combined HR.

Considerations regarding future research
This study demonstrates the usefulness of the currently available literature on pediatric PAH. Nevertheless, available data are limited by relatively small sample sizes, insufficiently explained discrepancies and inevitable potential duplicate patient inclusion. Current international collaborative initiatives aim to overcome these limitations. The ongoing Tracking Outcomes and Practice in Pediatric PH (TOPP) registry encompasses the largest cohort of children with PAH to date and is expected to yield important new insights in survival and prognostic factors in pediatric PAH. Although a powerful tool with regard to sample size, the usefulness of any registry depends on the predefined aims and might be hampered by the fact that frequency and mode of follow-up are often not dictated.47

To be able to further investigate reported discrepancies and to increase sample size and statistical power, it could also be considered to merge existing patient cohorts on an individual patient level. Recently, a direct comparison has been made between three major pediatric PAH referral centers, which allowed for analyzing differences in survival rates between centers.4 Such initiatives could be further expanded in the future. To provide transparency in the degree of duplicate patient inclusion throughout different reports, it could be considered to publish lists of unique patient codes with every paper.

To be able to identify which prognostic factors could also qualify in defining treatment goals, future research should also focus on assessing the prognostic value of treatment-induced changes in these variables.34,48

Conclusions
This systematic review combined with separate meta-analyses shows that WHO-FC, (NT-pro)BNP, mRAP, PVRi, cardiac index and acute vasodilator response are consistently reported prognostic factors in pediatric PAH. These variables are validated and useful clinical tools to assess prognosis. The current recapitulation of scientific evidence will provide an important basis for defining treatment strategies and developing practice guidelines for children with PAH. This systematic review does not preclude the potential of the other reported candidate prognostic factors, but rather identifies directions for further research to address gaps in current evidence.
REFERENCES

Chapter 6


## SUPPLEMENTARY DATA

**Table A.2. Studies included during full text review**

<table>
<thead>
<tr>
<th>First author</th>
<th>Abbreviated Journal Title</th>
<th>Year</th>
<th>Study Site</th>
<th>N</th>
<th>Inclusion period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apitz [21]</td>
<td>J Am Coll Cardiol</td>
<td>2012</td>
<td>Giessen</td>
<td>43</td>
<td>Not reported</td>
</tr>
<tr>
<td>Douwes [22]</td>
<td>Int J Cardiol</td>
<td>2013</td>
<td>Groningen</td>
<td>52</td>
<td>1993 - 2010</td>
</tr>
<tr>
<td>Chida [26]</td>
<td>Circ J</td>
<td>2014</td>
<td>Tokyo</td>
<td>59</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Citations are listed in a supplementary references section within this data supplement.

US = United States; NL = Netherlands.
Table A.1. Search strings used and number of identified abstracts per literature database

<table>
<thead>
<tr>
<th>Component</th>
<th>Search String</th>
<th>MEDLINE n hits</th>
<th>EMBASE n hits</th>
<th>Cochrane Library n hits</th>
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</thead>
<tbody>
<tr>
<td><strong>PAH</strong></td>
<td>&quot;Pulmonary arterial hypertension&quot; OR &quot;primary pulmonary arterial hypertension&quot; OR &quot;IPAH&quot; OR &quot;pediatric pulmonary hypertension&quot;</td>
<td>8419</td>
<td>10738</td>
<td>419</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>&quot;Pediatrics&quot; OR &quot;Child&quot; OR &quot;Adolescent&quot; OR &quot;Infant&quot; OR Pediatric OR Pediatrics OR child OR childhood OR kids OR adolescent OR infancy OR baby OR infants OR babies</td>
<td>3119773</td>
<td>1928580</td>
<td>77154</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>&quot;Survival&quot; OR &quot;Survival Analysis&quot; OR &quot;Survival Rate&quot; OR &quot;Mortality&quot; OR &quot;Outcome Assessment (Health Care)&quot; OR &quot;Prognosis (Health Care)&quot; OR Survival OR mortality OR &quot;outcome (Health Care)&quot;</td>
<td>2792649</td>
<td>2918321</td>
<td>150197</td>
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<tr>
<td>Combined</td>
<td>#1 AND #2 AND #3</td>
<td>746</td>
<td>705</td>
<td>9</td>
</tr>
</tbody>
</table>

Values represent the number of identified abstracts for every separate search string at April 1st 2014. Combining the final MEDLINE, EMBASE and Cochrane searches yielded 1053 unique abstracts. PAH = pulmonary arterial hypertension.
Figure A.1. Forest plot showing combined prognostic value of brain natriuretic peptide
Area of each diamond is proportional to the sample size of the studied cohort. * HRs are estimated from survival curve. Between brackets are the cut-off values used in dichotomizing BNP.
BNP = brain natriuretic peptide; HR = hazard ratio; CI = confidence interval.
# Table A.3. Studies excluded during full text review

<table>
<thead>
<tr>
<th>First author</th>
<th>Abbreviated Journal Title</th>
<th>Year</th>
<th>Reason for exclusion</th>
</tr>
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<tbody>
<tr>
<td>Houde [28]</td>
<td>Br Heart J</td>
<td>1993</td>
<td>PAH not main topic</td>
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<tr>
<td>Kerstein [29]</td>
<td>Circulation</td>
<td>1995</td>
<td>No survival analysis performed*</td>
</tr>
<tr>
<td>Rosenzweig [31]</td>
<td>Circulation</td>
<td>1999</td>
<td>No survival analysis performed*</td>
</tr>
<tr>
<td>Humpl [33]</td>
<td>Circulation</td>
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<td>No survival analysis performed*</td>
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<td>Endpoint other than Dt or Dt/LTx</td>
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<td>Simpson [35]</td>
<td>J Heart Lung Transplant</td>
<td>2006</td>
<td>No survival analysis performed*</td>
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<td>Lammers [36]</td>
<td>Heart</td>
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<td>Duffels [37]</td>
<td>Int J Cardiol</td>
<td>2007</td>
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</tr>
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<td>Taylor [38]</td>
<td>Br J Anaesth</td>
<td>2007</td>
<td>No survival analysis performed*</td>
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<td>Fasnacht [40]</td>
<td>Swiss Med Wkly</td>
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<td>Joshi [41]</td>
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<td>Ivy [42]</td>
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<td>2008</td>
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<td>Kim [43]</td>
<td>Korean Circ J</td>
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<td>Dickinson [44]</td>
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<td>Fraisse [45]</td>
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<td>2010</td>
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<td>Barst [46]</td>
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<td>Takatsuki [51]</td>
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<td>Yeager [52]</td>
<td>Proteomics Clin Appl</td>
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<td>Baruteau [53]</td>
<td>Ann Thorac Surg</td>
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<td>Takatsuki [54]</td>
<td>J Pediatr</td>
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<td>Krishnan [55]</td>
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<td>Duncan [56]</td>
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<td>Barst [65]</td>
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<td>No survival analysis performed*</td>
</tr>
</tbody>
</table>

Citations are listed in a supplementary references section within this data supplement.

* Survival analysis in which a candidate prognostic factor is evaluated using Cox regression analysis or Kaplan Meier analysis (not: comparison of treatment group survival).

Dt = death; Dt/LTx = death or lung-transplantation.
SUPPLEMENTARY REFERENCES


