Identification of treatment goals in paediatric pulmonary arterial hypertension

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ABSTRACT To be able to design goal-oriented treatment strategies in paediatric pulmonary arterial hypertension (PAH), we aimed to identify treatment goals by investigating the prognostic value of treatment-induced changes in noninvasive predictors of transplant-free survival.

66 consecutive, treatment-naïve paediatric PAH patients in the Dutch National Network for Paediatric Pulmonary Hypertension who started taking PAH-targeted drugs between January 2000 and April 2013 underwent prospective, standardised follow-up. Clinical, biochemical and echocardiographic measures were longitudinally collected at treatment initiation and follow-up, and their respective predictive values for transplant-free survival were assessed. Furthermore, the predictive values of treatment-induced changes were assessed.

From the identified set of baseline predictors, the variables World Health Organization functional class (WHO-FC), N-terminal pro-brain natriuretic peptide (NT-proBNP) and tricuspid annular plane systolic excursion (TAPSE) were identified as follow-up predictors in which treatment-induced changes were associated with survival. Patients in whom these variables improved after treatment showed better survival ($p<0.002$).

Therefore, WHO-FC, NT-proBNP and TAPSE are not only predictors of transplant-free survival in paediatric PAH but can also be used as treatment goals, as treatment-induced improvements in these variables are associated with improved survival. The identification of these variables allows for the introduction of goal-oriented treatment strategies in paediatric PAH.

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Introduction

Pulmonary arterial hypertension (PAH) is a severe, progressive disease of the precapillary pulmonary vessels, leading to increased pulmonary vascular resistance (PVR), right ventricular (RV) failure and death [1, 2]. Since the recent introduction of specific PAH-targeted drugs, quality of life and survival in both children and adults have been improved but remain unsatisfactory [3–11]. In adult PAH patients, a goal-oriented treatment strategy is recommended in which validated clinical and laboratory variables are used to guide the clinician in the timing of therapy escalations or lung transplantation [12, 13]. In children, such a strategy is hampered by the lack of validated treatment goals [14].

The first step in defining such treatment goals is assessing which variables qualify as surrogates for survival. A true surrogate meets at least the following criteria: 1) a strong correlation with survival; 2) values can be influenced by treatment; and 3) treatment-induced changes reflect changes in survival [15, 16]. Ideally, intra- and interobserver variability is low and the surrogate is part of the causal pathway of the disease [15]. A treatment goal could subsequently be defined using a clinically and prognostically relevant threshold value for such a variable.

Several simple predictors of survival have been identified in both adults and children but validated survival surrogates are scarce. Predictors of survival include World Health Organization functional class (WHO-FC), 6-min walking distance (6MWD), resting heart rate, serum levels of brain natriuretic peptide (BNP) or its precursor N-terminal pro-brain natriuretic peptide (NT-proBNP), noradrenaline, uric acid, troponin-T and haemodynamic variables, such as cardiac index, mixed venous oxygen saturation, mean right atrial pressure and PVR index [4–11, 17–27]. In addition, measures derived by echocardiography and cardiac magnetic resonance imaging (CMR) are shown to have prognostic value, including tricuspid annular plane systolic excursion (TAPSE), ratio of right-to-left ventricular dimensions (RV/left ventricular (LV) ratio) and the presence of pericardial effusion [28–32]. Nevertheless, such predictors of survival can only be used as treatment goals when treatment-induced changes are correlated with survival as well [15, 16]. It has recently been demonstrated in adults that improvements in WHO-FC, NT-proBNP, cardiac index and mixed venous oxygen saturation are associated with improvements in survival, supporting their role as treatment goals in adults [33, 34].

No such treatment goals have yet been identified in children with PAH. Because of the drawbacks of serial follow-up catheterisations in children (need for anaesthesia and relatively high complication rate), there is a particular need for noninvasive treatment goals [35]. The current study aimed to identify noninvasive treatment goals in paediatric PAH by investigating the prognostic value of treatment-induced changes in noninvasive predictors of transplant-free survival.

Methods

We performed a registry-based, prospective, observational study. In the Netherlands, all children with PAH are referred to the University Medical Center Groningen, the national referral centre of the Dutch National Network for Paediatric Pulmonary Hypertension [5]. Patients are followed and registered prospectively according to a standardised protocol. Ethical approval for this ongoing registry was obtained from the Medical Ethics Review Board of the University Medical Center Groningen and the subjects (and/or their guardians) provided written informed consent at enrolment.

Patients

All consecutive, treatment-naïve children with PAH who were started on PAH-targeted drugs between January 2000 and April 2013 were included. PAH-targeted therapies consisted of endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin analogues or a combination of these. Diagnosis of PAH was confirmed with cardiac catheterisation, and defined as mean pulmonary artery pressure $\geqslant$25 mmHg with a mean pulmonary capillary wedge pressure $\leqslant$15 mmHg and PVR index $\geqslant$3 Wood unit·m^2. In cases of clinical instability, diagnosis was made by echocardiography, defined as either the presence of right-to-left shunting in the case of congenital heart defects or a maximum systolic tricuspid regurgitant velocity $>$2.8 m·s^{-1} accompanied by septal flattening and/or RV hypertrophy [36]. Exclusion criteria were the presence of LV dysfunction or the start of PAH-targeted therapy $>$3 months before confirmation of diagnosis.

Baseline and clinical follow-up

Treatment initiation was defined as baseline and treatment effect was assessed at the follow-up visit $\geqslant$2 months after treatment initiation. WHO-FC, 6MWD, blood pressure, heart rate, NT-proBNP, creatine kinase, creatine kinase-MB fraction, uric acid, adrenaline, noradrenaline, (high-sensitivity) troponin-T, echocardiography including TAPSE, RV/LV ratio (parasternal short-axis view at end-diastole) and the

presence of pericardial effusion were assessed both at treatment initiation and follow-up. Haemodynamic variables were collected from the cardiac catheterisation at diagnosis. The main outcome parameter was defined as lung transplantation-free survival.

Data analysis

Data are presented as mean±SD, median (interquartile range (IQR)) or frequencies (percentage). In the analyses, logarithmic transformation was used to normalise the distribution of NT-proBNP. In order to ensure the reliability of the 6MWD, only those tests performed at an age $\geqslant$7 years were analysed [37]. Characteristics before and after treatment initiation were compared by paired-samples t-test, McNemar test or Wilcoxon signed-rank test where appropriate.

The combined end-point of transplant-free survival was estimated from time of treatment initiation until the last visit. Cox regression analysis was performed to evaluate the predictive value of variables before and after treatment initiation, and of the changes in-between. Follow-up measurements and treatment-induced changes were included as segmented time-dependent covariates in order to correct for potential time variability in the follow-up visits. Hazard ratios of treatment-induced changes were corrected for the initial baseline values at the time of treatment initiation. Variables with $p<0.100$ in the univariable model were adjusted for age, sex and diagnosis.

For significant predictors at follow-up in which a treatment-induced change was also associated with survival, prognostically distinctive thresholds were estimated using survival time-dependent receiver operating characteristic (ROC) analysis [38]. Kaplan–Meier curves were generated to illustrate the survival difference between high and low values. To study the prognostic implications of increases and decreases, we further estimated Kaplan–Meier curves according to four predefined risk profiles, as proposed previously in adult PAH patients [33]. We defined these profiles as 1) low risk both before and after treatment initiation, 2) high risk before but low risk after treatment initiation, 3) low risk before but high risk after treatment initiation and 4) high risk both before and after treatment initiation. Survival differences were compared by log-rank testing.

Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) and RStudio 0.98.501 (www.rstudio.com). All statistical tests were two-sided and p-values <0.05 were considered statistically significant.

Results

70 consecutive, treatment-naïve children were started on PAH-targeted drugs between January 2000 and April 2013. 66 of these were eligible for inclusion and four were excluded: two had LV dysfunction and in the other two cases, therapy had started >3 months before the confirmation of PAH diagnosis. In 59 cases, PAH was confirmed with cardiac catheterisation at a median (IQR) of 0.3 (0–6.4) months prior to treatment initiation. In the remaining seven cases, diagnosis was echocardiographically confirmed.

Treatment initiation

Patient characteristics at treatment initiation (baseline) are shown in table 1. Median (IQR) age was 8.0 (2.9–13.7) years and 38 patients were $\geqslant$7 years old. The majority of patients were diagnosed with idiopathic PAH (IPAH) or heritable PAH, or congenital heart disease (CHD)-associated PAH (APAH). Of the 24 CHD-APAH patients, two had a pre-tricuspid, 17 a post-tricuspid and five a corrected shunt. All patients were treatment naïve with respect to PAH-targeted therapy at baseline; three were already on a calcium channel blocker. Therapy consisted of monotherapy or combination therapy of endothelin receptor antagonists (56%), phosphodiesterase-5 inhibitors (30%) or prostanoids (24%). Patients were followed for a median (IQR) of 39 (10–75) months. In this period, 25 (38%) patients died and six (9%) underwent lung transplantation.

Univariable cox regression analysis in the full cohort revealed the baseline variables diagnosis, heart rate, WHO-FC, NT-proBNP, noradrenaline, troponin, TAPSE, RV/LV ratio and pericardial effusion as predictors of outcome (online supplementary table S1). No association with survival was demonstrated for the variables sex, age, blood pressure, 6MWD, creatine kinase (total and MB fraction), uric acid or adrenaline.

Treatment-induced changes

Treatment effect was evaluated at a median (IQR) of 4 (3–5) months after treatment initiation. Between treatment initiation and the first follow-up, nine (14%) patients died, leaving 57 (86%) patients available for baseline and follow-up comparison. Table 2 shows these comparisons for clinical, biochemical and echocardiographic variables, and the treatment-induced changes between variables at baseline and follow-up.

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TABLE 1 Patient characteristics stratified by diagnosis

	Total	IPAH/HPAH	APAH	
			CHD	Non-CHD
Patients n	66	34	24	8
Patient characteristics				
Males	23/66 (34.8)	22/34 (64.7)	19/24 (79.2)	2/8 (25.0)
Age at treatment initiation years	8.0 (2.9–13.7)	7.9 (2.9–13.7)	9.5 (1.4–15.1)	7.6 (6.2–11.5)
Heart rate beats per min	100±24.9 (n=63)	99±23.6 (n=32)	103±27.2 (n=23)	98±25.8
Systolic blood pressure mmHg	105±17.7 (n=55)	107±17.2 (n=28)	97±11.6 (n=19)	115±24.8
Diastolic blood pressure mmHg	62±12.5 (n=55)	63±14 (n=28)	58±8.1 (n=19)	69±13.4
WHO-FC				
I or II	13/66 (19.7)	7/34 (20.6)	1/24 (20.8)	1/8 (12.5)
III	32/66 (48.5)	17/34 (50.0)	11/24 (45.8)	4/8 (50.0)
IV	21/66 (31.8)	10/34 (29.4)	8/24 (33.3)	3/8 (37.5)
6MWD[#] m	350±91.7 (n=32)	377±80.6 (n=18)	315±100.4 (n=13)	324 (n=1)
Biochemical characteristics				
NT-proBNP ng·L^{-1}	875 (176–3090) (n=48)	1391 (202–4414) (n=24)	854 (86–1456) (n=17)	497 (115–7653) (n=7)
CK U·L^{-1}	67 (33–125) (n=32)	66 (25–133) (n=17)	71 (39–90) (n=10)	106 (44–211) (n=5)
CK-MB U·L^{-1}	21 (9–33) (n=31)	20 (8–32) (n=16)	24 (11–42) (n=10)	22 (14–30) (n=5)
Uric acid mmol·L^{-1}	0.3±0.09 (n=40)	0.3±0.07 (n=20)	0.3±0.09 (n=15)	0.4±0.17 (n=5)
Noradrenaline nmol·L^{-1}	1.5 (0.94–2.62) (n=23)	2.0 (1.3–5.9) (n=13)	1.3 (0.8–1.95) (n=9)	1.0 (n=1)
Adrenaline nmol·L^{-1}	0.2 (0.12–0.54) (n=22)	0.3 (0.2–0.85) (n=13)	0.1 (0.05–0.18) (n=8)	0.13 (n=1)
Detectable troponin	11/33 (33.3)	8/17 (47.1)	1/11 (9.1)	2/5 (40.0)
Echocardiographic characteristics				
TAPSE mm	15 (11.3–17.0) (n=49)	15 (11.1–16.8) (n=28)	15 (9.8–18.0) (n=14)	16 (12.5–19.5) (n=7)
RV/LV ratio	1.0 (0.71–1.57) (n=48)	1.2 (0.9–1.6) (n=27)	0.8 (0.6–1.2) (n=13)	0.8 (0.6–1.7) (n=8)
Presence of pericardial effusion	6/50 (12.0)	4/28 (14.3)	0/14 (0.0)	2/8 (25.0)
Diagnostic cardiac catheterisation				
Cardiac index L·min^{-1}·m^{-2}	2.8 (2.3–4.0) (n=53)	2.8 (2.0–3.5) (n=27)	2.7 (2.3–3.8) (n=19)	4.4 (2.4–4.7) (n=7)
mRAP mmHg	6 (5–8) (n=59)	6 (5–9) (n=31)	7 (5–8) (n=21)	5 (4–8) (n=7)
mPAP mmHg	50 (36–64) (n=59)	54 (36–64) (n=31)	49 (38–68) (n=21)	47 (30–61) (n=7)
PVRI WU·m^2	15.3 (8.1–26.8) (n=-53)	18.8 (8.3–27.8) (n=27)	15.3 (7.1–32.7) (n=19)	8.5 (4.7–18.5) (n=7)
Sv_{O_2} %	63.8 (56.0–71.5) (n=56)	64.9 (55.2–71.4) (n=28)	63.0 (54.1–67.4) (n=21)	69.8 (59.7–76.2) (n=7)
Acute response to vasodilator testing[¶]	4/47 (8.5)	3/24 (12.5)	1/16 (6.3)	0/7 (0.0)
Medication started at treatment initiation				
Medication				
ERA	37/66 (56.1)	18/34 (52.9)	18/24 (75)	1/8 (12.5)
PDE5i	20/66 (30.3)	11/34 (32.4)	5/24 (20.8)	4/8 (50.0)
Prostanoid	16/66 (24.2)	10/34 (29.4)	2/24 (8.3)	4/8 (50.0)
Therapy intensity				
Monotherapy	60/66 (90.9)	30/34 (88.2)	23/24 (95.8)	7/8 (87.5)
Upfront dual therapy	5/66 (7.6)	3/34 (8.8)	1/24 (4.2)	1/8 (12.5)
Upfront triple therapy	1/66 (1.5)	1/34 (2.9)	0/24 (0.0)	0/8 (0.0)

Data are presented as n/N (%), median (interquartile range) or mean± SD, unless otherwise stated. IPAH: idiopathic pulmonary arterial hypertension; HPAH: hereditary pulmonary arterial hypertension; CHD: congenital heart disease; APAH: associated pulmonary arterial hypertension; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; CK: creatine kinase; TAPSE: tricuspid annular plane systolic excursion; RV: right ventricular; LV: left ventricular; mRAP: mean right atrial pressure; mPAP: mean pulmonary artery pressure; PVRI: pulmonary vascular resistance index; WU: Wood unit; Sv_{O_2}: mixed venous oxygen saturation; ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase-5 inhibitor. [#]: only in children ⩾7 years old; [¶]: according to Sitbon criteria (decrease in mPAP of ⩾10 mmHg to an absolute mPAP ⩽40 mmHg without a decrease in cardiac output).

TABLE 2 Comparison of characteristics before and after treatment initiation[#]

	Before treatment initiation	After treatment initiation	Treatment-induced change	p-value[¶]
Clinical diagnostics				
Heart rate beats per min	97±23.3 (n=50)	92±24.0 (n=50)	-5±18.4 (n=50)	0.090
Systolic blood pressure mmHg	104±16.4 (n=44)	97±10.8 (n=44)	-7±12.6 (n=44)	0.001
Diastolic blood pressure mmHg	63±10.7 (n=41)	59±7.8 (n=41)	-3±12.2 (n=41)	0.104
WHO-FC				
I or II	11/55 (20.0)	19/55 (34.5)	-0.3±0.66	0.003
III	29/55 (52.7)	29/55 (52.7)		
IV	15/55 (27.3)	7/55 (12.7)		
6MWD[+] m	349±97.5 (n=28)	371±97.1 (n=28)	22±57.0 (n=28)	0.050
Biochemical characteristics				
NT-proBNP ng·L^{-1}	666 (96–1543) (n=36)	243 (101–686) (n=36)	-54 (-673–31) (n=36)	0.011
CK U·L^{-1}	67 (33-106) (n=23)	83 (56-112) (n=23)	13 (-13–40) (n=23)	0.066
CK-MB U·L^{-1}	21 (9–33) (n=23)	19 (11–29) (n=23)	-2 (-10–4) (n=23)	0.242
Uric acid mmol·L^{-1}	0.3±0.07 (n=33)	0.3±0.10 (n=33)	0.0±0.07 (n=33)	0.695
Noradrenaline nmol·L^{-1}	1.5 (0.85–1.99) (n=16)	1.9 (1.25–2.90) (n=16)	0.4 (-0.62–1.00) (n=16)	0.179
Adrenaline nmol·L^{-1}	0.2 (0.13–0.75) (n=16)	0.3 (0.20–0.39) (n=16)	0.1 (-0.13–0.15) (n=16)	0.698
Detectable troponin	6/26 (23.1)	6/26 (23.1)	6/26 (23.1)	>0.999
Echocardiographic characteristics				
TAPSE mm	15 (11.8–17.0) (n=41)	16 (13.0–17.8) (n=41)	1 (-1.0–2.6) (n=41)	0.077
RV/LV ratio	0.96 (0.69–1.47) (n=40)	0.84 (0.67–1.20) (n=40)	-0.06 (-0.23–0.05) (n=40)	0.029
Presence of pericardial effusion	4/42 (9.5)	5/42 (11.9)	1/42 (2.4)	>0.999

Data are presented as mean±SD, n/N (%) or median (interquartile range), unless otherwise stated. WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; CK: creatine kinase; TAPSE: tricuspid annular plane systolic excursion; RV: right ventricular; LV: left ventricular. [#]: this table encompasses only patients who survived until the first follow-up (n=57); [¶]: comparison between before and after treatment initiation, with paired-samples t-test, Wilcoxon signed rank test or McNemar test where appropriate; [+]: only children ⩾7 years old.

Systolic blood pressure, WHO-FC, NT-proBNP and RV/LV ratio had significantly decreased after treatment initiation, whereas 6MWD had increased.

The most clinically relevant candidate-predictors derived from time-dependent Cox regression analysis are shown in figure 1. The full time-dependent Cox regression analysis is shown in table S2. After adjusting for age, sex and diagnosis, and taking into account both baseline and follow-up measurements, and the prognostic value of treatment-induced changes, only three predictors remained associated with survival: WHO-FC, NT-proBNP and TAPSE.

Survival differences

For WHO-FC, NT-proBNP and TAPSE, Kaplan–Meier curves were estimated for high values in comparison with low values at treatment initiation and first follow-up (figs 2–4). Patients with lower WHO-FC and NT-proBNP, and higher TAPSE had higher survival rates, either when measured at treatment initiation or at the first follow-up after treatment initiation. Optimal thresholds determined using survival time-dependent ROC analysis were NT-proBNP ⩽1200 ng·L^{-1} and TAPSE ⩾12 mm. According to the univariable baseline analysis, the threshold for WHO-FC was set to ⩽III in the Kaplan–Meier analysis. Individual changes in WHO-FC in survivors and nonsurvivors are shown in figure 5.

Prognostic implications of treatment-induced changes according to the four predefined risk profiles are also illustrated in figures 2–4. Patients with low WHO-FC, low NT-proBNP and high TAPSE who remained stable after treatment initiation (profile 1) had the best survival rates. Patients who improved from initial high WHO-FC, high NT-proBNP and low TAPSE after treatment initiation (profile 2) had almost equally survival rates compared to profile 1, whereas patients in profile 4, who did not improve and remained at high risk (WHO-FC IV, NT-proBNP >1200 ng·L^{-1} or TAPSE <12 mm), showed significantly worse survival ($p<0.001$, $p<0.001$ and $p=0.002$, respectively). The "deterioration after treatment initiation" profile (profile 3) was exceptional: except from one patient who deteriorated from WHO-FC ⩽III to IV and died within 5 months, there were no deteriorations from low to high values for NT-proBNP or high to low values for TAPSE.

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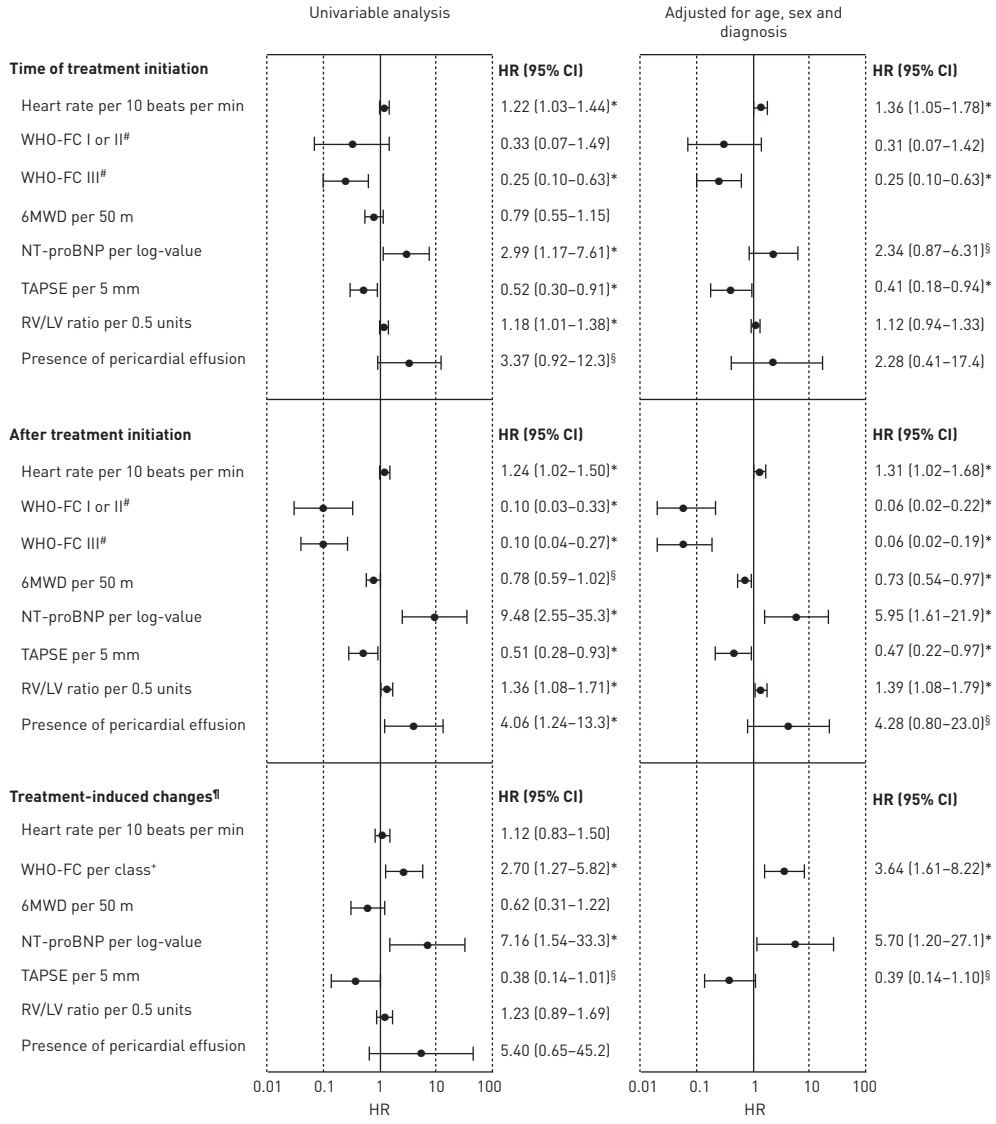

FIGURE 1 Forest plots showing the prognostic value of the most clinically relevant candidate-predictors for death or transplantation at treatment initiation, after treatment initiation and of the treatment-induced changes. This analysis encompasses only patients who survived until the first follow-up (n=57). Data are presented as hazard ratios (HR) with 95% confidence intervals, derived by segmented time-dependent Cox regression. For the numbers of patients for whom data were available, see table 2. WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; TAPSE: tricuspid annular plane systolic excursion; RV: right ventricular; LV: left ventricular. #: WHO-FC IV was used as the reference category; ¶: HRs of treatment-induced changes are adjusted for baseline; +: change in WHO-FC was handled as a continuous variable in the regression analysis; §: $p<0.10$; *: $p<0.05$.

Discussion

In the perspective of the high unmet need for goal-oriented treatment strategies in paediatric PAH, the identification of treatment goals is of great clinical importance. Although predictors of survival may be important when starting treatment for PAH, this does not mean that they can be used as treatment goals. To qualify as a treatment goal, it is imperative that the variable is changed by treatment and that this change is associated with a change in outcome [15, 16]. In the current study, baseline predictors were identified that are in line with previous reports. Of these, only WHO-FC, NT-proBNP and TAPSE showed treatment-induced changes that were associated with survival. These results indicate that improving WHO-FC, NT-proBNP and TAPSE qualify as treatment goals in children with PAH.

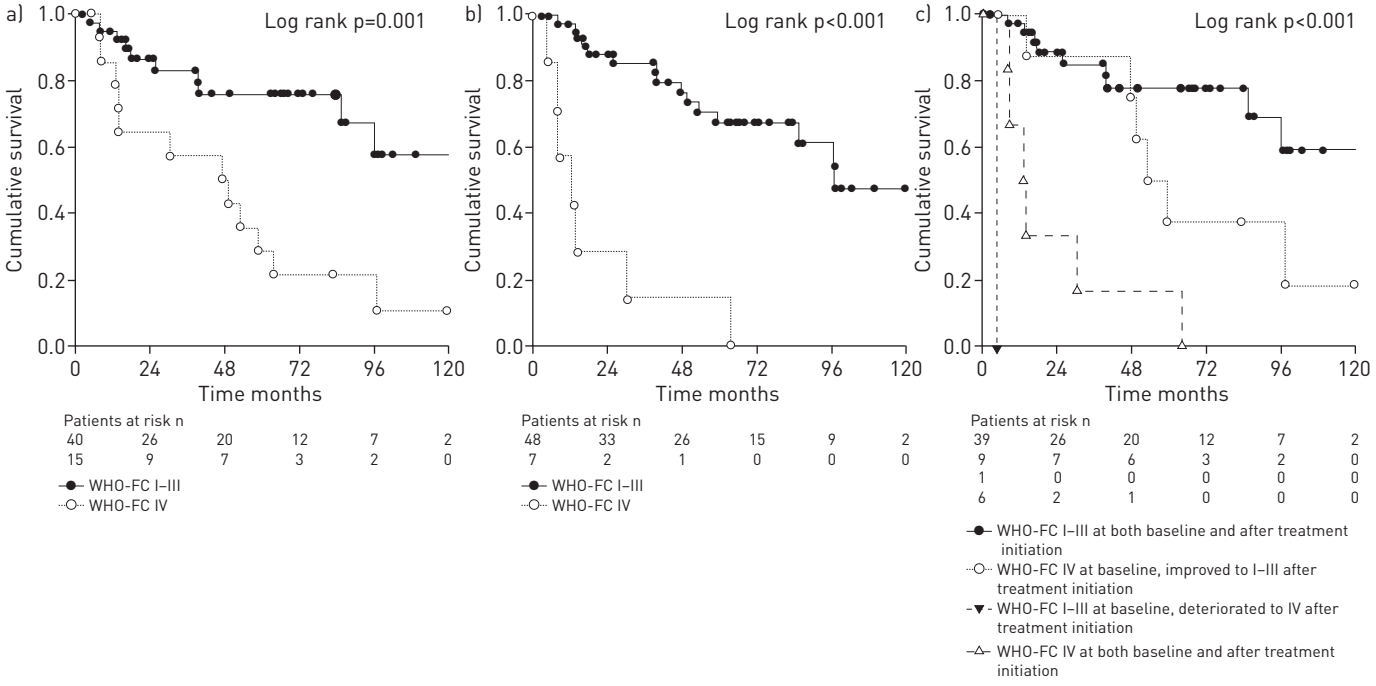

FIGURE 2 Transplant-free survival of patients with low and high World Health Organization functional class (WHO-FC) a) at treatment initiation, b) after treatment initiation, and c) according to risk profile categorisation by low or high WHO-FC before and after treatment initiation.

World Health Organization functional class

Our finding that WHO-FC is predictive of outcome at the time of treatment initiation is consistent with previous paediatric and adult outcome studies [5–8]. The enhanced prognostic value of WHO-FC after treatment initiation has been shown previously in adults but is now also confirmed in children. Treatment-induced changes in WHO-FC were also predictive of outcome in this paediatric cohort, which is in line with

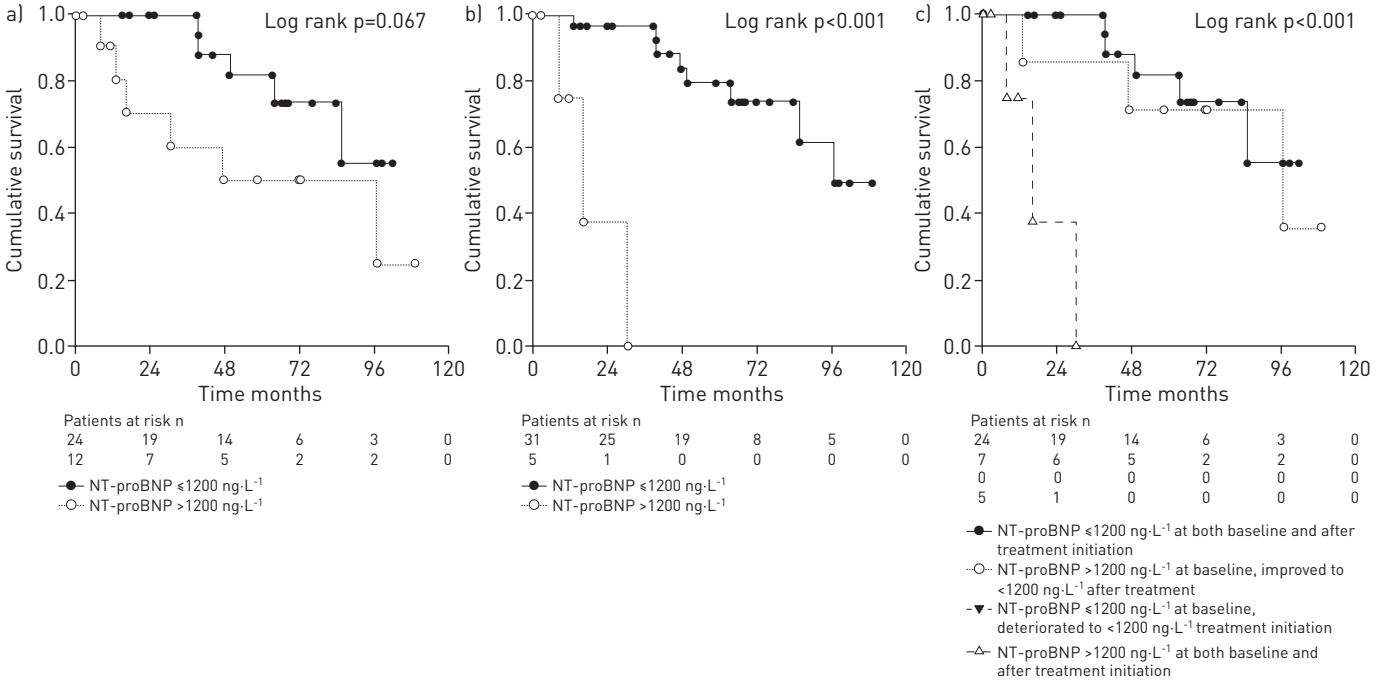

FIGURE 3 Transplant-free survival of patients with low and high N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations a) at treatment initiation, b) after treatment initiation, and c) according to risk profile categorisation by low or high NT-proBNP before and after treatment initiation.

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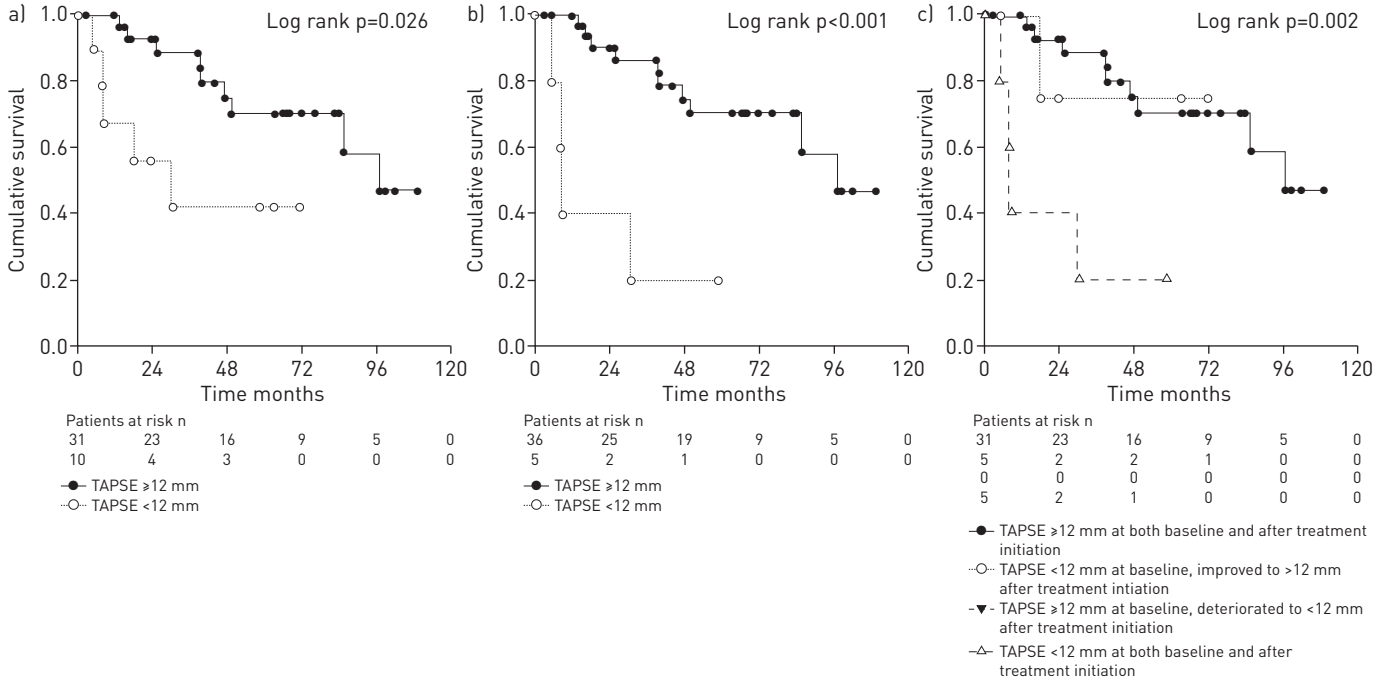

FIGURE 4 Transplant-free survival of patients with low and high tricuspid annular plane systolic excursion (TAPSE) a) at treatment initiation, b) after treatment initiation, and c) according to risk profile categorisation by low or high TAPSE before and after treatment initiation.

findings of NICKEL *et al.* [33] in an adult IPAH cohort, where a change in WHO-FC was an independent predictor of transplant-free survival. Our finding that improvements from WHO-FC IV to a lower class were associated with increased survival also corresponds with recent data from REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) showing that adult PAH patients who improved in WHO-FC from III to I or II had better survival [34]. The findings in the current study reinforce the clinical importance of repeated WHO-FC assessment also in children with PAH. In adults, it is recommended to achieve WHO-FC $\leqslant$II during treatment. Our study shows that WHO-FC IV should be avoided in children. Although the current study was not able to demonstrate additional value of improving WHO-FC III, this may be due to a lack of statistical power. The authors do certainly not want to suggest that WHO-FC III is acceptable in paediatric PAH. On the basis of adult data and clinical grounds, it seems obvious to exert every effort to reach WHO-FC $\leqslant$II during treatment in children too.

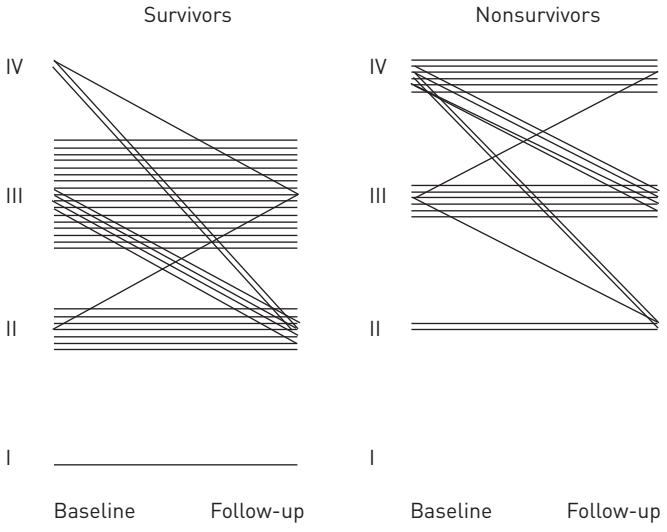

FIGURE 5 Individual treatment-induced changes in World Health Organization functional class (WHO-FC) stratified by survivors and nonsurvivors.

The applicability of WHO-FC in young children has been questioned in the past; however, WHO-FC has now been demonstrated to be a strong predictor of survival in several paediatric studies. The concept of WHO-FC is to describe symptoms at various levels of physical effort. Symptoms of dyspnoea on exertion in PAH are similar in children and adults, while physical effort should be adapted appropriately in relation to the age of the child (*e.g.* feeding as the physical effort for an infant and holding pace with peers at kindergarten for a toddler). Using such an approach, assessment of WHO-FC has been shown to be reliable and reproducible in every age group.

N-terminal pro-brain natriuretic peptide

NT-proBNP is presumably related to the degree of RV dysfunction and might thereby indicate one of the pathobiological processes in PAH, which is a major strength of this biomarker [39]. It is already known from several adult and paediatric studies that both BNP and NT-proBNP are baseline predictors of survival, and that baseline values and changes correlate with WHO-FC, 6MWD and haemodynamic variables [20–24]. Our study adds that NT-proBNP is also a follow-up predictor and that treatment-induced change predicts a change in survival.

It was shown previously that adults with an initial NT-proBNP level >1800 ng·L^{-1} that subsequently reached values below this threshold have identical outcomes to patients with low levels at baseline that remain low at follow-up [33]. We found the same pattern in children with PAH when using a threshold of 1200 ng·L^{-1}. Therefore, NT-proBNP seems suitable to incorporate in a goal-oriented treatment strategy in children. Although further research in larger paediatric cohorts may be needed to validate the current findings, we believe that it is justified to strive to achieve a NT-proBNP level of, at least, lower than 1200 ng·L^{-1} in the treatment of paediatric PAH.

Echocardiography

Echocardiography and CMR have previously been shown to yield prognostically important measures in both adults and children [28–32]. In contrast to CMR, echocardiography is a generally accessible follow-up tool and is also feasible in young children, without the need for sedation or anaesthesia.

The variables TAPSE, RV/LV ratio and pericardial effusion are determinants of RV function and, at baseline, showed a significant association with survival. In the current study, a treatment-induced improvement in TAPSE tended to be related to survival as well. The poor prognosis of patients in whom TAPSE did not improve to $\geqslant 12$ mm with treatment indicates that aiming for higher TAPSE in patients with values <12 mm seems a relevant treatment goal. However, since it is known that absolute values of TAPSE may vary considerably in young children, the appropriateness of such an absolute cut-off may be questioned in children <3 years of age [40]. Nevertheless, additional analysis in the current cohort demonstrated that changes both in TAPSE Z-scores and absolute values carry similar prognostic information (table S2).

Other potential treatment goals

Both baseline and follow-up values, and changes in heart rate have been shown to have prognostic value in adults with PAH [18, 19, 41]. In children, heart rate and heart rate variability at time of diagnosis have been shown to predict survival [17]. Our study confirms the predictive value of heart rate but a significant treatment-induced change could not be demonstrated, arguing against a role in defining treatment goals.

6MWD is a predictor of mortality in adult PAH and has been used as an end-point in clinical trials [42]. However, the prognostic value of 6MWD in adult PAH patients is a topic of debate since a recent meta-analysis showed that changes in 6MWD do not reflect changes in outcome [43]. Although the prognostic value of treatment-induced changes remains in question, it should be recognised that 6MWD also offers a direct measure of the patient's functional capacity, which might be regarded as an important aspect of quality of life [44]. Initiation of PAH-targeted treatment did improve 6MWD by a mean of 22 m, which could be regarded as a clinically meaningful effect. Considering quality of life, 6MWD could play a role in goal-oriented treatment strategies in children, albeit in the knowledge that changes in 6MWD do not necessarily implicate changes in survival.

Invasively obtained haemodynamic measures have been frequently studied and are well established predictors of outcome in both adult and paediatric PAH [5–11]. Cardiac catheterisation is required to confirm a diagnosis of PAH. However, serial follow-up catheterisations are controversial in paediatric PAH due to the frequent need for sedation or general anaesthesia and the relatively high complication rates in children [35]. Therefore, the current study aimed to assess the value of noninvasive treatment goals, irrespective of the availability of haemodynamic data.

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Clinical implications

This study showed substantial survival differences between children with PAH above and below the thresholds of WHO-FC $\leqslant$III, NT-proBNP $\leqslant$1200 ng·L^{-1} and TAPSE $\geqslant$12 mm. Failing to reach values below (WHO-FC and NT-proBNP) or above (TAPSE) these thresholds resulted in significantly worse survival, suggesting that treatment should be escalated rapidly in these children. In the absence of previously validated treatment goals, the identification of these variables allows for the introduction of goal-oriented treatment strategies in paediatric PAH.

Strengths and limitations

As paediatric pulmonary hypertension is a very rare disease, data on survival surrogates are extremely limited. The Dutch nationwide registry for pulmonary hypertension in childhood encompasses all diagnosed children with PAH in the Netherlands, representing a national cohort, and the long-term prospective and standardised follow-up makes this cohort uniquely qualified to identify treatment goals in paediatric PAH. Although absolute patient numbers might be relatively small, they did allow for the identification of at least three noninvasive treatment goals. We were able to perform longitudinal analyses for all clinically relevant noninvasive variables; however, number and time-points of follow-up cardiac catheterisation were not predefined in the protocol. Consequently, selection bias and time variability prohibited investigation of the prognostic implications of treatment-induced changes in haemodynamic variables. Whether the type of initiated treatment affected the observed treatment effect was not studied. Profile 3 was exceptional in the studied cohort, which hampers conclusions regarding the prognostic value of worsening in the identified variables. Nevertheless, the survival difference between improvers and nonimprovers is clear, and underlines the usefulness of the variables as treatment goals.

Conclusion

WHO-FC, NT-proBNP and TAPSE are not only predictors of transplant-free survival in paediatric PAH but can also be used as treatment goals, as treatment-induced improvements in these variables are associated with improved survival. The identification of these variables allows for the introduction of goal-oriented treatment strategies in paediatric PAH.

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