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Serial Measurements of N-Terminal Pro-B-Type Natriuretic Peptide Serum Level for Monitoring Pulmonary Arterial Hypertension in Children

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Objective To assess the association between serially measured N-terminal pro-B-type natriuretic peptide (NT-proBNP) serum levels and disease severity in children with pulmonary arterial hypertension (PAH), and to assess its predictive value for death or (heart-)lung transplantation.

Study design This was a longitudinal cohort study of the Dutch National Network for Pediatric Pulmonary Hypertension conducted between 2003 and 2017. Data on NT-proBNP and disease severity markers (World Health Organization Functional Class [WHO-FC], 6-minute walking distance [6MWD], and tricuspid annular plane systolic excursion [TAPSE]) were collected every 3 to 6 months from 82 children with PAH. The outcome measure was death or (heart-)lung transplantation. Also, NT-proBNP levels over time were compared between survivors and nonsurvivors.

Results The median patient age was 8.8 years (IQR, 4.6-13.5 years), and 61% were female. The median duration of follow-up was 4.8 years (IQR, 1.9-10.0 years). At all times during the course of disease, higher NT-proBNP levels were associated with higher WHO-FC ($\beta = 0.526$; 95% CI, 0.451-0.600), lower 6MWD z-score ($\beta = -0.587$; 95% CI, -0.828 to -0.346), lower TAPSE z-score ($\beta = -0.783$; 95% CI, -1.016 to -0.549), and elevated risk of death or (heart-)lung transplantation (hazard ratio 16.61; 95% CI, 7.81-35.33). Compared with survivors, nonsurvivors had NT-proBNP levels that were higher at first measurement and increased exponentially over time ($P = .005$). Changes in NT-proBNP serum level over time were predictive of outcome.

Conclusions Throughout the disease course of pediatric PAH, serial measurements of NT-proBNP are associated with disease severity and transplant-free survival. Monitoring NT-proBNP levels over time provides important prognostic information that can support clinical decision making in combination with other established prognostic markers. (*J Pediatr* 2020;220:139-45).

Pediatric pulmonary arterial hypertension (PAH) is a rare and severe disease with a broad spectrum of etiologies.¹ PAH is characterized by a progressive rise in pulmonary vascular resistance in the precapillary pulmonary vasculature, eventually leading to right ventricular (RV) failure and death.² Despite the growing availability of effective PAH-targeted therapies and the emergence of treatment guidelines, PAH remains fatal, with a variable disease course that is often unpredictable in individual patients. This underscores the need for optimization or, better, individual customization of treatment strategies.³ For this, noninvasive serum biomarkers that accurately reflect disease severity and are prognostic for outcome at any time in the disease course are needed.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a biomarker thought to be released into the circulation from cardiomyocytes in response to increased ventricular wall stress.^{4,5} In adults with PAH, NT-proBNP serum levels, both at first measurement and at follow-up, have been associated with RV function and long-term outcome.^{6,7} In children with PAH, NT-proBNP measured at the time of diagnosis has been shown to have prognostic value, and its change after initiation of PAH-targeted treatment was predictive for outcome.^{8,9} Accordingly, NT-proBNP may be a reliable biomarker in pediatric PAH, which accurately reflects disease severity and outcome at any time in the disease course. If so, NT-proBNP serum levels could be used to guide and improve individual treatment strategies. However, in pediatric PAH, the prognostic value of serially measured NT-proBNP during the course of disease has not been studied previously.

The aim of the present study was to assess the correlation between NT-proBNP serum level measured serially throughout the disease course and disease severity. We also aimed to determine its value in predicting transplant-free survival in children with PAH.

6MWD	6-minute walking distance
AVT	Acute response to vasodilator testing
HR	Hazard ratio
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAH	Pulmonary arterial hypertension
RV	Right ventricular
TAPSE	Tricuspid annular plane systolic excursion
WHO-FC	World Health Organization Function Class

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Methods

This was a longitudinal study of data obtained from a prospective clinical registry. In the Netherlands, children with PAH are referred to the national referral center of the Dutch National Network for Pediatric Pulmonary Hypertension, University Medical Center Groningen, and are prospectively enrolled in the National Registry for Pulmonary Hypertension in Childhood. All patients are diagnosed and followed according to a standardized protocol. Ethical approval was obtained from the Medical Ethics Review Board, and written informed consent was obtained from each patient and/or their guardian at enrollment. In the present study, we included children with idiopathic PAH or hereditary PAH, PAH associated with congenital heart disease, and PAH associated with other conditions between 2003 and 2017, with serial measurements (>1) of NT-proBNP and disease severity markers. PAH diagnosis was confirmed by right heart catheterization, with PAH defined as mean pulmonary artery pressure ≥ 25 mm Hg, pulmonary vascular resistance index ≥ 3 WU $\cdot$ m 2 , and mean pulmonary capillary wedge pressure ≤ 15 mm Hg. In cases of clinical instability ($n = 8$), PAH was diagnosed by echocardiography, with PAH defined as either the presence of right-to-left shunting in cases of congenital heart defects in the absence of outflow tract obstruction or systemic right-sided pressure (maximum systolic tricuspid regurgitant velocity >2.8 m/s accompanied by ventricular septal flattening and/or RV hypertrophy).¹⁰

Disease severity markers and NT-proBNP levels were assessed every 3–6 months. Blood specimens were obtained from peripheral veins with the patient at rest, and plasma NT-proBNP plasma levels were measured in fresh serum samples using electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland). Disease severity was assessed using World Health Organization Functional Class (WHO-FC), the 6-minute walking distance (6MWD), and echocardiographic assessment of RV function as measured by tricuspid annular plane systolic excursion (TAPSE). In addition, we calculated z -scores for 6MWD and TAPSE to adjust for age and sex, based on reported reference values.^{11,12} Invasive hemodynamic variables, including acute response to vasodilator testing (AVT) with nitric oxide according to the Sitbon criteria,¹³ were collected only if cardiac catheterization had been performed within 3 months from the first NT-proBNP measurement. Outcome was defined as death or (heart-)lung transplantation. The observation time was calculated from first measurement of NT-proBNP until death, (heart-)lung transplantation, or the last follow-up visit before October 2017.

Statistical Analyses

Continuous data are presented as mean $\pm$ SD when normally distributed and as median and IQR when not normally distributed. Values of NT-proBNP were normalized using log₁₀ transformation. Categorical data are presented as number and percentage. Because NT-proBNP values in children

depend on age and sex, analyses were also performed with adjustment for age and sex.¹⁴ Analyses were also corrected for PAH diagnosis. Statistical analyses were performed using IBM SPSS 23.0 (Armonk, New York) and Stata 13.0 (Stata-Corp, College Station, Texas). A P value $<.05$ was considered to indicate statistical significance.

We analyzed the association between serum NT-proBNP and disease severity markers including hemodynamic measures at time of first NT-proBNP measurement using linear regression analysis (yielding β coefficients with 95% CIs). To determine the relationship between serial NT-proBNP levels and disease severity markers during the disease course, we used linear mixed-effects modeling with random intercepts to correct for repeated measurements.

We used Cox regression analysis to assess the predictive value of first measurement of NT-proBNP levels for outcome. We evaluated the predictive value throughout the disease course using time-dependent Cox regression analysis. To do so, we created 2 time-dependent models, one model including all serial NT-proBNP measurements as time-varying covariates and the other model evaluating the occurrence of a doubling in the NT-proBNP level since the first NT-proBNP measurement as a dichotomous time-varying covariate. In this latter analysis, we corrected the hazard ratios (HRs) for NT-proBNP level at first measurement.

To study differences in survival between patients with a clinically relevant increase ($>10\%$) in NT-proBNP at first follow-up after the first NT-proBNP measurement and patients with decreased/stable/ $\leq 10\%$ increase in NT-proBNP (later referred to as patients with a $\leq 10\%$ increase), we used Kaplan-Meier analysis with log-rank testing with follow-up time starting at the first measurement after the first NT-proBNP measurement. In addition, we assessed the association with transplant-free survival in patients with a $>10\%$ increase in NT-proBNP at first follow-up using Cox regression analysis.

We performed 2 exploratory analyses. Owing to the evolution of therapeutic management, patients enrolled later in the study period might have been treated more aggressively compared with those enrolled in the first years of the inclusion period. Therefore, we performed an exploratory analysis to compare outcomes and percentage change in NT-proBNP levels between patients included in the first 7 years and those included in the second 7 years. We also performed an exploratory analysis to compare NT-proBNP levels at first measurement and the percentage change in NT-proBNP levels between responders to AVT and nonresponders to AVT according to the Sitbon criteria.¹³

We used linear mixed-effects modeling to compare changes in NT-proBNP over time between survivors and nonsurvivors. We constructed random intercept models with log₁₀ NT-proBNP as the dependent variable and observation time, transplant-free survival, and the interaction of observation time with outcome at last visit as independent variables. We considered linear and quadratic time transformations (because of sample size). The best fit for the fixed-effects structure was selected based on the Akaike

information criterion and Bayesian information criterion (measures for model fit; lower is better). This longitudinal analysis yielded separate regression equations for survivors and nonsurvivors with the ability to evaluate the statistical significance of the differences in intercept and linear and quadratic time coefficients between the 2 groups. Furthermore, we compared the evolution of NT-proBNP over time between Sitbon responders and nonresponders.

Results

A total of 82 patients (61% female) with a median age of 8.8 years (range, 0.3–18.3 years) were included for analyses (Table I). The median NT-proBNP levels were 193 ng/L (IQR, 75–1012 ng/L) in patients in WHO-FC I and II, 590 ng/L (IQR, 178–1578 ng/L) patients in WHO-FC III, and 2696 ng/L (IQR, 785–7418 ng/L) in patients in WHO-FC IV.

In univariable analysis, NT-proBNP levels at first measurement were significantly associated with WHO-FC (Table II). After adjustment for age, sex, and PAH diagnosis, higher NT-proBNP levels at first measurement were correlated with lower 6MWD (z-score) and higher WHO-FC. No significant association was found with TAPSE (z-score) (Table II). NT-proBNP correlated significantly with mean

right atrial pressure and cardiac index, also after adjustment for age, sex, and PAH diagnosis (Table II). No significant correlation was demonstrated between NT-proBNP serum level and mean pulmonary arterial pressure and pulmonary vascular resistance index. The levels of NT-proBNP at first measurement did not differ between Sitbon responders ($n = 8$) and nonresponders.

NT-proBNP at first measurement was associated with transplant-free survival, also after adjustment for age, sex, and PAH diagnosis. When comparing tertiles of first measurement NT-proBNP values (Figure 1, A), patients in the highest tertile (NT-proBNP >1271 ng/L) showed significantly worse survival compared with patients with lower NT-proBNP levels (log-rank, $P = .015$). Survival did not differ between patients included in the first 7 years and those included in the second 7 years (log-rank, $P = .443$).

At the first follow-up, patients with a >10% increase in NT-proBNP level over their first measurement had significantly worse survival compared with patients with a ≤10% increase in NT-proBNP (log-rank, $P = .033$) (Figure 1, B). Patients with an increase of NT-proBNP of >10% had a higher risk for death or (heart-)lung transplantation compared with patients with ≤10% increase (HR, 2.021; 95% CI, 1.046–3.906; $P = .036$). This HR did not change substantially after correcting for age, sex, and PAH diagnosis (HR, 2.039; 95% CI, 0.991–4.198; $P = .053$). The percentage change in NT-proBNP between first measurement and first follow-up was not different between patients included in the first 7 years and those included in the second 7 years. The percentage change in NT-proBNP at follow-up tended to be higher in Sitbon responders compared with nonresponders; however, this difference did not show statistical significance.

The results of linear mixed-effects modeling including all follow-up measurements of WHO-FC, 6MWD z-score, and TAPSE z-score as dependent outcome variables are shown in Table II. Higher NT-proBNP levels measured at any time throughout the disease course were significantly associated with simultaneous higher WHO-FC, lower 6MWD z-score, and lower TAPSE z-score, also after adjustment for age, sex, and PAH diagnosis. Time-dependent Cox regression analysis, with all available serial NT-proBNP measurements as time-varying covariates, showed that each unit increase in log₁₀ NT-proBNP was associated with worse transplant-free survival, also after adjustment for age, sex, and PAH diagnosis (Table II). A doubling of NT-proBNP level since the first measurement at any time during the disease course was also associated with worse transplant-free survival (HR, 5.696; 95% CI, 2.699–12.019; $P < .001$), also after adjustment for age, sex, and PAH diagnosis (HR, 7.349; 95% CI, 3.370–16.025; $P < .001$).

The evolution of NT-proBNP level over time is depicted in Figure 2, stratified by survival status at end of follow-up. The longitudinal trajectories of NT-proBNP level differed significantly between survivors and nonsurvivors. Nonsurvivors had higher first measurement values of

Table I. Patient characteristics at first measurement of NT-proBNP

Patient characteristics	N	Value
Female sex, n (%)	82	50 (61)
Age, y, median (IQR)	82	8.8 (4.6–13.5)
Follow-up, y, median (IQR)	82	4.8 (1.9–10.0)
Etiology, n (%)	82	
IPAH/HPAH		48 (59)
PAH-CHD		29 (35)
PAH-PVOD		3 (4)
PAH-other		2 (2)
WHO-FC, n (%)	82	
I + II		28 (34)
III		38 (46)
IV		16 (20)
NT-proBNP serum level	82	
ng/L, median (IQR)		606 (137–1830)
log ₁₀ , mean (SD)		2.8 (0.8)
6MWD		
m, mean (SD)	49	342 (91)
z-score, mean (SD)	49	−4.8 (1.8)
TAPSE		
mm, mean (SD)	64	14.9 (3.6)
z-score, mean (SD)	64	−3.2 (2.0)
Treatment intensity at first	82	
NT-proBNP measurement, n (%)		
No therapy		61 (74)
Monotherapy*		12 (15)
Dual therapy*		5 (6)
Triple therapy*		1 (1)
Calcium channel blockers		4 (5)

HPAH, hereditary pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PAH-other, PAH associated with portal hypertension and connective tissue disease; PVOD, pulmonary veno-occlusive disease.

*AH-targeted therapies.

Table II. Association of log₁₀ NT-proBNP with disease severity markers, hemodynamic measures, and outcome at first measurement and with disease severity markers and outcome serially

Disease severity and outcome measures	Associations at first measurement				Associations throughout the disease course			
	Univariable analysis		Adjusted for age, sex, and PAH diagnosis		Univariable analysis		Adjusted for age, sex, and PAH diagnosis	
	N	β /HR (95% CI)	P value	β /HR (95% CI)	N*	β /HR (95% CI)	P value	β /HR (95% CI)
Disease severity markers								
WHO-FC	82	0.311 (0.118-0.505)	.002	0.363 (0.183-0.544)	1096/81	0.526 (0.451-0.600)	<.001	0.526 (0.451-0.601)
6MWD z-score	49	-0.098 (-0.202 to 0.006)	.064	-0.130 (-0.237 to -0.024) [†]	1015/67	-0.587 (-0.828 to -0.346)	<.001	-0.582 (-0.819 to -0.344) [†]
TAPSE z-score	64	-0.072 (-0.170 to 0.026)	.147	-0.066 (-0.165 to 0.032) [‡]	1023/77	-0.783 (-1.016 to -0.549)	<.001	-0.772 (-1.006 to -0.538) [‡]
Hemodynamic measures								
mRAP, log	63	1.254 (0.436-2.072)	.003	1.210 (0.397-2.023)				
mPAP	62	0.005 (-0.004 to 0.015)	.257	0.006 (-0.004 to 0.015)				
CI, log	62	-1.220 (-2.400 to -0.040)	.043	-1.272 (-2.457 to -0.087)				
PVRi, log	62	0.257 (-0.368 to 0.882)	.414	0.351 (-0.302 to 1.003)				
Outcome	82	2.274 (1.383-3.738)	.001	2.535 (1.498-4.290)	1094/82	16.613 (7.811-35.331) [§]	<.001	17.676 (8.105-38.549) [§]

CI, cardiac index; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PVRi, pulmonary vascular resistance index. Data presented as β or HR with respective 95% CI per log₁₀ value change of NT-proBNP.

*Number of log₁₀ NT-proBNP measurements involved in analysis/number of patients involved in analysis.

[†]Only adjusted for PAH diagnosis.

[‡]Only adjusted for sex and PAH diagnosis.

[§]Predictive value of time-varying log₁₀ NT-proBNP for death/(H)Tx with adjustment of log₁₀ NT-proBNP level at first measurement.

NT-proBNP and showed an exponential increase in NT-proBNP over time compared with survivors whose NT-proBNP level remained stable or even slightly decreased (both $P = .005$). We could not demonstrate significant differences in the trajectories of NT-proBNP between Sitbon responders and nonresponders.

Discussion

In this nationwide longitudinal cohort study incorporating 14 years of outcome data, serial measurements of NT-proBNP throughout the disease course were strongly correlated with clinical disease severity and were predictive of transplant-free survival. The evolution of NT-proBNP during follow-up differed markedly between survivors and non-survivors.

Our study confirms the prognostic value of NT-proBNP at first measurement as demonstrated in previous studies of pediatric PAH.^{8,15,16} However, to inform clinical decision making, reliable prognostic biomarkers are needed not only at first measurement but also throughout the disease course. Here we report that a doubling of NT-proBNP level compared with the first measurement at any time in the disease course is predictive of worse survival. This observation is in line with findings in adults with PAH and adults with congenital heart disease, showing that serial NT-proBNP measurements provide clinically important additional prognostic information relative to a single baseline measurement.^{17,18}

We further found that children with an increase of >10% from first measurement to first follow-up visit had worse survival compared with those with a $\leq 10\%$ increase, independent of the absolute NT-proBNP value at first measurement. This cut-off value of 10% is exploratory and has not been previously reported in pediatric PAH. In clinical practice, monitoring a change in NT-proBNP level after treatment initiation or escalation can support the assessment of treatment effect and guide treatment decisions on whether to escalate treatment. Although sensitivity and specificity analyses of this percentage increase were not performed in the present study, the predictive properties of the exploratory cut-off point of 10% can be considered as a further tool for treatment decision making in pediatric PAH in addition to the previously reported treatment goal cut-off value of 1200 ng/L NT-proBNP.¹⁵ Using this criterion of a >10% increase from the first measurement may detect children at risk at an earlier stage before they reach an absolute NT-proBNP level of >1200 ng/L. The differences that we observed between survivors and nonsurvivors in the first measurement NT-proBNP value and the evolution of NT-proBNP levels over time are also in line with previously reported data for adults with PAH.^{7,18}

A recent study in adults with PAH, using data from the GRIPHON trial (Prostacyclin Receptor Agonist in PAH), reported that the risk of morbidity/mortality was lowest for patients with a stable low (<271 ng/L) or improved NT-proBNP level.⁷ We found that in nonsurvivors, serial serum levels may

Figure 1. Survival based on NT-proBNP level at first measurement. **A**, Survival of patients by tertile of NT-proBNP level at first measurement. **B**, Survival of patients with a >10% increase in NT-proBNP level and patients with a decreased, stable, or ≤10% increase since the first measurement at first follow-up. The number of patients at risk at each time point is shown on the x-axis.

remain stable for several years but then increase exponentially shortly before death or transplantation (Figure 2). We also found that survivors had a stable rather than a decreasing trajectory of NT-proBNP, which likely reflects the irreversible nature of PAH and the inability of PAH-targeted drugs to cure the disease. Accordingly, in pediatric PAH, any increase in NT-proBNP should be taken seriously as a signal to consider treatment escalation, because it is associated with worse clinical outcome. In addition, the higher NT-proBNP values in nonsurvivors at first measurement suggest that children who have an NT-proBNP serum level above a certain threshold at presentation may be at risk for adverse outcome and may benefit from a more intense initial therapeutic regimen

compared with patients with lower NT-proBNP at first measurement. Similarly, consideration of treatment escalation is suggested for adults who consistently have high (>1400) or deteriorate to high NT-proBNP levels while receiving selexipag.⁷ When stratified for tertiles of NT-proBNP at first measurement, survival curves showed that a value of ≥1271 ng/L indicated significantly worse survival, which is comparable with findings from Mauritz et al who reported a baseline value of ≥1256 ng/L to be associated with worse survival also in adults with PAH.¹⁸ Previously, Ploegstra et al reported a value of 1200 ng/L after treatment initiation as a treatment goal in pediatric PAH.¹⁵ Taken together, our findings support a further refinement of this treatment goal in pediatric PAH,

Figure 2. **A**, Longitudinal evolution of serum NT-proBNP in survivors with PAH. **B**, Longitudinal evolution of serum NT-proBNP in nonsurvivors with PAH.

suggesting consideration of absolute values as well as avoidance of an >10% increase in NT-proBNP serum level at first follow-up measurement.

Patients with PAH that show a positive response to AVT according to the Sitbon criteria have a significantly more favorable outcome when treated with calcium channel blockers compared with nonresponders.¹³ The number of responders to AVT according to the Sitbon criteria was small in the present study ($n = 8$). Our exploratory analyses did not show a difference in NT-proBNP levels at first measurement or over time between responders and nonresponders, although the percentage change in NT-proBNP at first follow-up tended to be higher in the responders. The proportion of children with a positive response to AVT according to the Sitbon criteria in our cohort (10%) is in line with previous reports; however, the absolute number of patients in this study precludes us from drawing definitive conclusions regarding potential differences in the evolution of NT-proBNP serum levels in responders and nonresponders.

In pediatric PAH, assessment of the effectiveness of PAH-targeted treatment is hampered by the lack of developmentally appropriate, age-specific and age-appropriate clinically meaningful endpoints.¹⁹ Clinical variables used in adults with PAH, such as WHO-FC, 6MWD, and cardiopulmonary exercise testing, have limitations for the assessment of children with PAH, particularly in the youngest pediatric age groups. Nonetheless, surrogate endpoints, such as biomarkers and hemodynamic and echocardiographic variables, require rigorous validation before they are acceptable as endpoints in clinical trials. Taking this into account, it is an important finding that serially measured serum levels of NT-proBNP measured at any time during follow-up correlated with WHO-FC, TAPSE, and 6MWD. The disease severity markers WHO-FC and TAPSE have been advocated previously to be both a predictor of survival and a treatment goal in pediatric PAH.^{15,20}

In children, data on the prognostic value of 6MWD, a clinically meaningful endpoint, are controversial. Yet, NT-proBNP serum levels have been reported to correlate with 6MWD in both children and adults^{9,19,21,22} and with invasive hemodynamics in children.²³ Taken together, these observational data indicate that NT-proBNP serum level is useful as a tool for monitoring disease severity and performing risk stratification in pediatric PAH. At the same time, it is important to emphasize that NT-proBNP serum levels should not be interpreted in isolation, but considered in conjunction with other clinical markers of disease severity and prognosticators in pediatric PAH. Haarman et al recently showed that in children, as in adults, clinical risk stratification tools composed of various clinical and biochemical variables (including NT-proBNP) as proposed in guidelines based on expert opinion are of clinical value in risk stratification and prognostication both at diagnosis and at follow-up.^{24,25}

The present study indicates that NT-proBNP has predictive value not only at diagnosis or after treatment initiation, but also throughout the entire disease course. The evolution of serum NT-proBNP levels over time reflects disease pro-

gression and predicts adverse patient outcome; thus, standardized serial monitoring can support clinical decision making regarding the timing of therapy escalation and listing for (heart-)lung transplantation.

Children diagnosed with PAH and a high NT-proBNP level at diagnosis are at risk for clinical deterioration and therefore may require more intense therapy than those newly diagnosed patients with low NT-proBNP levels. Similarly, children with increasing NT-proBNP over time may require more frequent follow-up visits and timely escalation of PAH-targeted therapy.

Several studies have shown a predictive value of specific markers of disease severity in children with PAH, including WHO-FC, invasive hemodynamics, echocardiographic variables, serum levels of NT-proBNP, and other biomarkers. However, only limited data are available on the diverse relationships between these biomarkers, including their relative superiority for predicting outcome or effect of treatment, or whether one variable can be substituted for by another (eg replacement of echocardiography with measurement of NT-proBNP serum levels). Similar to adult studies, we suggest that all these reported biomarkers, including NT-proBNP, should be serially monitored to predict outcome and optimize risk stratification in pediatric PAH.²⁴⁻²⁶ Future clinical studies are warranted to confirm whether clinical decision making guided or supported by NT-proBNP serum levels will change outcomes of children with PAH.

Strengths of this study are the use of prospective, standardized collection of data over a substantial period of time, the consistency of follow-up visits, and the completeness of the data collected at follow-up. A limitation of this study was that the sample size hampered extensive multivariable modeling. However, the number of included patients was relatively robust for a rare disease such as pediatric PAH. Further, because of the invasiveness and associated risks of heart catheterization, the relationship of NT-proBNP with hemodynamic measures could not be evaluated longitudinally. Due to the observational nature of the registry, this study does not allow any conclusions on the role of NT-proBNP in the disease mechanism of pediatric PAH, a formal requirement for surrogate endpoints for clinical trials. This does not preclude the utility of NT-proBNP levels in assessing disease severity and predicting transplant-free survival in children with PAH.

In conclusion, we found that at any time during the disease course of PAH in children, NT-proBNP serum levels corresponded with disease severity and predict transplant-free survival. In addition, independent of its absolute value, an increase of >10% in serially measured NT-proBNP serum levels over time predicted an adverse outcome. Further studies are warranted to investigate whether NT-proBNP-level-guided treatment strategies will ultimately improve outcome in pediatric PAH. ■

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