JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 78, NO. 19, 2021

PUBLISHED BY ELSEVIER

Predicting Major Adverse Cardiovascular Events in Children With Age-Adjusted NT-proBNP

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ABSTRACT

BACKGROUND N-terminal pro-B-type natriuretic peptide (NT-proBNP) is frequently used as a valuable prognostic biomarker in cardiac diseases. In children, however, it has not been established because of its strong age dependency. To overcome this obstacle, we recently introduced the zlog value of N-terminal pro-B-type natriuretic peptide (zlog-proBNP) as an age-adjusted reference.

OBJECTIVES This study evaluates the prognostic power of zlog-proBNP for the occurrence of major adverse cardiovascular events (MACE) throughout childhood in patients with congenital heart diseases (CHD).

METHODS A total of 910 children with CHD (median age 5 months; range 0.0-18.0 years) were included. MACE was defined as death, resuscitation, mechanical circulatory support, or hospitalization caused by cardiac decompensation. Because the physiological NT-proBNP concentration decreases significantly during childhood, zlog values were applied for an age-independent evaluation.

RESULTS MACE occurred in 138 children during a median follow-up of 6 months (range 1 day to 7.6 years). High zlog-proBNP values (>+3.0) were most strongly associated with adverse events (n = 93; adjusted HR: 21.1; 95% CI: 2.9-154.2; $P < 0.001$). Among all evaluated indicators, zlog-proBNP was the best predictor for MACE (adjusted HR: 1.52; 95% CI: 1.31-1.76; $P < 0.001$) along with age and predictively superior to absolute NT-proBNP values. A cutoff value of +1.96 (age-independent upper limit of the physiological NT-proBNP concentration) achieved a negative predictive value of >96%.

CONCLUSIONS Zlog-proBNP overcomes the strong age dependency of NT-proBNP and is a powerful prognostic marker for age-independent exclusion and prediction of MACE in children with CHD. We therefore expect zlog-proBNP to play a pivotal role in the future management of children with heart diseases. (J Am Coll Cardiol 2021;78:1890–1900)

B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have had a major impact on cardiovascular research and the clinical management of cardiac diseases over the last 2 decades. Both biomarkers are routinely used as valuable prognostic tools, with NT-proBNP being slightly superior in predicting the outcome of heart diseases in adults (1).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 6, 2021; revised manuscript received August 18, 2021, accepted August 20, 2021.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2021.08.056

In contrast, data for children with heart diseases are scarce (2). First, the number of cases is limited because of ethical constraints involving children in health research and a low prevalence of pediatric heart diseases (2). Second, the major obstacle for clinical use of NT-proBNP is the extreme age dependency of physiological concentrations (3). Until the third day of life, the 97.5th percentile of NT-proBNP exceeds 13,000 pg/mL, then rapidly decreases to 1,000 pg/mL during the first month of life, and gradually converges to adult reference values until the age of 18 years (207 pg/mL) (4). Thus, absolute concentrations have to be interpreted with respect to various age-specific reference intervals. In particular, studies investigating NT-proBNP in childhood did not sufficiently consider this highly significant age dynamic. Unfortunately, this combination of a low caseload, ethical issues, and extreme age dependency considerably impeded the scientific evaluation of NT-proBNP in children.

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To overcome these drawbacks, we recently introduced the zlog value of N-terminal pro-B-type natriuretic peptide (zlog-proBNP) (5). Analogous to a z-score, zlog-proBNP indicates the number of logarithmized SDs by which the measured NT-proBNP concentration is above or below the age-specific logarithmic mean (5,6). Thus, its age-independent reference interval ranges between −1.96 and +1.96, and subgrouping by age to address different reference intervals is not necessary.

The aim of the present study was to evaluate the prognostic power of zlog-proBNP for the occurrence of major adverse cardiac events (MACE) in a large cohort of pediatric patients throughout the entire period of childhood.

METHODS

STUDY POPULATION. At the German Heart Center Munich, a tertiary center for pediatric heart diseases, a database query was conducted to retrospectively identify all patients with at least 1 NT-proBNP measurement between January 1, 2011, and December 31, 2017. In addition, the following biomarkers were queried: creatinine, C-reactive protein (CRP), hemoglobin, hematocrit, sodium, potassium, and alanine transaminase. All of these parameters are part of our admission laboratory.

Datasets with at least 1 missing biomarker concentration (eg, caused by insufficient sample material) were removed. The baseline was defined as the earliest point within the specified time frame when both a complete set of laboratory values and medical records were available. Only patients with CHD under 18 years of age at the baseline were included. Patients with Fontan circulation (ie, total cavopulmonary connection) were excluded from this study.

The data were collected from the hospital information system. At baseline, the patients' age, sex, and diagnosis were recorded. Furthermore, a 30-day MACE history was evaluated, meaning that each subject was screened for adverse cardiovascular events (see endpoints) within 30 days prior to their individual baseline (eg, patients presenting because of cardiac decompensation or inpatient admissions after previous resuscitation). This is to prevent patients from being in an unstable condition at the beginning of the observation period.

The authors attest they are in compliance with human studies committees and that the study (**Central Illustration**) was approved by the Institutional Review Board (ethics commission) of The Technical University Munich, Munich, Germany.

ENDPOINTS. MACE was defined as follows: death (from any cause), resuscitation, necessity of mechanical circulatory support (extracorporeal membrane oxygenation or ventricular assist device), and hospital admission caused by cardiac decompensation. Because there is no common definition of cardiac decompensation in pediatrics, it was defined in this study as (at least subacute) worsening of echocardiographic functional parameters and/or worsening of heart failure symptoms requiring inpatient recompensation. Each event that had occurred since the beginning of the observation period was recorded separately, with the earliest event defining the end of the follow-up. If no MACE had occurred since the baseline, the follow-up ended with the last elective outpatient presentation or inpatient discharge from elective hospital stays.

ZLOG VALUES, ZLOG-proBNP AND OTHER BIOMARKERS. Zlog values in general are interpreted the same way as regular z-scores as they are used in pediatrics or echocardiography (eg, aortic root diameter) (7). Both measures indicate the number of SDs (σ) by which a variable (eg, a biomarker concentration) is above or below the mean value (μ), with 95% of physiological values ranging between $\mu \pm 1.96\ \sigma$ ($\approx$ mean ± 2 SD). However, zlog values operate with logarithms and therefore are suitable for non-normally distributed parameters such as NT-proBNP concentrations (6).

Zlog-proBNP in particular constitutes the zlog value of NT-proBNP, where μ and σ are expressed as a

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CHD = congenital heart disease

CRP = C-reactive protein

MACE = major adverse cardiovascular events

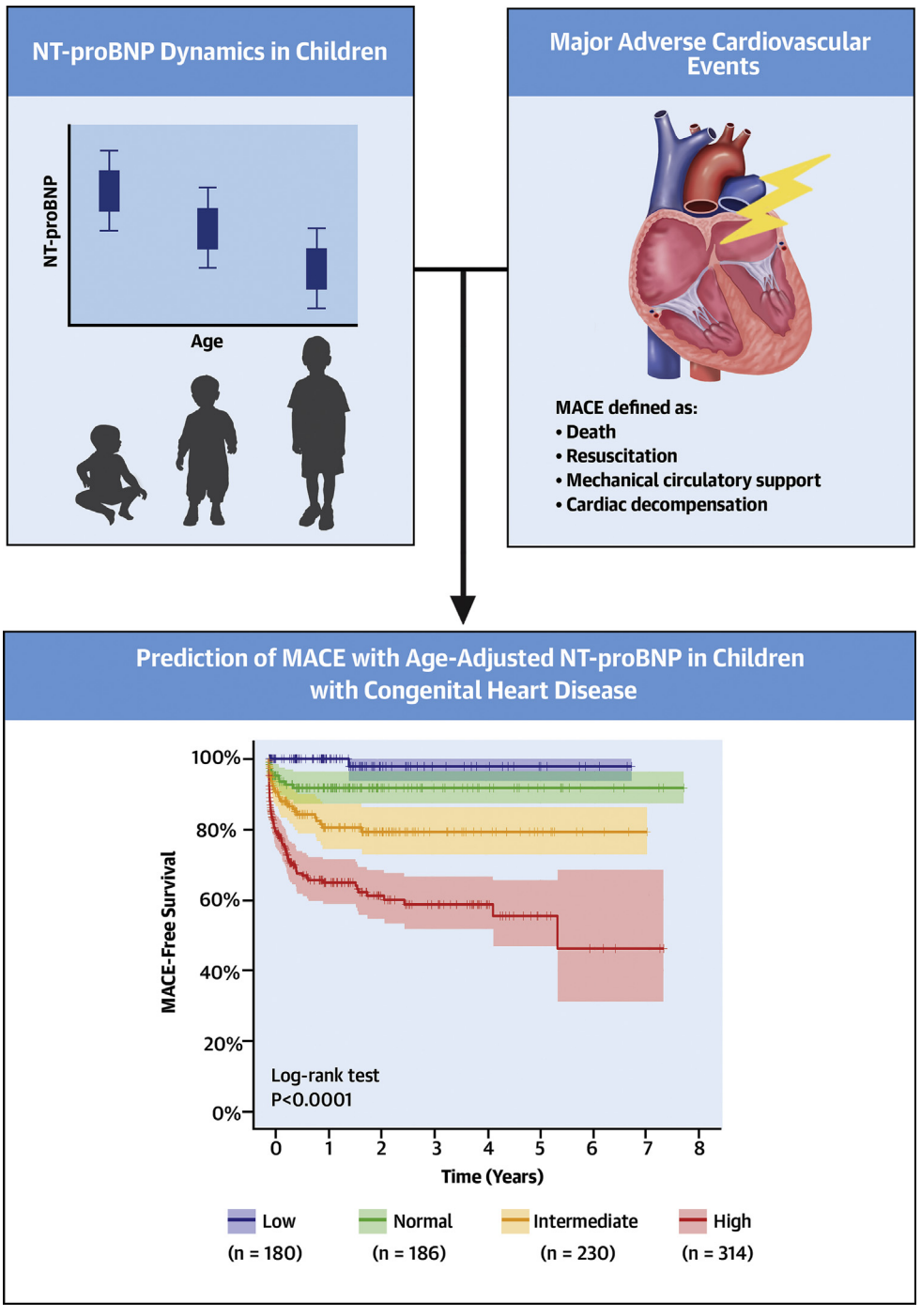
NT-proBNP = N-terminal pro-B-type natriuretic peptide

ROC = receiver-operating characteristic

zlog-proBNP = zlog value of N-terminal pro-B-type natriuretic peptide

JACC VOL. 78, NO. 19, 2021
NOVEMBER 9, 2021:1890–1900

CENTRAL ILLUSTRATION **Prediction of Major Adverse Cardiovascular Events With Age-Adjusted N-Terminal Pro-B-Type Natriuretic Peptide in Children With Congenital Heart Disease**



Palm, J. et al. J Am Coll Cardiol. 2021;78(19):1890–1900.

Due to the highly age-dependent N-terminal pro-B-type natriuretic peptide (NT-proBNP) dynamics during childhood, we recently introduced the zlog value of N-terminal pro-B-type natriuretic peptide as an age-adjusted reference. Of 910 children with congenital heart disease (CHD) enrolled in this study, 138 children experienced major adverse cardiovascular events (MACE) during follow-up. Statistical analysis revealed the zlog value of N-terminal pro-B-type natriuretic peptide to be a powerful prognostic marker for age-independent exclusion and prediction of MACE in children with CHD.

TABLE 1 Baseline Characteristics of the Study Population

	All Patients (N = 910)	zlog-proBNP Level				*P* Value[a]
		Low (n = 180)	Normal (n = 186)	Intermediate (n = 230)	High (n = 314)	
Zlog-proBNP range	−2.2 to +6.9	−2.2 to +1.0	+1.0 to +1.96	+1.96 to +3.0	+3.0 to +6.9	
Age, y	0.4 (0.1-8.8)	10.8 (5.1-14.9)	5.4 (0.3-13.2)	0.2 (0.1-1.8)	0.1 (0.0-0.5)	<0.001
Range	0.0-18.0	0.0-18.0	0.0-17.9	0.0-17.8	0.0-17.5	
Age group						<0.001
Newborns (birth to 4 wks)	242 (27)	14 (8)	29 (16)	73 (32)	126 (40)	
Infants (4 wks to 1 y)	291 (32)	16 (9)	46 (25)	95 (41)	134 (43)	
Kids (1 to 10 y)	165 (18)	56 (31)	39 (21)	38 (17)	32 (10)	
Adolescents (10 to 18 y)	212 (23)	94 (52)	72 (39)	24 (10)	22 (7)	
Sex						0.28
Male	509 (56)	100 (56)	113 (61)	116 (50)	180 (57)	
Female	401 (44)	80 (44)	73 (39)	114 (50)	134 (43)	
History of MACE[b]						<0.001
Positive	61 (7)	2 (1)	2 (1)	21 (9)	36 (11)	
Negative	849 (93)	178 (99)	184 (99)	209 (91)	278 (89)	
Laboratory						
Hemoglobin, g/dL	13.3 (12.1-14.8)	13.7 (12.6-15.1)	13.5 (12.4-14.6)	13.2 (11.8-14.6)	13.0 (11.6-14.6)	<0.001
Hematocrit, %	38.6 (35.1-42.2)	39.4 (36.5-43.2)	38.8 (36.1-42.0)	38.1 (34.1-41.7)	38.1 (33.6-42.0)	<0.001
Sodium, mmol/L	138 (136-141)	139 (137-141)	139 (136-140)	138 (135-141)	137 (134-140)	0.023
Potassium, mmol/L	4.2 (3.9-4.7)	4.1 (3.9-4.3)	4.1 (3.9-4.6)	4.3 (4.0-4.8)	4.4 (4.0-4.9)	<0.001
Creatinine, mg/dL	0.5 (0.3-0.6)	0.6 (0.4-0.8)	0.5 (0.3-0.7)	0.4 (0.3-0.5)	0.4 (0.3-0.6)	<0.001
ALT, U/L	21 (15-31)	18 (14-21)	20 (15-27)	22 (15-33)	24 (17-43)	<0.001
CRP, mg/L	2.1 (0.6-15.9)	0.6 (0.6-1.7)	0.8 (0.6-3.4)	6.6 (0.7-25.2)	8.9 (1.1-30.7)	<0.001
NT-proBNP, pg/mL	1,910 (172-8,483)	62 (34-98)	214 (130-977)	2,700 (955-5,340)	11,550 (5,945-24,100)	<0.001
Events during follow-up						
≥1 MACE	138 (15)	1 (1)	12 (6)	32 (14)	93 (30)	
Thereof deceased	55	0	3	8	44	
No events	772 (85)	179 (99)	174 (94)	198 (86)	221 (70)	

Values are median (interquartile range), n (%), or n, unless otherwise indicated. [a]The corresponding p values refer to the difference between physiological (low and normal) and pathological (intermediate and high) zlog-proBNP levels. [b]Patients with at least 1 major adverse cardiovascular event 30 days prior to the individual baseline.

ALT = alanine transaminase; CRP = C-reactive protein; MACE = major adverse cardiovascular events; zlog-proBNP = zlog value of N-terminal pro-B-type natriuretic peptide.

function of age and thus provide reference intervals on a daily age basis (5). This gauging allows NT-proBNP concentrations among different age groups to be compared. To ease the practicability of zlog-proBNP in everyday practice, we developed an online calculator (8) by means of which the zlog transform of NT-proBNP values can be reproduced with own laboratory results.

Besides age, further confounders affecting NT-proBNP concentrations are infections (CRP), anemia (hemoglobin, hematocrit), renal function (creatinine) and liver diseases (alanine transaminase) (9). Additionally, some of these biomarkers have an independent prognostic impact on mortality and morbidity in adults with congenital (creatinine, CRP) or acquired heart disease (hemoglobin, hematocrit) (10-12). In heart failure patients, sodium and potassium are predictors of mortality (13,14).

Peripheral blood was collected using standard collection techniques during inpatient hospital stays or on the day of the clinical visit in outpatients. NT-proBNP was measured using the Roche Diagnostics Elecsys proBNP II assay on a Cobas E411 system. For CRP, a high-sensitivity assay was used. Standard assays were used for all other biomarkers. More information is provided in Supplemental Table 1.

STATISTICAL ANALYSIS. Patients were divided into groups according to zlog-proBNP levels: low (≤1.0), normal (>1.0 and ≤1.96), intermediate (>1.96 and ≤3.0), and high (>3.0). Categorical variables representing baseline characteristics were expressed as percentages, and continuous variables were reported as medians with interquartile ranges (IQRs) or total ranges. For numerical variables, the Wilcoxon Mann-Whitney test was applied, and for contingency tables, the Fisher exact and chi-square test were used.

Cumulative endpoint-free survival curves for zlog-proBNP groups were derived using the Kaplan-Meier method and compared with the log-rank test. Cox regression analysis was performed to identify those indicators associated with MACE, where zlog-proBNP

TABLE 2 Underlying Diagnosis in Study Subjects

Main Cardiac Malformation	Patients
Anomalous left coronary artery from the pulmonary artery	12 (1.3)
Anomalous pulmonary venous connection	
Partial anomalous pulmonary venous connection	7 (0.8)
Total anomalous pulmonary venous connection	7 (0.8)
Aortic valve diseases	49 (5.4)
Aortopulmonary window	2 (0.2)
Atrial septal defect	61 (6.7)
Atrioventricular septal defect	
Partial atrioventricular septal defect	5 (0.5)
Complete atrioventricular septal defect	63 (6.9)
Coarctation of the aorta	62 (6.8)
Double inlet left ventricle	15 (1.6)
Double outlet right ventricle	52 (5.7)
Ebstein's anomaly	12 (1.3)
Hypoplastic left heart syndrome	93 (10.2)
Interrupted aortic arch	6 (0.7)
Mitral valve diseases	7 (0.8)
Patent ductus arteriosus	26 (2.9)
Pulmonary atresia	
Pulmonary atresia with intact ventricular septum	22 (2.4)
Pulmonary atresia with ventricular septal defect	55 (6.0)
Pulmonary valve disease	27 (3.0)
Shone's complex	13 (1.4)
Tetralogy of Fallot	86 (9.5)
Transposition of the great vessels	
dextro-Transposition of the great arteries	58 (6.4)
levo-Transposition of the great arteries	13 (1.4)
Tricuspid atresia	14 (1.5)
Tricuspid valve disease	5 (0.5)
Truncus arteriosus	25 (2.7)
Ventricular septal defect	61 (6.7)
Miscellaneous	
Complex malformations	37 (4.1)
Other minor defects	15 (1.6)

Values are n (%).

was analyzed both as a categorical ("low" as reference group) and as a continuous variable. To consider age-dependent reference intervals and thus achieve a fair comparison, zlog values were calculated for other biomarkers as well (based on the manufacturers' reference values [Supplemental Table 1]). For this analysis, zlog-proBNP was used instead of NT-proBNP. Thereafter, receiver-operating characteristic (ROC) analysis was performed to determine the prognostic validity of zlog-proBNP for predicting both MACE and death within 1 year after observation began. The same analyses were repeated for zlog-proBNP in combination with other significant predictors obtained from the Cox regression analysis.

To rule out the effect of age, paired age matching was conducted by finding a similarly aged patient without MACE for each patient with MACE. Cox regression was then applied as described in the previous text to this reduced data set, but this time it included both zlog-proBNP and absolute NT-proBNP concentrations for a head-to-head comparison and adjusted for other baseline characteristics. Age matching was conducted by a heuristic optimization algorithm that aims to minimize the sum of the absolute age differences of the log-ages of the MACE/non-MACE pairs. To resolve ties of the log-age values, the matching algorithm used random selection so that repeated runs of the algorithm led to slightly different matchings. The matching was repeated 1,000 times.

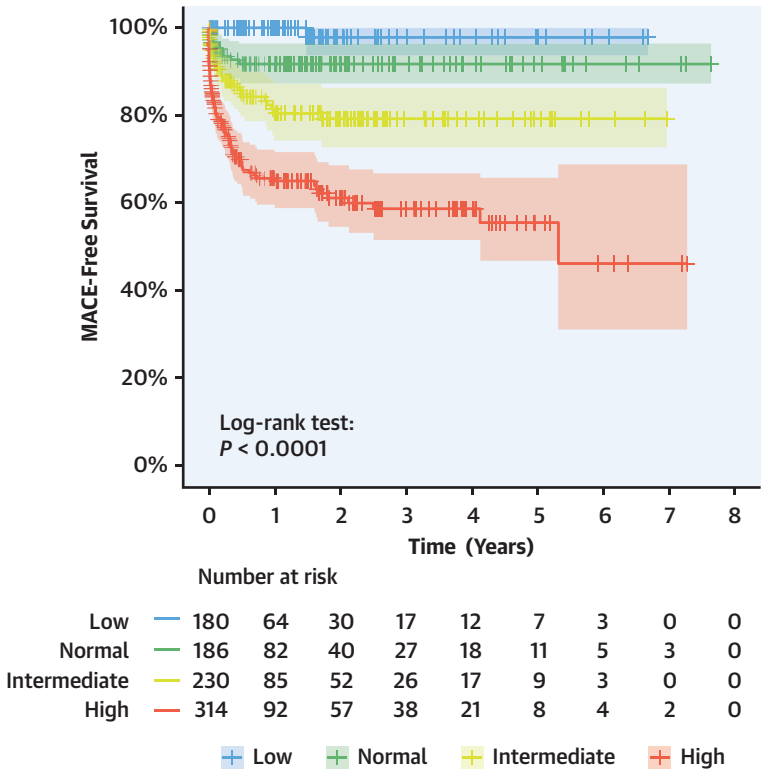
All 2-sided P values <0.05 were considered statistically significant. Analyses were conducted using R version 4.0.0 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS. Of the 1,420 patients with a complete laboratory record, 910 children with CHD met the eligibility criteria (Supplemental Figure 1). **Table 1** depicts the baseline characteristics of these subjects. A total of 27% were newborns (birth to ≤28 days), 32% were infants (>28 days to ≤1 year), 18% were children (>1 to ≤10 years) and 23% were adolescents (>10 years to their 18th birthday). The median age was 5 months (mean 4.5 years; range 0.0-18.0 years), and 56% were boys. Because the German Heart Center Munich is a tertiary center for congenital heart defects, complex heart diseases such as hypoplastic left heart syndrome, tricuspid atresia, or pulmonary atresia with intact ventricular septum accounted for a disproportionately large share. Whereas univentricular hearts usually account for only 2.8% of all congenital heart diseases, in our cohort, these patients represented 19.5% (n = 177) (15). Other severe or complex defects were also more frequent than average in our study population, which in turn conferred a significantly increased risk for the occurrence of MACE. The underlying diagnoses are presented in **Table 2**. A separate analysis according to each diagnosis was deliberately omitted here because this would exceed this paper's scope. Further baseline characteristics are reported in **Table 1**.

FOLLOW-UP AND MACE. The median observation time was 6 months (range 1 day to 7.6 years). A total of 138 patients (15%) with MACE were identified. Of these cases, 50.0% were resuscitations (n = 69, of which 62 were primarily successful and 7 fatal), 25.4% were extracorporeal membrane oxygenation implantations (n = 35, of which 12 were performed under resuscitation), 17.4% were hospitalizations caused by

FIGURE 1 Kaplan-Meier Curves for Different zlog-proBNP Levels



Patients were divided into groups according to zlog-proBNP levels: low (≤1.0), normal (>1.0 and ≤1.96), intermediate (>1.96 and ≤3.0), and high (>3.0). For these groups, Kaplan-Meier MACE-free survival curves with 95% CIs were derived. The log-rank test yielded a *P* value <0.001. MACE = major adverse cardiovascular events; zlog-proBNP = zlog value of N-terminal pro-B-type natriuretic peptide.

TABLE 3 Risk of MACE and Death According to zlog-proBNP Groups

	zlog-proBNP Level				
	Low (n = 180)	**Normal (n = 186)**	**Intermediate (n = 230)**	**High (n = 314)**	***P* Value**[a]
Major adverse cardiovascular events					
Patients with ≥1 event	1	12	32	93	
Total events during follow-up	1	16	43	163	
Person years[b]	181	242	261	302	
1-year MACE incidence,[c] %	0.0	8.3	19.5	35.1	
Crude HR (95% CI)	Reference	10.3 (1.3-79.0)	22.8 (3.1-167.0)	54.2 (7.6-388.8)	<0.001
Adjusted HR (95% CI)	Reference	8.5 (1.1-65.9)	10.3 (1.4-76.4)	21.1 (2.9-154.2)	<0.001
Death from any cause					
Deaths	0	3	8	44	
Person years[b]	248	317	261	281	
1-year survival rate,[c] %	100	97.9	95.8	82.7	
Crude HR (95% CI)		Reference[d]	3.9 (1.0-14.5)	16.0 (5.0-51.6)	<0.001
Adjusted HR (95% CI)		Reference[d]	1.5 (0.4-5.9)	6.1 (1.8-20.6)	0.027

[a]The corresponding *P* values refer to the difference between physiological (low and normal) and pathological (intermediate and high) zlog-proBNP levels. [b]Total of the entire observation period to the first event (in years). [c]Estimated with the Kaplan-Meier method. [d]Because no patients with low zlog-proBNP levels died during follow-up, these subjects were merged with the "normal" group.

TABLE 4 HRs for MACE and Mortality According to Indicators

	MACE		Death	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
zlog-proBNP	1.52 (1.31-1.76)[a]	<0.001	1.84 (1.42-2.39)[a]	<0.001
Age				
Increase by log-age, days	0.47 (0.38-0.60)[a]	<0.001	0.36 (0.23-0.56)[a]	<0.001
Sex				
Male	Reference		Reference	
Female	0.96 (0.69-1.35)[b]	0.83	0.90 (0.52-1.53)[b]	0.69
History of MACE[c]				
Negative	Reference		Reference	
Positive	2.29 (1.45-3.60)[a]	<0.001	3.66 (1.89-7.09)[a]	<0.001
Laboratory, 1-SD increase				
Hemoglobin	1.06 (0.96-1.17)[a]	0.22	1.10 (0.94-1.29)[a]	0.24
Hematocrit	0.95 (0.89-1.03)[b]	0.21	1.02 (0.91-1.14)[b]	0.78
Sodium	1.12 (0.98-1.29)[b]	0.10	1.17 (0.96-1.44)[a]	0.13
Potassium	1.05 (0.92-1.20)[b]	0.47	1.16 (0.94-1.42)[b]	0.16
Creatinine	1.12 (1.03-1.22)[a]	0.01	1.09 (0.95-1.24)[a]	0.22
ALT	1.09 (0.89-1.34)[a]	0.38	1.24 (0.91-1.69)[a]	0.18
CRP	1.00 (0.90-1.10)[a]	0.93	0.93 (0.78-1.10)[a]	0.40

[a]Result of the multivariate Cox regression analysis caused by significant association in the univariate analysis. [b]Result of the univariate Cox regression analysis (crude HR). [c]Patients with at least 1 major adverse cardiovascular event 30 days prior to individual baseline.

Abbreviations as in Table 1.

cardiac decompensation (n = 24), and 7.2% were deaths despite maximally exhausted therapy (n = 10). The median time from the beginning of observation to the onset of MACE was 20 days (IQR: 2-117 days). The vast majority of primary events occurred within the first year of life (84.8% of MACE). Similar observations were made concerning mortality. Throughout the entire observation period, a total of 55 patients (6.0%) died, with most deaths taking place within the first year of life (85.5% of fatalities).

Subjects with MACE revealed significantly higher zlog-proBNP values (median 3.6; IQR: 2.7-4.1; $P < 0.001$) than patients without events (median 2.2; IQR: 1.1-3.2) and were more likely to have a positive 30-day MACE history (5% vs 18%). Further characteristics of patients with and without MACE are provided in Supplemental Table 2.

TABLE 5 Prediction of 1-Year MACE Incidence and Mortality

Cutoff for zlog-proBNP	Sensitivity, %	Specificity, %	NPV, %	PPV, %	AUC (95% CI)
Major adverse cardiovascular events (Figure 2A)					
+1.0	100	17.9	100	14.2	0.76 (0.72-0.81)
+1.96	89.5	41.4	96.7	17.2	
+3.0	68.4	65.9	93.9	21.4	
+4.0	31.6	86.6	90.3	24.2	
Death (Figure 2B)					
+1.0	100	18.2	100	16.0	0.80 (0.74-0.86)
+1.96	94.5	41.2	98.0	20.1	
+3.0	80.0	68.2	95.6	28.2	
+4.0	43.6	88.9	91.0	38.1	

PROGNOSTIC ACCURACY OF ZLOG-proBNP. Figure 1 shows the Kaplan-Meier survival curves with 95% CIs according to zlog-proBNP groups. The log-rank test yielded a *P* value <0.001.

Kaplan-Meier estimates for the occurrence of MACE at 1 year were 0.0% for children with low zlog-proBNP levels, 8.3% for children with normal zlog-proBNP levels, 19.5% for children with intermediate zlog-proBNP levels, and 35.1% for children with high zlog-proBNP levels. Similar results were observed concerning mortality: 94.5% of deaths occurred in children with intermediate or high zlog-proBNP values, whereas no fatalities occurred in the low group. Kaplan-Meier estimates for survival rates at 1 year were 100% for subjects with low zlog-proBNP levels but 82.7% for those with high zlog-proBNP levels. Further results are depicted in Table 3.

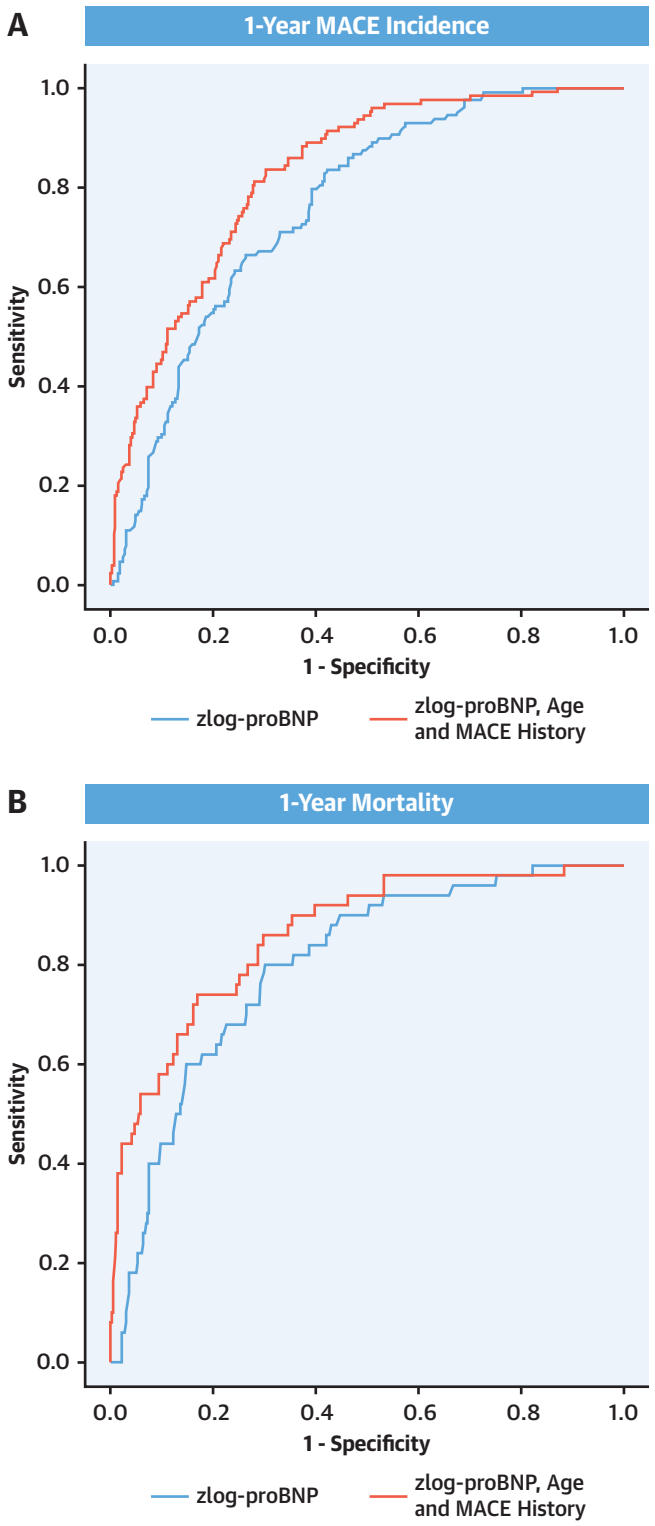
In the Cox regression analysis, zlog-proBNP was strongly associated with both MACE and death, irrespective of whether it was analyzed as a categorical (Table 3) or continuous variable (Table 4). After adjustment for confounders, zlog-proBNP remained a highly significant predictor. The HRs of all baseline characteristics are shown in Table 4.

For the prediction of 1-year MACE incidence and 1-year mortality, zlog-proBNP yielded areas under the curve (AUCs) of 0.76 (95% CI: 0.72-0.81; $P < 0.001$) and 0.80 (95% CI: 0.74-0.86; $P < 0.001$), respectively. Table 5 provides the prognostic findings of different zlog-proBNP levels. Corresponding ROC curves are depicted in Figures 2A and 2B.

EFFECT OF AGE. Of the 1,000 age matches performed, zlog-proBNP was significantly associated with MACE 956 times. In contrast, the absolute NT-proBNP concentration did not achieve significance even once. Cox regression analysis obtained an average adjusted HR of 1.09 (95% CI: 0.63-1.86; $P = 0.76$) for NT-proBNP and 1.35 (95% CI: 1.08-1.69; $P = 0.009$) for zlog-proBNP.

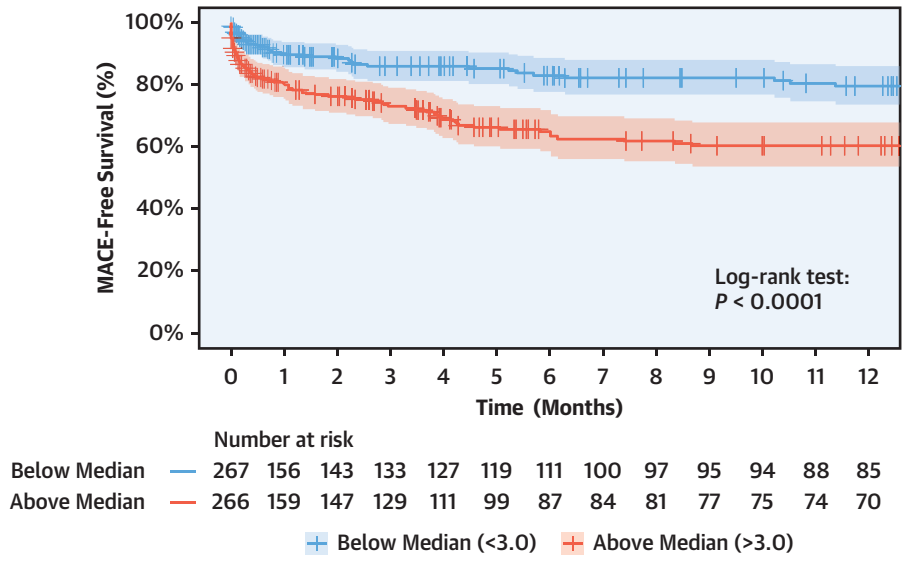
HIGH-RISK PATIENTS: NEONATES AND INFANTS. As 84.8% of major adverse cardiovascular events and 85.5% of deaths occurred during the first year of life, we performed an additional Kaplan-Meier survival analysis for this population (Figure 3). Because NT-proBNP in neonates and infants (<1 year of age) reveals a strong age dependency, as described in the previous text, applying zlog-proBNP is a particular advantage (3). First, NT-proBNP values can be assessed easily (eg, with our online calculator) without knowledge of different age-dependent reference intervals, because its reference interval

FIGURE 2 **Prediction of 1-Year MACE Incidence and Mortality**



For the prediction of 1-year MACE incidence **(A)** and 1-year mortality **(B)**, a receiver-operating characteristic analysis was performed on zlog-proBNP. The prognostic findings of different cutoff values are provided in Table 4. A joint model of zlog-proBNP, age (as a continuous variable, logarithmized), and 30-day MACE history yielded an area under the curve of 0.83 (95% CI: 0.79-0.87; $P < 0.001$) for predicting MACE and 0.86 (95% CI: 0.81-0.92; $P < 0.001$) for mortality. Abbreviations as in Figure 1.

FIGURE 3 Kaplan-Meier Survival Curves of Neonates and Infants According to zlog-proBNP



Patients were divided into 2 groups according to the median zlog-proBNP level in neonates and infants (+3.0). For these groups, Kaplan-Meier MACE-free survival curves with 95% CIs were derived. The log-rank test yielded a *P* value <0.001.

ranges from −1.96 to +1.96 age-independently. Second, this facilitates comparison with previously measured NT-proBNP values and thus the assessment of the progression in the first place. As indicated by the Kaplan-Meier survival curve (**Figure 3**), it is possible to identify high-risk patients on the basis of zlog-proBNP.

DISCUSSION

To the best of our knowledge, no previous study has investigated the predictive value of NT-proBNP in children with CHD. Therefore, in the following comparisons with other studies, only studies that include patients with acquired structural heart diseases (eg, cardiomyopathies) or use BNP instead will be referenced. A major difference between NT-proBNP and its active peptide BNP is the different half-life time (1-2 hours vs 15-20 minutes) (16). As a result, NT-proBNP reveals higher plasma concentrations and a more pronounced age dynamic (16). Furthermore, only 1 assay (Roche proBNP II kit) is routinely used for NT-proBNP, facilitating the comparison of different studies. In contrast, several assays with variable reference intervals exist for BNP (9). Of course, one may also calculate zlog values for BNP, but in this case, for each assay, a specific zlog formula will be needed (5).

ROLE OF AGE. As demonstrated in previous studies, physiological NT-proBNP dynamics have been characterized by exceptionally high concentrations within the first days of life, followed by an exponential decline, especially during the first year (3,4). The same dynamics are described in preterm infants (17). The reference intervals assessed by Nir et al (4), on which zlog-proBNP is based, are consistent with recently established reference intervals of very and extremely preterm infants (17). Precisely this first year of life also constitutes the most critical period in patients with CHD (18). First, decisive cardiosurgical procedures with their intrinsic risks are still pending. Second, the underlying hemodynamic condition of complex CHD entails severe strain on the myocardium, ultimately causing acute or chronic heart failure (16,19). It is thus not surprising that in children with CHD, mortality and the occurrence of MACE depend on age as well (18). In our cohort, we observed a similar age dependence: approximately 85% of both deaths and major adverse cardiovascular events occurred during the first year of life.

RELATIONSHIP AMONG AGE, MACE, AND NT-proBNP. Based on these 2 facts, a correlation between MACE and NT-proBNP that is interlinked by age exists. However, this coincidental effect with time as a mediator must not be mistaken for a cause-and-effect relationship, because correlation does not imply causation. To overcome this logical fallacy and to truly assess whether there is a relationship between NT-proBNP and MACE, age must be dissociated as the

common factor before performing statistical analyses. In our study, this was achieved by using zlog-proBNP instead of absolute NT-proBNP values. Our findings proved zlog-proBNP to predict both MACE and mortality at a high level of significance. Even after adjustment for age and other confounders, it constituted the strongest predictor besides age. In the age-matched analysis, zlog-proBNP remained a highly significant predictor, whereas the absolute NT-proBNP concentration was no longer predictive of the occurrence of MACE. Due to its age independence, the provided zlog-proBNP cutoff values are applicable for the entire childhood and adolescence (5).

COMPARISON WITH PREVIOUS STUDIES. Until recently, the simultaneous decay of MACE and NT-proBNP dynamics with age could only be solved by forming age-related subgroups. However, this creates implausible jumps at the boundaries between groups and can cause these groups to become too small for statistical analysis (5). However, only the largest study (n = 138; median age 3.4 years; IQR: 1.1-11.0 years) performed such a subgrouping (20). Although the authors were able to demonstrate a prognostic value for BNP predicting MACE, a uniform cutoff value not considering age-dependent reference intervals was established (16,20). ROC analysis revealed an AUC of 0.71 (95% CI: 0.60-0.81) (20). We obtained a similar but better result for zlog-proBNP (AUC: 0.76 [95% CI: 0.72-0.81]). Comparatively, our cohort was considerably larger, exclusively consisted of children with CHD of all ages, and investigated NT-proBNP by means of zlog-proBNP.

Another study revealed BNP to have a high prognostic value in children with dilated cardiomyopathy and ventricular dysfunction (n = 56; median age 9.3 years; IQR: 2.7-15.1 years) for predicting cardiac death, cardiac hospitalization, and listing for heart transplantation (21). Further evidence for the prognostic role of NT-proBNP was given by a prospective study with 65 children with CHD in which deceased patients had higher NT-proBNP concentrations than surviving patients (22). Although no survival analysis was performed, all of these findings are consistent with our results.

OUTLOOK. Given the limited data available in children, it is no surprise that thus far, no biomarkers have been included in the guidelines for the treatment of children with CHD (2). With our findings, for the first time, we demonstrated the high prognostic value of zlog-proBNP in a large cohort of children of all ages over the entire range of CHD. These by far represent the main group of pediatric cardiological diagnoses in industrialized nations. Additionally, the age independence of zlog-proBNP permits the determination of cutoff values valid throughout the entirety of childhood (5). Due to its high prognostic validity and superiority, zlog-proBNP is of high clinical value. We therefore expect zlog-proBNP to play a pivotal role in the future management of children with both congenital and acquired heart diseases. Theoretically, it would also be suitable for use in cardiovascular medicine in adulthood to consider the—albeit less pronounced—age-related dynamics (23).

STUDY LIMITATIONS. This study is a retrospective analysis. We have deliberately omitted echocardiographic parameters such as the ejection fraction, as, because of their anatomical heterogeneity, they have not been standardized for different ventricle geometries in many complex heart diseases (eg, those with systemic right ventricle). Additionally, functional classes were not evaluated because they can be confounded by subjective parents' reporting and are difficult to assess in a clinical setting after surgical or transcatheter interventions.

CONCLUSIONS

In the largest pediatric cardiological cohort to date, our findings reveal zlog-proBNP to reliably predict the risk of MACE. Of all indicators evaluated, zlog-proBNP was the best predictor besides age. After age matching was performed, the absolute NT-proBNP concentration no longer predicted the occurrence of MACE. In contrast, zlog-proBNP remained a highly significant predictor. Due to its age independence, the cutoff values presented in our study are valid for risk stratification throughout childhood. Therefore, its usage may reduce mortality and morbidity in everyday clinical practice and has the capability to play a pivotal role in the management of children with heart diseases. Furthermore, zlog-proBNP has the potential to profoundly influence clinical research in pediatric cardiology, similar to NT-proBNP in cardiovascular medicine in adults.

ACKNOWLEDGMENT The authors thank Dr Laura Wiegand for her support in the database query of the laboratory values.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL OUTCOMES: zlog-proBNP, an age-adjusted z-score of plasma NT-proBNP level, reliably predicts major adverse cardiovascular events in children with CHD.

TRANSLATIONAL OUTLOOK: Further research is needed to determine the prognostic value of zlog-proBNP in acquired forms of pediatric heart disease and to define its role in relation to other risk assessment tools.

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KEY WORDS congenital heart disease, MACE, mortality pediatrics, N-terminal pro-B-type natriuretic peptide, zlog-proBNP

APPENDIX For supplemental tables and a figure, please see the online version of this paper.