Cardiology in the Young

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Perioperative prediction of adverse events with age-adjusted NT-proBNP in children undergoing Norwood surgery

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Abstract

Background: Due to the high postoperative mortality, tools for an adaequate risk stratification are important to identify high-risk patients undergoing the Norwood procedure. As a marker of ventricular wall stress, NT-proBNP might be of particular interest in these children. *Objectives:* This study evaluated whether NT-proBNP's age-adjusted z-score ("zlog-NT-proBNP") predicts outcomes after stage I Norwood procedure. *Methods:* Patients who underwent the Norwood procedure between 1 January 2011 and 31 December 2022, with perioperative NT-proBNP measurements available were enrolled. Since reference intervals of NT-proBNP are highly age-dependent, age-adjusted zlog-NT-proBNP was used. Serial zlog-NT-proBNP values were analysed to predict the occurrence of major adverse cardiovascular events after the Norwood procedure. Major adverse cardiovascular events was defined as death, resuscitation, or mechanical circulatory support. Secondary endpoints were re-operation and re-intervention for shunt. *Results:* A total of 139 patients underwent the Norwood procedure and had at least one NT-proBNP measurement available. Preoperative zlog-NT-proBNP measurements (median 3.7, interquartile range 3.1–4.19) showed no association with the occurrence of major adverse cardiovascular events or mortality. Zlog-NT-proBNP early after ICU admission (3.2, interquartile range 2.4–3.8) was predictive of mortality but showed no association with the occurrence of major adverse cardiovascular events. Zlog-NT-proBNP before ICU discharge (3.2, interquartile range 2.8–3.8) was significantly associated with the occurrence of both major adverse cardiovascular events (hazard ratio 1.83, 95% confidence interval 1.25–2.67, $P = 0.002$) and death (hazard ratio 2.1, 95% CI 1.4–3.2, $P < 0.001$). *Conclusions:* High zlog-NT-proBNP levels after the Norwood surgery were strongly associated with the occurrence of major adverse cardiovascular events and death. Therefore, zlog-NT-proBNP has the potential to identify high-risk patients before life-threatening complications occur.

Introduction

The Norwood procedure (stage-1-palliation; S1P) is the first step in the renowned 3-staged Fontan palliation for infants born with univentricular heart. Through improvements in surgical techniques and perioperative management, mortality has decreased during the past three decades, since the Norwood procedure was described first in 1983 by Norwood et al.[1,2]. Nevertheless, it is considered a high-risk procedure due to various intra- and postoperative risks, including a considerable risk for adverse cardiovascular events like the necessity of mechanical circulatory support and death in the postoperative course.[3,4] Above all, this is due to the shunt-dependent physiology, corresponding with instable coronary perfusion, dysfunction of the (systemic) right ventricle, regurgitation of the systemic atrioventricular valve, and an underdeveloped, stenotic aorta.

Consequently, tools for predicting adverse events after surgery are profoundly valuable components for providing appropriate care in the ICU and during follow-up until patients undergo bidirectional cavopulmonary shunt (stage 2 palliation, S2P) as the second step of Fontan palliation. With 30-day mortality rates around 12%, perioperative mortality is still a matter of concern, mainly due to the occurrence of major adverse cardiovascular events in the postoperative period.[4,5]

In a recently published study from our research group, we demonstrated that zlog-NT-proBNP – a special type of z-score for NT-proBNP adjusted for its highly age-dependent reference intervals – is a reliable predictor of major adverse cardiovascular events in children with CHD and even is superior to absolute NT-proBNP concentrations.[6,7] As NT-proBNP is a sensitive marker for cardiac wall stress, ventricular overload, and myocardial dysfunction, it might be a useful tool in children with univentricular heart.[8] However, zlog-NT-proBNP within these patients highly depends on the stage of Fontan palliation as well.[9] Therefore, within the present study, we enrolled children with univentricular heart undergoing serial NT-proBNP measurements at the time around the Norwood procedure and evaluated zlog-NT-proBNP as a potential tool for predicting adverse events in the early and late postoperative course.

Materials and methods

Study population and baseline characteristics

Patients who underwent the Norwood procedure at the German Heart Center Munich, a tertiary centre of care for paediatric heart diseases, between 2011 and 2022 were enrolled. Out of these, subjects with at least one NT-proBNP measurement before the Norwood procedure or in the postoperative course until dismission from ICU were included. Data were abstracted from medical records, including clinical, surgical, echocardiographic data, and events in the postoperative course. Age, sex, and underlying diagnosis were determined preoperatively. The body surface area was calculated using the standard Mosteller formula.[10]

Finally, patients were screened for the occurrence of major adverse cardiovascular events after Norwood surgery until they were discharged home. For those who were transferred to another hospital before discharge, those medical reports were reviewed as well. Therefore, follow-up ended when events occurred or patients were discharged home.

Endpoints

The primary endpoint was major adverse cardiovascular events, defined as death from any cause, resuscitation and the need for mechanical circulatory support (extracorporeal membrane oxygenation). Secondary endpoints, re-operation (i.e. shunt revision), and shunt re-intervention (i.e., stent implantation and/or balloon dilatation) were analysed in addition. Each event that had occurred since the time of Norwood surgery was recorded, with the earliest event defining the end of follow-up time. If no major adverse cardiovascular events had occurred since baseline, follow-up ended when the patients were discharged home. If the patients were hospitalised throughout the entire time until the next surgical step (bidirectional cavopulmonary shunt), follow-up ended one day before surgery.

Operative techniques and shunt size

The Norwood procedure was executed under standard cardiopulmonary bypass. Selective cerebral perfusion was performed during the reconstruction of aortic arch. The patients' surgeons and cardiologists decided on either modified Blalock–Taussig shunt or right ventricle-to-pulmonary artery conduit procedure. For those patients who underwent modified Blalock–Taussig shunt, a 3.5 mm non-ringed Gore-Tex graft was routinely used. For most of those who underwent right ventricle-to-pulmonary artery conduit, a 5.0 mm ringed Gore-Tex shunt was utilised. Technical details and considerations behind the chosen technique were described in our previous studies.[11,12]

The following variables in relation to surgical strategy were also taken into account in the assessment of the occurrence of modified Blalock–Taussig shunt: the ratio of shunt size (mm) to body weight (kg) and a graft index, which is the ratio of graft cross-sectional area (cross-sectional area, mm^2) to body surface area (m^2). Separate analyses were done for each shunt type.

Measurement of NT-proBNP and calculation of zlog-NT-proBNP

Blood samples were drawn during inpatient hospital stay using standard collection techniques, via a central venous catheter or an arterial line. NT-proBNP values were measured using the Roche Diagnostics Elecsys proBNP II assay on a Cobas E411 system. The assay ranges from 5 to 35,000 ng/L. Higher concentrations were routinely diluted and remeasured to determine exact concentrations above.

Physiologic NT-proBNP levels are characterised by markedly elevated concentrations during infancy, followed by a steady decline until adulthood.[13,14] During the first three days of life, the upper limit of NT-proBNP concentration reaches as high as 13,000 ng/L, and then declines to 1,000 ng/L during the first month of life. This rapid change in reference intervals for NT-proBNP during the first weeks of life particularly constitutes the time when the Norwood procedure is performed. Therefore, we applied age-adjusted zlog values (zlog-NT-proBNP) and used these instead of absolute concentrations. Eliminating the age dependency is the prerequisite to enable comparison over time in this specific study population. Zlog-NT-proBNP values were calculated as previously described (online calculator available at http://bit.ly/zlogNTproBNP).[6]

Timing of NT-proBNP measurements

NT-proBNP is an integral part of our admission laboratory since 2016. Serial NT-proBNP measurements during the postoperative course have been routinely obtained for several years as well, regardless of the child's condition. For the risk factor analysis, we considered three points in time: The first was "preoperatively", the second was "early postoperatively", which was the first measurement on ICU within 7 days after surgery, and the third was "late postoperatively", i.e. the last measurement on ICU at most 7 days before referral to normal ward. A flow chart of the patient selection is depicted in the appendix (Supplemental Figure 1).

For the preoperative zlog-NT-proBNP measurement, the Norwood operation was used as the baseline, whereas for the early and late postoperative measurements, the time of the corresponding laboratory measurement was used as baseline. Preoperative NT-proBNP was measured within up to 7 days before surgery. Previous measurements were not taken into account because they were not considered representative of the child's condition at the time of surgery. In addition, the intermediate postoperative period from day 7 to day 21 was evaluated and minima analysed.

Ethical statement

The study was approved by the Institutional Review Board of the Technical University of Munich (approval number of 2023-422-S-KR on August 14, 2023). Because of the retrospective and

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Table 1. Baseline characteristics

Characteristic	Patients
Subjects — no. (%)	139
Age at surgery in days — median (IQR)	8 (6–11)
Sex — no. (%)	
Male	94 (68)
Female	45 (32)
Preoperative data — median (IQR)	
Height — cm	51 (49–53)
Weight — kg	3.2 (2.9–3.6)
Body surface area (BSA) — m^2	0.21 (0.20–0.23)
Gestational data	
Gestational age — median (IQR)	39 (38–40)
Premature birth — no. (%)	27 (20)
Norwood procedure — median (IQR)	
Operation time — min	282 (241–343)
Cardiopulmonary bypass time (CPB) — min	156 (137–188)
Aortic cross clamp (AXC) — min	54 (46–68)
Deep hypothermic circulatory arrest (DHCA) — min	38 (3–46)
Lowest temperature — °C	21.1 (18.0–24.0)
Shunt type	
Modified Blalock–Taussig shunt (MBTS) — no. (%)	89 (64)
Right ventricle-to-pulmonary artery conduit (RVPAC) — no. (%)	47 (34)
Other — no. (%)	3 (2.1)
Shunt size MBTS — no. (%)	
3 — mm	5 (3.6)
3.5 — mm	70 (50)
4 — mm	15 (11)
Shunt size RVPAC — no. (%)	
5 — mm	48 (35)
6 — mm	1 (0.7)
Shunt size to weight ratio	
Modified Blalock–Taussig shunt (MBTS)	1.09 (1.03–1.25)
Right ventricle-to-pulmonary artery conduit (RVPAC)	1.61 (1.47–1.75)
Shunt cross-sectional area (CSA) to BSA ratio	
Modified Blalock–Taussig shunt (MBTS)	46.69 (43.58–52.46)
Right ventricle-to-pulmonary artery conduit (RVPAC)	92.22 (86.95–99.57)
Shnt size to BSA ratio	
Modified Blalock–Taussig shunt (MBTS)	16.81 (15.85–17.68)
Right ventricle-to-pulmonary artery conduit (RVPAC)	23.48 (22.14–25.17)
Postoperative data — median (IQR)	
Intubation — days	6 (4–13)
Secondary chest closure — days	3 (2–6)
ICU stay — days	15 (10–25)
Overall hospital stay — days	37 (23–65)
MACE (death, resuscitation, ECMO implantation) — no. (%)	61 (44)
thereof deceased	35 (25)
Re-intervention or re-operation for shunt — no. (%)	30 (22)

observational nature of the study, the need for individual patient consent was waived.

Statistical analysis

Categorical variables were presented as absolute numbers and percentages, depicting the patients' baseline characteristics and diagnosis. The Mann–Whitney *U* test was used to compare non-normally distributed numerical variables, while Student's *t*-test was applied to normally distributed data. Continuous variables were expressed as median with interquartile range or total range. Fisher's exact and the chi-squared tests were used for contingency tables. The Kaplan–Meier method was performed to obtain cumulative endpoint-free survival curves for zlog-NT-proBNP groups (below and above median) and compared with the log-rank test. Cox regression was used to evaluate the association between major adverse cardiovascular events and zlog-NT-proBNP as a categorical and continuous variable and as a change from preoperative value. The association between major adverse cardiovascular events and other baseline characteristics was analysed in addition. Primary endpoints were major adverse cardiovascular events and secondary endpoints were events as described above. Variables with a total range smaller than one were multiplied by a factor of 100 for the Cox regression, as noted in the table. Backward stepwise Cox regression was used for multivariate analysis, including parameters which were significantly associated with events in the univariate analysis.

p values < 0.05 for two-sided tests were considered significant. Data analysis and graphing were performed using the Statistical Package for the Social Sciences version 28 for Windows (IBM, Ehningen, Germany) and R version 4.0.0.

Results

Baseline characteristics and diagnoses

Out of 213 patients who underwent the Norwood procedure, 139 had at least one NT-proBNP measurement available. Tables 1 and 2 depict the baseline characteristics of the study population. The median age at Norwood procedure was 8 days (interquartile range 6–11 days, range 2–141 days), and 68% ($n = 94$) were male. Median weight at surgery was 3.2 kg (interquartile range 2.9–3.6 kg). Modified Blalock–Taussig shunt was used in 64% ($n = 89$) while right ventricle-to-pulmonary artery conduit was chosen in 34%

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Table 2. NT-proBNP measurements

	Preoperative	Early after ICU admission	Before ICU dismission
Zlog-NT-proBNP — median (IQR)	3.69 (3.05-4.07)	3.21 (2.42-3.82)	3.23 (2.81-3.84)
Days to surgery — median (IQR)	2 (1-3)	6 (3-10)	13 (7-23)
Measurements — no. (%)	72	81	110

Table 3. Underlying diagnosis

Characteristic	Patients
Subjects — no. (%)	139
Primary diagnosis — no. (%)	
Congenitally corrected transposition of the great arteries (ccTGA)	2 (1.4)
Double inlet left ventricle (DILV)	15 (11)
Double outlet right ventricle (DORV)	10 (7.2)
Hypoplastic left heart syndrome (HLHS)	97 (70)
Tricuspid atresia (TA)	1 (0.7)
Unbalanced atrioventricular septal defect (UAVSD)	8 (5.8)
Others: (complex) functional single ventricles (SV)	6 (4.3)
Associated cardiac anomaly — no. (%)	
(Hemi-)azygos vein	1 (0.7)
Anomalous pulmonary vein return (APVR)	3 (2.2)
Aortic anomalies (hypoplasic arch, CoA, IAA)	132 (95)
Common atrioventricular valve (CAVV)	8 (5.8)
Dextrocardia	2 (1.4)
Heterotaxy	0 (0)
Persistent left superior vena cava (PLSVC)	11 (7.9)
Trans-/malposition of the great arteries (TGA, MGA)	31 (22)
Dominant ventricle — no. (%)	
Dominant left ventricle (LV)	20 (14)
Dominant right ventricle (RV)	119 (86)

($n = 47$) of cases. The median of preoperative zlog-NT-proBNP was 3.69 (interquartile range 3.05–4.07). Early postoperative zlog-NT-proBNP (after ICU admission) was at a median of 3.21 (interquartile range 2.42–3.82) and late postoperative (before ICU discharge) was 3.23 (interquartile range 2.81–3.84). In the majority of patients (70%, $n = 97$), hypoplastic left heart syndrome was the primary underlying cardiac diagnosis. In total, 86% ($n = 119$) of the patients had a dominant right ventricle. Further diagnosis and associated anomalies are reported in Table 3.

Follow-up and major adverse cardiovascular events

The median ICU stay was 15 days (interquartile range 10–25 days), and the median overall hospital stay was 37 days (interquartile range 23–65 days). At least one primary endpoint (death, resuscitation or extracorporeal membrane oxygenation implantation) was met in 61 patients (44%). 30 patients (22%) reached the secondary endpoint (re-operation or re-intervention for shunt). In total, 35 patients (25%) died before they could be discharged home, despite maximally exhausted therapy.

When interpreting zlog-NT-proBNP levels before ICU discharge in patients with at least one adverse event in the following compared to patients without events, those with major adverse cardiovascular events revealed higher values than patients without (median 3.72, interquartile range 3.21–4.63 vs. median 3.20, interquartile range 3.09–3.27, $P < 0.001$). Supplemental Figure 2a shows zlog-NT-proBNP measurements during the first 30 postoperative days according to events. In those who did not have an event, zlog-NT-proBNP fell continuously after surgery. Patients who died by time of discharge had a steady increase in zlog-NT-proBNP in the early postoperative period (Supplemental Figure 2b). In patients with resuscitation or the need of extracorporeal membrane oxygenation, zlog-NT-proBNP values tended to rise after surgery but then declined. In patients with an event, zlog-NT-proBNP values increased immediately after surgery, whereas zlog-NT-proBNP values usually decreased in the first postoperative days in those who did not have an event.

Prognostic accuracy of zlog-NT-proBNP after surgery

Table 4 shows the hazard ratios of the baseline characteristics. The late postoperative zlog-NT-proBNP measurement showed a strong association with major adverse cardiovascular events (hazard ratio 1.83, 95% confidence interval 1.25–2.67, $P = 0.002$). Kaplan–Meier survival curves for late-postoperative zlog-NT-proBNP groups are depicted in Figure 1 (log-rank test, $P = 0.003$). Association with mortality was even more significant (hazard ratio 2.14, 95% CI 1.43–3.21, $P < 0.001$). The early postoperative zlog-NT-proBNP measurement revealed a significant association with mortality as well (hazard ratio 1.70, 95% confidence interval 1.08–2.68, $P = 0.02$). Figure 2 shows Kaplan–Meier survival curves for early postoperative zlog-NT-proBNP (log-rank test, $P = 0.005$).

The preoperative zlog-NT-proBNP measurement did not show an association with the occurrence of major adverse cardiovascular events, nor did the early postoperative zlog-NT-proBNP measurement.

Apart from that, operation time, and in specific cardiopulmonary bypass time, revealed significant associations with the occurrence of major adverse cardiovascular events in the univariate analysis. Also, body height and body surface area showed significant associations with the occurrence of major adverse cardiovascular events. Of the shunt parameters analysed, only the right ventricle-to-pulmonary artery conduit shunt type showed a significant association between the shunt size to body surface area ratio and the occurrence of adverse events.

In the multivariate analysis, the late postoperative zlog-NT-proBNP remained a highly significant predictor of both major adverse cardiovascular events and mortality (major adverse cardiovascular events: hazard ratio 1.74, 95% confidence interval

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Table 4. Hazard ratios for MACE and mortality according to indicators - univariate analysis

	MACE		Death	
Characteristic	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Laboratory data				
Preoperative zlog-NT-proBNP	0.97 (0.66-1.44)	0.897	1.38 (0.81-2.36)	0.242
Early postoperative zlog-NT-proBNP (after ICU admission)	1.28 (0.87-1.88)	0.213	1.70 (1.08-2.68)	0.022
Late postoperative zlog-NT-proBNP (before ICU dismission)	1.83 (1.25-2.67)	0.002	2.14 (1.43-3.21)	<0.001
Age — log days	1.00 (0.99-1.02)	0.587	1.00 (0.97-1.02)	0.890
Sex				
Male	Reference		Reference	
Female	0.67 (0.38-1.19)	0.172	0.96 (0.47-1.95)	0.899
Height	0.92 (0.86-1.00)	0.042	0.88 (0.79-0.98)	0.018
Weight	0.62 (0.38-1.02)	0.058	0.35 (0.18-0.69)	0.002
Body surface area (BSA)*	0.89 (0.80-0.99)	0.038	0.80 (0.69-0.93)	0.003
Gestational age				
Mature	Reference		Reference	
Premature	1.14 (0.60-2.17)	0.679	1.09 (0.47-2.50)	0.846
HLHS	0.75 (0.44-1.27)	0.285	0.97 (0.48-1.99)	0.936
Associated cardiac anomaly				
(Hemi-) azygos vein	0.05 (0.0-10^4)	0.650	0.05 (0.00-10^7)	0.761
Anomalous pulmonary vein return (APVR)	2.22 (0.54-9.14)	0.269	1.50 (0.20-11.05)	0.692
Aortic anomalies (hypoplasic arch, CoA, IAA)	0.54 (0.21-1.35)	0.184	0.35 (0.10-1.16)	0.087
Common atrioventricular valve (CAVV)	1.12 (0.40-3.14)	0.824	0.67 (016-2.84)	0.586
Dextrocardia	0.48 (0.00-173)	0.467	0.05 (0.00-5411)	0.609
Persistent left superior vena cava (PLSVC)	0.30 (0.07-1.24)	0.096	0.47 (0.11-2.03)	0.312
Trans-/malposition of the great arteries (TGA, MGA)	1.45 (0.81-2.58)	0.212	1.18 (0.54-2.62)	0.676
Dominant ventricle				
Left ventricle	Reference		Reference	
Right ventricle	1.13 (0.51-2.51)	0.757	2.14 (0.51-9.04)	0.300
Echocardiography				
Systemic ventricular function (moderate or higher)	0.99 (0.36-2.73)	0.981	0.96 (0.23-4.03)	0.957
Systemic AV valve regurgitation (moderate or higher)	1.34 (0.80-2.24)	0.266	1.28 (0.65-2.50)	0.480
Restrictive PFO/ASD	0.86 (0.46-1.59)	0.631	0.72 (0.30-1.75)	0.468
Aortic atresia	1.23 (0.74-2.04)	0.428	1.37 (0.70-2.65)	0.358
Shunt type				
Modified Blalock–Taussig shunt (MBTS)	Reference		Reference	
Right ventricle-to-pulmonary artery conduit (RVPAC)	1.38 (0.81-2.36)	0.236	1.01 (0.50-2.05)	0.976
Other	2.59 (0.62-10.9)	0.194	1.19 (0.16-8.9)	0.867
Shunt variables				
Modified Blalock–Taussig shunt (MBTS)				
Shunt size to weight ratio	1.63 (0.38-6.95)	0.513	4.36 (0.78-24.2)	0.092
Shunt cross-sectional area (CSA) to BSA	0.99 (0.95-1.03)	0.558	1.00 (0.97-1.04)	0.730
Shunt size to BSA	1.02 (0.88-1.18)	0.838	1.12 (0.94-1.32)	0.209

(*Continued*)

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Table 4. (*Continued*)

Characteristic	MACE Hazard ratio (95% CI)	MACE p value	Death Hazard ratio (95% CI)	Death p value
Right ventricle-to-pulmonary artery conduit (RVPAC)				
Shunt size to weight ratio	4.42 (0.66-29.7)	0.127	6.21 (0.71-54.7)	0.100
Shunt cross-sectional area (CSA) to BSA	1.04 (0.99-1.09)	0.086	1.05 (0.99-1.10)	0.107
Shunt size to BSA	1.25 (1.02-1.54)	0.031	1.22 (0.98-1.52)	0.074
Operation time	1.00 (1.00-1.01)	<0.001	1.00 (1.00-1.01)	0.024
Cardiopulmonary bypass time (CPB)	1.01 (1.00-1.02)	<0.001	1.01 (1.01-1.02)	<0.001
Aortic cross clamp (AXC)	1.01 (0.99-1.03)	0.289	1.02 (0.99-1.03)	0.178
Deep hypothermic circulatory arrest (DHCA)	1.01 (0.99-1.02)	0.426	1.01 (0.99-1.02)	0.404

*Hazard ratios refer to 100-fold value, see statistical analysis.

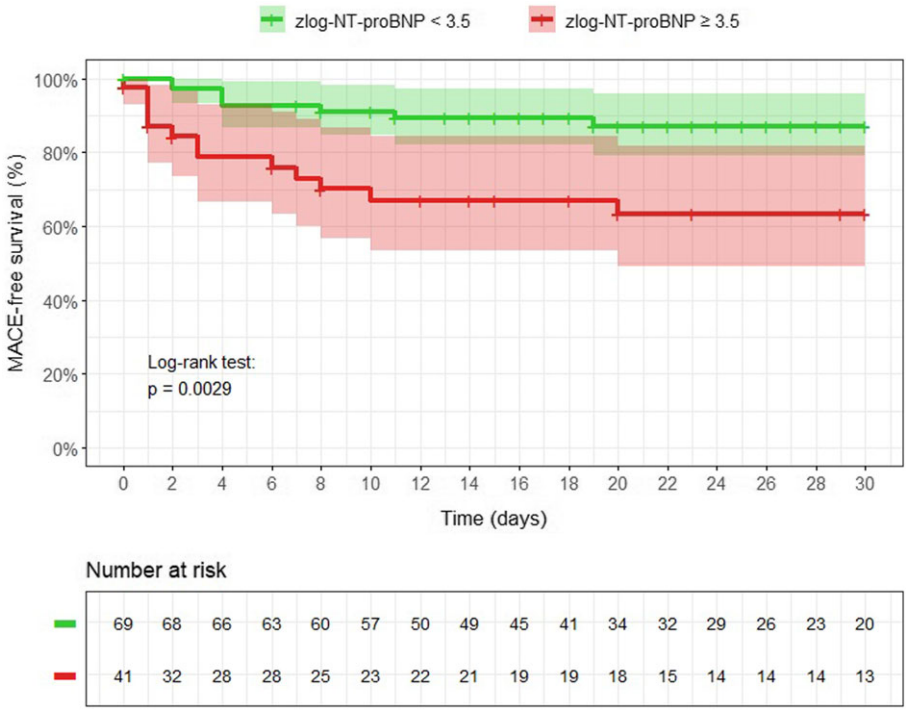

Figure 1. Kaplan–Meier MACE-free survival curve according to late postoperative zlog-NT-proBNP. Patients were divided into two groups according to zlog-NT-proBNP levels before discharge from ICU (below and above 3.5). The log-rank test yielded a p value 0.003.

1.18–2.57, $P = 0.005$ and death: hazard ratio 2.07, 95% confidence interval 1.32–3.25, $P = 0.002$). A strong association with mortality was observed for early postoperative zlog-NT-proBNP as well (hazard ratio 2.19, 95% confidence interval 1.20–4.01, $P = 0.01$). Further predictors for major adverse cardiovascular events were body surface area and cardiopulmonary bypass time. Other predictive parameters regarding mortality were shunt size to weight ratio, shunt size to body surface area, operation time, and cardiopulmonary bypass time. Hazard ratios for major adverse cardiovascular events and mortality in the multivariate analysis are presented in Table 5.

When analysing the minimum postoperative zlog-NT-proBNP value, measured in the intermediate postoperative period from day 7 to day 21, the receiver operating characteristic (ROC) analysis for mortality revealed an area under the curve of 0.77 (95% confid 0.67–0.88, Figure 3a). Corresponding boxplots of the minimum zlog-NT-proBNP values of patients who died vs. those who survived are depicted in Figure 3b.

Discussion

Our data showed that postoperative zlog-NT-proBNP close to discharge from ICU to normal ward predicted the occurrence of major adverse cardiovascular events and death until dismission home. In addition, early postoperative zlog-NT-proBNP predicted mortality in the postoperative course.

Comparison with previous studies on Norwood procedure

The early outcome after the Norwood procedure has improved over the past three decades. While Mahle et al. reported a hospital survival rate of 63.7% for patients with hypoplastic left heart

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Table 5. Hazard ratios for MACE and mortality according to indicators - multivariate analysis

	MACE		Death	
Characteristic	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Laboratory data				
Preoperative zlog-NT-proBNP	0.85 (0.55-1.30)	0.443	0.94 (0.48-1.85)	0.868
Early postoperative zlog-NT-proBNP (after ICU admission)	1.37 (0.81-2.31)	0.243	2.19 (1.20-4.01)	0.011
Late postoperative zlog-NT-proBNP (before ICU dismission)	1.74 (1.18-2.57)	0.005	2.07 (1.32-3.25)	0.002
Height	2.53 (0.047-13.7)	0.282	2.52 (0.03-246)	0.692
Weight	2.66 (0.06-129)	0.621	319 (0.02-10^7)	0.255
Body surface area (BSA)*	0.76 (0.63-0.92)	0.005	0.87 (0.59-1.29)	0.492
Dominant ventricle	1.56 (0.45-5.42)	0.484	3.56 (0.44-28)	0.234
Shunt type				
Modified Blalock–Taussig shunt (MBTS)	Reference		Reference	
Right ventricle-to-pulmonary artery conduit (RVPAC)	0.76 (0.06-9.88)	0.832	42 (0.26-6805)	0.149
Other	1.74 (0.22-14.1)	0.604	1.02 (0.12-8.45)	0.983
Shunt size to weight	2.12 (0.48-9.36)	0.320	3144 (3.78-10^6)	0.019
Shunt size to BSA	0.85 (0.08-8.72)	0.894	0.57 (0.34-0.95)	0.030
Operation time	1.00 (0.99-1.00)	0.207	0.99 (0.98-1.00)	0.040
Cardiopulmonary bypass time (CPB)	1.01 (1.01-1.02)	<0.001	1.02 (1.01-1.04)	0.003

*Hazard ratios refer to 100-fold value, see statistical analysis.

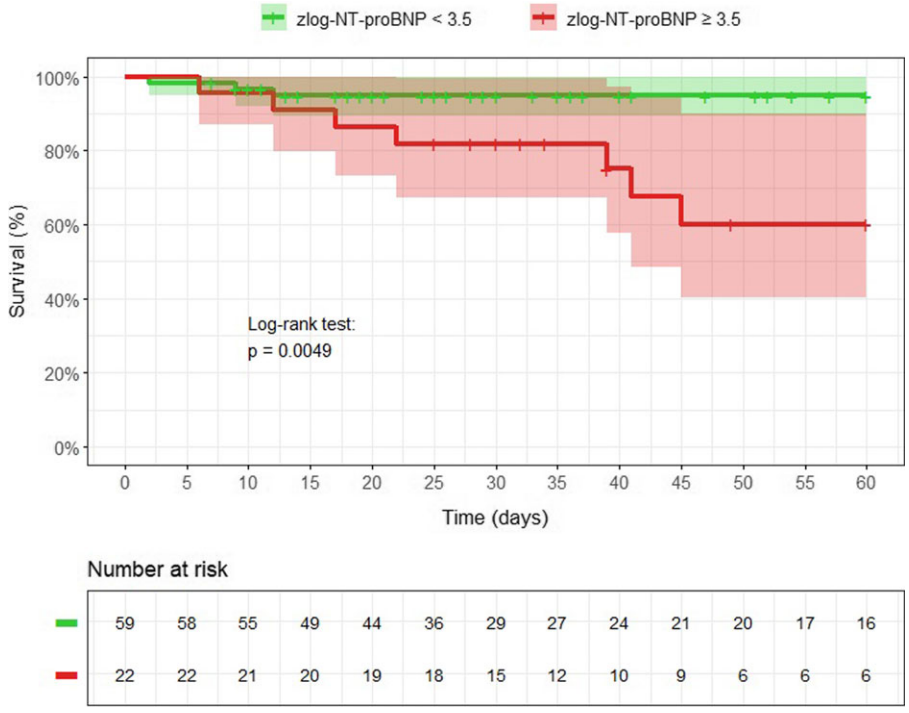

Figure 2. Kaplan–Meier survival curve according to zlog-NT-proBNP. Patients were divided into two groups according to early postoperative zlog-NT-proBNP levels (below and above 3.5). The log-rank test yielded a p value of 0.005.

syndrome who underwent the Norwood procedure between 1984 and 1999, recent 30-day survival rates reached 88% over the past 20 years.[5,15] Risk factors for early mortality have been extensively studied: Previous studies identified a birth weight lower than 2.5 kg as an independent predictor for early mortality after the S1P, and lower birth weight as a continuous variable was an independent risk factor for late mortality after the S1P. Univariate analysis also identified weight at the S1P as a risk for both early and late death.[5] In this study, we were also able to identify weight, height and, in particular, body surface area as important factors influencing

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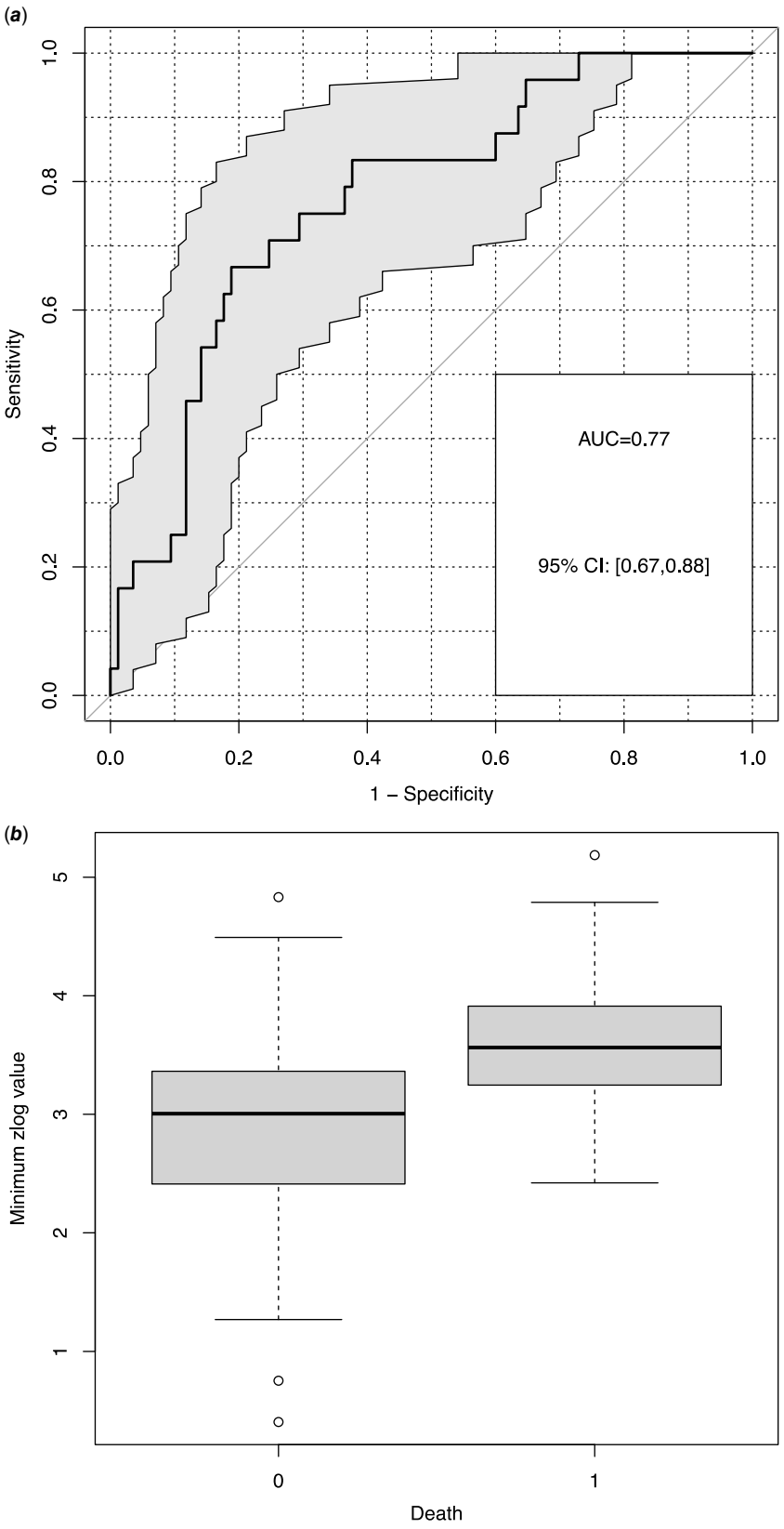

Figure 3 *a*. ROC curve for death according to the minimum zlog-NT-proBNP value measured in the intermediate postoperative period from day 7 to day 21. The area under the curve was 0.77 (95% CI 0.67–0.88). *b*. Boxplots according to the minimum zlog-NT-proBNP value measured in the intermediate postoperative period from day 7 to day 21 in patients who died and patients who survived. Patients who died had elevated levels compared to those who survived (median 3.56, IQR 3.25–3.91 vs. 3.0, IQR 2.41–3.36).

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major adverse cardiovascular events and death. Higher weight, height and body surface area were protective against major adverse cardiovascular events and especially mortality, with death and body surface area being the strongest factors.

Lubert et al. reported that patients' risk for requiring extracorporeal membrane oxygenation support after Norwood procedure was a longer cardiopulmonary bypass time in addition to birth weight.[16] This study also demonstrated that cardiopulmonary bypass time was predictive of the occurrence of adverse events and survival. Among others, Tabbutt et al. found aortic atresia as a factor for early mortality.[17] However, in our cohort, aortic atresia was not associated with mortality.

In 2008, Ohye et al. published the multi-centre randomised single ventricle reconstruction trial to compare modified Blalock–Taussig shunt and right ventricle-to-pulmonary artery conduit in the Norwood procedure. Results of the single ventricle reconstruction trial have been serially reported. On the one hand, Ohye reported in 2010 that there were more resuscitations in the modified Blalock–Taussig shunt group during Norwood hospitalisation, and on the other hand, there were more cardiovascular interventions in the right ventricle-to-pulmonary artery conduit group.[18,19] In the most recent publication, transplant-free survival at 6 years did not differ significantly between right ventricle-to-pulmonary artery conduit and modified Blalock–Taussig shunt groups (64% vs. 59%, $p = 0.25$).[20] In accordance with this study, we did not find a difference in survival between both shunt types.

However, through this study, we demonstrated that zlog-NT-proBNP is a parameter that allows to anticipate the occurrence of adverse events in the postoperative course.

Zlog-NT-proBNP as predictive marker after Norwood procedure

Previous studies have shown that NT-proBNP levels tend to decrease during staged Fontan palliation.[21,22] This decrease represents the release of volume overload and cardiac wall stress, mainly on the right ventricle, especially after bidirectional cavopulmonary shunt. During Fontan palliation, S1P is especially critical, with the highest risks for early death and the occurrence of other major adverse cardiovascular events compared to the second and third step.[5] In 2008, Berry et al. reported on BNP measurements 6 to 12 hours after surgery, that were of predictive value for duration of inotropic support and length of hospital stay.[23] Similar results were described by Nahum et al. in 2013, when he found BNP to be predictive for inotropic support and longer ICU stay.[24] However, none of these studies took account for the distinct age dynamics of this biomarker. In addition, unlike BNP, NT-proBNP has different reference intervals and dynamics, probably due to its longer half-life.[25] Yet, no literature can be found on NT-proBNP as a predictive marker for adverse cardiovascular events during hospitalisation for the Norwood procedure. Interesting is that, e.g. in cases of death, depicted in graph (B) in Supplemental Figure 2a and b, zlog-NT-proBNP levels increase continuously after surgery, which is consistent with clinical experience of patients with steadily rising zlog-NT-proBNP levels who often experience adverse events in the following.

Outlook

Our study is the first to investigate zlog-NT-proBNP in children undergoing the Norwood procedure and its impact on early postoperative outcome. In the future, clinicians should consider this biomarker in patients that underwent Norwood procedure as a tool for postoperative care and follow-up. Especially in more protracted and difficult cases, serial zlog-NT-proBNP measurements might be useful. Longitudinal measurements of zlog-NT-proBNP can provide an indication of future adverse events, as the dyamics in Supplemental Figure 2a and b suggest. This can help the clinician decide whether a child can be discharged from ICU and transferred home or to another hospital, depending on the likelihood of life-threatening events.

Study limitations

This study was limited by its retrospective, non-randomised and single-centre design. The limited number of available NT-proBNP measurements might have diminished the reliability of analysis and added additional variability. Diagnostic methods, surgical, interventional, and perioperative management may have changed during the relative long study period, probably influencing the outcomes and adding further variability. In addition, before 2016, NT-proBNP was often measured upon clinical indication, possibly resulting in a selection bias towards sicker patients and a higher mortality rate. However, these subjects are the ones who benefit from further tools for risk stratification the most.

Another limitation, which specifically affects Supplemental Figures 2a and b, is that NT-proBNP measurements were not taken at fixed times (i.e., POD 1, 3, 7, 14) for each patient, but varied, with some patients having multiple measurements and others only a few, making comparisons more difficult. The variability in NT-proBNP measurements could also lead to bias when considering the minimum zlog-NT-proBNP value for each patient, as in Figure 3a and b. In principle, a higher number of measurements increases the probability of a lower minimum value. However, patients with a higher number of measurements are likely to be those in a more critical condition and tend to have higher values. In this sense, the possible bias due to the higher number of measurements makes our results appear worse than if all patients had the same number of measurements, and therefore tends to underestimate the likelihood of events and the corresponding hazard ratio.

Conclusions

In this study, zlog-NT-proBNP measurements were assessed before Norwood, early postoperatively, i.e. after ICU admission, and late postoperatively, i.e. before ICU discharge to the normal ward. A significant association was found between late postoperative zlog-NT-proBNP levels and the occurrence of major adverse cardiovascular events and, in particular, death. In addition, elevated early postoperative zlog-NT-proBNP levels were predictive of mortality in the subsequent postoperative period. Furthermore, higher minimum values between POD 7 and 21 correlated with worse outcome. Accordingly, we expect zlog-NT-proBNP to play an important role in the future monitoring of high-risk inpatients as well as in the outpatient management of infants and toddlers with univentricular hearts until Fontan completion.

Perspectives

Competency in medical knowledge

The occurrence of major adverse cardiovascular events, i.e. death, in the postoperative course of patients who have undergone the Norwood procedure is strongly associated with

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the level of zlog-NT-proBNP in the ICU. Evidence of this association may help healthcare professionals to use zlog-NT-proBNP as a tool for postoperative care and follow-up. Especially to estimate the probability of the occurrence of an adverse event, regular zlog-NT-proBNP measurements might be useful.

Translational outlook

Prospective studies, including additional confounders such as echocardiographic parameters, could establish postoperative zlog-NT-proBNP cut-off values for patients who have undergone the Norwood procedure to help clinicians estimate the likelihood of an adverse event occurring in the postoperative course. Thus, zlog-NT-proBNP reference values could be used as benchmarks to develop the best strategy for the postoperative management of these patients in order to avoid the occurrence of adverse events through appropriate treatment.

Data availability statement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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