Brain injury and neurodevelopmental outcomes in children undergoing surgery for congenital heart disease

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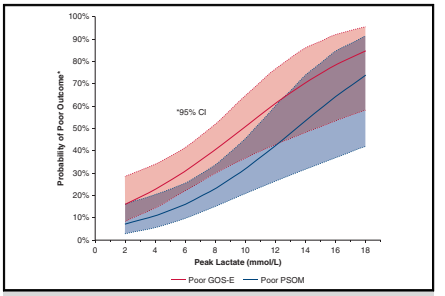
ABSTRACT

Objectives: Brain injury is commonly seen on magnetic resonance imaging in infants with complex congenital heart disease. The impact of perioperative brain injury on neurodevelopmental outcomes is not well understood. We evaluate the association of brain injury and other markers on neurodevelopmental outcomes in patients undergoing surgery for congenital heart surgery during infancy.

Methods: Term newborns with infant cardiac surgery performed between 2008 and 2019 at a single tertiary center, and both preoperative and postoperative brain magnetic resonance imaging were included. Those with underlying genetic conditions were excluded. Brain injury was characterized using an magnetic resonance imaging scoring system. Neurodevelopmental outcomes were assigned using the Pediatric Stroke Outcome Measure and Glasgow Outcome Scale Extended. Independent risk factors for poor neurodevelopmental outcomes were determined by multivariable Cox regression.

Results: A total of 122 patients were included. New or progressive postoperative brain injury was noted in 69 patients (57%). A total of 101 patients (83%) had at least 1 neurodevelopmental assessment (median age 36 months) with an early assessment (5-24 months) performed in 95 children. Multivariable Cox regression analysis of early neurodevelopmental outcomes identified new stroke on postoperative magnetic resonance imaging to be an independent predictor of poor neurodevelopmental outcome. Postoperative peak lactate was an independent predictor of poor outcome assessed by the Pediatric Stroke Outcome Measure and Glasgow Outcome Scale Extended.

Conclusions: Our study reveals that evidence of new stroke on magnetic resonance imaging after infant congenital heart surgery is a predictor of poor neurodevelopmental outcomes in early childhood. Postoperative lactic acidosis is associated with poor neurodevelopmental outcome and may be a surrogate biomarker for ischemic brain injury. (JTCVS Open 2024;17:229-47)



Elevated postoperative serum lactate levels are a useful clinical biomarker to identify patients at risk for ischemic brain injury with impact on ND outcome in childhood.

CENTRAL MESSAGE

New stroke on postoperative brain MRI after infant congenital heart surgery is predictive for early-onset ND disability. An elevated postoperative peak lactate level is a predictor of adverse ND outcome in childhood.

PERSPECTIVE

Children with new stroke after infant heart surgery are at risk for adverse ND outcome early in childhood and may benefit from screening for ND disability between 5 and 24 months of age.

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Abbreviations and Acronyms

AUC = area under the curve
CHD = congenital heart disease
DHCA = deep hypothermic cardiac arrest
GOS-E = Glasgow Outcome Scale Extended
ICU = intensive care unit
MRI = magnetic resonance imaging
ND = neurodevelopmental
PSOM = Pediatric Stroke Outcome Measure
WMI = white matter injury

Life expectancy is steadily increasing for patients with congenital heart disease (CHD). The majority of children with CHD will reach adulthood.[1] Current estimates report neurodevelopmental (ND) disorders impact more than 50% of children with severe CHD.[2] Efforts to ensure positive long-term neurologic outcomes for patients with CHD are imperative.

A variety of independent risk factors for ND impairment in children with CHD are reported. When predicting an individual's prognosis, a combination of risk factors need to be considered. Not only are there significant differences between the many subtypes of CHD, but within each subgroup individual defects vary significantly. Patients with CHD are heterogenous in their extracardiac risk factors as well. Studies have shown elements inherent to the patient (ie, genetic vulnerabilities,[3] low birth weight), environment (ie, lower socioeconomic status), and clinical course (eg, prolonged mechanical ventilation, longer stay in the intensive care unit [ICU][4]) all have an impact on the ND outcome.

Several different types of brain injuries are known to be common in patients with CHD. Magnetic resonance imaging (MRI) abnormalities commonly include white matter injury (WMI) and stroke (Table E6). Despite the extensive evaluation of brain injuries in infants with CHD, there are gaps in our understanding of how these radiographic injuries impact the ND outcome. Some studies have shown brain immaturity, but not brain injury, predicts impaired neurodevelopment at 2 years.[5] Andropoulos and colleagues[6] demonstrated that new postoperative injury predicts lower cognitive scores, but Claessens and colleagues[7] found that moderate to severe WMI is associated with lower cognitive scores at 2 years and full-scale IQ at 6 years of age.

There are several explanations for why studies linking infant brain injury to ND outcome may have inconsistent findings. First, the small numbers of patients studied and the inherent variability among patients with CHD make it difficult to generalize ND outcomes. Further, within the body of literature, outcomes are measured at a variety of ages, using different tools and thresholds for poor outcome. Timing of the ND assessment appears to be particularly important when considering the impact of specific brain injury subtypes, because earlier assessments have more of an emphasis on motor skills and later assessments on social/emotional and cognitive skills.[8] Finally, the timing (eg, perinatal vs perioperative) and location of the brain injury may alter the impact of the brain injury subtypes on outcome.[9]

Despite the complexity of predicting ND outcome in patients with CHD, some commonalities exist. For example, length of ICU stay and duration of mechanical ventilation are shown to consistently have a negative association with ND outcome. As such, modifiable determinants of outcome likely can be found in the perioperative care of these patients. In this study, we investigated the timing and subtype of acute brain injury on the risk for poor ND outcome in patients with surgery for CHD during infancy. Clinical biomarkers were also evaluated that may portend when a patient is at risk for an unfavorable ND outcome.

We hypothesize that ischemic brain injury acquired during the perioperative course may have an adverse impact on ND outcome. Furthermore, we propose that elevations of serum lactate during the perioperative period may be a useful clinical biomarker to identify patients at risk for ischemic brain injury.

MATERIAL AND METHODS

Patient Cohort

Term infants who underwent congenital cardiac surgery at a single tertiary care center between 2008 and 2019 were retrospectively identified from the cardiac surgery database. Patients with surgery performed within the first 90 days of life and with both preoperative and postoperative brain MRIs were included in the analysis. Patients born before 37 weeks gestation and those with multiple congenital malformations or a suspected/confirmed genetic condition were excluded. ND assessments were evaluated as part of clinical care.

The study was approved by the Institutional Review Board of Children's National Hospital (Pro00009673, approved 7/19/2014). Patient consent was waived due to the retrospective design of this study and de-identified data.

Clinical Data

Patient demographics and clinical data were extracted from the database and supplemented from the electronic medical record. Patient characteristics included gestational age, birth weight, birth head circumference, and age at the time of MRI. Intraoperative data captured included age and weight at time of surgery, aortic crossclamp time, duration of deep hypothermic circulatory arrest (DHCA), and procedure performed. Markers of oxygenation and perfusion in the postoperative period were collected and consisted of highest arterial lactate, highest arterial pCO2, and lowest arterial pH. Peak values were defined as highest value in the postoperative ICU course after initial surgery and before postoperative MRI. Clinical events recorded were time from surgery to postoperative MRI, duration of intubation, length of stay in the ICU, length of hospital stay, cardiac arrest, need for extracorporeal membrane oxygenation support, subsequent cardiac surgery or catheterization, and presence of clinical seizures. Only clinical seizures confirmed on electroencephalogram were counted as seizures but not subclinical seizures because not all patients in the cohort had continuous

electroencephalogram monitoring. Outcome variables comprised mortality, ND evaluations, and gastrointestinal tube placement before discharge.

Magnetic Resonance Imaging

Preoperative brain MRI scans were obtained as soon as the newborn could be safely transported to the MRI scanner as determined by the clinical team. Postoperative studies were performed after the patient's condition stabilized and the pacing wires were removed. MRI scans were acquired as part of clinical care. Patients did not undergo brain MRI as part of clinical care if the clinical team deemed that the scans might adversely impact the course of the patients because of clinical or administrative reasons.

Preoperative and postoperative MRI studies were performed on a 1.5 T (Discovery MR450; GE Healthcare or Siemens Avanto) or 3.0 T scanner (Discovery MR750; GE Healthcare). The MRI scans consisted of T1- and T2-weighted images, susceptibility-weighted images, diffusion-weighted imaging, and magnetic resonance spectroscopy.

MRI scans were scored for brain injury by a pediatric neuroradiologist or pediatric neurologist. Scores were assigned outside of routine clinical care without relating to clinical data other than the patient's age and sex; formal blinding was not performed. Brain injury on preoperative and postoperative brain MRI scans was characterized using the brain injury score devised by Andropoulos and colleagues[10] and as previously described.[4,11] Brain injury scores 5 or greater were defined as moderate or severe brain injury (Table E1).

Neurodevelopmental Outcome Assessments

Per institutional routine, patients with CHD and cardiac surgery during the first year of life are referred for outpatient ND evaluation. ND assessments are performed by a pediatric neurologist or a developmental psychologist at recommended intervals during childhood. Inpatient assessments were excluded from this study. ND outcome scores were retrospectively assigned using both the Pediatric Stroke Outcome Measure (PSOM) and Glasgow Outcome Scale Extended (GOS-E) as previously described.[4,11] Outcomes were assigned as *early* ND outcome (5-24 months) and *latest* ND outcome (as defined by the most recent ND assessment). Adverse outcome was defined as a PSOM score greater than 2 and for GOS-E as a score greater than 2.

Statistical Analysis

Independent risk factors for poor *early* and *latest* ND outcomes were identified by Cox regression analysis with date of surgery and date of follow-up to determine time-to-event for adverse GOS-E and PSOM. Variables included in multivariable Cox regression analyses were those with P less than .05 in univariate Cox analysis. Hazard ratios and 95% CIs were calculated as the measure of risk and presented as Forest plots. For significant variables in the multivariable Cox regression analysis, the area under the curve (AUC) was calculated and a probability model calculated based on logistic regression. Bootstrap validation with 2000 bootstrap resamples with replacement was performed to evaluate internal validation of the multivariable predictive outcome models.[12] Analysis of the data was performed using Stata version 16.1 (StataCorp LLC).

RESULTS

A total of 1061 infants underwent congenital heart surgery within the first 90 days of life between 2008 and 2019. Among them, 204 had preoperative and postoperative brain MRI and were eligible for inclusion in this study. Of those, 21 were excluded because of preterm birth and 48 because of genetic malformations or suspected syndromes. Specifically, among the patients excluded for genetic syndromes, 7 were diagnosed with trisomy 21, 9 with DiGeorge, 3 with Turner, 2 with Vaterl, 2 with Kabuki, 1 with Charge, and 1 with Noonan syndrome. Additionally, 2 had cerebral dysgeneses and 19 exhibited other genetic variations. Thirteen patients were not included in the analysis because of incomplete MRI studies. The final study cohort comprised 122 patients (Table 1).

Diagnoses and Surgeries Performed

Forty-two patients (34%) had single ventricular circulation, and 80 patients (66%) had biventricular circulation. A total of 103 patients (84%) underwent surgery with cardiopulmonary bypass. Deep hypothermic cardiac arrest (DHCA) was exclusively used in patients undergoing arch reconstruction until 2017, covering most of the study period (2008-2019). After 2017, 1 single surgeon used selective cerebral perfusion for arch reconstructions. During 75 surgeries (62%), DHCA was used, and in 31 cases (25%) DHCA was 40 minutes or longer (Table 1). Details are given in Table E2.

Diagnostic Assessments

Preoperative brain injury was present in 53% (n = 64), and injury was characterized as moderate or severe in 16% (n = 19). Injury was noted on the postoperative scan in 74% of patients (n = 90), with 33% (n = 40) having moderate or severe injuries. Fifty-seven percent (n = 69) of the injuries identified on the postoperative MRI scan were defined as new or expanded injury. The median age (SD) at preoperative MRI was 3 (5.8) days with the scan occurring a median (SD) of 3 (9.2) days before surgery. The median (SD) age at postoperative MRI was 25 (18.3) days, occurring at a median (SD) of 15 (17.1) days after surgery (Table 2 and Table E3).

A total of 101 patients (83%) had at least 1 ND assessment. The median (interquartile range) age was 36 (18-53) months. Ninety-five children (78%) had an *early* assessment (at 5-24 months) at a median (SD) age of 8 (4.5) months. Sixty-seven (55%) of the children had 2 assessments at least 12 months apart. The median (SD) time between the 2 assessments was 34 (20.8) months.

Of the 122 patients studied, 10 died. Three died before 5 months of age and had no ND assessment. Consequently, those 3 were not included in the analysis of ND outcomes. All 7 patients who died after 5 months of age had an adverse ND assessment before death.

An *early* ND outcome assessment was obtained in 95 children. Thirteen children (7%) had a poor outcome by PSOM, and 21 children (22%) had a poor outcome by GOS-E. A poor PSOM score was found on the *latest* ND assessment in 21 children (21%), whereas a poor GOS-E was assigned in 35 (35%) of the *latest* follow-ups. Of the 67 children with 2 assessments at least 12 months apart, 31 (46%) ND assessments (both PSOM and GOS-E)

TABLE 1. Cohort characteristics

Variable	Total
Cohort, n (%)	122 (100)
Gender, n (%)	
Male	80 (66)
Ethnicity, n (%)	
White	63 (52)
Black	32 (26)
Hispanic	16 (13)
Other	11 (9)
Gestational age at birth, median wk (IQR)	39 (38-39)
Birth weight, median kg (IQR)	3.23 (2.9-3.5)
Head circumference at birth, median cm (IQR)	34 (33-35)
CHD Class, n (%)	
I + II = biventricular	55 (41) + 25 (25)
III + IV = single ventricle	13 (11) + 29 (22)
Lowest pO2 preoperative, median mm Hg (IQR)	34 (26-43)
Lowest pH preoperative, median (IQR)	7.32 (7.27-7.35)
Highest lactate preoperative, median (IQR)	2.9 (1.9-4.6)
Lowest SBP preoperative, median (IQR)	51 (47-57)
Lowest DBP preoperative, median (IQR)	25 (20-29)
PGE used, n (%)	112 (92%)
PGE duration, median d (IQR)	5 (3-7)
Mechanical ventilation preoperative, n (%)	63 (52)
Duration ventilation preoperative, median d (IQR)	2 (1-5)
Inotropic support used preoperative, n (%)	23 (19%)
Age at cardiac surgery, median d (IQR)	7 (5-10)
Weight at surgery, median kg (IQR)	3.26 (2.96-3.63)
Surgery with CPB, n (%)	103 (84)
Surgery without CPB, n (%)	19 (16)
DHCA, n (%)	75 (62)
DHCA ≥40 min	31 (25)
Highest lactate postoperative, median (IQR)	5.9 (3.2-8.2)
Lowest pH immediately postoperative, median (IQR)	7.18 (7.09-7.27)
Lowest pH postoperative later, median (IQR)	7.29 (7.15-7.34)
Cardiac arrest, n (%)	
Between MRIs	11 (9)
Before discharge	14
Overall	20
Fever, n (%)	
Between MRIs/perioperative	20 (16)
Before discharge	27 (22)
ECMO, n (%)	
Between MRIs	7 (6)
Before discharge	7 (6)
Overall	10
Venous vascular thrombosis (initial hospitalization), n (%)	20 (16)
Clinical seizures confirmed on electroencephalogram, n (%)	16 (13)
Duration of ICU stay, median d (IQR)	17 (13-28)
Duration of hospital stay, median d, (IQR)	26 (18-48)
Duration of mechanical ventilation total, median d (IQR)	7 (4-11)
Duration surgery to postoperative MRI, median d (IQR)	14 (8-29)
Tracheostomy, n (%)	3 (2.5)
G-tube, n (%)	28 (23)
Subsequent cardiac surgery performed, n (%)	60 (49)
Subsequent surgery >1 time, n (%)	37 (30)
Early follow-up at 5-24 mo	
n (%)	95 (78)
Age (without deaths), median mo (SD)	8 (4.5)
Latest follow-up ≥5 mo	
n (%)	101 (83)
Age (without deaths), median mo (IQR)	36 (18-53)
2 follow-ups (at 5-24 mo and >24 mo, at least 12 mo apart)	
n (%)	67 (55)
Time difference, mo (without deaths), median (SD)	34 (20.8)
PSOM recent follow-up (deaths included) worse/better than first follow-up, n (%)	31 (46)/6 (9)

(Continued)

TABLE 1. Continued

Variable	Total
GOS-E recent follow-up (deaths included) worse/better than first follow-up, n (%)	31 (46)/11 (16)
Death, n (%)	10 (8)
Age, mean/median, wk (IQR)	116/66 (35-184)
Age, mean/median, y (IQR)	2.2/1.3 (0.7-3.5)

IQR, Interquartile range; *CHD*, congenital heart disease; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *PGE*, prostaglandin; *DHCA*, deep hypothermic cardiac arrest; *MRI*, magnetic resonance imaging; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit; *SD*, standard deviation; *PSOM*, Pediatric Stroke Outcome Measure; *GOS-E*, Glasgow Outcome Scale Extended.

were worse at the second assessment compared with the first. Alternatively, at the second assessment, 6 children (9%) had a better PSOM score and 11 children (16%) a better GOS-E score.

An ischemic stroke was present on 14 (11%) of the preoperative MRIs. Twenty-three (19%) of the postoperative MRI scans contained an ischemic stroke, of which 17 (14%) were new or expanded ischemic injury. ND follow-ups were obtained in 12 of the 14 patients with stroke on preoperative MRI and 21 of the 23 patients with stroke on postoperative MRI. A total of 16 of the 17 patients with new stroke on postoperative MRI were assigned an ND outcome score. Adverse ND outcome was present only in the patients with new postoperative stroke (Figure 1).

Statistical Analysis

Multivariable Cox regression of the *early* (5-24 months) ND outcomes confirmed that new or worse stroke on postoperative MRI and cardiac arrest before initial discharge are significant independent predictors of poor outcome by GOS-E assessment (Figure 2 and Table 3), whereas stroke on postoperative MRI is the only significant independent predictor of poor PSOM outcome (Figure E1 and Table E4). Notably, postoperative moderate to severe brain injury and stroke on postoperative MRI (a component of the total brain injury score) were colinear in the univariate model; therefore, only new stroke on postoperative MRI was included in the multivariable analysis.

For the GOS-E model, the 2 independent risk factors (stroke and cardiac arrest) provide an AUC of 0.833 (95% CI, 0.732-0.934). Doing a bootstrap validation with 2000 bootstrap resamples with replacement, this model demonstrates robust internal model performance with regard to discrimination (bootstrap AUC = 0.833) and calibration (Brier Score = 0.10, Hosmer-Lemeshow goodness-of-fit test $P = .887$). A bootstrap validation with 2000 bootstrap resamples for stroke on MRI predicts poor PSOM outcome at 5 to 24 months. Based on the numbers below, the bootstrap validation indicates good discrimination and calibration: bias-corrected AUC = 0.727, bias-corrected Somers' D = 0.45, bias-corrected Brier score = 0.10.

Looking at the *latest* follow-up, in a multivariable model, peak lactate (adjusted HR, 1.22 per mmol/dL; 95% CI, 1.1-1.34; $P < .001$) and subsequent surgery (adjusted HR, 4.32; 95% CI, 1.22-15.3; $P = .023$) are significant independent predictors of poor GOS-E (Table 4). Peak lactate (adjusted HR, 1.17 per mmol/dL; 95% CI, 1.02-1.34; $P = .024$) was the only significant independent predictor of poor PSOM (Table E5). Peak lactate demonstrated good prognostic accuracy in identifying children with poor outcome assessed by PSOM (AUC = 0.728, 95% CI, 0.618-0.875, $P < .001$) and poor outcome assessed by GOS-E (AUC = 0.728, 95% CI, 0.625-0.876). Figure 3 shows the probability curves for poor outcome according to peak lactate level based on logistic regression, depicting a steadily increasing risk of poor outcome for both PSOM and GOS-E. Specific probabilities of poor outcome according to peak lactate and corresponding 95% CIs are presented in the table included in Figure 3.

DISCUSSION

We aimed to evaluate brain injury subtypes and timing of the injury as potential clinical biomarkers to signal an

TABLE 2. Brain injuries

Variable	Preoperative MRI				Postoperative MRI					
Median age in d at time of MRI, n (SD)	3 (2-5)				25 (18.25-36)					
Brain injury present, n (%)	64 (52.5%)				90 (73.8%)					
New brain injury, n (%)	N/A				69 (56.6%)					
Brain injury subtype, n (%)										
	Injury overall		Moderate/severe injury		Total					
					Injury overall		Moderate/severe injury		New injury post vs pre	
WMI	23	18.9%	6	5%	39	32.0%	11	9%	25	20.5%
Infarction	14	11.5%	6	5%	23	18.9%	17	14%	17	13.9%

MRI, Magnetic resonance imaging; *SD*, standard deviation; *N/A*, not available; *WMI*, white matter injury.

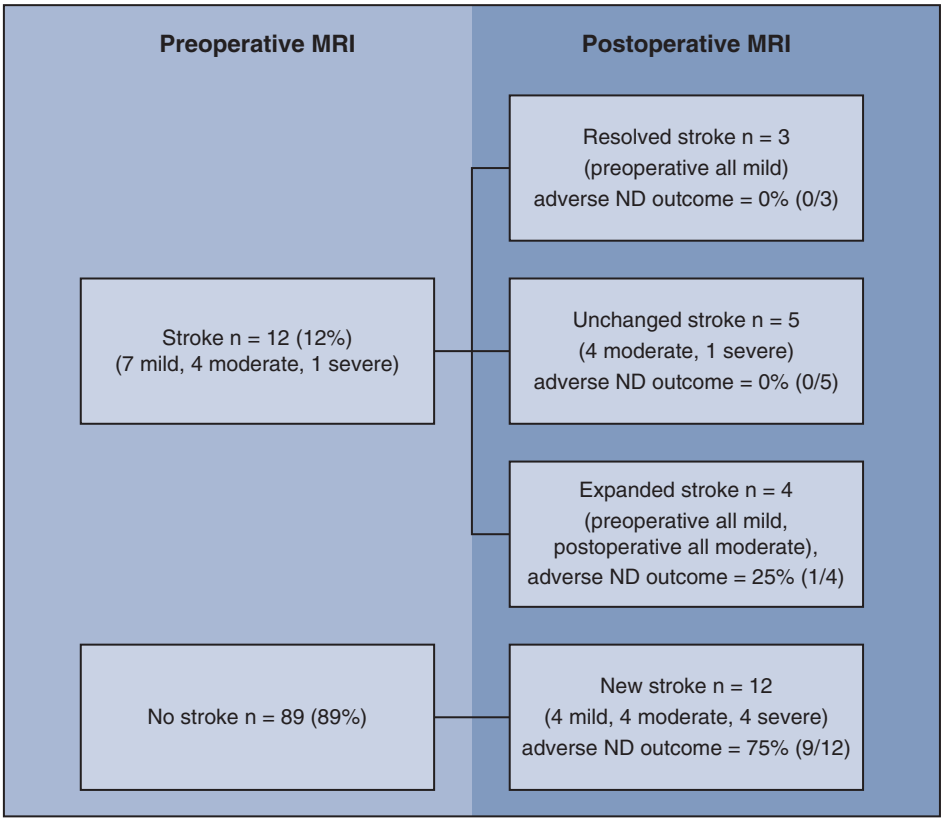


FIGURE 1. ND outcome by stroke time and severity (includes only patients with ND assessment). Mild: less than 1/3 of vascular territory of ACA, MCA, or PCA in 1 hemisphere, total size 1 to 5 mm. Moderate: 1/3 to 2/3 of vascular territory, total size 6 to 15 mm. Severe: greater than 2/3 of vascular territory, total size greater than 15 mm. *MRI*, Magnetic resonance imaging; *ND*, neurodevelopmental.

elevated risk for poor ND outcome in patients with surgery for CHD during infancy.

To our knowledge, this is the largest cohort of patients with cardiac surgery in infancy and both preoperative and postoperative brain MRI as well as ND follow-up (Table E6).

Our analyses revealed 2 novel clinical biomarkers for predicting ND outcome in children with surgery for CHD in infancy. First, new ischemic stroke on postoperative MRI increases the risk for *early* ND disability. Second, elevated lactate (peak) during the postoperative course is a predictor for poor ND outcome in childhood (Figure 4).

Radiographic evidence of brain injury in infants with CHD is well documented, with multiple studies describing the incidence and subtypes of injury in cohorts with preoperative and postoperative MRI.[5,8,10] Yet, associations between brain

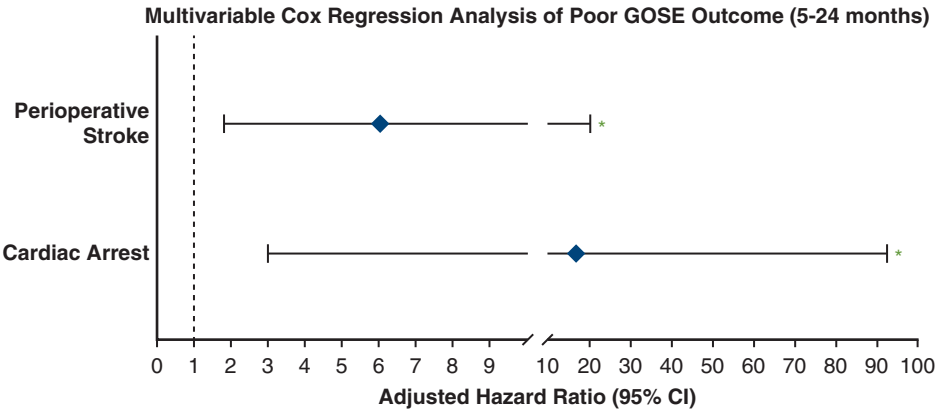


FIGURE 2. Significant risk factors in multivariable analysis for poor ND outcome (*GOS-E*) at 5 to 24 months of age. *CI*, Confidence interval.

TABLE 3. Univariate and multivariable Cox regression analysis of poor Glasgow Outcome Scale Extended outcome (5-24 months)

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Perioperative stroke	3.6 (1.51-8.57)	**.004***	6.04 (1.81-20.1)	**.003***
Moderate/severe brain injury	2.68 (1.12-6.37)	**.026***	Omitted due to collinearity	
Single ventricle	6.02 (2.02-17.9)	**<.001***	3.3 (0.94-11.5)	.062
Cardiac arrest	9.26 (3.6-23.9)	**<.001***	16.7 (3-92.5)	**<.001***
Thrombosis	2.45 (0.99-6.09)	.053		
Peak lactate†	1.21 (1.1-1.34)	**<.001***	0.92 (0.8-1.07)	.275
Seizure‡	2.65 (1.09-6.42)	**.031***	Omitted due to collinearity	
Duration of ventilation	1.03 (1.02-1.04)	**<.001***	1 (0.98-1.03)	.736
ICU length of stay	1.02 (1.01-1.03)	**<.001***	1 (0.99-1.02)	.409
DHCA				
No DHCA	Reference	.	.	
1-39 min of DHCA	0.65 (0.16-2.56)	.537		
40+ min of DHCA	1.99 (0.77-5.15)	.157		

Variables with $P < .05$ in univariate analysis were included in the multivariable model. *HR*, Hazard ratio; *CI*, confidence interval; *ICU*, intensive care unit; *DHCA*, deep hypothermic cardiac arrest. *Statistically significant. †Peak lactate after surgery and before postoperative MRI. ‡Clinical seizure confirmed on electroencephalogram.

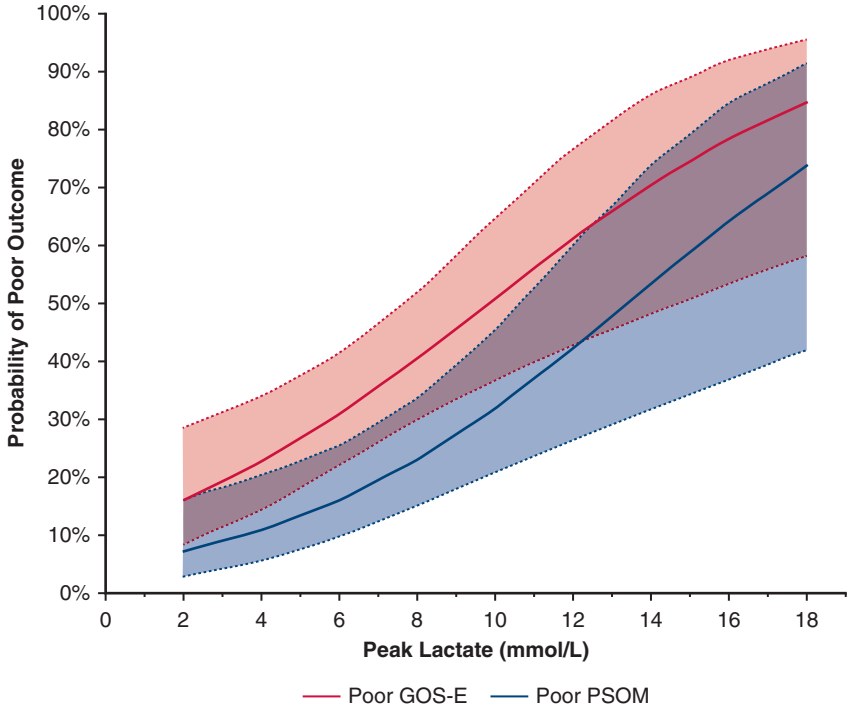
injury and ND outcome are not well understood, in part because only a few studies include brain imaging before and after surgery and ND outcome.[5,8] WMI is the subtype studied in the greatest detail. Multiple studies have described an association with white matter lesions on MRI in infancy and cognitive impairment when assessed after 3 years of age.

ND disabilities are commonly present in patients with CHD before 3 years of age; thus, we aimed to explore brain injury subtypes predictive of poor early outcome. Although WMI appears to have a deleterious effect on long-term outcome, multiple studies have shown no significant impact on early ND outcome assessments.[5,8] Ischemic infarction is also common in this population, and yet, less is known about the impact of stroke on outcome. Similar to other studies, our patients had high rates of ischemic infarction before (11%) and after surgery (total 19%, new 14%).

TABLE 4. Univariate and multivariable Cox regression analysis of poor Glasgow Outcome Scale Extended outcome at latest assessment (median age 36 months)

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Diagnosis				
BV	Reference	.	Reference	.
SV (not HLHS)	1.79 (0.66-4.86)	.255	0.83 (0.23-2.93)	.769
HLHS	2.51 (1.14-5.49)	**.022***	0.32 (0.08-1.22)	.096
Perioperative stroke	1.42 (0.66-3.09)	.373		
DHCA				
No DHCA	Reference	.	Reference	.
1-39 min of DHCA	1.56 (0.58-4.19)	.375	2.11 (0.7-6.35)	.184
40+ min of DHCA	2.51 (1.09-5.81)	**.031***	2.62 (0.86-7.98)	.089
Peak lactate†	1.21 (1.11-1.31)	**<.001***	1.22 (1.1-1.34)	**<.001***
Duration of ventilation	1.01 (0.99-1.02)	.159		
Seizure‡	1.23 (0.59-2.56)	.587		
Thrombosis	1.04 (0.48-2.25)	.927		
Subsequent surgery	4.04 (1.41-11.6)	**.009***	4.32 (1.22-15.3)	**.023***

Variables with $P < .05$ in univariate analysis were included in the multivariable model. *HR*, Hazard ratio; *CI*, confidence interval; *BV*, biventricular; *SV*, single ventricle; *HLHS*, hypoplastic left heart syndrome; *DHCA*, deep hypothermic cardiac arrest. *Statistically significant. †Peak lactate after surgery and before postoperative MRI. ‡Clinical seizure confirmed on electroencephalogram.



Predicted Probability of Poor Neurological Outcome based on Peak Lactate

Peak Lactate (mmol/L)	Probability of poor GOSE	95% CI	Probability of poor PSOM	95% CI
2	16.2%	(8.5%, 28.6%)	7.3%	(3%, 16.5%)
4	22.7%	(14.4%, 34%)	10.9%	(5.6%, 20.3%)
6	30.9%	(22.1%, 41.4%)	16.1%	(9.7%, 25.6%)
8	40.5%	(30.1%, 51.9%)	23.1%	(15.1%, 33.6%)
10	50.9%	(36.9%, 64.8%)	31.9%	(20.9%, 45.5%)
12	61.2%	(42.8%, 76.9%)	42.3%	(26.4%, 60.1%)
14	70.6%	(48.3%, 86.1%)	53.5%	(31.7%, 74%)
16	78.5%	(53.4%, 92.1%)	64.3%	(36.9%, 84.7%)
18	84.8%	(58.3%, 95.7%)	73.8%	(42.1%, 91.6%)

FIGURE 3. Predicted probability of poor neurological outcome based on peak lactate. *GOS-E*, Glasgow Outcome Scale Extended; *PSOM*, Pediatric Stroke Outcome Measure; *CI*, confidence interval.

In our cohort, all 8 patients with stroke on preoperative MRI and no progression of stroke on postoperative MRI and ND outcome assessments had good ND outcome, including 1 with a stroke characterized as severe (Figure 1). In contrast, 10 of 16 patients (63%) with new or expanded stroke on the postoperative MRI had adverse ND outcomes. These patients accounted for more than half (7/13, 54%) of all the patients with adverse PSOM scores on *early* assessment. New or expanded stroke was a significant predictor for adverse outcome at early ND assessments (Table 3).

Although new or expanded stroke was not a predictor of outcome for the group at large at the last ND assessment, deficits were persistent. For all 7 children with new or expanded stroke by postoperative MRI and poor *early* ND outcome, outcome assessment remained poor on the latest assessment (mean interval of repeat testing was 4 years).

The incidence of stroke in our cohort was higher than in some other studies with similar patient populations (Table E5). Timing of postoperative MRI is a consideration when comparing studies. For example, in our cohort, postoperative MRI was performed after patients were stabilized, whereas in other studies postoperative MRI was performed closer to the operative date, and thus medically unstable patients were excluded. An example of this can be seen in the study by Beca and colleagues,[5] where 9 patients were

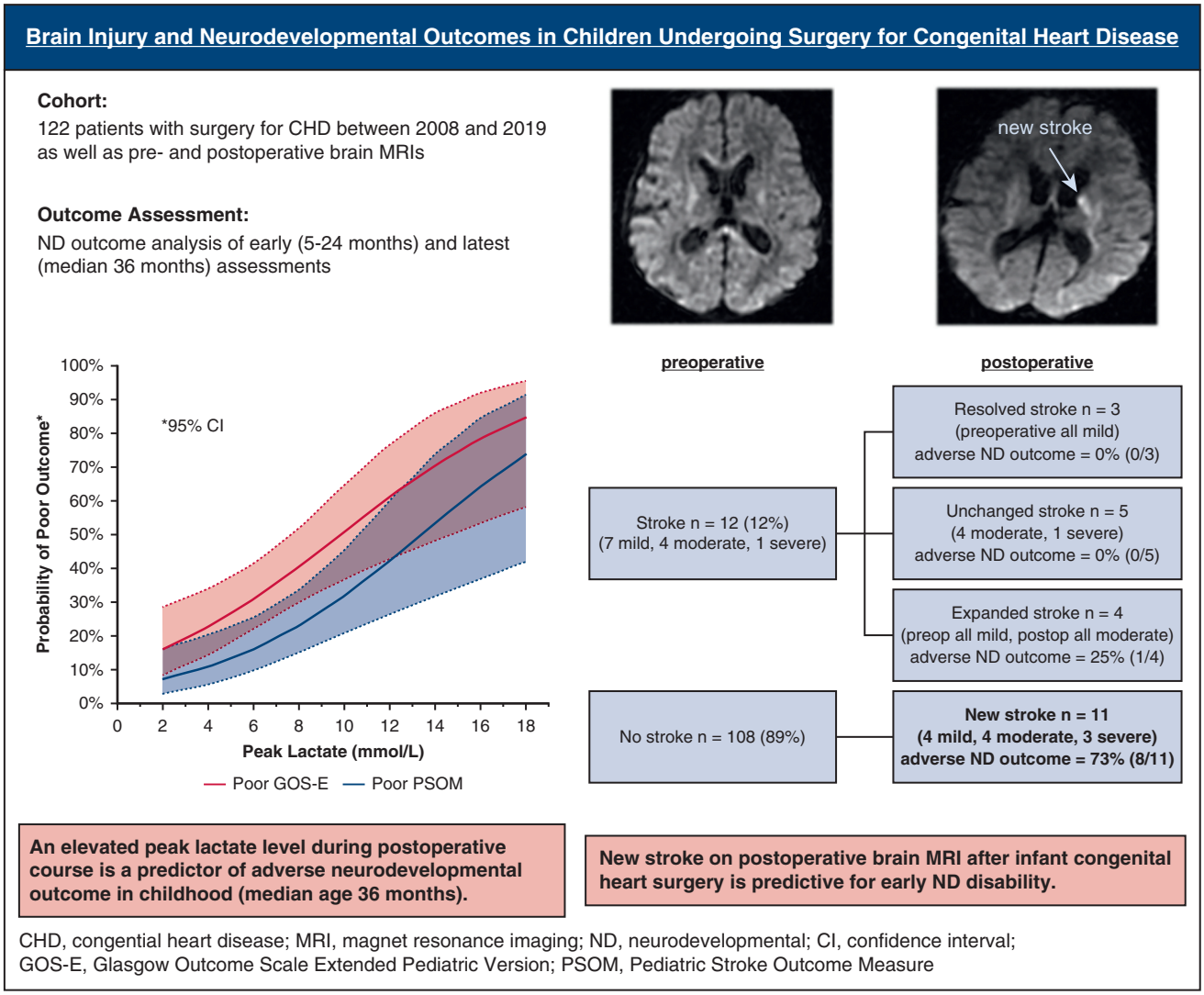


FIGURE 4. Graphical Abstract: new ischemic stroke on postoperative MRI increases the risk for early ND disability and lactate peaks during the postoperative course is a predictor for poor ND outcome in childhood. *CHD*, Congenital heart disease; *ND*, neurodevelopmental; *CI*, confidence interval; *GOS-E*, Glasgow Outcome Scale Extended; *PSOM*, Pediatric Stroke Outcome Measure.

excluded due to ongoing extracorporeal membrane oxygenation support. We chose to use the PSOM and GOS-E scoring systems because of their primary focus on assessing the quality of life and their ability to capture impairments in specific subcategories among children with brain injuries. Notably, their reliability is high even when applied retrospectively. We have previously used these scoring systems in 2 separate studies and were able to demonstrate their consistency and reliability.[4,11]

The prevalence of a poor outcome in our cohort increased more broadly when considering the latest ND assessment. Adverse GOS-E/PSOM scores were noted in 22%/14% of *early* outcomes, whereas 35%/21% of children had impaired ND outcome at the latest assessment. Sixty-seven children had 2 ND assessments at least 12 months apart. In 31 children (46%), both PSOM and GOS-E were worse at the second assessment compared with the first. In comparison, only 9%/16% had better PSOM/GOS-E scores at the second assessment. Likewise, Peyvandi and colleagues[8] demonstrated a decline in ND assessment in children with CHD and perioperative brain injury when measures were obtained at 12 and 30 months of age.

The reasoning for this perceived deterioration is inherent to children's development; the testing and skills evolve with age. Early assessments are heavily weighted toward motor skills, whereas later assessments have a greater emphasis on cognition and language. Of the 4 subcategories of PSOM (motor, cognitive, language comprehension, language production), the highest percentage of limitations in the *early* assessments was in the motor subcategory. At the *latest* ND assessment, the rate of impairments in the motor subcategory remained the same (25%), whereas the prevalence of cognitive impairment increased from 7% to 32%.

Brain injury was not the only factor predictive of poor outcome. Several other clinical variables were also found to correlated with outcome. Cardiac arrest was a predictor of poor *early* outcome in our multivariable model (Table 3), whereas subsequent surgery and postoperative peak lactate were associated with poor outcome when the latest assessment was studied (Table 4).

Lactic acidosis is a clinical measure of metabolic failure and a surrogate marker for hypoxia and hypoperfusion. Lactate is an appealing clinical biomarker because of its common availability, rapid turnaround time, and broad application. Also, unlike MRI, lactate levels can be obtained frequently and in patients who are clinically unstable. There are numerous articles that describe goal-directed therapies based on elevated lactate levels, especially in adult cardiac surgery. In pediatric cardiac surgery, investigations of its association with morbidity and mortality have produced inconsistent results. Hatherill and colleagues[13] found no correlation between peak lactate and mortality, whereas Siegel and colleagues[14] found the opposite. Charpie and colleagues[15] described a correlation between peak lactate and early outcome after pediatric cardiac surgery. One possible explanation for these incongruent results might be that most studies relied only on a single lactate measurement. With a focus on the impact of lactate on ND outcome, there is only 1 study investigating the predictive value of cerebral tissue oxygenation index on ND outcome that includes lactate as additional marker. Lactate values were gathered prospectively at different time up to 24 hours postoperatively.[16] Adding 24-hour lactate values to the cerebral tissue oxygenation index model improved predictive accuracy on ND outcome at assessments up to 21 months of age. In addition, Beca and colleagues[5] showed that higher serum lactate 6 hours after surgery was a significant independent predictor for new WMI in postoperative MRI. In our cohort, we captured all lactate values from an arterial source during the postoperative ICU course. For most patients, lactate was mildly elevated immediately after surgery and declined within hours. In patients with complicated postoperative course, a second lactate peak could be observed. We found elevated lactate (peak value) during the postoperative course was a strong predictor for adverse *latest* ND outcome in our multivariable model. A probability model of poor ND outcome based on lactate values is presented in Figure 3. The higher the peak lactate value, the greater the expected risk of poor ND outcomes.

Although the association needs to be explored further, it seems reasonable to consider modifying therapies in real time when lactate values are climbing to reduce exposure to hypoperfusion and hypoxia. Furthermore, identifying lactate elevations early may have downstream effects on clinical variables consistently identified to impact ND outcome, such as length of ICU stay and duration of mechanical ventilation.[4,11]

Study Limitations

Our cohort includes a mixture of patients with different CHD subtypes. Because of the small sample sizes, it was not feasible in this study to look within each subtype to assess patterns of vulnerability regarding poor ND outcomes during follow-up. Studies with larger sample sizes in each subcategory of CHD are required to allow for adequate analysis of potential clinical biomarkers for poor ND outcome.

Perhaps the greatest limitation of this study is its retrospective design. Only patients retrospectively identified to have both preoperative and postoperative MRI scans were included, and patients who were not included because they did not receive brain MRI might have different clinical characteristics. ND follow-up was absent in 17% of our cohort. We used Cox regression analysis to address the varying ages at follow-up in the statistical analysis, although a prospective longitudinal study design with predetermined assessment intervals would allow for a more precise temporal analysis.

CONCLUSIONS

New or expanded ischemic stroke on postoperative MRI is predictive of poor early outcome in patients receiving CHD surgery in infancy. Stroke deficits were primarily defined by motor impairments and did not improve on repeat clinical assessments. High peak lactate levels in the postoperative period are a predictor of adverse ND outcome in childhood. In children with increasing lactate values, therapeutic options should be discussed for improving perfusion and oxygenation. Further studies are needed to explore the potential utility of lactate as a predictive biomarker for poor ND outcome and opportunities for intervention.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: brain injury, cardiac surgery, congenital heart disease, magnetic resonance imaging, neurodevelopmental outcome, stroke

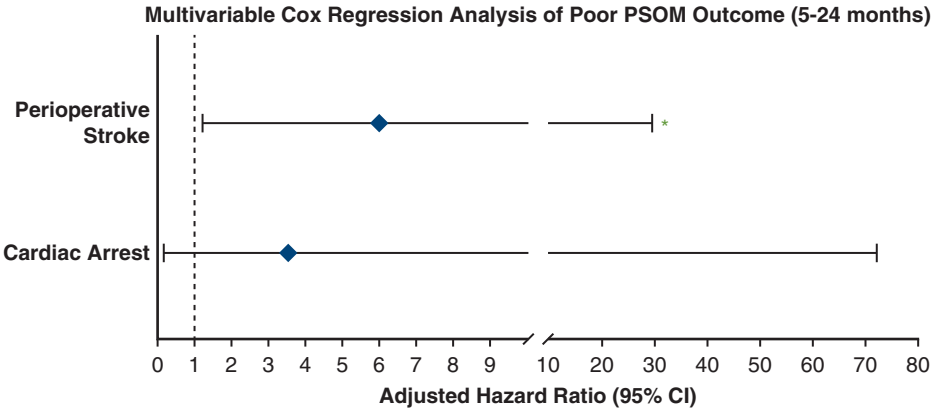

FIGURE E1. Significant risk factors in multivariable analysis for PSOM at 5 to 24 months of age.

TABLE E1. Brain injury score calculation

Subcategory	Outcome significance multiplier	Score	Definition	Size (total mm, largest diameter, add all lesions)
WMI	3	0	none	0
		1	mild: ≤3, <2 mm	1-5 mm
		2	moderate: >3, >2 mm	6-15 mm
		3	severe: 10% white matter	>15 mm
Infarction (stroke-ischemic)	3	0	none	0
		1	<1/3 of vascular territory of ACA, MCA, or PCA in 1 hemisphere	1 to 5 mm
		2	1/3-2/3 vascular territory	6 to 15 mm
		3	>2/3 vascular territory	>15 mm
IP hemorrhage (stroke-hemorrhagic)	3	0		0
		1		1-5 mm
		2		6-15 mm
		3		>15 mm
Punctate lesions	2	0	none	0
		1	1-3 lesions	all ≤2 mm
		2	4-6 lesions	all ≤2 mm
		3	>6 lesions	all ≤2 mm
↑Lactate on MRS	2	0	none to lactate/creatinine ratio of 0.15	NA
		1	lactate/creatinine ratio of 0.16-0.5	
		2	lactate/creatinine 0.5-1	
		3	lactate/creatinine >1	
IVH	1	0	0	
		1	subependymal/germinal matrix hemorrhage /choroid plexus hemorrhage	1-5 mm
		2	IVH isolated	6-15 mm
		3	IVH with ventricular dilation	>15 mm
SDH	1	0	Subdural blood above tentorium; minimal SDH below tentorium frequently 2° birth process and not considered abnormal	
		1	Minimal just above tentorium	
		2	Spread to interhemispheric fissure in occipital area	
		3	Larger hemorrhage; interhemispheric to parietal or frontal area; any mass effect	
DVST	1	0	Flow voids in dural venous sinuses, confirmed by magnetic resonance venogram	0
		1		Right or left transverse alone
		2		Bilateral right and left
		3		Straight or sagittal sinus
All categories	Total score 0	None	Multiply score in each of 9 categories by outcome significance multiplier	
	Total score 1-5	Mild	Sum all 9 subscores for total score	
	Total score 6-10	Moderate	Range of scores: 0-51	
	Total score >10	Severe		

Modified from Andropoulos and colleagues.[10] *WMI*, White matter injury; infarction, ischemic stroke including both thromboembolic and watershed distribution; *ACA*, anterior cerebral artery; *MCA*, middle cerebral artery; *PCA*, posterior cerebral artery; *IP*, intraparenchymal; *MRS*, magnetic resonance spectroscopy; *NA*, not available; *IVH*, intraventricular hemorrhage; *SDH*, subdural hemorrhage; *DVST*, dural sinovenous thrombosis.

TABLE E2. Cohort characteristics

Variable	Total
Diagnosis, n (%)	37 (30)
TGA	24 (20)
HLHS	15 (12)
DORV	6 (5)
Other SV	14 (11)
Coarctation of aorta	10 (8)
TOF	5 (4)
Truncus arteriosus	3 (2)
VSD	3 (2)
TAPVR	5 (4)
Procedure, n (%)	
Arterial switch operation	35 (29)
Norwood	27 (22)
Coarctation of aorta repair	14 (12)
BT shunt	13 (11)
ToF repair	10 (8)
Truncus repair	5 (4)
VSD repair	3 (3)
DORV repair	3 (3)
TAPVR repair	3 (3)
Other	9 (7)
Lowest spO2 preoperative, median % (IQR)	73 (55-87)
Highest pCO2 preoperative, median mm Hg (IQR)	48 (43-58)
iNO used preoperative, n (%)	10 (8%)
Balloon atrial septostomy, n (%)	33 (27)
CPB duration, median min (IQR)	150 (122-180)
Clamp aorta, n (%)	93 (76)
Clamp duration time, median min (IQR)	79 (51-111)
DHCA duration, median min (IQR)	33 (9-49)
Lowest temp during surgery in °C, median (IQR)	15 (14-24)
Cardiac index	0.49 (0.46-0.53)
Open chest after surgery, n (%)	72 (59%)
Open chest duration after surgery, median d (IQR)	3 (3-4)
Highest pCO2 immediately postoperative, median (IQR)	75 (64-95)
Highest pCO2 postoperative later, median (IQR)	65 (59-74)
Antiepileptic drug given, n (%)	24 (20)
spO2 at discharge, median % (IQR)	95 (83-99)
Need for subsequent cardiac catheterizations, n (%)	47 (39)
Subsequent surgery with CPB, n (%)	55 (45)
Subsequent surgery not palliation, n (%)	29 (24)

TGA, Transposition of the great arteries; *HLHS*, hypoplastic left heart syndrome; *DORV*, double outlet right ventricle; *SV*, single ventricle; *ToF*, tetralogy of Fallot; *VSD*, ventricular septal defect; *BT*, Blalock-Taussig; *TAPVR*, total anomalous pulmonary venous return; *IQR*, interquartile range; *iNO*, inhaled nitric oxide; *CPB*, cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest.

TABLE E3. Brain injury subtypes

	Brain injury subtype, n (%)									
					Total					
	Performed and injury		Unable to perform		Performed and injury		Unable to perform		New injury post vs pre	
WMI	23	18.85%	1	0.82%	39	31.97%	3	2.46%	25	20.49%
Infarction	14	11.48%	1	0.82%	23	18.85%	0	0.00%	17	13.93%
IPH	6	4.92%	0	0.00%	9	7.38%	0	0.00%	4	3.28%
SDH	24	19.67%	1	0.82%	23	18.85%	0	0.00%	14	11.48%
IVH	14	11.48%	0	0.00%	19	15.57%	0	0.00%	10	8.20%

WMI, White matter injury; *IPH*, intraparenchymal hemorrhage; *SDH*, subdural hemorrhage; *IVH*, intraventricular hemorrhage.

TABLE E4. Univariate and multivariable Cox regression analysis of poor Pediatric Stroke Outcome Measure outcome at early assessment (age 5-24 months)

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Perioperative stroke	5.57 (1.86-16.6)	**.002***	6 (1.22-29.5)	**.028***
Moderate/severe brain injury	4.41 (1.35-14.4)	**.014***	Omitted due to collinearity	
Single ventricle	7.9 (1.75-35.7)	**.007***	2.6 (0.45-14.4)	.289
Cardiac arrest	7.43 (2.07-26.6)	**.002***	3.54 (0.17-72.1)	.411
Thrombosis	2.98 (0.97-9.16)	.057		
Peak lactate†	1.28 (1.12-1.47)	<**.001***	1.01 (0.82-1.23)	.95
Seizure	4.82 (1.61-14.5)	**.005***	Omitted due to collinearity	
Duration of ventilation	1.03 (1.02-1.04)	<**.001***	1 (0.98-1.03)	.582
ICU length of stay	1.02 (1.01-1.03)	<**.001***	1.01 (0.99-1.04)	.228
DHCA				
No DHCA	Reference	.	.	
DHCA	0.81 (0.14-4.59)	.816		
≥40 min of DHCA	2.24 (0.65-7.69)	.231		

Variables with $P < .05$ in univariate analysis were included in the multivariable model. *HR*, Hazard ratio; *CI*, confidence interval; *ICU*, intensive care unit; *DHCA*, deep hypothermic cardiac arrest. *Statistically significant. †Peak lactate after surgery and before postoperative MRI.

TABLE E5. Univariate and multivariable Cox regression analysis of poor Pediatric Stroke Outcome Measure outcome at latest assessment (median age 36 months)

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Diagnosis				
BV	Reference	.	Reference	.
SV (not HLHS)	3.32 (0.91-12)	.067	1.5 (0.3-7.5)	.622
HLHS	4.07 (1.38-11.9)	**.01***	0.91 (0.22-3.77)	.892
Perioperative stroke	2.09 (0.83-5.26)	.119		
DHCA				
No DHCA	Reference	.	.	.
1-39 min of DHCA	1.24 (0.37-4.2)	.727		
40+ min of DHCA	2.1 (0.74-5.94)	.162		
Peak lactate†	1.21 (1.1-1.34)	**<.001***	1.17 (1.02-1.34)	**.024***
Duration of ventilation	1.01 (1.01-1.03)	**.021***	1 (0.99-1.02)	.646
Seizure	2.15 (0.88-5.23)	.092		
Thrombosis	2.26 (0.93-5.46)	.071		
Subsequent surgery	5.81 (1.34-25.2)	**.019***	3.59 (0.58-22.2)	.17

Variables with $P < .05$ in univariate analysis were included in the multivariable model. *HR*, Hazard ratio; *CI*, confidence interval; *BV*, biventricular; *SV*, single ventricle; *HLHS*, hypoplastic left heart syndrome; *DHCA*, deep hypothermic cardiac arrest. *Statistically significant. †Peak lactate after surgery and before postoperative MRI.

TABLE E6. Literature investigating pre- and postoperative brain injuries

First author	Year	Institution	n	Age surgery	Main diagnoses	CPB	DHCA	MRI												ND assessments				Key findings
								Preoperative					Postoperative											
								n	Any injury		WMI	Stroke	Age (d)	n	Any		WMI	Stroke	Comment	Scoring	Age	Percentage	Score	
Mahle	2002	CHOP	24	<1 mo	13 SV, 8 HLHS		88%	79%	7	37%	16%	8%	5-12	88%	14	67%	42%	19%	Postoperative new injuries; third scan at 3-6 mo	NA				• Established high frequency of asymptomatic ischemic lesions on preoperative and postoperative brain MRI in neonates with surgery for CHD. • At third scan resolution of early lesions in 8 and mild cerebral atrophy in 2.
McQuillen	2007	UCSF	62		18 SV	91%	23%	100%		39%	18%	21%		85%	19	35%	26%	9%		NA				• BAS increased the risk for preoperative brain injury • Low mean BP on POD 1 increases the risk for postoperative WMI. • Risk for postoperative brain injury was increased in (1) SV with a Norwood and (2) CBP with RCP.
Chen	2009	CHOP	122	<6 mo		100%	62%						3-14					10%		NA				Included stroke risk with lower birth weight, preoperative intubation, lower intraoperative HCT, higher SBP on CICU admission.
Andropoulos	2010	TCH	68	<30 d	36 SV, 35 HLHS	100%	50%	99%	38	57%	16%	18%	7-10	82%	43	77%	15%	22%	6 patients had resolution of mild WMI between the scans; third scan at 3-6 mo	NA				• Risk factors for preoperative injury was low brain maturity score, for postoperative WMI: preoperative injury, low brain maturation and SV; • at third scan 27% incidence of new minor lesions, but 58% of previous lesions partially or completely resolved.
Dimitro poulos	2013	UCSF/ UCB	120	<3 mo	71 TGA, 36 SV	?	?	100%	49	41%	21%	19%	median 10	87%	75	72%	38%	31%	23 (19%) stroke preoperative, 10 (10%) new postoperative	NA				• Higher SNAP-PE, lower preoperative O2 saturation, lowest postoperative BP mean, and BAS (in TGA) predicted higher preoperative BIS. • New postoperative BIS was assoc. with lower postoperative systolic and mean BP.
Beca	2013	SCH/ RCH	153	<8 wk	62 SV, 34 Nor-wood	84%	39%	96%	38	26%	20%	5%	7	88%	59	44%	42%	4%	Postoperative new injuries; third scan at 3 mo	Bayley	2 y	?	cognitive 94 ± 15, language 94 ± 16, motor 97 ± 12	• New postoperative WMI predicted by longer duration of CPB, 6 h postoperative lactate, brain maturity and preoperative WMI. • Brain immaturity, but not brain injury predicted impaired neurodevelopment at 2 y. • MRI at 3 mo: WMI resolved at 3 mo in 75%, no new WMI, stroke, or hemorrhage.

(Continued)

TABLE E6. Continued

First author	Year	Institution	n	Age surgery	Main diagnoses	CPB	DHCA	MRI												ND assessments				Key findings
								Preoperative					Postoperative											
								n	Any injury		WMI	Stroke	Age (d)	n	Any		WMI	Stroke	Comment	Scoring	Age	Percentage	Score	
Andropoulos	2014	TCH	59	<30 d	28 SV, 20 TGA	100%		66%	18	46%	31%	23%	0-7	66%	28	72%	36%	26%	Postoperative new injuries	Bayley-III	1 y	71%	cognitive 102.1 ± 13.3, language 87.8 ± 12.5, motor 89.6 ± 14.1; initially 93 enrolled	New postoperative MRI injury, higher VAA exposure and increased ICU LOS each predicted lower cognitive scores
Classens	2018	UMCU	34	<4 mo	all arch obstruction	100%	51%	100%	NA	NA	47%	NA	mean 10	NA	NA	NA	79%	NA		Bayley/ Wechsler	2 y/6 y	86%/81%	initially 37 patients enrolled	• Moderate-severe WMI was assoc. with lower cognitive scores at 2 y and full-scale IQ at 6 y. • Grey matter, focal infarctions did not impact outcome (n = 9, 26%) - pre vs post not distinguished in the article.
Peyvandi	2018	UCSF/ UBC	104	?	84 TGA, 20 SV	100%	?	100%			Did not differentiate between pre and post in the article		?	100%	56	54%	38%	26%	Total injury rates, did not differentiate between pre and post in the article	Bayley-III	12 mo/30 mo	67%/46%	initially 165 patients enrolled	• At 12 mo, only clinical variables associated with outcome. • At 30 mo, subjects with moderate-severe WMI had significantly lower psychomotor development index score. • Stroke (total pre- and postoperative) was not associated with outcome at 30 mo
Kuhn	2020	CNH	53	<1 mo	29 TGA, 24 HLHS	100%	94%	100%	29	55%	22%	11%	mean 25	100%	41	77%	35%	20%		PSOM and GOS-E	10 mo	85%	82% of the HLHS patients and 17% of the d-TGA patients had adverse outcome	• BAS not associated with included preoperative injury or stroke. • HLHS included risk for postoperative stroke in moderate-severe range. • ICU duration included risk for postoperative injury in moderative-severe range
Kosiorek	2022	CNH	42	<10 wk	13 SV	57%	0%	100%	21	50%	19%	17%	mean 33	100%	28	67%	36%	14%		PSOM and GOS-E	28 mo	69%	45% had adverse GOS-E outcome	Adverse outcome associated with longer ICU stay, mechanical ventilation, MBT shunt procedure and postoperative seizures. Total BIS did not predict outcome. Post infarction or IPH was associated with worse outcome

(Continued)

TABLE E6. Continued

First author	Year	Institution	n	Age surgery	Main diagnoses	CPB	DHCA	MRI											ND assessments				Key findings
								Preoperative					Postoperative										
								n	Any injury	WMI	Stroke	Age (d)	n	Any	WMI	Stroke	Comment	Scoring	Age	Percentage	Score	
Reitz	2023	CNH	122	<90 d	37 TGA, 42 SV	84%	62%	100%	64 52%	23%	14%	median 25	100%	90 74%	32%	19%		PSOM and GOS-E	8 mo/ 36 mo	78%/ 83%	adverse outcome: PSOM 7% and GOS-E 21%/PSOM 21% GOS-E 35%	• New or expanded ischemic stroke on postoperative brain MRI is predictive of poor early outcome, mainly defined by poor motor outcomes, did not improve on repeat assessment. • Elevated lactate in the postoperative period is a predictor of adverse ND outcome in childhood.

CPB, Cardiopulmonary bypass; *DHCA*, deep hypothermic cardiac arres; *MRI*, magnetic resonance imagingt; *WMI*, white matter injury; *ND*, neurodevelopmental; *CHOP*, Children's Hospital of Philadelphia; *HLHS*, hypoplastic left heart syndrome; *NA*, not available; *CHD*, congenital heart disease; *UCSF*, University of California, San Francisco Medical Center; *SV*, single ventricle; *BAS*, balloon atrial septostomy; *BP*, blood pressure; *POD*, postoperative day; *RCP*, regional cerebral perfusion; *HCT*, hematocrit; *SBP*, systolic blood pressure; *CICU*, cardiac intensive care unit; *TCH*, Texas Children's Hospital; *UBC*, University of British Columbia Hospital; *TGA*, transposition of the great arteries; *SNAP-PE*, Score for Neonatal Acute Physiology–Perinatal Extension; *BIS*, brain injury score; *SCH/RCH*, Starship Children's Hospital Auckland/Royal Children's Hospital Melbourne; *VAA*, Volatile Anesthetics; *ICU*, intensive care unit; *LOS*, lenghts of stay; *UMCU*, University Medical Center Utrecht; *IQ*, intelligent quotient; *CNH*, Children's National Hospital; *PSOM*, Pediatric Stroke Outcome Measure; *GOS-E*, Glasgow Outcome Scale Extended; *DTGA*, dextro-transposition of great arteries; *MBT*, modified Blalock-Taussig Shunt; *IPH*, intraparenchymal hemorrhage.