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Association between Z-score for birth weight and postoperative outcomes in neonates and infants with congenital heart disease

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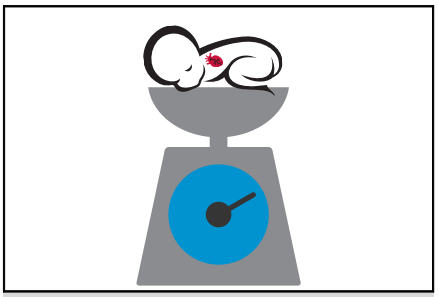
ABSTRACT

Objective: We hypothesized that infants with fetal growth restrictions have increased mortality and morbidity after congenital heart disease surgery.

Methods: The study included patients in The Society of Thoracic Surgeons Congenital Heart Surgery Database (2010-2016) who underwent cardiac surgery at a corrected gestational age of ≤44 weeks. Patients were classified as severely (birth weight Z-score −4 to −2), moderately (Z-score −2 to −1), and mildly growth restricted (Z-score −1.0 to −0.5) and compared with a reference population (Z-score 0-0.5). Multivariable logistic regression clustering on center was used to evaluate the association of birth weight Z-score with operative mortality and postoperative complications and its interaction with gestational age was assessed.

Results: In 25,244 patients, operative mortality was 8.6% and major complications occurred in 19.4%. Compared with the reference group, the adjusted odds ratio (AOR) of mortality was increased in infants with severe (AOR, 2.4; 95% confidence interval [CI], 2.0-3.0), moderate (AOR, 1.7; 95% CI, 1.4-2.0), and mild growth restriction (AOR, 1.4; 95% CI, 1.2-1.6). The AOR for major postoperative complications was increased for severe (AOR, 1.4; 95% CI, 1.2-1.7) and moderate growth restriction (AOR, 1.2; 95% CI, 1.1-1.4). There was significant interaction between birth weight Z-score and gestational age ($P = .007$).

Conclusions: Even birth weight Z-scores slightly below average are independent risk factors for mortality and morbidity in infants who undergo cardiac surgery. The strongest association between poor fetal growth and operative mortality exists in early-term infants. These novel findings might account for some of the previously unexplained variation in cardiac surgical outcomes. (J Thorac Cardiovasc Surg 2021;■:1-10)



Infant on scale.

CENTRAL MESSAGE

Even mild fetal growth restriction measured as birth weight Z-score slightly below average is an independent risk factor for mortality and morbidity in infants who undergo cardiac surgery.

PERSPECTIVE

The effect of poor fetal growth on outcomes in infants with congenital heart disease is not well understood. We show that even mild fetal growth restriction measured as birth weight Z-scores slightly below average are independent risk factors for mortality and morbidity after cardiac surgery. These findings might account for some of the previously unexplained variation in cardiac surgical outcomes.

See Commentary on page XXX.

CONG

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Abbreviations and Acronyms

AOR	= adjusted odds ratio
CHD	= congenital heart disease
CI	= confidence interval
CPB	= cardiopulmonary bypass
GA	= gestational age
PLOS	= postoperative hospital length of stay
STS	= The Society of Thoracic Surgeons
STS-CHSD	= The Society of Thoracic Surgeons Congenital Heart Surgery Database

Scanning this QR code will take you to the table of contents to access supplementary information.

CONG

Neonatal congenital heart disease (CHD) encompasses a variety of cardiac lesions with variable mortality risks.[1,2] Several risk adjustment tools were developed to account for case mix and compare outcomes within and across centers, including the Risk Adjustment in Congenital Heart Surgery[3] method, the Aristotle score,[4] and The Society of Thoracic Surgeons (STS)-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Score and associated categories (STAT Mortality Categories).[5] The Aristotle[4] and the Risk Adjustment in Congenital Heart Surgery[3] score accounted for a limited number of patient-level risk factors such as prematurity and noncardiac comorbidities. Most recently, the STS Congenital Heart Surgery Database (STS-CHSD) Mortality Risk Model was developed. It includes several nonprocedural variables, including age, prematurity, presence of chromosomal abnormalities, and certain preoperative conditions such as shock or mechanical ventilation.[6] Although our ability to predict mortality after congenital heart surgery has been refined by these models, substantial variation in mortality remains incompletely explained.[7]

The shortcomings of current models might be most relevant to newborns because of the strong effect of some patient-specific risk factors such as gestational age (GA) at birth.[8-10] Low birth weight as a predictor of outcome is problematic because it is highly associated with prematurity. Neonates born more preterm are more likely to have lower birth weights. However, the low birth weight population itself is very heterogeneous because it consists of preterm infants with weight appropriate for GA and term infants with birth weight small for GA. Expressing birth weight as a GA adjusted standard deviation (birth weight Z-score) addresses the collinearity between birth weight and GA and allows investigation of the effect of fetal growth on outcomes independent of GA. It is known that neonates with CHD are more likely to have poor fetal growth and consequently the incidence of small for GA in the CHD population is increased.[11,12] However, the effect of poor fetal growth on outcomes is less well studied. In this study, we use the STS-CHSD because it contains more detailed anatomic, procedural, and patient-level detail to evaluate the independent effect of birth weight Z-score on mortality and postoperative complications. A secondary aim was to understand how birth weight Z-score interacts with GA with regard to mortality. We hypothesized that low birth weight Z-score is associated with worse outcomes in preterm and term infants.

METHODS

Data Source

Deidentified data were obtained from the STS-CHSD through the Participant User File (PUF) Research Program after scientific review and approval by the PUF Research Program Committee. The STS-CHSD includes data from 127 institutions (95% in North America) where pediatric and congenital heart surgery is performed. Data from these centers are reported to the STS-CHSD using standardized data collection as part of a quality improvement initiative.[13] Perioperative, operative, and outcomes data are collected on all of the patients who undergo pediatric and congenital heart surgery at participating centers using standard definitions (STS-CHSD data specifications, available at https://www.sts.org/registries-research-center/sts-national-database/congenital-heart-surgery-database/data-collection). The PUF file includes data on the demographic, preoperative, intraoperative, and postoperative variables relevant to our study that were selected by the study team. Review by the Duke University institutional review board determined the study to be exempt from review in accordance with the Common Rule (45 CFR 46.102[f]). As an analysis of a deidentified data set provided by STS Research Center, patient consent was not required for this study. The project proposal and resulting report were approved by STS PUF Task Force.

Study Population and Primary Exposure Variables

Starting with the STS-CHSD PUF file of patients who underwent procedures between January 1, 2010, and December 31, 2016, the study population was determined as follows. We first identified all records of neonates and infants with corrected GA $\leq$ 44 weeks at the time of a cardiovascular surgical operation of the STS-CHSD operation type "cardiopulmonary bypass," "CPB," or operation type "no CPB cardiovascular," which included at least 1 procedure code that falls into one of the 5 STS-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Categories (STAT Mortality Categories). For 39,288 qualifying records, we assigned the primary procedure and the STAT Mortality Categories according to standard STS-CHSD definitions and rules.[5,14] STAT Mortality Category 1 corresponds to procedures associated with the lowest predicted mortality risk, and Category 5 corresponds to procedures with the highest predicted mortality risk. We excluded 8261 records with isolated surgical closure of patent ductus arteriosus and 581 records with isolated pacemaker placement as the only cardiovascular surgical procedure. In addition, 1910 records with missing key exposure data were excluded (Figure 1). Because the exported PUF data file does not contain a patient identification number, a given patient might have multiple records if they underwent more than 1 procedure during the period of eligibility. To identify multiple records corresponding to a single patient, the remaining

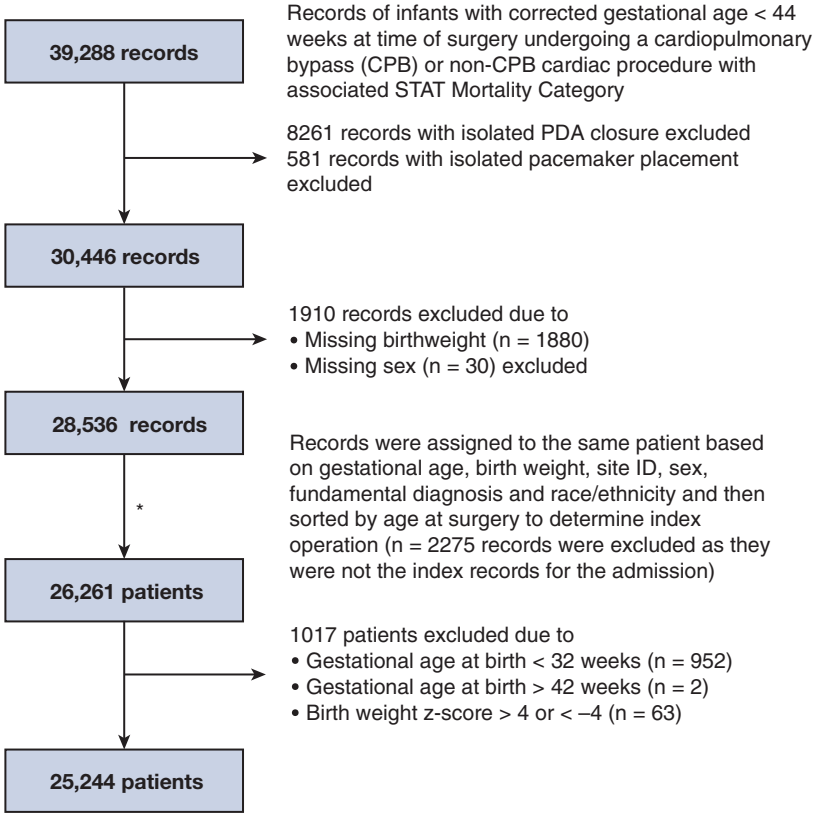

FIGURE 1. Flow chart; inclusion and exclusion criteria for selection of the study cohort. *CPB*, Cardiopulmonary bypass; *PDA*, persistent ductus arteriosus.

CONG

records (n = 28,536) were assessed using probabilistic matching on the basis of GA at birth, birth weight, site identification number, sex, fundamental diagnosis, and race/ethnicity. The 26,261 unique patients identified in this fashion were then sorted according to age at the time of the respective procedures. The index operation for each patient was defined according to STS criteria as the first operation of the given hospitalization that has an operation type of "CPB" or "no CPB cardiovascular" (https://www.sts.org/registries-research-center/sts-national-database/congenital-heart-surgery-database/data-collection).

Because of the relatively small number, patients with a GA at birth < 32 completed weeks or > 42 completed weeks were excluded from further analysis (n = 954; Figure 1). Our primary predictor was birth weight Z-score. It was assigned to each patient on the basis of weight at birth using the lambda for the skew, mu for the median, and sigma for the generalized coefficient of variation method with GA and sex-specific data provided by Fenton and colleagues.[15,16] For each week of GA at birth the distribution of birth weights for that specific week was taken into account and the Z-score for birth weight was calculated from this distribution. This method eliminates concern for collinearity between birth weight and GA in our modeling.

Patients with a resulting Z-score > 4 or < −4 were excluded from further analysis (n = 63; Figure 1). After these exclusions, the analytic cohort comprised 25,244 patients.

Outcomes

The primary outcome for this study was operative mortality of the index operation defined as (1) all deaths occurring during the hospitalization in which the index operation was performed, even if after 30 days, and (2) all deaths occurring after discharge from the hospital, but before the end of the 30th postoperative day.[17] Data on operative mortality was missing in 165 patients (0.7%); these subjects were excluded from the mortality analysis.

The secondary outcome analyzed was the occurrence of at least 1 major postoperative complication. We also secondarily evaluated postoperative hospital length of stay (PLOS) because this is likely to be an important outcome for families and stakeholders, although it is likely confounded by the occurrence of complications.

Major postoperative complications were defined according to STS-CHSD standard definitions as at least 1 of the following postoperative events occurring before hospital discharge: mechanical circulatory support, renal failure requiring dialysis, neurologic deficit persisting at discharge, stroke, unplanned cardiac reoperation or unanticipated postoperative interventional cardiovascular catheterization, and heart block requiring permanent pacemaker. Patients with missing data for operative mortality or major postoperative complications were excluded from the respective primary analyses. However, to assess for potential bias associated with missing outcome data, we performed sensitivity analyses: first, all subjects missing outcome data were assumed to have died or experienced major complications; second, all subjects with missing outcomes data were assumed to have survived or to have avoided any major complication.

Analysis

Summary statistics were reported as count (percentage) or median with 25th-75th percentiles, as appropriate. The Wilcoxon rank sum test was used to compare medians and the χ^2 test was used to compare proportions. To present summary statistics of the entire population, we divided the cohort into the 2 groups: growth restricted versus adequately grown at the time of birth. Growth restriction is commonly defined as a birth weight below the

10th percentile for GA and sex, corresponding to a birth weight Z-score below −1.28. For a more detailed analysis of the effect of birth weight Z-score on outcomes, this variable was grouped into 8 predefined categories (−4 to < −2, −2 to < −1, −1 to < −0.5, −0.5 to < 0, 0 to < 0.5, 0.5 to < 1, 1 to < 2, and 2 to < 4), corresponding to the following percentiles: Z-score −4 (0 percentile), Z-score −2 (second percentile), Z-score −1 (16th percentile), Z-score −0.5 (31st percentile), Z-score 0 (50th percentile), Z-score 0.5 (69th percentile), Z-score 1 (84th percentile), Z-score 3 (98th percentile), and Z-score 4 (100th percentile). For ease of reading, we further defined severe growth restriction as Z-score −4 to < −2, moderate growth restriction as Z-score −2 to < −1, and mild growth restriction as Z-score −1 to −0.5, acknowledging that the latter category could be considered to have low normal growth. We chose a birth weight Z-score of 0 to 0.5 as the reference category.

To model the relationship between mortality risk and birth weight Z-score, restricted cubic spline transformation was applied to the continuous Z-score variable, allowing the model to accommodate nonlinear relationships. The knots were chosen without knowledge of the clinical outcomes and on the basis of the distribution of the Z-score variable in the data set as recommended by Harrell.[18] The knots used in all of the models were Harrell −1.7, −0.4, and 1.0 corresponding to the 10th, 50th and 90th percentiles of the Z-score for birth weight distribution in the data set.

Because it is known that treatment and outcomes might vary across centers,[19] our analytic approach to evaluate the relationship between birth weight Z-score and outcomes accommodated for confounding according to center using conditional logistic regression and approaches clustering on the center level. Results were adjusted for previously identified factors associated with outcome in this population, including GA at birth, male sex, STAT Mortality Category of the primary procedure, weight and age at surgery, the presence of any STS-CHSD preoperative risk factor, the presence of any noncardiac anatomic or genetic abnormality/syndrome, and use of CPB for the index procedure. Multicollinearity between birth weight Z-score, GA at birth, and weight at surgery was checked by calculating correlation coefficients and variance inflation factors. Unadjusted and adjusted odds ratios (AORs) and 95% confidence intervals (CIs) are presented using models that account for clustering according to center.

For postoperative hospital PLOS, competing risk regression analysis was performed with in-hospital mortality as the competing risk. The model included indicator variables for centers and other covariates as noted previously. Competing risk regression calculates subhazard ratios for discharge with a comparison of each Z-score category with the reference of 0 to 1 (ie, a subhazard ratio < 1) indicates a longer hospital stay and a decreased likelihood of discharge over time. Because competing risk analyses are difficult to conceptualize, we also performed a traditional proportional hazard analysis in the subgroup of infants who survived until hospital discharge.

To investigate a potential interaction between GA and Z-score for birth weight an interaction terms was fitted for the operative mortality model and tested for statistical significance. All analyses were performed using Stata version 16.0 (StataCorp LP).

RESULTS

Study Population

Of the 25,244 study subjects, growth restriction, using the traditional definition of birth weight < the 10th percentile (corresponding Z-score < −1.28) was present in 17.9% of all infants (4524/25,244). Growth restricted infants were more likely to have STS-CHSD preoperative risk factors ($P < .001$), 1 or more noncardiac anatomic or chromosomal abnormalities ($P < .001$), be older at the time of surgery ($P < .001$), and were less likely to undergo surgery on CPB ($P < .001$; Table 1). A higher proportion of growth restricted infants and infants with low Z-scores received a pulmonary artery band or hybrid procedure (Table E1). Multicollinearity between birth weight Z-score, GA, and weight at surgery was low with correlation indices < 0.3 and variance inflation factors < 1.2 for all 3 variables.

Operative Mortality

The overall operative mortality was 8.6%. The highest operative mortality occurred in the group of infants with severe growth restriction (birth weight Z-score between −4 and < −2; mortality, 14.9%; 95% CI, 13.2%-16.6%) compared with the reference group with a birth weight Z-score between 0 and 0.5 (mortality, 6.7%; 95% CI, 6.0%-7.5%). In multivariable analysis, the AOR of mortality was increased 2.43-fold (95% CI, 1.96-3.02) in infants with severe growth restriction compared with the reference group. Interestingly, infants who were smaller than average though not technically growth restricted (birth weight Z-score between −1 and < −0.5, corresponding to 16%-31% percentile) also had higher operative mortality than the reference group (AOR, 1.38; 95% CI, 1.17-1.64). Birth weight Z-scores above 0.5 were not associated with an increased risk of operative mortality (Table 2). Table E2 contains the unadjusted and adjusted associations of other covariates and operative mortality. Operative mortality was missing in 165 patients (0.7%), Table E3 shows the results of the sensitivity analysis. To assess Z-score in a more granular manner, Figure 2, *A* contains the AOR plot with 95% CIs for operative mortality using birth weight Z-score as a restricted cubic spline with all other model covariates set to their mean value. The graph shows that the AOR for operative mortality continues to decline as the birth weight Z-score increases; this finding is statistically significant (95% CI not crossing 1 in the illustration) up to a Z-score of 0.5.

Major Postoperative Complications and PLOS

Overall, major postoperative complications occurred in 19.4%. The rate of major postoperative complications in infants with severe growth restriction was 23.4% (95% CI, 21.2%-25.8%), and 18.3% (95% CI, 17.1%-19.6%) the reference group. The AOR for major postoperative complications was increased for infants with severe (AOR, 1.44; 95% CI, 1.22-1.71) and moderate growth restriction (AOR, 1.22; 95% CI, 1.08-1.38), but not in mildly growth restricted infants (AOR, 1.06; 95% CI, 0.94-1.19) compared with the reference group (Table 2). Major postoperative complications were missing in 1614 patients (6.4%); Table E3 shows the results of the sensitivity analysis. The AOR curve for major postoperative complications using Z-score as a restricted cubic spline (Figure 2, *B*) has a parabolic shape, although a statistically significant association is only present for birth weight Z-scores less than −0.5. The results for PLOS are shown in Table E4.

TABLE 1. Preoperative characteristics and operative variables

Variable	Not growth restricted (n = 20,720)*	Growth restricted (n = 4524)*	*P* value	Missing data, %
Preoperative Characteristics				
Male sex	12,235 (59.1)	2635 (58.2)	.32	0
Race			**<.001**	2.0
White	14,183 (68.5)	2774 (61.3)		
African American	2770 (12.9)	803 (17.8)		
Asian	664 (3.2)	226 (5.0)		
Native American	199 (1.0)	42 (0.9)		
Pacific Islander	135 (0.7)	37 (0.8)		
Other	2471 (11.9)	548 (12.1)		
Hispanic or Latino ethnicity	4073 (19.7)	868 (19.2)	.36	4.8
Gestational age at birth, wk	39 (37-39)	38 (37-39)	**.004**	0
Any STS-CHSD preoperative risk factor	9402 (45.4)	2197 (48.6)	**<.001**	1.5
Any noncardiac anatomic or chromosomal abnormality	3691 (17.8)	1199 (26.5)	**<.001**	0.3
Operative variables				
STAT Mortality Category of the index operation			**<.001**	0
1	1105 (5.3)	239 (5.3)		
2	2613 (12.6)	653 (14.4)		
3	2790 (13.4)	426 (9.4)		
4	10,204 (49.3)	2451 (54.2)		
5	4008 (19.4)	755 (16.7)		
Cardiopulmonary bypass used	14,825 (71.6)	3015 (66.6)	**<.001**	0
Cardiopulmonary bypass time	134 (92-177)	127 (87-173)	**<.001**	1.1
Aortic cross clamp time, min	63 (37-94)	58 (32-89)	**<.001**	1.3
Delayed sternal closure	6357 (30.7)	1408 (31.1)	.53	6.4
Growth variables				
Weight at birth, g	3200 (2900-3540)	2455 (2100-2700)	**<.001**	0
Weight at surgery, g	3300 (2990-3640)	2600 (2300-2900)	**<.001**	0.1
Weight at surgery < 2500 g	1323 (6.4)	1681 (37.2)	**<.001**	0.1
Age at surgery, d	7 (5-13)	8 (5-17)	**<.001**	0
Outcomes				
Operative mortality	1597 (7.8)	570 (12.7)	**<.001**	0.7
Any major complications	3663 (18.9)	924 (21.8)	**<.001**	6.4
Mechanical circulatory support	1347 (7.0)	378 (8.9)	**<.001**	
Renal failure requiring dialysis	592 (3.1)	164 (3.9)	**.006**	
Neurologic deficit persisting at discharge	189 (1.0)	58 (1.4)	**.023**	
Stroke	297 (1.5)	77 (1.8)	.18	
Unplanned cardiac reoperation or unanticipated postoperative interventional cardiovascular catheterization	2501 (12.9)	655 (15.4)	**<.001**	
Heart block requiring permanent pacemaker	207 (1.1)	37 (0.9)	.25	

Data are reported as median (25th, 75th percentiles) or n (%). Point estimates shown in bold are statistically significant with a *P* value < .05. χ^2 Test used for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. *STS-CHSD*, The Society of Thoracic Surgeons Congenital Heart Surgery Database. *Birth weight less than the 10th percentile (corresponding to Z-score < −1.28) for gestational age and sex.

Effect of GA at Birth

There was a statistically significant interaction between birth weight Z-score and GA at birth for operative mortality ($P = .007$), indicating that the strength of the association between a given birth weight Z-score and mortality differs on the basis of GA at birth. Thus, we investigated the association between birth weight Z-score and operative mortality separately for preterm (GA < 37 weeks), early term (GA

TABLE 2. Unadjusted and adjusted analysis for associations between Z-score for birth weight and operative mortality and major postoperative complications

Z-score for birth weight	Patients, n	Observed rate (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Operative mortality				
−4 to < −2	1398	14.9 (13.1-16.8)	**2.41 (2.00-2.94)**	**2.43 (1.96-3.02)**
−2 to < −1	5273	10.7 (9.9-11.6)	**1.69 (1.45-1.97)**	**1.67 (1.41-1.97)**
−1 to < −0.5	4622	9.4 (8.6-10.3)	**1.46 (1.24-1.71)**	**1.38 (1.17-1.64)**
−0.5 to < 0	4913	7.8 (7.1-8.6)	**1.19 (1.01-1.40)**	1.17 (0.98-1.39)
0 to < 0.5	3899	6.7 (6.0-7.5)	Reference	Reference
0.5 to < 1	2540	5.9 (5.1-6.9)	0.90 (0.73-1.11)	0.94 (0.75-1.17)
1 to < 2	1984	6.4 (5.4-7.6)	0.97 (0.78-1.21)	1.00 (0.79-1.25)
2 to < 4	450	8.2 (6.0-11.2)	1.24 (0.86-1.78)	1.04 (0.70-1.53)
Major postoperative complications				
−4 to < −2	1335	23.4 (21.2-25.8)	**1.42 (1.21-1.65)**	**1.44 (1.22-1.71)**
−2 to < −1	4962	20.9 (19.8-22.1)	**1.22 (1.10-1.37)**	**1.22 (1.08-1.38)**
−1 to < −0.5	4356	19.2 (18.0-20.4)	1.09 (0.97-1.22)	1.06 (0.94-1.19)
−0.5 to < 0	4625	18.7 (17.6-19.9)	1.05 (0.94-1.18)	1.04 (0.92-1.17)
0 to < 0.5	3663	18.3 (17.1-19.6)	Reference	Reference
0.5 to < 1	2392	18.3 (16.8-19.9)	1.02 (0.89-1.17)	1.07 (0.92-1.23)
1 to < 2	1882	18.2 (16.5-20.0)	1.01 (0.87-1.17)	1.07 (0.92-1.25)
2 to < 4	415	20.7 (17.1-24.9)	1.20 (0.93-1.56)	1.13 (0.86-1.50)

Operative mortality of the index operation defined as: (1) all deaths occurring during the hospitalization in which the index operation was performed, even if after 30 days; and (2) all deaths occurring after discharge from the hospital, but before the end of the 30th postoperative day. Major postoperative complications defined as the occurrence of at least 1 of the following: postoperative mechanical circulatory support, renal failure requiring dialysis, neurologic deficit persisting at discharge, stroke, unplanned cardiac reoperation or interventional cardiovascular catheterization during the postoperative time period, and heart block requiring permanent pacemaker. Unadjusted values were estimated using models that included a center variable but did not include other patient-level characteristics. Adjusted associations included a center variable and were controlled for sex, race, gestational age, STAT Mortality Category of the index operation, presence of any STS-CHSD preoperative risk factors, genetic or extracardiac anatomic anomaly, use of cardiopulmonary bypass, weight at surgery, and age at surgery. Point estimates shown in bold are statistically significant with a P value < .05. *CI*, Confidence interval; *OR*, odds ratio.

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37-38 weeks), and term (GA 39-42 weeks) infants (Table 3 and Figure E1). Figure E1 shows that the effect of birth weight Z-score on operative mortality is strongest in early term infants. The relationship between birth weight Z-scores, GA at birth, and operative mortality is depicted in a contour plot (Figure 3).

DISCUSSION

In neonates and infants who underwent cardiac surgery, in our study even infants with a very mild reduction in birth weight Z-score had higher mortality compared with infants with normal fetal growth. Growth restricted and smaller infants up to a birth weight Z-score of −0.5 also had higher

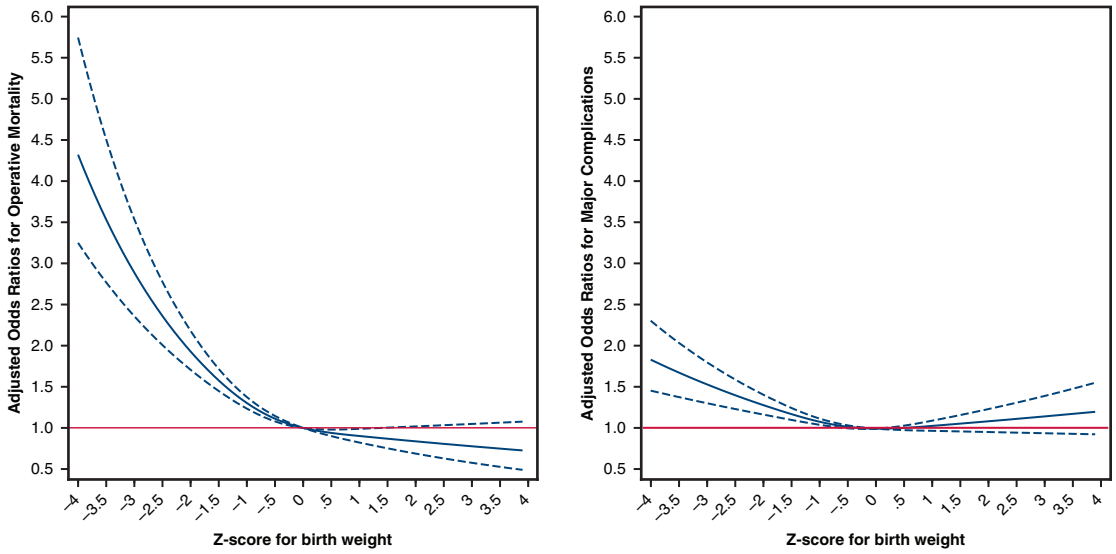


FIGURE 2. Adjusted odds ratio (*solid line*) and 95% confidence interval (*dashed lines*) for (*left*) operative mortality and (*right*) postoperative complications fitting Z-score for birth weight as a restricted cubic with 3 prespecified knots. The knots were −1.7, −0.4, and 1.0, corresponding to the 10th, 50th, and 90th percentile of the Z-score for birth weight distribution in the data set. All other variables were set to their mean values.

TABLE 3. Adjusted analysis for associations between Z-score for birth weight and operative mortality according to GA group

Z-score for birth weight	Adjusted OR (95% CI)		
	Preterm (GA <37 wk)	Early-term (GA 37-38 wk)	Term (GA 39-42 wk)
−4 to < −2	**1.80 (1.11-2.92)**	**2.87 (2.00-4.10)**	**2.26 (1.59-3.19)**
−2 to < −1	**1.55 (1.10-2.19)**	**1.90 (1.43-2.53)**	**1.49 (1.15-1.93)**
−1 to < −0.5	1.31 (0.93-1.84)	**1.41 (1.04-1.92)**	**1.40 (1.08-1.82)**
−0.5 to < 0	1.12 (0.79-1.59)	1.31 (0.96-1.78)	1.10 (0.84-1.43)
0 to < 0.5	Reference	Reference	Reference
0.5 to < 1	0.94 (0.60-1.47)	1.09 (0.76-1.56)	0.81 (0.57-1.17)
1 to < 2	1.03 (0.66-1.59)	1.12 (0.76-1.64)	0.86 (0.57-1.30)
2 to < 4	1.53 (0.87-2.70)	0.65 (0.29-1.47)	0.88 (0.34-2.27)

Adjusted associations included a center variable and were controlled for sex, race, STAT Mortality Category of the index operation, presence of any STS-CHSD preoperative risk factors, genetic or anatomic anomaly, use of cardiopulmonary bypass and weight at surgery and age at surgery. Point estimates shown in bold are statistically significant with a *P* value < .05. *GA*, Gestational age; *OR*, odds ratio; *CI*, confidence interval.

rates of postoperative complications. We further show that although the association between birth weight Z-score and operative mortality existed in all GA groups, it was most pronounced in early-term neonates (GA 37-38 weeks). These findings suggest that incorporation of birth weight Z-score into standard risk models will promote more accurate benchmarking, prognostication, and counseling (Figure 4). The study design and main findings are presented in Video 1.

Three previous studies reported on the association between birth weight Z-score and outcomes in neonates with CHD. One was a small single-center study (n = 230)[20]; the other two used population-based data sets. Best and colleagues reported a cohort of 5093 infants with CHD born between the years 1985 and 2003 in England.[21] These investigators used 3 birth weight Z-score categories (Z < −1, Z −1 to 1, and Z > 1) and reported that infants with birth weight Z-score < −1 had a higher

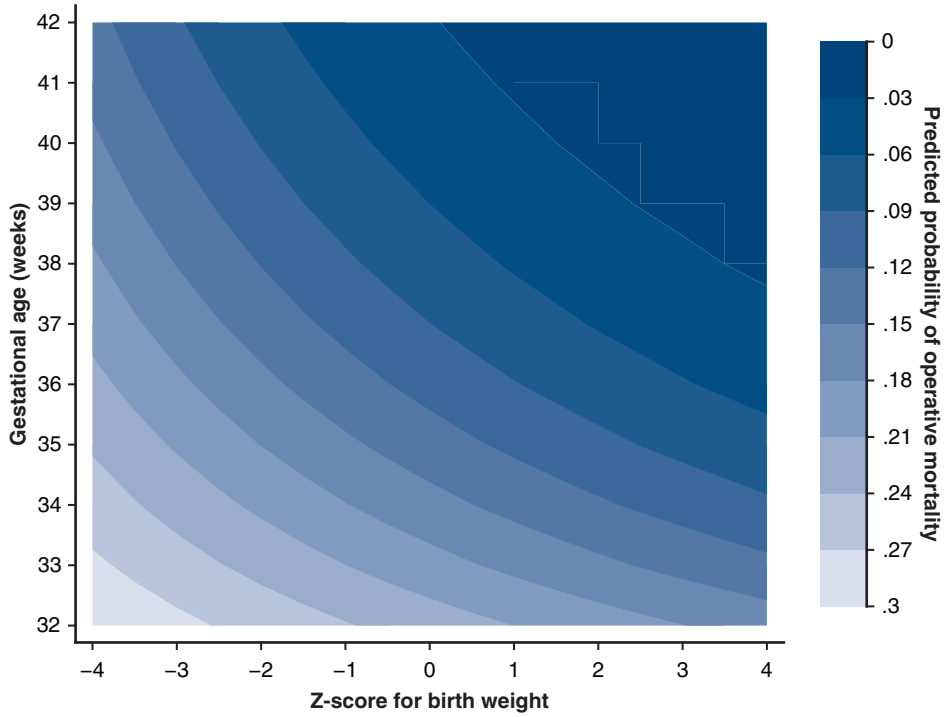


FIGURE 3. Contour plot showing interaction between Z-score for birth weight and gestational age at birth on operative mortality. The different *gray shaded areas* correspond to different predicted probabilities of mortality while holding all confounders at their mean values. The interaction term ($P = .007$) in the model causes the curvature of the contour lines in the graph (ie, without interaction, the contour lines would be straight lines). The contour plot can be used to find infants with similar predicted mortality; for example, an infant born at 37 weeks with a Z-score for birth weight of −4 has approximately the same predicted operative mortality risk as an infant born at 33 weeks with a Z-score of 0.

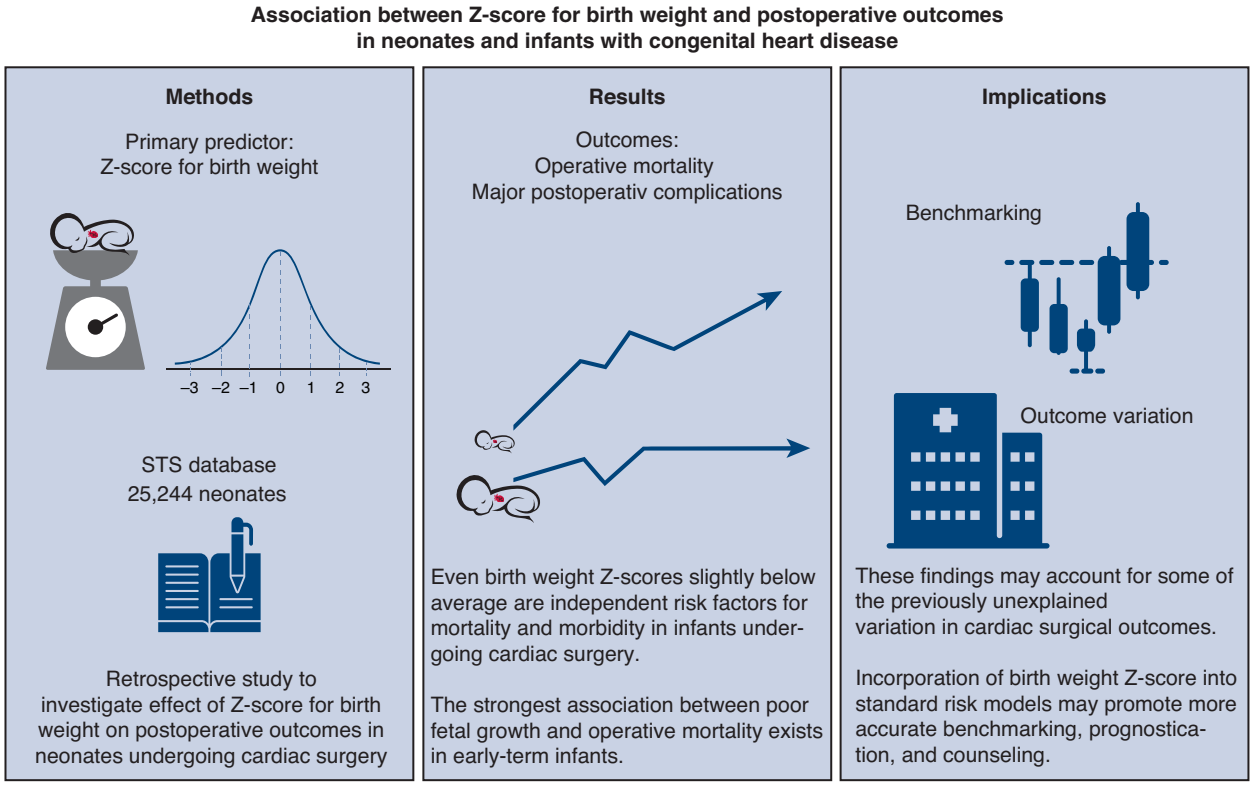
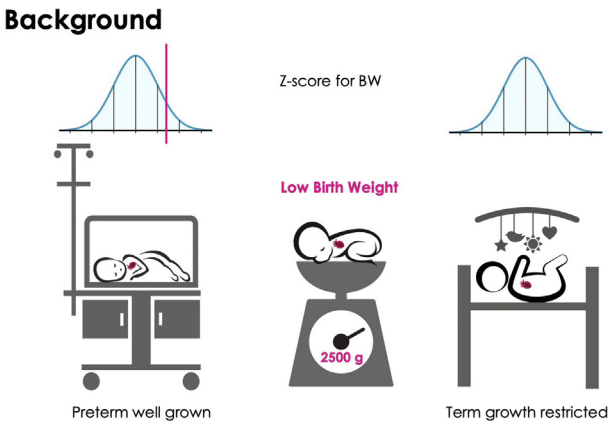


FIGURE 4. Methods, main results, and implications of this study. This was a retrospective study using The Society of Thoracic Surgeons database to evaluate Z-score for birth weight as a predictor for mortality and postoperative complications in neonates who underwent congenital heart surgery.

crude and adjusted hazard ratio for 5-year mortality than infants with a birth weight Z-score of −1 to 1, who in turn were slightly less likely to survive than infants with a birth weight Z-score > 1. Another study from our group included infants born between 2007 and 2012 in California (n = 6903).[22] The Z-score was modeled as a categorical variable similar to the current study. In this study, the association between birth weight Z-score and 1-year mortality differed between GA categories: in preterm and full-term infants, only the most growth restricted babies (birth weight Z-score < −2) were at increased risk for mortality, whereas in early-term infants, the risk extended to those who were less growth restricted (birth weight Z-score < −0.5). Because of the population-based nature of both of these studies, they captured all postnatal mortalities regardless of referral to a tertiary care center, but risk adjustment was limited by the use of administrative data sets with International Classification of Diseases Ninth Revision codes and the only outcome assessed was mortality. In the present study, the use of rich clinical registry data allowed for more comprehensive risk adjustment and assessment of postoperative complications. Additionally, the large multicenter cohort of patients captured by the STS-CHSD makes our findings highly generalizable.



VIDEO 1. Narrative of background, aim, methods, results, and conclusions of the study. Video available at: https://www.jtcvs.org/article/S0022-5223(21)00164-1/fulltext.

The variable effect of birth weight Z-score on mortality across GA categories warrants further discussion. Our findings mirror those of the population-based California cohort study.[22] In the current study, there was a significant interaction between GA and birth weight Z-score, strongest in early-term infants and weakest in preterm infants. A

possible explanation for these findings is that in preterm infants, GA as an indicator of organ maturity is a much stronger driver of mortality than fetal growth. Additionally, there have been several reports of accelerated fetal pulmonary maturation in association with intrauterine growth restriction possibly due to the fetus's response to a stressful environment by increasing adrenal glucocorticoid production,[23] which might mitigate the effect of poor fetal growth on mortality in preterm infants. Along similar lines, in term infants, Z-score for birth weight might not be as important because the full GA makes them more robust, even if the birth weight Z-score is lower. This leaves the late preterm infants as the most vulnerable group. However, most importantly, although the magnitude of the effect of birth weight Z-score varies among GA groups, Z-score influences mortality across all GAs. The current study illustrates that even slight reductions in birth weight Z-score are independent risk factors for morbidity and mortality.

Existing metrics that address the issue of case mix in the context of congenital heart surgery outcomes do include various combinations of patient age, weight at surgery, and prematurity.[3,5,24] Whether birth weight Z-score could improve existing risk adjustment models for the neonatal age group needs further investigation. In future studies, the methodology of Birkmeyer and colleagues could be used to investigate mitigating influences of related variables such as surgeon and center volume,[25,26] data that were not available for this analysis. Specifically, the influence of center volume on outcomes in growth restricted infants should be addressed. Additionally, timing of surgery specifically for infants with lower Z-score warrants further investigation and might influence the debate of ideal time of surgery for preterm neonates with CHD. Another interesting question that warrants further study is whether certain types of palliative surgeries would benefit infants with severe growth restriction as opposed to a 1-stage complete repair.

Although it is likely that the underlying cause of growth restriction might also influence postnatal outcomes, we were unfortunately unable to study the etiologic nature of abnormal fetal growth because prenatal and obstetric factors are not available in the STS-CHSD. The reason for the high incidence of poor fetal growth in infants with CHD is not well understood but is most likely multifactorial.[27-30] First, maternal pregnancy complications such as preeclampsia or gestational hypertension are higher in fetuses with CHD[31] and are associated with poor fetal growth.[32] Such pregnancy complications likely adversely affect the "maternal-fetal environment" and have been associated with adverse outcomes after neonatal cardiac surgery.[27,28] Second, the rates of chromosomal anomalies/syndromes are higher in infants with CHD and these infants often have low birth weight Z-scores.[29] We adjusted for noncardiac anomalies and genetic syndromes in our multivariable models, however, this adjustment might be imperfect. Finally, a third group might have poor fetal growth due to the underlying cardiac lesion itself. Lutin and colleagues showed that hemodynamic abnormalities in the fetus with CHD are present before birth.[30] It has not been investigated whether impaired fetal growth might be related to inadequate fetal cardiac output. The underlying reason for growth restriction might influence postnatal outcomes. Further studies should focus on identifying the different etiologies of growth restriction in neonates with CHD and investigate whether these are associated with mortality. As such it is worth considering adding additional prenatal and obstetric variables to CHD registries.

The most important strengths of this study are the size of the cohort, the detailed data on cardiac diagnoses and procedures, and that the patients were cared for in a large number of centers, which make the findings highly generalizable to all neonates and infants with CHD who receive surgery during the neonatal period. It is however important to recognize that the use of a surgical registry inherently creates selection bias in that only neonates who actually receive surgery are included. If some infants with important growth restriction are less likely to be offered surgery or are more likely to be offered non-CPB palliative surgeries initially followed by additional surgery later in infancy, then the true effect of birth weight Z-score would be underestimated using the STS data set.

In our study birth weight Z-scores that are only slightly below average are independent risk factors for mortality and morbidity in neonates and infants who undergo cardiac surgery. The strongest association between poor fetal growth and operative mortality exists in early-term infants. These novel findings might account for some of the previously unexplained variation in cardiac surgical outcomes.

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: congenital heart disease, fetal growth restriction, Z-score for birth weight, postoperative outcomes

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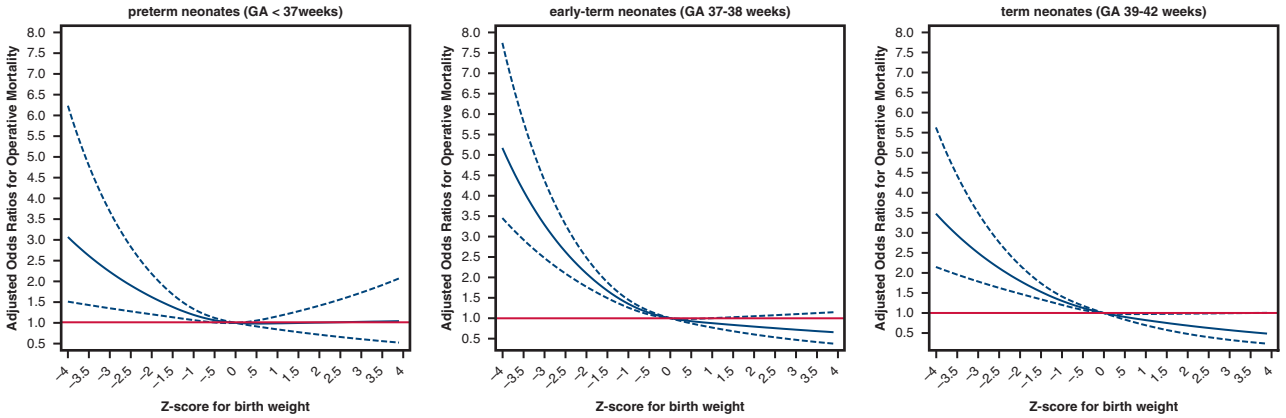

FIGURE E1. Adjusted odds ratio and 95% confidence interval for operative mortality fitting birth weight Z-score as a restricted cubic spline according to gestational age (*GA*) group. The knots were −1.7, −0.4, and 1.0 corresponding to the 10th, 50th, and 90th percentile of the Z-score for birth weight distribution in the data set. All other variables were set to their mean values.

TABLE E1. Non-CPB procedures according to growth restriction and Z-score for birth weight

Variable	CPB surgery	No CPB surgery	Central shunt	Pulmonary artery band	Hybrid procedure	CoA/arch repair	Other non-CPB procedure
Growth restriction (<10th percentile)							
Yes	3015 (66.6)	1509 (33.4)	424 (9.3)	296 (6.5)	54 (1.2)	515 (11.4)	220 (4.9)
No	14,825 (71.6)	5895 (28.5)	1600 (7.7)	978 (4.7)	147 (0.7)	2306 (11.1)	864 (4.2)
Z-score for birth weight							
−4 to < −2	864 (61.5)	544 (38.6)	134 (9.5)	117 (8.3)	24 (1.7)	192 (13.6)	77 (5.5)
−2 to < −1	3702 (69.7)	1609 (30.3)	484 (9.1)	296 (5.6)	48 (0.9)	545 (10.3)	236 (4.4)
−1 to < −0.5	3328 (71.6)	1322 (28.4)	380 (8.2)	228 (4.9)	42 (0.9)	477 (10.3)	195 (4.2)
−0.5 to < 0	3544 (71.6)	1405 (28.4)	412 (8.3)	312 (4.3)	35 (0.7)	545 (11.0)	200 (4.1)
0 to < 0.5	2868 (73.1)	1053 (26.9)	250 (6.3)	160 (4.1)	27 (0.7)	439 (11.2)	177 (4.5)
0.5 to < 1	1831 (71.6)	725 (28.4)	177 (6.9)	116 (4.5)	12 (0.5)	324 (12.7)	96 (3.8)
1 to < 2	1397 (69.9)	602 (30.1)	36 (8.0)	33 (7.3)	3 (0.7)	246 (12.3)	84 (4.2)
2 to < 4	306 (68.0)	144 (32.0)	36 (8.0)	33 (7.3)	3 (0.7)	53 (11.8)	19 (4.2)

Data are presented as n (%). *CBP*, Cardiopulmonary bypass; *CoA*, coarctation of the aorta.

TABLE E2. Unadjusted and adjusted analysis for operative mortality for all included covariates

Variable	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Z-score for birth weight category		
−4 to < −2	**2.41 (2.00-2.94)**	**2.43 (1.96-3.02)**
−2 to < −1	**1.69 (1.45-1.97)**	**1.67 (1.42-1.97)**
−1 to < −0.5	**1.46 (1.24-1.71)**	**1.38 (1.17-1.64)**
−0.5 to < 0	**1.19 (1.01-1.40)**	1.17 (0.98-1.39)
0 to < 0.5	Reference	Reference
0.5 to < 1	0.90 (0.73-1.11)	0.94 (0.75-1.17)
1 to < 2	0.97 (0.78-1.21)	1.00 (0.79-1.25)
2 to < 4	1.24 (0.86-1.78)	1.04 (0.70-1.53)
Gestational age at birth category		
32-33 wk	**2.67 (2.18-3.27)**	**4.40 (3.44-5.62)**
34-36 wk	**2.01 (1.77-2.28)**	**2.30 (2.00-2.65)**
37-38 wk	**1.53 (1.38-1.70)**	**1.45 (1.30-1.62)**
39-40 wk	Reference	Reference
41-42 wk	**0.57 (0.39-0.84)**	**0.52 (0.34-0.78)**
STAT Mortality Category of index operation		
1	Reference	Reference
2	0.77 (0.56-1.06)	0.90 (0.64-1.26)
3	0.92 (0.67-1.26)	0.90 (0.64-1.27)
4	**2.08 (1.59-2.71)**	**1.93 (1.44-2.57)**
5	**4.42 (3.37-5.79)**	**4.30 (3.20-5.80)**
Female sex	**1.21 (1.10-1.32)**	**1.17 (1.06-1.29)**
Race		
Caucasian	Reference	Reference
African American	**1.63 (1.44-1.85)**	**1.42 (1.25-1.63)**
Asian	1.23 (0.95-1.58)	1.32 (1.02-1.72)
Native American	1.48 (0.95-2.31)	1.32 (0.83-2.10)
Pacific Islander	1.29 (0.71-2.32)	1.29 (0.69-2.38)
Other	**1.66 (1.43-1.92)**	**1.72 (1.47-2.00)**
Any noncardiac anatomic or chromosomal abnormality	**1.91 (1.73-2.11)**	**1.58 (1.41-1.76)**
Any STS-CHSD preoperative risk factor	**2.64 (2.39-2.91)**	**2.38 (2.15-2.64)**
Cardiopulmonary bypass used	**1.53 (1.37-1.71)**	**1.40 (1.24-1.59)**
Weight at surgery, kg	**0.61 (0.56-0.65)**	1.01 (0.97-1.04)
Age at surgery, d	**0.99 (0.99-0.99)**	**0.98 (0.98-0.99)**

Operative mortality of the index operation defined as (1) all deaths occurring during the hospitalization in which the index operation was performed, even if after 30 days; and (2) all deaths occurring after discharge from the hospital, but before the end of the 30th postoperative day. Unadjusted values were estimated using models that included a center variable but did not include other patient-level characteristics. Point estimates in bold are statistically significant with P value < .05. *OR*, Odds ratio; *CI*, confidence interval; *STS-CHSD*, The Society of Thoracic Surgeons Congenital Heart Surgery Database. *Adjusted for all variables in the presented in the table.

TABLE E3. Unadjusted and adjusted analysis for associations between Z-score for birth weight and operative mortality and major postoperative complications

Z-score for birth weight	All missing experienced outcome Adjusted OR (95% CI)	None of the missing experienced the outcome Adjusted OR (95% CI)
Operative mortality		
−4 to < −2	**2.50 (2.02-3.09)**	**2.41 (1.94-2.99)**
−2 to < −1	**1.70 (1.45-2.00)**	**1.66 (1.41-1.96)**
−1 to < −0.5	**1.39 (1.18-1.65)**	**1.38 (1.17-1.64)**
−0.5 to < 0	1.18 (0.99-1.40)	1.16 (0.98-1.38)
0 to < 0.5	Reference	Reference
0.5 to <1	0.96 (0.77-1.18)	0.93 (0.75-1.16)
1 to <2	1.04 (0.83-1.30)	0.99 (0.78-1.24)
2 to <4	1.00 (0.68-1.48)	1.04 (0.70-1.53)
Major postoperative complications		
−4 to < −2	**1.27 (1.08-1.48)**	**1.46 (1.24-1.73)**
−2 to < −1	**1.15 (1.03-1.28)**	**1.22 (1.09-1.38)**
−1 to < −0.5	1.02 (0.91-1.14)	1.06 (0.94-1.20)
−0.5 to < 0	1.05 (0.93-1.20)	1.04 (0.93-1.17)
0 to < 0.5	Reference	Reference
0.5 to < 1	1.05 (0.89-1.18)	1.06 (0.92-1.22)
1 to < 2	1.02 (0.89-1.18)	1.08 (0.93-1.26)
2 to < 4	1.14 (0.89-1.47)	1.12 (0.85-1.49)

Operative mortality of the index operation defined as (1) all deaths occurring during the hospitalization in which the index operation was performed, even if after 30 days; and (2) all deaths occurring after discharge from the hospital, but before the end of the 30th postoperative day. Major postoperative complications defined as the occurrence of at least 1 of the following: postoperative mechanical circulatory support, renal failure requiring dialysis, neurologic deficit persisting at discharge, stroke, unplanned cardiac reoperation or interventional cardiovascular catheterization during the postoperative time period, and heart block requiring permanent pacemaker. Unadjusted values were estimated using models that included a center variable but did not include other patient-level characteristics. Adjusted associations included a center variable and were controlled for sex, race, gestational age, STAT Mortality Category of the index operation, presence of any STS-CHSD preoperative risk factors, genetic or extracardiac anatomic anomaly, use of cardiopulmonary bypass, weight at surgery, and age at surgery. Point estimates in bold are statistically significant with *P* value < .05. *OR*, Odds ratio; *CI*, confidence interval; *STS-CHSD*, The Society of Thoracic Surgeons Congenital Heart Surgery Database.

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TABLE E4. Unadjusted and adjusted competing risk analysis for postoperative length of stay according to Z-score for birth weight

Z-score for birth weight	Observed PLOS in days, median (IQR)*	Competing risk analysis		Proportional hazard model	
		Unadjusted SHR (95% CI)	Adjusted SHR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
−4 to < −2	22 (12-43)	**0.65 (0.61-0.69)**	**0.64 (0.60-0.68)**	**0.73 (0.68-0.78)**	**0.71 (0.66-0.76)**
−2 to < −1	19 (10-37)	**0.80 (0.77-0.83)**	**0.81 (0.77-0.85)**	**0.84 (0.81-0.88)**	**0.85 (0.82-0.89)**
−1 to < −0.5	17 (9-35)	**0.86 (0.82-0.89)**	**0.87 (0.83-0.92)**	**0.90 (0.86-0.94)**	**0.90 (0.86-0.94)**
−0.5 to < 0	16 (9-31)	**0.95 (0.91-0.98)**	**0.95 (0.91-0.99)**	**0.94 (0.90-0.99)**	**0.95 (0.91-0.99)**
0 to < 0.5	15 (9-30)	Reference	Reference	Reference	Reference
0.5 to < 1	15 (8-30)	1.02 (0.97-1.07)	0.99 (0.94-1.06)	0.98 (0.93-1.03)	0.95 (0.91-1.01)
1 to < 2	16 (9-33)	0.97 (0.92-1.02)	0.95 (0.90-1.01)	**0.94 (0.89-0.99)**	**0.91 (0.86-0.96)**
2 to < 4	21 (10-39)	**0.83 (0.75-0.93)**	**0.84 (0.75-0.94)**	**0.83 (0.75-0.91)**	**0.78 (0.70-0.86)**

Lower HR or SHR is associated with longer PLOS. Death before hospital discharge was treated as competing risk. Unadjusted values were estimated using models that included a center variable but did not include other patient-level characteristics. Adjusted associations included a center variable and were controlled for sex, race, gestational age, STAT Mortality Category of the index operation, presence of any STS-CHSD preoperative risk factors, genetic or extracardiac anatomic anomaly, use of cardiopulmonary bypass,