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Authors
Savorgnan, Fabio
Elhoff, Justin J
Guffey, Danielle
et al.

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Relationship between gestational age and outcomes after congenital heart surgery

Fabio Savorgnan, MD[*,1], Justin J Elhoff, MD[*,1], Danielle Guffey[1], David Axelrod, MD[2], Jason R Buckley, MD[3], Michael Gaies, MD[4], Nancy S Ghanayem, MD[1], Javier J Lasa, MD[1], Lara Shekerdemian, MD[1], James S Tweddell, MD[5], David K Werho, MD[6], Justin Yeh, MD[7], Martina A Steurer, MD[8]

[1]Baylor College of Medicine, Houston, TX

[2]Stanford University, Palo Alto, CA

[3]Medical University of South Carolina, Charleston, SC

[4]University of Michigan, Ann Arbor, MI

[5]University of Cincinnati, Cincinnati, OH

[6]University of California-San Diego, San Diego, CA

[7]University of Pittsburgh, Pittsburgh, PA

[8]University of California-San Francisco, CA

Abstract

Background: Previous studies suggest that birth prior to 39 weeks gestational age (GA) is associated with higher perioperative mortality and morbidity after congenital heart surgery. The optimal approach to timing of surgery in premature infants remains unclear. We investigated the impact of GA at birth and corrected GA at surgery on post-operative outcomes using the Pediatric Cardiac Critical Care Consortium (PC[4]) database.

Methods: Infants undergoing selected index cardiac operations before the end of the neonatal period were included (n=2,298). GA at birth and corrected GA at the time of index cardiac surgery were used as categorical predictors and fitted as a cubic spline to assess non-linear relationships. The primary outcome was hospital mortality. Multivariable logistic regression models assessed the association between predictors and outcomes while adjusting for confounders.

Results: Late-preterm birth (34–36 weeks) was associated with increased odds of mortality compared to full-term (39–40 weeks) birth while early-term birth (37–38 weeks) was not associated with increased mortality. Corrected GA at surgery of 34–37 weeks compared to 40–

Corresponding author: Justin Elhoff, Texas Children's Hospital, 6651 Main Street, MC E1420, Houston, TX 77030, jxelhoff@texaschildrens.org.
*Co-first authors

44 weeks was associated with increased mortality. When analyzing corrected GA at surgery as a continuous predictor of outcome, odds of survival improve as patients approach 39 weeks corrected GA.

Conclusions: Contrary to previous literature, we did not find an association between early-term birth and hospital mortality at PC^4 hospitals. Our analysis of the relationship between corrected GA and mortality suggests that operating closer to full-term corrected GA may improve survival.

Gestational age (GA) is an important factor when considering assessment of outcomes, planning cardiac interventions, and counseling families of newborns with congenital heart disease (CHD). Prematurity has been traditionally defined as birth prior to 37 weeks GA. Several studies of premature newborns with CHD have demonstrated higher morbidity and mortality after congenital heart surgery [1–4].

There is increasing neonatology literature demonstrating worse hospital and neurodevelopmental outcomes for "term" infants born outside of the 39–40 week interval [5]. In 2013 the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine issued the recommendation to divide "term gestation" into "early-term" (37–38 weeks), "full-term" (39–40 weeks), and "late-term" (41 weeks) [6]. Similarly, recent studies have provided evidence of worse outcomes for children undergoing neonatal congenital heart surgery who were born at early-term [7]. A 2014 analysis of the Society of Thoracic Surgeons (STS) database found that compared to infants born at 39.5 weeks GA, those born at 37 weeks GA and below had increased adjusted odds of mortality, and those born at 38 weeks GA or less had increased surgical complications [7]. An administrative database analysis found that patients born at 37–38 weeks GA with critical CHD had increased mortality and neonatal morbidity compared to those born at 39–42 weeks GA [8].

Assessment of the relationship between GA and outcomes in neonates with critical CHD is further complicated as the risks of cardiac surgery on immature organs must be weighed against the competing risk of delayed intervention and protracted exposure to an abnormal circulation and/or hypoxemia. Some studies demonstrate acceptable outcomes for early primary repair of cardiac defects in premature or low birth weight infants, although the mortality rate remained high compared to what has been reported in term infants [2–4,9–11]. None of those studies compared early to late repair in this patient group. Thus, it remains unclear whether decisions regarding timing of surgery may be different across subgroups of premature or early-term infants to optimize outcomes.

In this current study, we aimed to examine the influence of preterm and early-term birth on perioperative outcomes using the Pediatric Critical Care Consortium (PC^4) database. We further sought to evaluate corrected GA at surgery as a predictor for outcomes to investigate the interplay between GA at birth and postnatal age at surgery. We hypothesize that corrected GA at the time of cardiac surgery is associated with post-operative outcomes; such an association would spur future efforts to understand the best approach to managing premature and early-term infants with critical CHD.

Patients and Methods

Data Source

The PC^4 is a quality improvement collaborative that collects data on all patients with primary cardiac disease admitted to the cardiac intensive care unit (CICU) service at participating hospitals. PC^4 maintains a clinical registry to support research and quality improvement initiatives as previously described [12]. The University of Michigan Institutional Review Board provides oversight for the PC^4 Data Coordinating Center and approved with waiver of informed consent. At the time of this analysis, 33 centers were submitting cases to the PC^4 registry.

Study population

Neonates with a GA at birth of between 34 and 41 weeks who were hospitalized between August 1, 2014 and January 2, 2019 and underwent selected STS defined cardiac operations before the end of the neonatal period (corrected GA of 44 weeks) were included. We excluded neonates who underwent surgery within the first 24 hours of life. Included operations were Norwood procedure, hybrid stage 1 palliation procedure, and benchmark biventricular repairs including arterial switch operation, arterial switch operation with ventricular septal defect closure, truncus arteriosus repair, and tetralogy of Fallot repair.

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes were 1) major postoperative complications in survivors, and 2) CICU length of stay (LOS) in survivors. Major postoperative complications were defined as any of the following: postoperative cardiac arrest, any postoperative extracorporeal membrane oxygenation use, neurological complication (seizures, stroke, intraventricular hemorrhage > grade II or intracerebral hemorrhage) or unplanned reoperation (any additional unplanned cardiac reoperation, including postoperative chest re-opening or unplanned interventional cardiac catheterization).

Predictors

The main predictor of interest was GA at birth and the secondary predictor of interest was corrected GA at surgery. Corrected GA at surgery was calculated by adding the age in days at surgery to GA (in weeks) at birth. If the result was 3 days or less (e.g. 39 3/7), it was rounded down (39 weeks); if the result was 4 days or more (e.g. 39 4/7) it was rounded up (40 weeks). We also explored the relationship between age at surgery and outcomes. However, recognizing that questions about the optimal age at surgery are fundamentally different based on GA at birth and diagnosis we elected to focus on corrected GA at surgery which represents the interplay between GA at birth and age at surgery.

Analysis

Patient characteristics and outcomes were reported using median with 25th and 75th percentiles and frequency with percentage as appropriate. Similarly, summary statistics were calculated using quantile regression, Chi-square test and Fisher's exact test to compare different GA groups.

To assess the relationship between GA at birth and our outcomes, we utilized the recognized GA categories of late-preterm (34–36 completed weeks of gestation), early-term (37–38 completed weeks), full-term (39–40 completed weeks) and late-term (41 completed weeks). The model with GA at birth as the primary predictor was adjusted for age at surgery.

To model the non-linear relationships between predictors and outcomes, a restricted cubic spline transformation was applied to the GA variable in weeks for all patients, and then separately for patients who survived to hospital discharge. The knots were chosen based on the distribution of the data.

As both treatment and outcomes may vary across centers, our analytic approach took into account the hierarchical structure of the data at the hospital level. For binary outcomes, logistic regression with clustering at the hospital level was used. For CICU LOS, competing risk regression analysis was performed with in-hospital mortality as the competing risk variable. Competing risk regression calculates subhazard ratios for discharge comparing each GA category to the reference (full-term infants), i.e. a subhazard ratio below 1 indicates a longer hospital stay and a decreased likelihood of discharge over time.

Crude and adjusted measures of association are reported. Models were adjusted for the following potential confounders: sex, birth weight for GA, antenatal diagnosis, presence of genetic syndrome or extracardiac anomaly, CICU admission prior to surgery, any preoperative risk factor (defined as preoperative mechanical circulatory support, preoperative mechanical ventilation, or presence of any STS low or high-risk factor), STS-EACTS STAT Mortality Category and age at surgery. Both unadjusted and adjusted models account for center differences.

All analyses were performed using Stata version 15.0 (StataCorp LP).

Results

A total of 2,298 patients met inclusion criteria with 52% classified as full-term, 34% born early-term, 11% late-preterm, and 2% late-term (Table 1). Fifty-four percent underwent one of the defined biventricular repairs, 40% underwent Norwood palliation, and 6% underwent a hybrid procedure. Patients born earlier were more likely to have a genetic syndrome or extracardiac anomaly and underwent surgery later following birth.

Postoperative outcomes for patients of different GA groups are described separately by surgical group in Supplemental Table 1. In patients undergoing the Norwood procedure, earlier GA at birth was associated with higher mortality and longer postoperative CICU LOS but not with major postoperative complications in survivors. In infants undergoing biventricular repairs, GA at birth was not associated with hospital mortality or major complications in survivors, however the CICU LOS was increased in survivors with lower GA.

Table 2 shows the unadjusted and adjusted odds ratio (aOR) for GA at birth and the binary outcomes. After adjustment, patients born late-preterm but not early-term had increased odds of mortality compared to full-term infants. In survivors, early-term but not late-preterm birth was associated with increased odds for major postoperative complications. Figure 1 shows the aOR with 95% CI for hospital mortality (panel A) and major postoperative complications in survivors (panel B) using GA at birth as a restricted cubic spline while keeping all covariates at their mean value. The graph shows that the aOR for hospital mortality has a parabolic shape; it continues to decline as the GA at birth increases with a nadir at 39 weeks, however, this relationship was only statistically significant when comparing 37 weeks or less to the reference of 39 weeks. The aOR curve for major postoperative complications in survivors is rather flat, indicating that the influence of GA is minimal.

Age at surgery was not associated with hospital mortality or major postoperative complications in survivors after adjustment (Table 2). When age at surgery was treated as a cubic spline, the point estimate for hospital mortality decreased with increased age at surgery; however, this did not reach statistical significance (Supplemental Figure 1).

Table 3 uses the same model as presented in Table 2 but applies corrected GA at surgery as the predictor. Hospital mortality and major postoperative complications in survivors were increased for corrected GA at surgery of 34–37 weeks compared to 40–44 weeks. Figure 2 plots the aOR with 95% CI for hospital mortality (panel A) and major postoperative complications in survivors (panel B) using corrected GA at surgery as a restricted cubic spline while keeping all covariates at their mean value. The graph shows that the aOR for hospital mortality decreases up to a corrected GA of 39 weeks. The graph for major postoperative complications in survivors shows an aOR of about 1 up to 39 weeks with a decrease afterwards.

Late-preterm and early-term patients were at increased risk for longer postoperative CICU stay compared to full-term infants (Supplemental Table 2 and Figure 3). Several other patient characteristics were also significantly associated with post-operative CICU LOS, including small for gestational age and genetic syndrome or extracardiac anomaly.

Comment

In this study of a contemporary, multicenter CICU registry, we have shown increased hospital mortality in late-preterm but not early-term infants when compared to full-term infants undergoing surgery for CHD during the neonatal period. Major postoperative complications in survivors were increased in early-term patients, and late-preterm and early-term infants had prolonged CICU LOS. Corrected GA at surgery of 34–37 weeks was significantly associated with mortality as well as with major postoperative complications in survivors. Most interestingly, fitting cubic splines for corrected GA at surgery showed that the odds of survival increased up to a corrected GA at surgery of 39 weeks, after which no additional survival benefits were observed.

Previous database studies of neonates with CHD have shown that early-term infants with CHD had higher odds for mortality and morbidity [7,8,13]. There are several potential explanations for the contrasting findings in our study. First, this could be in part related to differences of the source populations and local models of care. One publication utilized an administrative database that included neonates who died prior to any cardiac intervention [8], and the other utilized a surgical registry that includes data from some institutions without a dedicated CICU [7]. By contrast, the PC^4 database includes a greater proportion of hospitals with dedicated CICUs and higher surgical volume. Furthermore, the epidemiology of mortality and complications may be different in this population of hospitals. Additionally, our patient population was more selective than that of the other studies. Although our sample size was smaller than the study from the STS registry (n = 2298 versus n = 3950 for early-term and full-term infants), retrospective power calculation revealed that our sample size was large enough to demonstrate a mortality difference of at least 3.2% between early and full-term infants, which is the same than the mortality difference found in the STS study [7].

There is evidence that late-preterm and early-term patients require increased resource utilization compared to their full-term counterparts. Unadjusted data identified increased duration of postoperative mechanical ventilation for patients undergoing Norwood and biventricular repairs and an adjusted competing risk analysis revealed that postoperative CICU LOS was significantly longer in the late-preterm and early-term groups compared to full-term patients. As CICU LOS and mechanical ventilation duration are increasingly utilized as outcome and quality benchmarking measures, it is important to recognize that the traditional risk factor of “prematurity” defined as <37 weeks GA is likely not appropriate, and more granular consideration of GA may be required. Moreover the importance of this observation cannot be overstated when we consider longer-term neurodevelopment in this highly vulnerable population, which is directly correlated with increased ICU LOS [14,15].

The optimal timing of cardiac surgery is often debated in preterm as well as full-term neonates with scarce literature available [16]. Neonates with critical CHD represent a group where, for the majority, an unfavorable and often unstable physiologic milieu exists pre-operatively that is ideally corrected or at least stabilized by surgery. Thus the pros and cons of interventions versus waiting longer for end-organ maturation and somatic growth for surgery are constantly weighed. In particular, we are aware that the brain development of neonates with CHD is relatively delayed compared to neonates without CHD [17–19].

While some studies have described successful early primary repair in preterm infants, [2,9,10] none addressed the challenging question of when to intervene. We did not find that age at surgery alone was associated with mortality or major complication. However, our analysis of the relationship between corrected GA and outcomes suggests that delaying the operation until the infant is corrected to full-term is associated with decreased odds of mortality. While our study assessed the neonatal cohort as a single group, different GA categories and cardiac lesions might require tailored approaches. While further dedicated investigations into optimal surgical timing are necessary, particularly in unique surgical subgroups, our findings support the concept of performing surgical intervention near full-term corrected GA for patients born preterm or early-term.

There are notable limitations to this study. Our investigation is limited to variables included in the clinical registry, and there may be important predictors not measured, particularly certain preoperative data in patients cared for outside the cardiac ICU. Importantly, GA at birth is captured only as “weeks” in the PC^4 database. This might have led to nondifferential misclassification of our predictor variable and bias towards the null. As such, a more nuanced analysis of GA and corrected GA based on an estimated weeks and days GA is not possible using this data source. Second, biventricular repairs examined in this study included only high-risk STS benchmark operations. The relationship between GA and outcomes may be different for non-benchmark operations. Third, this analysis does not consider outcomes for patients who did not undergo cardiac operations. Specifically, it is possible that some patients with similar anatomy were not surgical candidates or underwent other procedures prior to or rather than one of the defined operations. Additionally, patient characteristics and practice patterns within centers participating in the PC^4 registry may vary compared to non-PC^4 centers, potentially limiting generalizability of our results. Lastly, as we consider timing of surgery and the association of corrected GA with outcomes, we acknowledge that we do not have complete information regarding what motivated timing of operation, and there are possible unmeasured factors leading to patients with more complex or emergent disease undergoing operation at an earlier corrected GA.

In summary, this contemporary study found that early-term infants are not at increased risk of mortality after selected cardiac surgical procedures of variable complexity when compared to full-term infants. Furthermore, GA at birth was not associated with major postoperative complications. Most importantly, our findings identify corrected GA at surgery as a potentially important factor associated with surgical outcomes and may be a critical consideration for planning cardiac interventions. Our data suggests the optimal timing for neonatal cardiac surgery may be at corrected GA of 39–40 weeks, but additional work is needed to know whether this recommendation applies equally across disease and operation subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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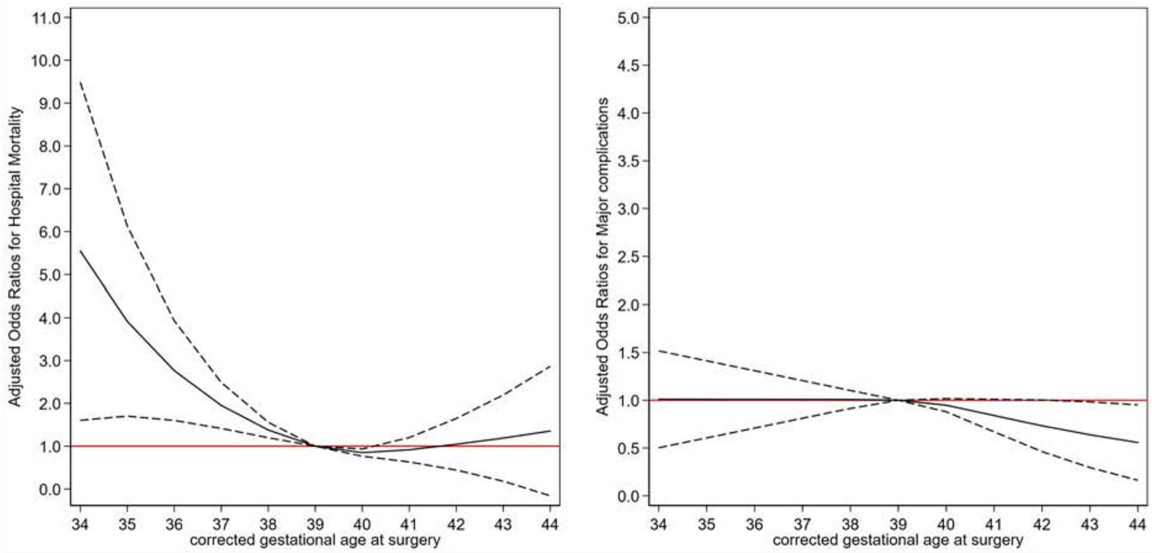

Figure 1: GA at birth as cubic spline for a) in hospital mortality and b) major postoperative complications in survivors

Knots for hospital mortality and postoperative complications in survivors at 36, 39 and 40 weeks GA

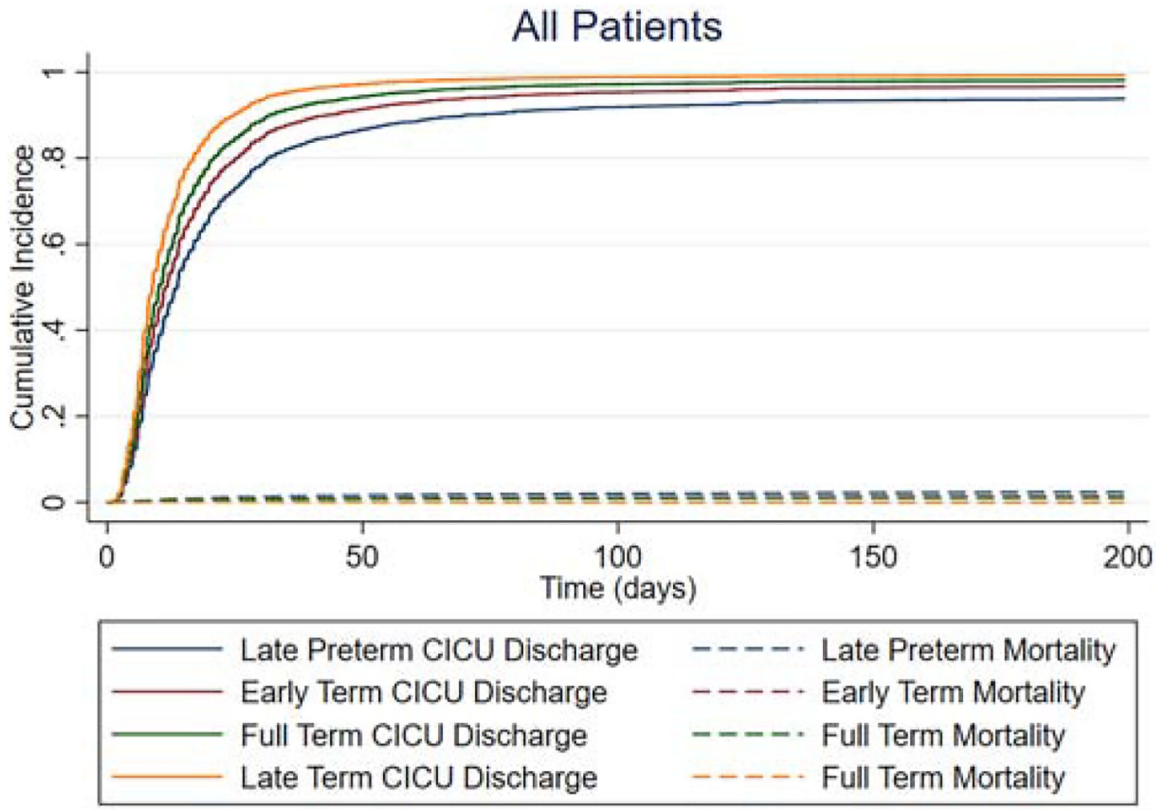

Figure 2: Corrected GA at surgery as cubic spline for a) in hospital mortality and b) major postoperative complications in survivors

Knots for hospital mortality and postoperative complications in survivor at 38, 40 and 41 weeks GA

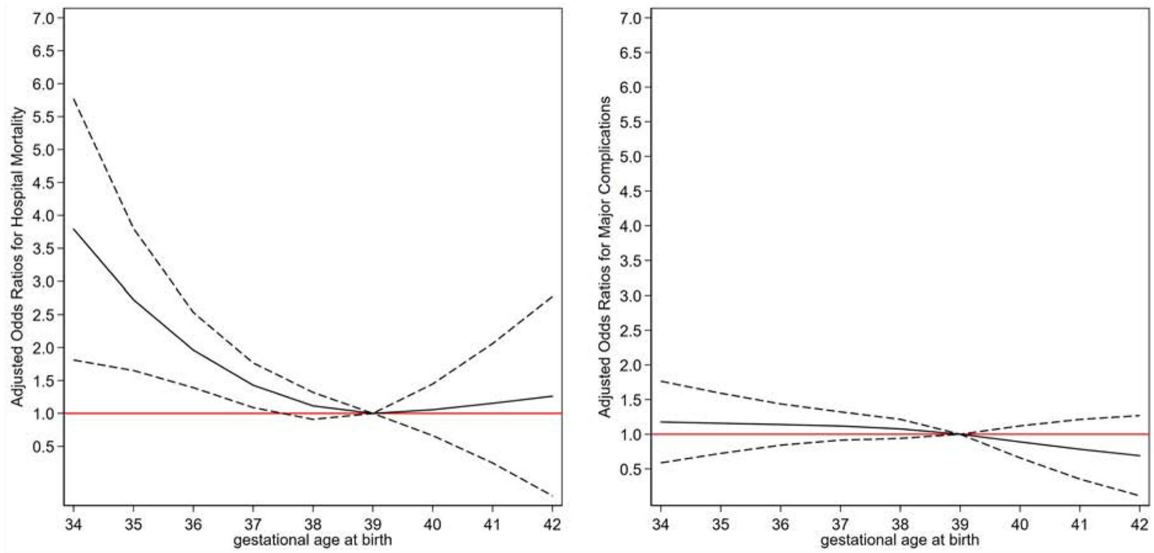

Figure 3: Competing risk regression for CICU LOS by GA category

Table 1:

Patient characteristics of the patient population by GA

	Late preterm (34–36 weeks) N=262	Early term (37–38 weeks) N=790	Full term (39–40 weeks) N=1192	Late term (41 weeks) N=54	p-value
Patient characteristics					
GA at birth, weeks	35 (35, 36)	38 (37, 38)	39 (39, 39)	41 (41,41)	<0.001
Male sex	165 (63.0)	488 (61.9)	750 (63.0)	36 (66.7)	.899
Birth weight for GA					<0.001
SGA	33 (13.3)	90 (11.7)	83 (7.1)	5 (9.6)	
AGA	187 (75.4)	596 (77.3)	998 (84.9)	45 (86.5)	
LGA	28 (11.3)	85 (11.0)	95 (8.1)	2 (3.8)	
Antenatal diagnosis	184 (70.8)	597 (76.1)	834 (70.1)	13 (24.1)	<0.001
Genetic syndrome or extracardiac anomaly	87 (33.2)	203 (25.7)	217 (18.2)	10 (18.5)	<0.001
Preoperative characteristics					
Preoperative CICU stay	189 (72.1)	624 (79.0)	968 (81.2)	45 (83.3)	.012
Preoperative MCS	1 (0.4)	7 (0.9)	8 (0.7)	0	.840
Preoperative mechanical ventilation	113 (43.1)	277 (35.1)	401 (33.6)	28 (51.9)	.002
STS low risk	67 (25.6)	182 (23.0)	232 (19.5)	16 (29.6)	.034
STS high risk	14 (5.3)	42 (5.3)	64 (5.4)	4 (7.4)	.878
Any preoperative risk factors *	146 (55.7)	372 (47.1)	537 (45.1)	35 (64.8)	.001
Operative characteristics					
STAT Category					<0.001
1	13 (5.0)	23 (2.9)	14 (1.2)	1 (19)	
2	27 (10.3)	47 (5.9)	38 (3.2)	4 (7.4)	
3	48 (18.3)	203 (25.7)	354 (29.7)	26 (48.1)	
4	82 (1.3)	156 (19.7)	253 (21.2)	11 (20.4)	
5	92 (35.1)	361 (45.7)	533 (44.7)	12 (22.2)	
Surgical Procedure					<0.001
Truncus arteriosus	33 (12.6)	56 (7.1)	85 (7.1)	3 (5.6)	
ASO	48 (18.3)	203 (25.7)	354 (29.7)	26 (48.1)	
ASO + VSD repair	30 (11.5)	77 (9.7)	148 (12.4)	7 (13.0)	
TOF repair	40 (15.3)	70 (8.9)	52 (4.4)	5 (9.3)	
Single ventricle palliation					
Norwood	70 (26.7)	329 (41.6)	514 (43.1)	10 (18.5)	
Hybrid	41 (15.6)	55 (7.0)	39 (3.3)	3 (5.6)	
Age at surgery, days	10 (6.0,20.0)	6 (4.0,9.0)	6(4.0,8.0)	6.5 (5, 9)	<0.001
Corrected GA at surgery, weeks	37 (36.0,38.0)	39 (38.0,39.0)	40 (40.0,41.0)	42 (42,42)	<0.001

GA = gestational age, SGA = small for GA, AGA = appropriate for GA, LGA = large for GA, CICU = cardiac intensive care unit, MCS = mechanical circulatory support, STAT = STS-European Association for Cardio-thoracic Surgery (EACTS), ASO = arterial switch operation, VSD = ventricular septal defect, TOF = tetralogy of Fallot,

*either preoperative mechanical circulatory support, preoperative mechanical ventilation, STS low risk or STS high risk

Table 2:

Unadjusted and adjusted predictors of mortality and major postoperative complications in survivors using GA at birth as the primary predictor

	Hospital mortality		**Major postoperative complications in survivors[@]**	
	Crude OR (95% CI)	**Adjusted OR[*] (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR[*] (95% CI)**
Patient characteristics				
GA at birth				
Late preterm	**2.19 (1.42, 3.37)**	**2.17 (1.44, 3.28)**	1.13 (0.77, 1.65)	1.22 (0.81, 1.83)
Early term	**1.36 (1.01, 1.84)**	1.18 (0.86, 1.61)	**1.27 (1.01, 1.58)**	**1.26 (1.00, 1.60)**
Full term	Reference	Reference	Reference	Reference
Late term	-	-	0.75 (0.30, 1.87)	0.83 (0.32, 2.16)
Male sex	**0.67 (0.51, 0.88)**	0.81 (0.61, 1.07)	1.00 (0.82, 1.22)	1.11 (0.87, 1.42)
Size for GA				
SGA	**2.16 (1.49, 3.15)**	**1.89 (1.27, 2.81)**	1.36 (0.90, 2.05)	1.25 (0.82, 1.91)
AGA	Reference	Reference	Reference	Reference
LGA	0.93 (0.48, 1.80)	0.87 (0.44, 1.70)	0.72 (0.44, 1.17)	0.70 (0.44, 1.13)
Antenatal diagnosis	**2.17 (1.60, 2.96)**	1.45 (0.96, 2.17)	1.20 (0.91, 1.59)	0.88 (0.62, 1.27)
Genetic syndrome or extracardiac anomaly	**3.18 (1.98, 5.10)**	**2.23 (1.43, 3.47)**	1.43 (0.99, 2.06)	1.20 (0.82, 1.74)
Preoperative characteristics				
Preoperative CICU stay	**1.71 (1.03, 2.84)**	1.33 (0.75, 2.36)	**1.65 (1.09, 2.50)**	**1.44 (1.03, 2.03)**
Any preoperative risk factors[#]	**1.41 (1.09, 1.84)**	**1.70 (1.36, 2.37)**	1.15 (0.89, 1.49)	**1.39 (1.05, 1.83)**
Operative characteristics				
STAT category				
1 −2	Reference	Reference	Reference	Reference
3	1.06 (0.19, 5.93)	1.08 (0.22, 5.36)	0.61 (0.36, 1.05)	**0.48 (0.28, 0.81)**
4	**16.35 (2.81, 94.97)**	**12.87 (2.38, 69.46)**	1.53 (0.93, 2.54)	1.32 (0.79, 2.18)
5	**24.20 (3.96, 147.82)**	**20.54 (3.73, 113.23)**	**2.42 (1.36, 4.31)**	**2.04 (1.09, 3.80)**
Age at surgery, days	0.98 (0.96, 1.00)	0.98 (0.95, 1.02)	0.99 (0.98, 1.01)	1.00 (0.98, 1.01)

GA = gestational age, SGA = small for GA, AGA = appropriate for GA LGA = large for GA, CICU = cardiac intensive care unit, STAT = STS-European Association for Cardio-thoracic Surgery (EACTS)

@ major postoperative complications defined as either postoperative cardiac arrest, postoperative ECMO use (any), neurological complication or unplanned reoperation

* Adjusted for all factors presented in the table

either preoperative mechanical circulatory support, preoperative mechanical ventilation, STS low risk or STS high risk

Table 3:

Unadjusted and adjusted predictors of mortality and major postoperative complications in survivors using corrected GA at surgery as the primary predictor

	Hospital mortality		Major postoperative complications in survivors@	
	Crude OR (95% CI)	**Adjusted OR* (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR* (95% CI)**
Patient characteristics				
Corrected GA at surgery				
34–37 weeks	**3.28 (2.22, 4.83)**	**2.65 (1.74, 4.03)**	1.07 (0.80, 1.45)	**1.43 (1.06, 1.91)**
38–39 weeks	1.26 (0.98, 1.63)	0.97 (0.71, 1.34)	1.22 (0.95, 1.56)	1.07 (0.84, 1.36)
40–44 weeks	Reference	Reference	Reference	Reference
Male sex	0.67 (0.51, 0.88)	0.81 (0.62, 1.06)	1.00 (0.82, 1.22)	1.00 (0.79, 1.26)
Size for GA				
SGA	**2.16 (1.49, 3.15)**	**1.91 (1.31, 2.80)**	1.36 (0.90, 2.05)	1.47 (0.99, 2.19)
AGA	Reference	Reference	Reference	Reference
LGA	0.93 (0.48, 1.80)	0.84 (0.43, 1.65)	0.72 (0.44, 1.17)	0.72 (0.47, 1.09)
Antenatal diagnosis	**2.17 (1.60, 2.96)**	**1.52 (1.03, 2.22)**	1.20 (0.91, 1.59)	0.99 (0.73, 1.34)
Genetic syndrome or extracardiac anomaly	**3.18 (1.98, 5.10)**	**2.20 (1.45, 3.34)**	1.43 (0.99, 2.06)	**1.32 (1.01, 1.74)**
Preoperative characteristics				
Preoperative CICU stay	**1.71 (1.03, 2.84)**	1.34 (0.76, 2.35)	**1.65 (1.09, 2.50)**	**1.43 (1.12, 1.83)**
Any preoperative risk factors#	**1.41 (1.09, 1.84)**	**1.79 (1.38, 2.31)**	1.15 (0.89, 1.49)	**1.48 (1.15, 1.89)**
Operative characteristics				
STAT category				
1 −2	Reference	Reference	Reference	Reference
3	1.06 (0.19, 5.93)	1.20 (0.24, 6.09)	0.61 (0.36, 1.05)	**0.55 (0.34, 0.88)**
4	**16.35 (2.81, 94.97)**	**14.56 (2.62, 80.92)**	1.53 (0.93, 2.54)	**1.93 (1.26, 2.94)**
5	**24.20 (3.96, 147.82)**	**24.28 (4.33, 136.19)**	**2.42 (1.36, 4.31)**	**2.95 (1.73, 5.03)**

-see table 2