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ORIGINAL RESEARCH

Predictors of postoperative outcomes in infants with low birth weight undergoing congenital heart surgery: a retrospective observational study

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Background: Despite improvements in neonatal cardiac surgery and postoperative care, hospitalized death for infants with low birth weight remains high.

Objective: This study sought to identify predictors of postoperative outcomes in low-birth-weight infants undergoing congenital heart surgery and establish nomograms to predict postoperative intensive-care unit (ICU) stay.

Methods: From June 2009 to June 2018, a retrospective review of 114 infants with low birth weight (≤2.5 kg) undergoing congenital heart surgery was conducted at Guangdong Provincial People's Hospital. Purely surgical ligation of patent ductus arteriosus was excluded from this study. A total of 26 clinical variables were chosen for univariate, multivariate, and Cox regression analysis, and 14 variables were analyzed as predictors of postoperative outcomes. Nomograms were established to predict risk of postoperative cardiac ICU (CICU) stay, postoperative neonatal ICU (NICU) stay, and total ICU length of stay in infants with cardiac diseases.

Results: Two variables were independent predictors in multiple logistic regression analysis of hospitalized death: operation weight and Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery (STAT) risk categories. Six variables were independent predictors in the Cox model of postoperative ICU length of stay, including sex, prematurity, birth weight, preoperative stay time in NICU, diagnostic classification, and STAT risk categories. We calculated concordance-index values to estimate the discriminative ability of models of risk of postoperative CICU stay, postoperative NICU stay, and total ICU length of stay, with values of 0.758 (95% CI 0.696–0.820), 0.604 (95% CI 0.525–0.682), and 0.716 (95% CI 0.657–0.776), which indicated the possibility of true-positive results.

Conclusion: Our findings might help clinicians predict postoperative outcomes and optimize therapeutic strategies.

Keywords: low birth weight, congenital heart disease, neonatal cardiac surgery, outcome prognosis, predictive tools, nomogram

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Introduction

The term "low birth weight" (LBW) denotes infants born weighing ≤2.5 kilograms, which includes those born preterm or small for gestational age.[1] The probability of cardiovascular malformation in preterm infants is double that of those born at term.[2] Infants with congenital heart disease have a high probability (8%–23%) of LBW, and vary in specific cardiac malformation.[2–4] While waiting for weight gain over the weeks, these infants are at greater risk of pulmonary infection, gastrointestinal ischemia, anemia, hypoxic ischemic encephalopathy, and myocardial dysplasia.[5]

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Despite improvements in surgical techniques, extracorporeal circulation, and intensive care over the last few decades, many cardiac centers have reported increased mortality rates of LBW infants with cardiac surgery — 10%–24%.[6–8] However, risk factors of LBW infants with cardiac surgery are still controversial, and there is no effective prediction system at present.[9] Furthermore, few researchers have paid attention to the impact of LBW on postoperative hospital stay.

The aim of this study was to investigate risk factors related to postoperative outcomes in LBW infants undergoing congenital heart surgery and establish nomograms that will predict postoperative intensive-care unit (ICU) length of stay.

Methods

Study design and patient population

This study was conducted in accordance with the Declaration of Helsinki and was also approved by the Medical Ethics Committee of Guangdong Provincial People's Hospital. Patient consent to review their medical records was not required, as this was an observational retrospective study that did not infringe upon the interests or rights of the patients. All data were strictly confidential. After acquiring institutional review board approval and permission to waive consent, the electronic medical records of 114 LBW infants undergoing congenital heart surgery from January 2009 to January 2018 were conducted. This article followed the STROBE checklist for observational studies. As a heart center of southern China, the quantity of our cardiac surgery has increased steadily every year, reaching 5,619 cases in 2017, over 100 of which were neonatal heart operations. The neonatal cardiac intensive-care section is staffed with highly trained neonatal cardiac intensive-care cardiologists and nurses, neonatal respiratory therapists, and neonatal nutritionists. Purely surgical ligation of patent ductus arteriosus was excluded from this study.

Data collection

We recorded characteristics of all patients from the electronic medical record systemas follows. The preoperative section comprised sex, prematurity (yes/no), gestational age, birth weight, age at operation, operation weight, preoperative concurrent diseases, preoperative ventilation (yes/no), preoperative pulmonary overcirculation (yes/no), preoperative stay in neonatal ICU (NICU), emergency operation (yes/no), diagnostic classification, and Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery (STAT risk categories). The intraoperative section comprised cardiopulmonary bypass (CPB) time, clamp time, deep hypothermic circulatory arrest (DHCA) (yes/no), DHCA time, and delayed sternal closure (yes/no). The postoperative section comprised trachea reintubation (yes/no), unplanned reoperation (yes/no), postoperative complications, postoperative ventilation time, postoperative stay in cardiac ICU (CICU), postoperative time in NICU, total ICU length of stay, hospitalized death (yes/no), and death cause.

STAT risk categories were based on the definition established by O'Brien et al,[10] and diagnostic classification was characterized as compound deformity, univentricular deformity, biventricular deformity, and macrovascular deformity. Preoperative pulmonary overcirculation was mainly diagnosed with chest radiography. Researchers and research assistants were trained and responsible for quality control of data acquisition and entry.

Statistical analysis

Catagorical data are expressed as proportions, and quantitive data as medians and ranges. Data were classified as characteristics before, at, and after surgery. Catagrical outcomes were regressed with a logistic model, in all independent variables that achieved a significance level of 20% in univariate analysis were included in a multivariate logistic regression model and examined by stepwise backward elimination. Likelihood-ratio tests were used to select variables in the multivariate model and check the goodness of fit. Quantitive outcomes were analysed with the Cox proportional-hazard model and examined by stepwise backward elimination with the Akaike information criterion (AIC). Models were validated by calibration plots and discrimination plot (C-index). Statistical analyses were conducted with R version 3.4.1. $P<0.05$ was considered statistically significant for all modeling.

Construction and calibration of nomograms

Perioperative deaths were deleted in the nomograms to predict risk for postoperative CICU stay, postoperative NICU stay, and total ICU length of stay in infants with cardiac diseases. Based on the results obtained from the Cox proportional-hazard model, nomograms were established to predict risk of postoperative outcomes using the R package. A score was assigned to identified factors according to their regression coefficients, which will be convenient for clinical usage. We calculated the C-index to estimate the discriminative ability of models of risk. The maximum value of the C-index is 1, referring to perfect discrimination, whereas 0 refers to no discrimination ability.[11]

Results

Patient characteristics

From January 2009 to January 2018, 185 LBW infants undergoing congenital heart surgery were included. Of these, 71 infants with purely surgical ligation of patent ductus arteriosus were removed. Therefore, our final comparative study comprised 114 infants, and patient characteristics (before, at, and after surgery) are shown in Table S1. Diagnosis, operation,and mortality of the infants are shown in Table 1. A total of 24 cases died during hospitalization, the overall mortality rate was 21.1%, of which four cases died during operation, 12 cases died early after operation (72 hrs), and 3 cases had treatment ceased.

Univariate and multivariate logistic analysis of hospitalized death

Ten risk factors were found to show significant differences in the univariate analysis of hospitalized death (Table 2). When these factors were further entered into the multivariate logistic model checked by the likelihood-ratio test, only two were independent predictors in multiple logistic regression analysis (Table 3: operation weight (OR 0.17, 95% CI 0.03–0.85; P=0.031) and STAT risk categories (OR 1.97, 95% CI 1.21–3.22; P=0.006).

Cox proportional-hazard model

Perioperative deaths were deleted in the Cox proportional-hazard model. Quantitive outcomes (postoperative CICU/

Table 1 Diagnosis, operation, and mortality of 114 infants

Diagnosis	Number	Operation	n	Death
CoA ± PDA	8	CoA correction ± PDA ligation	8	1
PA + IVS	5	AP shunt + Brock Reconstruction of RVOT	4 1	2
PA + VSD	8	Blalock–Taussig shunt Reconstruction of RVOT	4 4	1 1
PS ± ASD or VSD	10	PS correction + ASD/VSD repair PS correction	6 4	1
VSD/ASD/PFO	36	VSD/ASD/PFO correction	36	3
ASD + AP window	2	ASD + AP window repair	2	
TOF	9	TOF radical correction TOF palliative correction	3 6	1 2
TAPVC	6	TAPVC correction	6	3
TGA + IVS	8	Switch Modified Rastelli Blalock–Taussig	6 1 1	1
TGA + VSD	7	Switch Modified Rastelli	6 1	2
CoA + VSD ± ASD	7	CoA correction+VSD± ASD	7	2
PTA ± VSD	4	PTA correction ±VSD repair	4	3
IAA ± VSD	4	IAA correction ±VSD repair IAA correction	3 1	1

Abbreviations: PDA, patent ductus arteriosus; CoA, coarctation of aorta; ASD, atrial septal defect; VSD, ventricular septal defect; PFO, patent foramen ovale; TOF, tetralogy of Fallot; TAPVC, total anomalous pulmonary venous drainage; TGA, (complete) transposition of great arteries; IVS, interventricular septum; PA, pulmonary atresia; PS, pulmonary artery stenosis; PTA, permanent trunk of artery; IAA, interruption of aortic arch; AP, aortopulmonary.

Table 2 Univariate risk analysis for hospitalized death in low-birth-weight infants

	Survivors (n=90)	Hospitalized deaths (n=24)	Wilcoxon rank-sum test with continuity correction, *P*-value
Gestational age (weeks)	36.00±2.87	35.26±3.35	0.346
Birth weight (kg)	1.96±0.43	1.98±0.38	0.9612
Operation weight (kg)	2.20±0.38	2.10±0.31	0.0388
Preoperative stay in NICU (days)	11.39±13.48	13.00±10.98	0.4904
CPB time (minutes)	86.38±59.72	133.67±97.51	0.0244
Clamp time (minutes)	46.08±39.01	72.75±60.37	0.0632
DHCA time (minutes)	4.43±11.75	9.29±18.05	0.2544
Postoperative ventilation time (days)	9.41±17.86	6.00±8.39	0.0043
Postoperative stay time in CICU (days)	3.78±3.49	3.08±3.68	0.0446
Total length of stay (days)	39.76±31.66	19.58±13.29	<0.001
Sex (male)	59 (65.6%)	15 (62.5%)	0.7847
Prematurity	55 (61.1%)	14 (58.3%)	0.8086
Preoperative ventilation	36 (40.0%)	6 (25.0%)	0.1791
Preoperative pulmonary overcirculation	47 (52.2%)	5 (20.8%)	0.0064
Emergency operation	8 (8.9%)	4 (16.7%)	0.2749
STAT risk categories			
1	18 (20.0%)	2 (8.3%)	0.1855
2	34 (37.8%)	4 (16.7%)	0.0528
3	16 (17.8%)	2 (8.3%)	0.264
4	19 (21.1%)	15 (62.5%)	<0.001
5	3 (3.3%)	1 (4.2%)	0.8529
Delayed sternal closure	35 (38.9%)	11 (45.8%)	0.5423
Trachea reintubation	19 (21.1%)	2 (8.3%)	0.1547
Unplanned reoperation	19 (21.1%)	5 (20.8%)	0.9804

Abbreviations: NICU, neonatal intensive-care unit; CICU, cardiac ICU; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery.

Table 3 Multivariate logistic analysis for hospitalized death in low-birth-weight infants

Outcome	Independent variables ($p \leq 0.2$)	Adjusted OR	95% CI	*P* (*Z*)	Model likelihood-ratio test
Death	Intercept	2.83	0.07–119.53	0.5867	LR 21.40 (χ^2)
	Operation Weight	0.17	0.03–0.85	0.0312	$P<0.0001$ (χ^2)
	STAT risk Categories	1.97	1.21–3.22	0.0062	

Abbreviation: STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery.

NICU stay, total ICU length of stay) were fitted to the model and covariates selected by stepwise backward elimination with the AIC (Table S2). Five variables were independent predictors in the Cox model for postoperative CICU stay: sex, prematurity, preoperative stay in NICU, diagnostic classification, and STAT risk categories. Two variables were independent predictors in the Cox model for postoperative NICU stay: gestational age and STAT risk categories. Three variables were independent predictors in the Cox model for total ICU length of stay: birth weight, preoperative stay in the NICU, and STAT risk categories.

Nomogram model

Based on the results obtained from multiple logistic regression and the Cox model, nomograms were established to predict risk of postoperative stay in the CICU and NICU and total ICU length of stay of LBW patients born with cardiac diseases (Figures 1–3). We calculated C-index values to estimate the discriminative ability of models of risk of postoperative stay in the CICU and NICU and total ICU length of stay — 0.758 (95% CI 0.696–0.820), 0.604 (95% CI 0.525–0.682), and 0.716 (95% CI 0.657–0.776), respectively — which indicated the possibility of true-positive results. AIC values for postoperative stay in the CICU and NICU and total ICU length of stay were 610.8, 600.1, and 577.5.

Discussion

Despite good outcomes for many infants, great challenges remain in improving outcomes in LBW infants with congenital

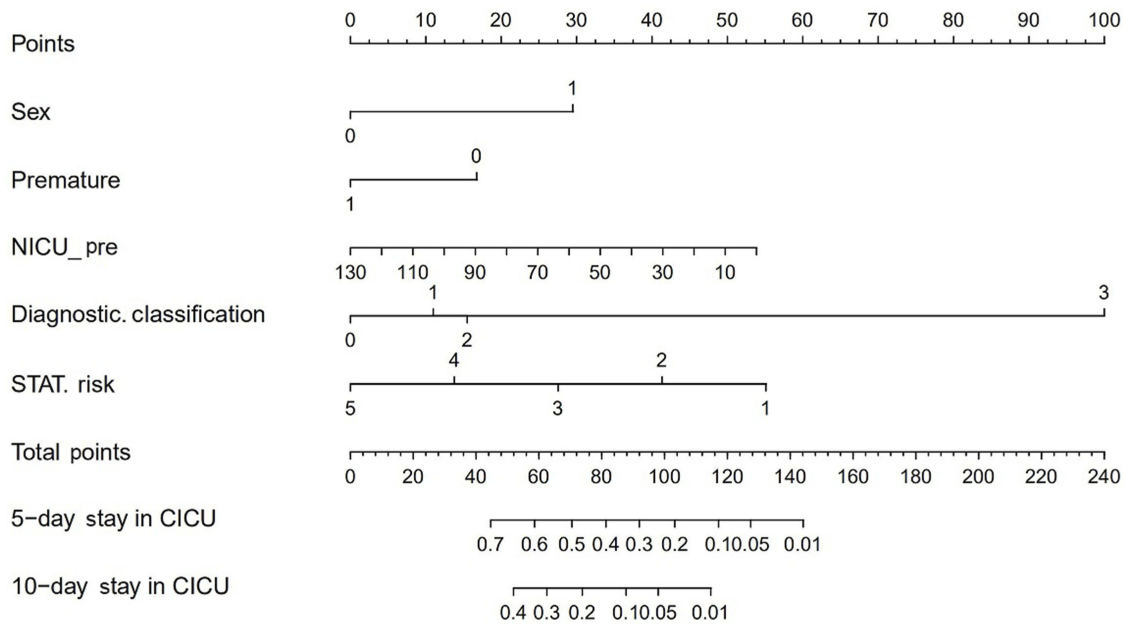

Figure 1 Nomogram prediction of postoperative stay time in CICU.
Abbreviations: STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery; NICU, neonatal intensive-care unit; CICU, cardiac ICU.

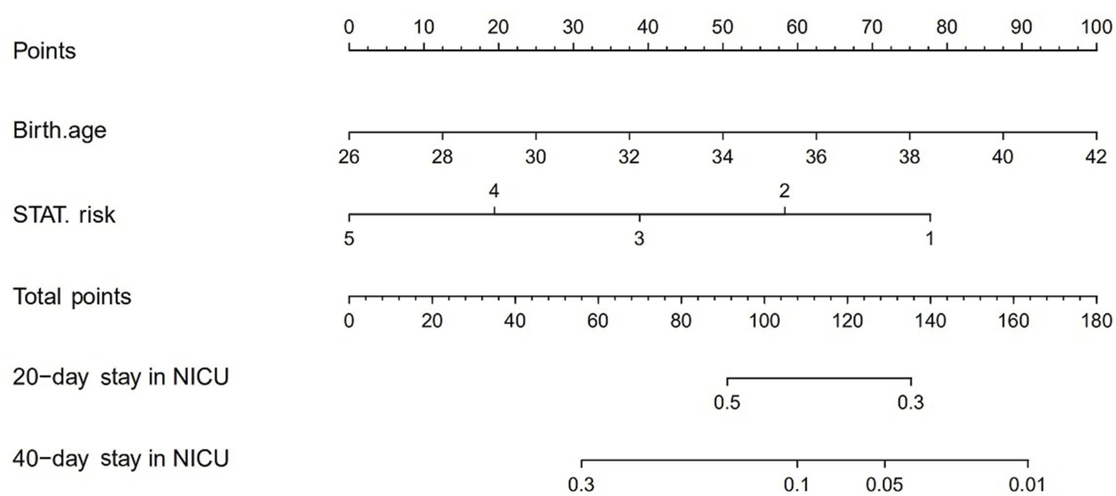

Figure 2 Nomogram prediction of postoperative stay time in NICU.
Abbreviations: STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery; NICU, neonatal intensive-care unit

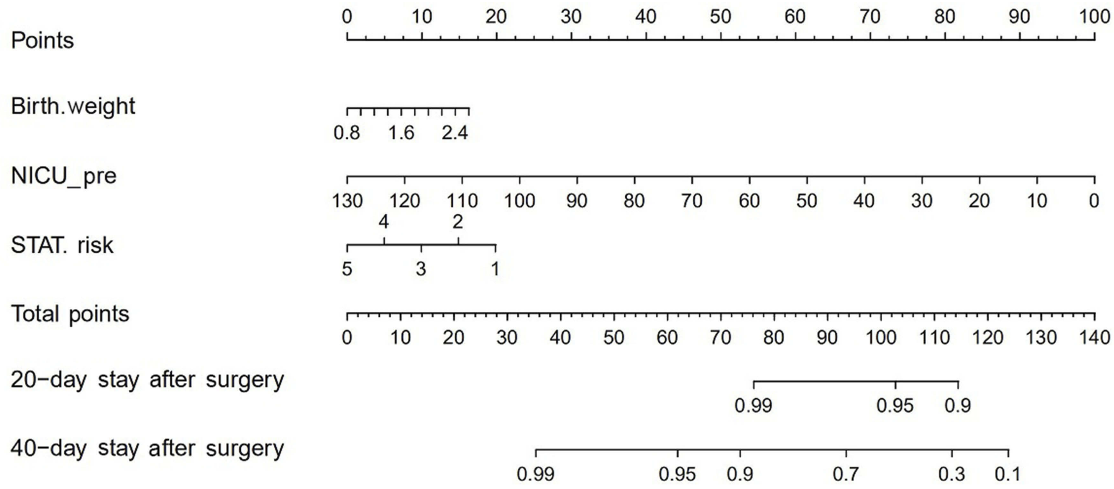

Figure 3 Nomogram prediction of total ICU length of stay.

Notes: Premature — 0 = no, 1 = yes; diagnostic classification — 0 = compound deformity, 1 = univentricular deformity, 2 = biventricular deformity, 3 = macrovascular deformity.

Abbreviations: Pre, preoperative; ICU, intensive-care unit; NICU, neonatal ICU; STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery.

heart disease.[12] Postoperative outcomes depend not only on surgical techniques but also on many other factors, such as anesthesia, intensive care and patient-specific characteristics.[13] Therefore, prognostic estimation and perioperative management of infants undergoing congenital cardiac surgery are critical for patients' health and prognosis.

A recent study from Westmead Children's Hospital in Australia reported that low operation weight remained associated with high mortality rates.[14] Analysis of the Society of Thoracic Surgeons Congenital Heart Surgery database from 32 participating centers reached a similar conclusion.[12] Consistently with previous studies, we found that low operation weight was a significant risk factor for mortality in LBW infants with congenital heart disease, which stresses the importance of understanding the certain danger. The Society of Thoracic Surgeons database indicated that lower weight consistently raised the risk of mortality after risk classification.[12] Our data confirmed the verification of STAT risk categories as these applied to the Chinese population, and indicated a strong relationship between STAT risk categories and postoperative mortality.

As far as we know, length of ICU stay, a principal indicator of medical quality, has a great impact on admission policy, surgical arrangement, and costs. Identification of risk factors influencing ICU hospitalization after cardiac surgery can not only provide reliable risk adjustment for administrative data but also enhance overall quality. Recently, several factors have been identifed as risk factors of prolonged ICU stay, such as gestational age, operation weight, preoperative ventilation, single-ventricle anomalies, STAT risk categories, CPB time, clamp time, and postoperative complications.[15–19] Consistently with Pagowska-Klimek's study, we have not found a close relationship between DHCA time and total postoperative ICU length of stay.[16] Our study confirmed the usefulness of STAT risk categories as means of predicting postoperative CICU stay, NICU stay, and total ICU length of stay, which was consistent with Brown et al.[18] CPB time is now well recognized as a risk factor associated with ICU length of stay in both children and adults.[20,21] However, our study found that CPB time was not an independent predictor of postoperative ICU stay in LBW infants. We identified sex as an independent predictor of postoperative CICU stay, largely due to differences in STAT risk categories between the sexes.

LBW infants often suffer from severe morbidity of prematurity and intrauterine growth restriction.[5] The latter raises rates of respiratory distress syndrome and bronchopulmonary dysplasia in premature babies.[22,23] Also, LBW infants with congenital heart disease tend to be critically ill and their condition complicated by noncardiac malformation. Over the past few decades, numerous single-center studies have documented increased morbidity and mortality correlated with cardiac surgery in LBW infants.[7–9] However, few studies have focused on the impact of LBW on postoperative length of hospitalization. As these LBW infants with varied adverse risk factors start to have advanced survival, the morbidity burden would be aggravated with a commensurate rise in the length of hospitalization. Our study showed that gestational age, birth weight, and STAT risk categories were significant predictors in postoperative NICU stay and total length of ICU stay. Nevertheless, further larger studies are needed to validate the impact of LBW on postoperative length of hospitalization.

To the best of our knowledge, no accurate prediction model specific for LBW infants with cardiac surgery exists. In the present study, we examined risk factors associated with postoperative outcomes and established nomograms to estimate the risk of postoperative length of hospitalization in LBW infants with cardiac surgery. Each factor included in the nomograms was attributed a risk score, and integration of these risk scores can provide potential incidence of postoperative length of hospitalization. Moreover, the nomograms that we have established had good discrimination ability and good concordance-index values in the present series.

Limitations

Several limitations have to be admitted in our study. First, it was a retrospective single-center study with a limited number of cases. Collecting and analyzing Chinese major cardiac multiinstitutional data set of LBW patients is thus an essential part of our plan, and will be the subject of communication in the future. Second, there was a lack of long-term postdischarge follow-up to predict long-term mortality and morbidity. Finally, while the nomograms indicated good efficacy to predict postoperative outcomes in our hospital, they may not apply to other patient populations. External validation of the nomograms in a multicenter database is thus necessary. Despite these limitations, our study has developed nomograms that will effectively predict postoperative outcomes for LBW infants undergoing congenital heart surgery.

Conclusion

Our novel nomogram predictions are tools that provide risk adjustment for administrative data that might help clinicians predict postoperative outcomes and optimize therapeutic strategies. Further studies with large samples are encouraged to ensure their application in multiple institutions.

Abbreviation list

PDA, patent ductus arteriosus; CoA, coarctation of aorta; ASD, atrial septal defect; VSD, ventricular septal defect; PFO, patent foramen ovale; TOF, tetralogy of Fallot; TAPVC, total anomalous pulmonary venous drainage; TGA, (complete) transposition of great arteries; IVS, interventricular septum; PA, pulmonary atresia; PS, pulmonary artery stenosis; PTA, permanent trunk of artery; IAA, interruption of aortic arch, AP, aortopulmonary, LBW, low birth weight, IGUR, intrauterine growth restriction, STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery; ICU, intensive-care unit; NICU, neonatal ICU; CICU, cardiac ICU; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest.

Availability of data and material

All data supporting our findings will be shared on request. Contact Sheng Wang via shengwang_gz@163.com.

Ethics approval and consent to participate

The Institutional Review Committee of Guangdong Provincial People's Hospital approved this study, and all investigations were conducted in accordance with ethical research principles. Patient consent was not required.

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Author contributions

SW, JZ, LY, and CL designed the study. CL, LY, SW, JZ, and JW gathered the data. JC, SW, JZ, LY, and CL analyzed the data. CL, LY, JW, JC, JZ, and SW wrote the manuscript and agree to be responsible for its contents. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work

Disclosure

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Supplementary material

Table S1 Patient characteristics of 114 infants undergoing congenital heart surgery

	Counts(%)
Sex (male)	65% (n=74)
Premature	61% (n=69)
Gestational age (weeks, median)	36.3 (range 25.1–42.0)
Birth weight (kg, median)	2.02 (range 0.9–2.5)
Age at operation (days, median)	27.0 (range 3–97)
Operation weight (kg, median)	2.25 (range 1.1–2.7)
STAT risk categories: -1 -2 -3 -4 -5	 17.5% (n=20) 33.3% (n=38) 15.8% (n=18) 29.8% (n=34) 3.5% (n=4)
CPB (minutes, median)	87.0 (range 0–326, n=112)
Clamp (minutes, median)	44.0 (range 0–195, n=112)
DHCA	19.5% (n=22, n=113)
DHCA (minutes, median)	20.0 (range 0–68, n=113)
Time of sternal closure -usual -delayed	 59.6% (n=68) 40.4% (n=46)
Unplanned reoperation	21.1% (n=24)
CICU after surgery (days, median)	3.0 (range 0–23)
Mechanical ventilation time after surgery (days, median)	5.0 (range 0–164)
NICU after surgery (days, median)	15.0 (range 0–245)
Total length of stay (days, median)	29.5 (range 0–267)

Abbreviations: NICU, neonatal intensive-care unit; CICU, cardiac ICU; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery.

Table S2 Cox proportional-hazard model of quantitive outcomes

	Covariates	OR	95% CI
CICU (days)	Sex = 1	2.1353	1.2401–3.489
	Premature = 1	0.6499	1.2401–3.490
	NICU Pre	0.9894	1.2401–3.491
	Diagnostic classification = 1	1.3264	1.2401–3.492
	Diagnostic classification = 2	1.4891	1.2401–3.493
	Diagnostic classification = 3	13.0881	1.2401–3.494
	STAT risk	0.7017	1.2401–3.495
NICU (days)	Gestational age	1.0811	1.2401–3.496
	STAT risk	0.7847	1.2401–3.497
Total stay (days)	Birth weight	1.7423	1.2401–3.498
	NICU Pre	0.9539	1.2401–3.499
	STAT risk	0.7376	1.2401–3.500

Abbreviations: Pre, preoperative; NICU, neonatal intensive care unit; CICU, cardiac ICU; STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery.