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ORIGINAL ARTICLE

Outcomes and Risk Factors for Mortality in Premature Neonates With Critical Congenital Heart Disease

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Abstract We sought to describe contemporary outcomes and identify risk factors for hospital mortality in premature neonates with critical congenital heart disease who were referred for early intervention. Neonates who were born before 37 weeks' gestation with critical congenital heart disease and admitted to our institution from 2002 to 2008 were included in this retrospective cohort study. Critical congenital heart disease was defined as a defect requiring surgical or transcatheter cardiac intervention or a defect resulting in death within the first 28 days of life. Logistic regression analyses were performed to identify risk factors for mortality before hospital discharge. The study included 180 premature neonates, of whom 37 (21%) died during their initial hospitalization, including 6 (4%) before cardiac intervention and 31 (17%) after cardiac intervention. For the 174 patients undergoing cardiac intervention, independent risk factors for mortality were a 5 min Apgar score $\leq$7, need for preintervention mechanical ventilation, and Risk Adjustment in Congenital Heart Surgery category $\geq$4 or not assignable. Mortality for premature infants with critical congenital heart disease who are referred for early intervention remains high. Patients with lower Apgar scores who receive preintervention mechanical ventilation and undergo more complex procedures are at greatest risk.

Keywords Gestational age · Heart defects, congenital · Intensive care · Premature birth

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Introduction

In the United States, it is estimated that congenital heart disease complicates the care of at least 6500 premature neonates annually [30]. Both prematurity and birth weight <2500 g are known risk factors for hospital mortality in neonates with congenital heart disease [1, 9, 13]. The small size of cardiovascular structures and immaturity of myocyte calcium handling proteins and multiple other organ systems are likely contributory [32].

The optimal timing and type of intervention in premature neonates with complex congenital heart disease remains controversial. In a cohort of low–birth weight patients with complex cardiac lesions who received care in our institution between 1987 and 1991, the overall early mortality rate was 30% [6]. Patients in that study undergoing early complete repair tended to have improved outcomes compared with those undergoing initial palliative surgery or prolonged medical management while awaiting weight gain or maturation. Thus, our general institutional strategy for premature or low–birth weight neonates with critical congenital heart disease has been to recommend early intervention with a preference for complete single-stage repair whenever possible.

More recently, we completed a study that sought to identify associations between gestational age and outcomes in 971 neonates with critical congenital heart disease [7]. Although the focus of that study was on the relation between gestational age and outcomes for patients born at term, we found that overall hospital survival for premature neonates in the cohort was only 79%, similar to the outcomes reported by several institutions during the last two decades in low–birth weight or premature neonates [1, 4, 6, 14, 24, 26]. These findings prompted the current detailed analysis of our contemporary experience with premature neonates having critical congenital heart disease. We sought to describe early outcomes and identify risk factors associated with increased mortality and morbidity.

Methods

In this retrospective single-center cohort study, we included all premature neonates <28 days of age with critical congenital heart disease who were referred to the cardiac intensive care unit (CICU) at Children's Hospital Boston for consideration of early cardiac intervention between January 1, 2002, and December 31, 2008. Prematurity was defined as birth before 37 weeks' completed gestation as assigned by obstetrical providers. Critical congenital heart disease was defined as a congenital heart defect requiring surgical or transcatheter cardiac intervention or a defect resulting in death within the first 28 days of life [10]. We excluded premature neonates who had congenital heart disease but who did not require a surgical or transcatheter intervention during the first 28 days of life, patients with structurally normal hearts who were admitted with isolated tachyarrhythmias, and patients who had a combination of critical congenital heart disease, severe chromosomal anomalies (e.g., trisomy 18), and/or multiple birth defects if the medical team and parents elected not to pursue cardiac surgical or transcatheter intervention. We also excluded patients who underwent an initial cardiac surgical procedure at another institution as well as those who only required ligation of a patent ductus arteriosus (PDA).

We reviewed medical records for each patient and recorded prenatal, postnatal, and intervention-related variables that were plausibly associated with the outcomes of interest. Prenatal and postnatal variables included several markers of nonreassuring fetal status before delivery (e.g., polyhydramnios, oligohydramnios, hydrops fetalis, or nonreassuring antepartum fetal testing). We noted whether the patient's congenital heart disease was diagnosed prenatally, the location of delivery (two adjacent hospitals: Brigham and Woman's Hospital or Beth Israel Deaconess Medical Center *vs*. other), and vaginal or Cesarean mode of delivery. We noted each patient's sex, 1- and 5-min Apgar scores, birth weight, and whether the birth weight was small for gestational age (defined as z-score <–2). We recorded the presence of major noncardiac structural (e.g., tracheoesophageal fistula, duodenal atresia) or chromosomal anomalies; respiratory distress syndrome (RDS; defined as the need for surfactant); use of prostaglandin-E1 (PGE) before intervention; and need for mechanical ventilation or inotropic support before intervention.

Intervention-related data collected included whether each patient underwent primary cardiac surgical or transcatheter intervention as well as the duration of cardiopulmonary bypass. The primary cardiac intervention was identified as the definitive procedure intended to allow the patient to be discharged from the hospital. The cardiac intervention was also designated as corrective (e.g., arterial switch surgery for transposition of the great arteries) or palliative (e.g., pulmonary artery banding in the presence of a ventricular septal defect [VSD]). We recorded patient age and corrected gestational age at time of initial intervention. Each patient was assigned a Risk Adjustment in Congenital Heart Surgery (RACHS)-1 category [13]. RACHS-1 is a validated risk adjustment method that groups cardiac surgical procedures with similar expected in-hospital mortality rates into six predefined risk categories, in which category 1 has the lowest risk for death (e.g., secundum atrial septal defect closure), and category 6 has the highest risk for death (e.g., stage 1 Norwood surgery). The RACHS-1 system was modified for the purposes of this study to include two additional patient categories: one for patients who underwent primary transcatheter intervention and another for surgical patients who could not be assigned an established RACHS-1 category (e.g., heart transplant, hybrid procedure for hypoplastic left heart syndrome consisting of bilateral pulmonary artery banding and ductus arteriosus stenting).

The primary outcome variable was in-hospital mortality for patients undergoing cardiac intervention. Secondary outcomes included morbid events, such as cardiopulmonary resuscitation (CPR; defined as need for chest compressions), need for extracorporeal membrane oxygenation (ECMO), occurrence of radiographically documented central nervous system (CNS) injury (grade II or higher intraventricular hemorrhage, ischemic stroke, or periventricular hemorrhagic infarction), necrotizing enterocolitis (NEC; defined by the presence of pneumatosis or free air on abdominal radiograph), and unplanned reoperation or interventional cardiac catheterization for one or more residual anatomic lesions during the same hospitalization. A composite morbidity outcome variable was created for surviving patients who experienced one or more of these five serious events: CPR, ECMO, CNS injury, NEC, or unplanned cardiac reintervention. Additional outcomes reported but not included in the composite outcome included the development of health care–associated infections (bloodstream, surgical site, or urinary tract), duration of mechanical ventilation, need for unplanned reintubation, unplanned CICU readmission (readmission to CICU during the same hospitalization after initial transfer to cardiac ward after intervention), duration of CICU and hospital stay, transfer to an outside institution for further convalescence, and unplanned readmission to our institution within 30 days of hospital discharge. Intermediate-term survival was determined by recording vital status at the time of the most recent clinical documentation (e.g., clinic note, outside hospital correspondence). This study was approved by the Committee on Clinical Investigation and Children's Hospital Boston, and the need for written, informed consent was waived.

Statistics

Descriptive statistics include frequencies and percentages for categorical variables and medians and ranges for continuous variables. Pearson's chi-square, Fisher's exact, and Wilcoxon rank sum tests were used, as appropriate, to compare patients with in-hospital mortality versus survivors. Variables with $P < 0.1$ in these univariable analyses were considered for stepwise model selection using multivariable logistic regression models to identify independent risk factors for mortality (adjusted $P < 0.05$) and the composite morbidity outcome. Patients who developed severe end-organ injury and died before attempted cardiac intervention were excluded from the primary analyses. Kaplan-Meier estimates were used to estimate survival time distributions. SAS Software, version 9.1, of the SAS System for Windows (SAS, Cary, NC) was used for statistical analysis.

Results

Study Patients

Between January 1, 2002, and December 31, 2008, 1245 neonates were admitted to our CICU, including 222 (18%) patients who were born prematurely. Of these 222 patients, 42 were excluded for the following reasons: no cardiac intervention performed during their first month of life ($n = 36$); significant chromosomal abnormalities or multiple birth defects and treatment withdrawn before any cardiac intervention ($n = 4$), initial cardiac intervention at an outside institution ($n = 1$), and isolated PDA ligation ($n = 1$).

One hundred eighty patients were therefore included in the study. Of these, 174 (97%) patients underwent primary cardiac intervention, and 6 patients (3%) died before cardiac intervention. The primary cardiac intervention was interventional cardiac catheterization in 25 (14%) patients, and 149 (83%) patients underwent surgery, which included 38 (21%) stage I Norwood operations. The median age at time of the primary cardiac intervention was 6 days (median corrected gestational age 36.4 weeks). Additional demographic information, comorbidities, and interventional variables for the 174 premature neonates who underwent cardiac intervention are listed in Table 1, and the specific cardiac interventions performed are listed in Table 2.

Patient Outcomes and Risk Factors for Mortality

Of the 174 patients who underwent cardiac intervention, 31 (18%) died during their initial hospitalization. Intervention-specific hospital mortality rates are listed in Table 2. For patients undergoing intervention, 1-year survival was 78% and 5-year survival was 77% during a median follow-up time of 3.3 years. Univariable risk factors for hospital mortality are listed in Table 3. Demographic and preintervention variables associated with mortality included lower gestational age, 5-min Apgar score ≤7, need for mechanical ventilation and inotropic support before cardiac intervention, aortic arch obstruction, and a diagnosis of RDS. Notable preintervention variables that were not significantly associated with mortality included prenatal diagnosis of congenital heart disease, birth weight, birth weight that was small for gestational age, presence of a major noncardiac structural anomaly, and single-ventricle physiology.

Interventional variables associated with increased hospital mortality were corrected gestational age at intervention <34 weeks, RACHS-1 category ≥4, and longer cardiopulmonary bypass time. The type of initial cardiac intervention (surgery versus catheterization) and absolute age at intervention were not associated with mortality.

With multivariable analysis, the independent predictors of hospital mortality were 5-min Apgar score ≤7 (adjusted odds ratio [OR] 3.0; 95% confidence interval [CI] 1.2–7.4; $P = 0.02$), preintervention mechanical ventilation (adjusted OR 5.1; 95% CI 1.4–18.4; $P = 0.01$), and RACHS-1 category ≥ 4 (adjusted OR 3.7; 95% CI 1.5–9.1; $P = 0.002$).

Morbid Events and Risk Factors for Composite Morbidity End Point

Of the 174 patients undergoing intervention, CPR was required in 38 (22%); 35 (20%) required an unplanned surgical or transcatheter cardiac reintervention during the same hospitalization; ECMO support was used for 27 (16%); central nervous system injury occurred in 23 (13%); and 8 (5%) developed NEC. Table 4 lists morbidity rates for these and other outcomes along with unadjusted hospital mortality rates for those patients experiencing each morbid event.

Table 1 Demographic and intervention characteristics for 174 premature neonates undergoing cardiac interventions

	$n = 174$ (100%)
Prenatal diagnosis of congenital heart disease	98 (56)
Multiple gestation	35 (20)
Nonreassuring fetal status[a]	29 (17)
Delivery at adjacent hospital	82 (47)
Cesarean delivery	97 (56)
Gestational age (wk) at birth (range)	35.6 (26.0–36.9)
<34 weeks gestational age at birth	40 (23)
Birth weight in kg (range)	2.32 (0.69–4.04)
Birth weight small for gestational age[b]	8 (5)
Male sex	100 (57)
Major noncardiac anomaly	28 (16)
Identifiable chromosomal anomaly	12 (7)
Preintervention mechanical ventilation	114 (66)
RDS	38 (22)
Preintervention inotropic support	96 (55)
Single ventricle	50 (29)
Aortic arch obstruction	86 (49)
Preintervention prostaglandin E1 use	127 (73)
Total days (range) prostaglandin E1[c]	2 (0–81)
Intervention characteristics	
Days of age (range) at first intervention	6 (0–26)
Corrected gestational age (wk) at first intervention (range)	36.4 (27.1–40.0)
Initial cardiac intervention	
Surgery	149 (86)
Cardiac catheterization	25 (14)
RACHS-1 category	
Cardiac catheterization	25 (14)
1	0 (0)
2	25 (14)
3	43 (25)
4	28 (16)
5	1 (1)
6	38 (22)
Not assignable	14 (8)

Data reported as number of patients (%) or median (range)

[a] Defined as intrauterine growth restriction, hydrops, nonreassuring fetal heart tracing, or failed stress test

[b] Defined as birth weight with Z-score < –2

[c] Including both preintervention and postintervention administration of prostaglandin E1

Table 2 Cardiac interventions and intervention-specific hospital mortality for 174 premature neonates

Intervention	No. (%) of interventions	No. (%) of intervention-specific hospital mortalities
Stage I Norwood surgery	38 (22)	9 (24)
Arterial switch		
Without additional lesion	18 (10)	1 (6)
With coarctation repair	1 (1)	0 (0)
With VSD closure	5 (3)	0 (0)
With VSD closure/ coarctation repair	4 (2)	3 (75)
Tetralogy of Fallot repair	18 (10)	3 (17)
Coarctation repair	15 (9)	1 (7)
Balloon dilation of pulmonary valve	12 (7)	0 (0)
Balloon dilation of aortic valve	8 (5)	1 (13)
Pacemaker placement	7 (4)	0 (0)
Repair of truncus arteriosus	7 (4)	1 (14)
VSD closure/coarctation repair	7 (4)	2 (29)
Blalock–Taussig shunt (modified)	6 (3)	0 (0)
Balloon dilation of coarctation	4 (2)	1 (25)
Hybrid procedure for hypoplastic left heart syndrome[a]	4 (2)	1 (25)
Total anomalous pulmonary venous return repair	4 (2)	1 (25)
Other[b]	16 (10)	7 (44)

Interventions reported as number of patients (% of total patients). Intervention-specific hospital mortality reported as number of patients (% within each intervention group)

[a] Bilateral pulmonary artery banding with ductus arteriosus stenting

[b] Includes procedures that occurred ≤2 times during study period (e.g., aortopulmonary window repair, balloon dilation of tricuspid valve, mitral/aortic valvuloplasty)

For patients who underwent a cardiac intervention and survived to hospital discharge ($n = 143$), 40 (28%) reached the composite morbidity outcome. Independent risk factors for reaching this end point were 5-minute Apgar score ≤7 (adjusted OR 3.7; 95% CI 1.4–9.8; $P = 0.009$), single-ventricle physiology (adjusted OR 2.7; 95% CI 1.2–6.2; $P = 0.02$), and corrected gestational age at first cardiac intervention < 35 weeks (adjusted OR 2.7; 95% CI 1.1–6.7; $P = 0.04$).

Discussion

Numerous advances in the care of patients with congenital heart disease have lead to a marked improvement in overall outcomes. However, this study demonstrates that premature neonates with critical congenital heart disease who are referred for early cardiac intervention remain at substantial risk for mortality and morbidity. The most

Table 3 Comparison of risk factors by mortality for 174 premature neonates who underwent cardiac intervention

Variable	Nonsurvivors ($n = 31$)	Survivors ($n = 143$)	p
Demographic and preintervention variables (%)			
Prenatal diagnosis congenital heart disease	20 (65)	78 (55)	0.31
Multiple gestation	5 (16)	30 (21)	0.54
Nonreassuring fetal status[a]	8 (26)	21 (15)	0.13
Delivery at adjacent hospital	18 (58)	64 (45)	0.18
Cesarean delivery	20 (65)	77 (54)	0.28
Gestational age at birth (weeks)			0.02
$34–36^{6/7}$	19 (61)	115 (80)	
$30–33^{6/7}$	9 (29)	26 (18)	
<30	3 (10)	2 (1)	
Birth weight (kg)			0.97
>2.5	12 (39)	58 (41)	
2.0–2.5	9 (29)	41 (29)	
<2.0	10 (32)	44 (31)	
Birth weight small for gestational age[b]	0 (0)	8 (6)	0.35
Male sex	22 (71)	78 (55)	0.09
1-min Apgar ≤ 7[c]	18 (58)	59 (41)	0.09
5-min Apgar ≤ 7[c]	13 (42)	23 (16)	0.001
Major noncardiac anomaly	5 (16)	23 (16)	1.00
Identifiable chromosomal anomaly	1 (3)	11 (8)	0.70
Preintervention mechanical ventilation	28 (90)	86 (60)	0.001
RDS	12 (39)	26 (18)	0.01
Preintervention inotropic support	23 (74)	73 (51)	0.02
Single ventricle	11 (35)	39 (27)	0.36
Aortic arch obstruction	21 (68)	65 (45)	0.02
Days (range) preintervention prostaglandin E1 use	25 (81)	102 (71)	0.28
Total days (range) prostaglandin E1	3 (0–16)	2 (0–81)	0.26
Intervention variables (%)			
Age at first intervention (d)			0.89
≤5	12 (39)	56 (39)	
6–10	10 (32)	51 (36)	
≥11	9 (29)	36 (25)	
Corrected gestational age at first intervention <34 weeks	9 (29)	16 (11)	0.02
Initial cardiac intervention			0.58
Surgery	28 (90)	121 (85)	
Cardiac catheterization	3 (10)	22 (15)	
RACHS-1 category ≥ 4 or not assignable	22 (71)	59 (41)	0.003
Cardiopulmonary bypass time (min)			0.02
0	6 (19)	50 (35)	
1–150	11 (36)	63 (44)	
>150	14 (45)	30 (21)	

Data reported as number of patients (%) or median (range)

[a] Defined as intrauterine growth restriction, hydrops, nonreassuring fetal heart tracing, or failed stress test

[b] Defined as birth weight with z-score < –2

[c] Apgar scores not known for six patients

important risk factors for hospital mortality were 5-min Apgar score ≤7, preintervention mechanical ventilation, and greater surgical complexity. Morbidity in surviving patients was associated with lower 5-min Apgar scores, younger gestational age at first cardiac intervention, and single-ventricle physiology.

The overall hospital mortality rate for the 180 premature neonates who had critical congenital heart disease and who were referred for early cardiac intervention during this study period was 21%. This mortality rate is significantly greater than that experienced by patients managed in our center during the same time period with critical congenital

Table 4 Morbid events for 174 premature neonates who underwent cardiac intervention

Outcome	No. (%) of morbid events	No. of morbidity-specific hospital mortality (%)
Cardiopulmonary resuscitation[a]	38 (22)	19 (50)
Unplanned cardiac reintervention[a]	35 (20)	16 (46)
Extracorporeal membrane oxygenation[a]	27 (16)	19 (70)
CNS injury[a]	23 (13)	13 (57)
Necrotizing enterocolitis[a]	8 (5)	2 (25)
Infection	40 (23)	15 (38)
Unplanned reintubation	38 (22)	7 (18)
Unplanned CICU readmission	13 (7)	0 (0)
Transfer to another hospital	45 (26)	–
Rehospitalization within 30 days	17 (10)	–

[a] Data reported as number of patients (% of total patients). Morbidity-specific hospital mortality reported as number of patients (% within each morbid event)

[a] Included within composite morbidity outcome. During their initial hospitalization, 26 patients underwent unplanned cardiac surgical reintervention; six patients underwent unplanned reintervention by way of cardiac catheterization; and three patients underwent both types of reintervention

heart disease who were born between 37 and 38 weeks' completed gestation ($n = 360$ [7% hospital mortality]) or between 39 and 40 weeks' gestation ($n = 378$ [3% hospital mortality]) [7]. We noted in our previous study that compared with patients born at term, those who were premature had greater rates of fetal compromise, birth weight that was small for gestational age, major noncardiac structural anomalies, and chromosomal anomalies [7]. In addition to the underlying immaturity of multiple organ systems, all of these factors may contribute to worse outcomes in premature neonates with critical congenital heart disease compared with those born at term.

Most of the outcomes literature pertaining to this challenging patient population focuses on patients with a birth or surgical weight <2500 g rather than prematurity *per se*. Weight at surgery <2500 g has been shown in a multicenter study to be a risk factor for mortality in neonates with congenital heart disease [8]. In single-center studies that included term and preterm neonates with a birth weight or weight at time of surgery <2500 g, reported hospital mortality rates ranged from 10% to 24% [1, 4, 6, 22, 24, 27]. Dees *et al*. described a cohort of patients born between 1976 and 1999 who were both preterm and weighed less than 2500 g at birth and reported that overall cardiac surgical mortality was 19% [9]. Although direct comparisons between the outcomes reported in these studies and our findings are limited by differences in inclusion criteria and surgical era, the overall mortality rates are similar. The general lack of improvement in hospital mortality rates for this patient population during the last two decades is likely explained in part by the fact that more complex procedures (e.g., stage 1 Norwood surgery) are attempted during the current era. Nevertheless, the similarity in outcomes stresses the importance of understanding risk factors that place premature patients at greatest risk.

Previous investigations of low–birth weight neonates with congenital heart disease reported no association between prematurity or gestational age and surgical mortality [1, 4, 14, 21, 22, 27]. In contrast, data from this study and our recent investigation indicate that gestational age, and thus maturity, may be a more important predictor of outcomes than birth weight or weight at intervention in neonates with critical congenital heart disease [7].

The association between lower Apgar scores and mortality in this study is consistent with previous reports in neonates without cardiac defects. In a study of 151,891 live-born singletons without major malformations, including 13,399 preterm infants, a lower 5-min Apgar score was associated with an increased relative risk of death within the first 28 days of life [5]. Apgar scores may be reflective of fetal well-being in late gestation, tolerance of labor, adequacy of transitional cardiopulmonary physiology during the first few minutes of life, or quality of initial resuscitation.

The need for inotropic support, mechanical ventilation, and the development of RDS before cardiac intervention were risk factors for mortality in our study. Although speculative, intensive medical management with inotropes and mechanical ventilation could be indicative of unstable cardiopulmonary status leading up to intervention. In premature neonates, possible underdevelopment of arterioles in the pulmonary vascular bed may predispose patients with the potential for left-to-right shunting to develop a prompt postnatal decrease in pulmonary vascular resistance and overcirculation compared with term neonates having similar cardiac anatomy [20, 31]. Furthermore, mechanical ventilation in patients with left-to-right shunts may recruit collapsed alveoli and thus poorly perfused lung areas, thereby decreasing pulmonary vascular resistance and enhancing the propensity for pulmonary overcirculation [29]. Additional periods of mechanical ventilation may play a role in lung injury and systemic inflammation, as had been proposed in patients with acute RDS [25]. Avoidance of mechanical ventilation when possible and meticulous attention to cardiopulmonary interactions may be beneficial in this patient population to avoid adverse changes in pulmonary vascular resistance, lung injury, and systemic inflammation.

Greater surgical complexity and longer cardiopulmonary bypass time were important predictors of hospital mortality in this study. Both are well-established risk factors for mortality for pediatric cardiac surgical procedures in general, and longer cardiopulmonary bypass times have been associated with increased mortality in low–birth weight infants [4, 14, 24]. Cardiopulmonary bypass is associated with inflammation, immunoparesis, and disturbances in the coagulation system. The premature lung often exhibits surfactant dysfunction, which may be further compromised by cardiopulmonary bypass [12, 23]. In light of the association we identified between markers of lung disease and mortality, future studies are warranted to determine whether a subset of premature neonates may benefit from empiric perioperative surfactant administration or other innovative pulmonary therapies.

Prematurity is a known risk factor for infection, and the risk of infection is inversely related to gestational age [3]. In our study cohort of premature neonates with critical congenital heart disease, 23% developed a nosocomial infection versus a 14% infection rate in similar neonates born at 39 to 40 weeks' gestation [7]. Previous work has shown that cardiopulmonary bypass significantly alters the immune system, particularly cell-mediated immunity [11, 18]. Medical treatments to alter immune response after cardiopulmonary bypass in efforts to either suppress or restore immune function have been attempted [18, 28]. However, data are lacking regarding possible relations between cardiopulmonary bypass-related immune suppression and infections in the high-risk premature population. Palliative transcatheter interventions or "hybrid" techniques, aimed at decreasing or eliminating the need for neonatal exposure to cardiopulmonary bypass, may warrant consideration in selected patients, but issues related to vascular access, regulation of pulmonary blood flow, and other technical issues complicate such procedures.

The ideal age for cardiac intervention in neonates with critical congenital heart disease is unknown. Interestingly, we found no association between corrected gestational age at first cardiac intervention and mortality, but we did identify an independent association between intervention before 35 weeks' corrected gestation and increased morbidity in survivors. Systematically delaying intervention in such patients while awaiting growth or further maturation, however, may not be warranted because previous studies from our institution and others suggest that efforts to substantially delay definitive cardiac intervention while awaiting weight gain are either of no benefit or are associated with worse outcomes [4, 6, 22, 27]. Given our institutional bias for early intervention during the study period, we do not have a comparable group of neonates who were medically managed for an extended period of time while awaiting growth and maturation.

For patients in our current study who survived to 1 year of age, late deaths were rare, a finding mirrored in other studies of similar patient populations [24, 26, 27]. However, systematic evaluation of neurodevelopment outcomes for this patient population has not been reported. When present in isolation, both prematurity and the presence of complex congenital heart disease are associated with worse neurodevelopmental outcomes [17, 19]. In fetuses and term neonates with selected complex congenital heart defects, structural and functional brain maturation are delayed, which may predispose these patients to brain injury during the perioperative period [2, 15, 16]. It is possible, but as yet unknown, whether these maturational phenomenon place premature neonates with critical congenital heart disease at additional risk.

Limitations

Our study is limited by its retrospective, single-center design. In addition, we only included patients who were admitted to our CICU. The number of premature neonates in our encatchment area who were not referred during the first month of life because of a presumed poor prognosis or because of a strategy to await further growth and maturity before intervention is unknown. In addition, our referral pattern led to a median gestation age of our study patients of 35.6 weeks, an age considered late preterm. Thus, our findings cannot be generalized to the larger population of premature neonates with congenital heart disease, but they are applicable to the subset of such patients that are referred for early intervention at gestational ages represented in our study.

Conclusion

During the current era, mortality for premature infants with critical congenital heart disease who are referred for intervention during the first month of life remains high. Patients with lower Apgar scores at birth who need pre-intervention mechanical ventilation and undergo more complex procedures are at greatest risk. Further studies are needed to better understand factors contributing to premature delivery and identify practice changes that will lead to improved short-term outcomes. In addition, investigation of long-term outcomes, including neurodevelopmental status, in this high-risk population should be pursued.

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