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ORIGINAL ARTICLE

Perinatal Decision Making for Preterm Infants with Congenital Heart Disease: Determinable Risk Factors for Mortality

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Abstract For premature infants with congenital heart disease (CHD), it may be unclear when the burdens of treatment outweigh potential benefits. Parents may thus have to choose between comfort care at birth and medical stabilization until surgical repair is feasible. Better defined outcome data, including risk factors for mortality, are needed to counsel expectant parents who are considering intensive care for premature infants with CHD. We sought to evaluate outcomes in this population to inform expectant parents considering intensive versus palliative care at birth. We performed a retrospective cohort study of infants born <34 weeks who received intensive care with critical or moderately severe CHD predicted to require surgery in the neonatal period or the first 6 months of life. 46 % of 54 infants survived. Among non-survivors, 74 % died prior to surgery (median age 24 days). Of the infants that underwent surgery, 75 % survived. Survival was lower among infants <32 weeks gestational age (GA) ($p = 0.013$), with birth weight (BW) <1500 g ($p = 0.011$), or with extra-cardiac anomalies (ECA) ($p = 0.015$). GA and ECA remained significant risk factors for mortality in multiple logistic regression analysis. In summary, GA < 32 weeks, BW < 1500 g, and ECA are determinable prenatally and were significant risk factors for mortality. The majority of infants who survived to cardiac intervention survived neonatal hospitalization, whereas most of the infants who died did so prior to surgery. For some expectant parents, this early declaration of mortality may support a trial of intensive care while avoiding burdensome interventions.

Keywords Antenatal counseling · Congenital heart disease · Premature · Trial of therapy

Abbreviations

BPD	Bronchopulmonary dysplasia
BW	Birth weight
CHD	Congenital heart disease
ECA	Extra-cardiac anomalies
ELBW	Extremely low birth weight
GA	Gestational age
IQR	Interquartile range
IUGR	Intrauterine growth restriction
IVH	Intra-ventricular hemorrhage
LBW	Low birth weight
NEC	Necrotizing enterocolitis
OR	Odds ratio
PPROM	Premature, prolonged rupture of membranes
PVL	Periventricular leukomalacia
ROP	Retinopathy of prematurity
SGA	Small for gestational age
VLBW	Very low birth weight

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Introduction

Prematurity and congenital heart disease (CHD) are major causes of morbidity and mortality among infants, and the two conditions often coexist [1, 2]. Previous reports have shown an increased occurrence of CHD in premature infants compared to term infants [1]. This may be explained by altered cardiac physiology in utero, poor fetal growth, or associated lesions or syndromes with CHD.

These infants have been shown to have a high mortality rate [1–6]. A large multicenter report demonstrated significantly higher mortality among very low birth weight (VLBW) (<1500 g) infants born <29 weeks gestational age (GA) with serious CHD compared to similar infants without CHD [2]. Similarly, Pappas reported higher risk of death among extremely low birth weight (ELBW) (<1000 g) infants with versus without CHD [4]. However, sequelae of prematurity such as bronchopulmonary dysplasia (BPD) confound survival, as described by McMahon who reported a higher incidence of 30-day postsurgical survival among preterm infants with CHD but without BPD (vs. with BPD) [7].

The high mortality rate among premature infants with CHD complicates decision making around delivery and resuscitation, as well as ongoing intensive care. Often, the goal of care is medical stabilization until surgical repair can be safely done. There are many unknowns, however, including whether a premature infant can tolerate the altered physiology of CHD [2], if cardiac surgery is even possible on very small infants, and if so whether the premature infant can survive such a surgery.

These unknowns may lead to questions about whether the burdens of intensive care for premature infants with CHD outweigh the benefits, and parents may be presented with the option or recommendation to forgo resuscitation and provide comfort care to the baby at delivery. Additional evidence is needed to understand the epidemiology of this patient population and to determine whether there are readily identifiable maternal or fetal characteristics which might allow for more precise, context-specific counseling. The goal of this study was to evaluate a group of premature infants with CHD in order to explore the potential value of a trial of medical support in the neonatal intensive care unit and to identify risk factors for mortality to guide antenatal counseling.

Methods

We conducted a retrospective cohort study of premature infants with CHD born between October 2007 and November 2012. Infants were included if live born at ≤33 6/7 weeks' GA with CHD. Out-born infants were included. This study was approved by the University of Michigan Institutional Review Board.

At our center, timing of surgery is based on consideration of multiple factors by the cardiologist and cardiothoracic surgeon, including GA, weight, clinical stability, cardiac lesion, complexity and type of cardiac surgery required, and the presence of non-cardiac morbidities. There are no predetermined GA or weight thresholds for surgery; however, the specific procedure offered may depend on the age or size of the infant. Typically, surgery is deferred in the first week of life to allow for stabilization and evaluation of the overall clinical status of the infant and is considered when the infant is physiologically stable and when non-cardiac morbidities are improving or resolved. Our clinical practice is to proceed with cardiac surgical intervention based on overall clinical stability. For infants requiring cardiac bypass for surgical repair who are without a palliative option, surgery is usually delayed until after 32 weeks gestation to allow for more brain maturation, due to our institution's findings demonstrating very low survival for Norwood palliation before this gestational age [6].

The types of CHD were subdivided into critical and moderately severe lesions. Critical lesions were those predicted to need surgery in the neonatal period. Moderately severe lesions were predicted to need surgery in the first 6 months of life. Patients with patent ductus arteriosus, isolated septal defects, and isolated fetal arrhythmia were excluded.

Our institutional fetal echocardiogram database, which contains maternal, fetal, and neonatal data was used to identify prenatally diagnosed infants. The local Vermont Oxford Network database was used to identify infants with a postnatal diagnosis of CHD or whose mothers did not have a fetal echocardiogram in our system, and who were treated in our neonatal intensive care unit.

Details of the infants' initial hospital stay were abstracted from the medical record. The primary outcome was survival to initial hospital discharge. Other data collected included maternal age, parity, reason for preterm delivery, the presence of intrauterine growth restriction (IUGR) as identified in the maternal record, gestational age, prolonged (>18 h) rupture of membranes (PPROM), chorioamnionitis, mode of delivery, administration of antenatal steroids, birth weight (BW), gender, small for gestational age (SGA) (defined as less than the 10th percentile for gestational age), and the presence of extra-cardiac anomalies (ECA) or chromosomal abnormalities. Additional diagnoses were noted, including BPD, defined as oxygen use at 28 days of life or 36 weeks corrected GA, necrotizing enterocolitis (NEC), intra-ventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and

retinopathy of prematurity (ROP). Information on the initial cardiac intervention, surgery, or therapeutic catheterization was obtained. The infants' status at discharge, i.e., home oxygen, tracheostomy, home ventilator, gastrostomy tube, ventricular shunt, and overall length of stay was recorded. Cause of death for non-surviving infants who were initially resuscitated was determined by individual chart review.

The infants were grouped into survivors versus non-survivors, and the frequencies of the above characteristics were compared. Univariate analysis was done using Chi-square and Fishers exact test for categorical variables and independent samples *t* test for continuous variables. Multivariate logistic regression analysis was performed on the variables that reached significance in univariate analysis and/or are likely to be known at the time of delivery. Statistical significance was determined with a p value <0.05 and 95 % confidence intervals. The data were analyzed with SPSS software, version 20 (SPSS Inc., Chicago, IL, USA), and Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA).

Results

Fifty-four infants were eligible as detailed in Fig. 1. Twenty-five (46 %) of the infants survived to hospital discharge. Seventeen of 40 (42 %) infants with critical CHD and eight of 14 (57 %) infants with moderately severe CHD survived (Table 1). There was no significant difference in survival based on the dichotomous severity of heart lesion ($p = 0.427$). Two of the infants with hypoplastic left heart syndrome were given comfort care only at delivery and thus excluded from further analysis.

Of the 27 deaths in the cohort, preoperative deaths followed withdrawal of intensive care after the development of multisystem organ dysfunction or failure ($n = 11$, 42 %), cardiac arrest ($n = 5$, 19 %), and complications of necrotizing enterocolitis (NEC) ($n = 4$, 15 %). Postoperative deaths followed redirection of care due to multisystem organ failure in 12 % ($n = 3$) and cardiac arrest for the remaining 12 % ($n = 3$). Cause of death for one back-transferred infant could not be determined.

Indications for preterm delivery were divided into four categories: preterm rupture of membranes (PROM), preterm labor (PTL), maternal indications (for example preeclampsia), or fetal indications (for non-reassuring testing for fetal well-being). Infants were assigned a primary indication based on chart review. These are shown in Fig. 2; indication for delivery was not a statistically significant predictor of mortality.

GA of the cohort ranged from 24 1/7 to 33 4/7 weeks (median 31 3/7 weeks, interquartile range (IQR) 29 5/7–33 weeks). Survivors had a higher mean GA of 31 6/7 weeks than non-survivors, which was 30 3/7 weeks ($p = 0.014$). We then grouped the infants categorically by those born prior to versus after 32 weeks (the approximate median GA) and compared survival (Fig. 3a). Nine of 28 (32 %) infants <32 weeks GA survived, versus 16 of 24 (67 %) >32 weeks ($p = 0.025$). BW also correlated with survival. The infants were grouped categorically by standard BW classifications, and we found a large increase in survival at 1500 g and above (Fig. 3b). Specifically, seven of 25 (28 %) of all VLBW infants survived, compared to 16 of 25 (64 %) of the infants born with BW > 1500 g ($p = 0.022$) (Fig. 3c).

Many of the infants (54 %) had ECA in addition to CHD. These included aneuploidy, renal, gastrointestinal, and neurologic anomalies. Significantly fewer infants with ECA survived, nine of 28 (32 %), compared to the infants who had CHD alone, 16 of 24 (67 %) ($p = 0.025$).

In univariate analyses, GA > 32 weeks, BW > 1500 g, and the absence of ECA were significant predictors of survival (Table 2). In multivariate logistic regression, GA and ECA remained independent risk factors for mortality (Table 3). Those born without ECA had increased odds of survival of 11.7, and for every week increase in GA at birth, the odds of survival increase by 1.7, while holding all other variables constant.

Secondary outcome measures included length of stay, co-morbidities during the clinical course, timing of cardiac intervention (surgery or therapeutic catheterization), and the infant's overall status at discharge. There were 11 cases of NEC in the cohort, with no difference in the incidence of NEC among survivors versus non-survivors. All the cases of NEC among survivors were Bell stage I or II, thus not requiring surgery, and all cases among non-survivors were the more severe Bell stage III, requiring surgery [8, 9]. There was one infant who was placed on ECMO; that infant did not survive.

When comparing the timing of death related to cardiac intervention, 20 (74 %) of the non-survivors died before any cardiac intervention, while only seven (26 %) died afterward. Median age at death for all non-survivors was 24 days (IQR 9–41). In contrast, 21 of the 28 infants (75 %) who received cardiac intervention ultimately survived to discharge. The median age at the time of initial procedure was 15 days of life (IQR 8–41), and the median length of hospital stay was 54 days (IQR 38–83).

Among survivors, fifteen (53 %) had BPD at discharge, including two infants discharged on home oxygen. No survivors required tracheostomy, gastric feeding tube, or ventricular shunt placement. Two of the survivors had IVH, one with grade 1 and the other with grade 2; both resolved without intervention. There was no PVL and no ROP requiring intervention.

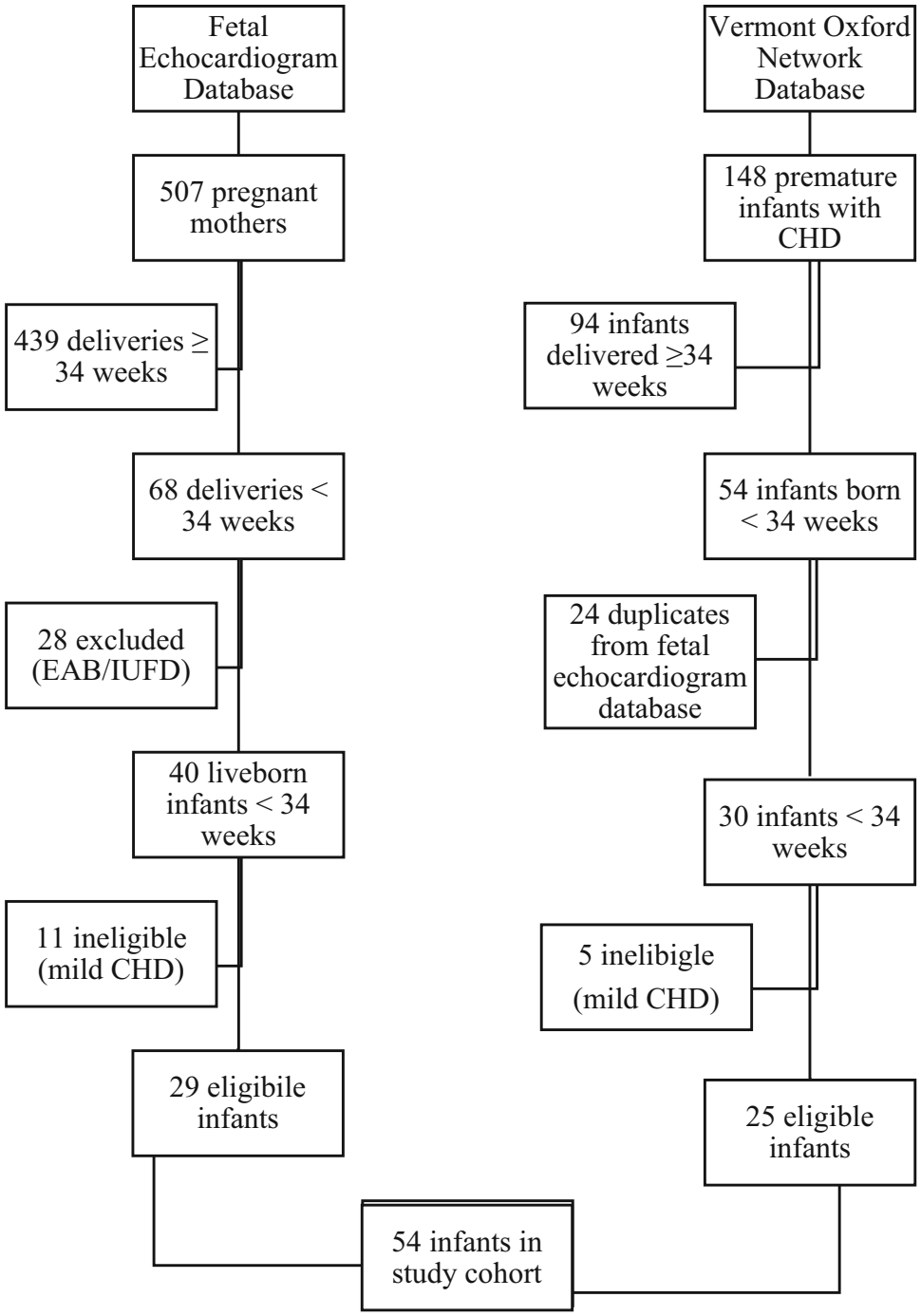

Fig. 1 Patient recruitment, inclusion and exclusion criteria. *EAB* elective abortion, *IUFD* intrauterine fetal demise, *CHD* congenital heart disease

Discussion

This study of 54 significantly premature infants with critical or moderately severe congenital heart disease of diverse etiology was undertaken with the goal of identifying risk factors for mortality which can be recognized before birth, ultimately leading to improved decision making around delivery and resuscitation, as well as ongoing intensive care.

We found improved survival with older and larger infants, specifically after 32 weeks GA, and at BW > 1500 g, consistent with other studies [5, 6]. Our results further validate those findings in a cohort exclusive of late preterm infants (34–36 6/7 weeks GA). While late preterm infants with CHD do have increased mortality over their term counterparts [10, 11], we excluded them in order to focus on the most vulnerable preterm infants. Mortality in late preterm infants with CHD is generally not so poor as to justify offering non-resuscitation at delivery.

Table 1 Distribution of CHD into critical and moderately severe subtypes and survival

n= CHD severity	Patients	Survivors	*n*=	Patients	Survivors
Critical	40	17	Moderately severe	14	8
Specific lesion					
HLHS	10	3	AVSD (balanced)	4	2
TOF (ductal dependent)	8	2	TOF (non-ductal dependent)	4	2
Ebstein anomaly	4	1	Non-critical aortic coarctation	3	2
Semilunar valve stenosis	4	2	DORV	2	1
d-TGA	3	1	AP window	1	1
PA-IVS	3	2			
Truncus arteriosus	3	3			
Critical aortic coarctation	2	1			
TAPVR	1	1			
AVSD (unbalanced)	1	0			
DILV	1	1			

HLHS hypoplastic left heart syndrome, *TOF* tetrology of fallot, *TGA* transposition of the great arteries. *PA-IVS* pulmonary atresia with intact ventricular septum, *TAPVR* total anomalous pulmonary venous return, *AVSD* atrioventricular septal defect, *DILV* double inlet left ventricle, *DORV* double outlet right ventricle, *AP* aortopulmonary

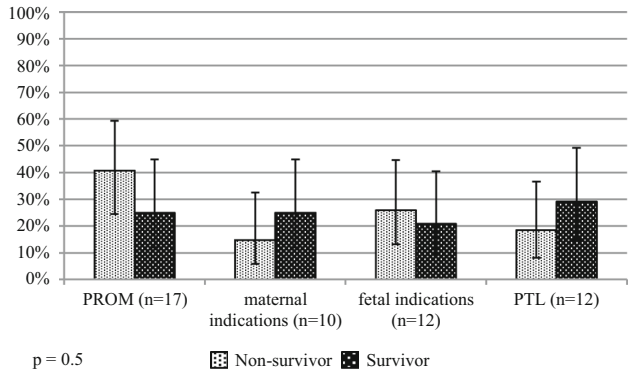

Fig. 2 Primary indications for delivery among survivors and non-survivors. Maternal indications: HELLP, abruption, preeclampsia, maternal thrombocytopenia. Fetal indications: abnormal Dopplers, hydrops, non-reassuring fetal heart tones, abnormal biophysical wellbeing, fetal supraventricular tachycardia, intrauterine growth restriction, fetal tachycardia, twin–twin transfusion syndrome. Whiskers indicate 95 % confidence interval. *PROM* prolonged rupture of membranes, *PTL* preterm labor, *HELLP* hemolysis, elevated liver enzymes, low platelet count

We found no difference in survival of infants who were growth restricted or with hydrops fetalis. This has been seen in other studies of neonates with CHD [6], but there were likely too few such infants in our study to reach significance. There was increased mortality in our study among infants with PPROM or chorioamnionitis, but this also did not reach statistical significance. Increased mortality in the presence of PPROM has been previously described [12]. The relationship between growth restriction, hydrops fetalis, or perinatal infection and mortality among preterm infants with CHD bears further study, as consideration of these states may be useful in antenatal counseling. We also identified increased mortality among infants with extra-cardiac anomalies (ECA). This has been previously reported [5, 6], yet it is not known in those studies or ours what impact the presence of an ECA, in addition to prematurity and CHD, had on treatment decisions and aggressiveness of care. This bias would be difficult to ascertain in a retrospective study.

Only critical or moderately severe CHD cases (lesions requiring intervention in the neonatal period or by 6 months of life) were included, similar to classifications used in other studies [2, 5]. This limited our cohort to the most vulnerable infants, excluding those with smaller septal defects or isolated arrhythmias, who do not have significant hemodynamic affect from their heart defects, and do not necessarily require cardiac intervention in the neonatal period. There was a fairly even distribution of type of lesion across the studied gestational age range, suggesting that lesion type was not as important as GA or BW for survival within our cohort. However, there may be lesion-specific physiology which is not represented in our study due to small sample size, and variation in lesion-specific mortality has been reported among premature infants with CHD [2].

In our study, the infants who ultimately survived to surgery were assessed as reasonable candidates for intervention, as clinical stability was the primary criterion for proceeding. The majority of infants who survived to surgery (75 %) ultimately survived their hospitalization, whereas the majority of those who died did so prior to

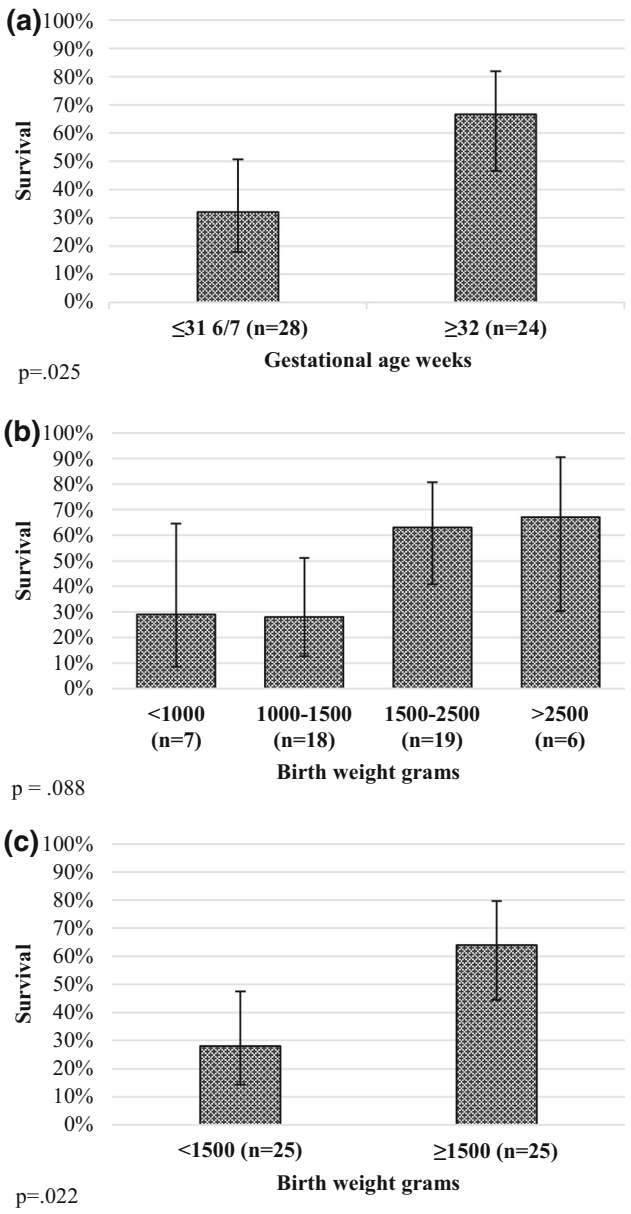

Fig. 3 Survival as a function of gestational age and birthweight. **a** Significantly more survivors among those infants born after 32 weeks versus those born earlier, $p = 0.025$. $p = 0.025$. **b** Survival by BW. <1000 g or ELBW, extremely low birth weight; 1000–1500 g or VLBW, very low birth weight; 1500–2500 g or LBW, low birth weight; >2500 g or normal birth weight. $p = 0.088$. **c** Decreased survival among VLBW (<1500 g) infants compared to non-VLBW (>1500 g) infants, $p = 0.022$. $p = 0.022$ [two infants with no BW recorded]. Whisker plots represent 95 % confidence intervals. *BW* birthweight, *ELBW* extremely low birthweight, *VLBW* very low birthweight

undergoing a major cardiac procedure. This suggests that a trial of medical stabilization to determine the added disease burden of prematurity and its potential complications may be justifiable. Both preoperative and postoperative deaths were equally divided in terms of negotiated death (i.e., following redirection of care) and unexpected death in the setting of clinical instability; this suggests that in both groups, heterogeneity in medical circumstances and parental values exists. This may be reassuring to parents who wish to retain autonomy over decision making and goals of care before and after surgical intervention, but complicates the creation of simple rules to determine who should be offered a trial of therapy and ultimately surgery.

Balancing the benefits of expedient surgery versus avoiding the risks of surgery for infants with deteriorating respiratory, neurologic, and other non-cardiac morbidities is challenging, and the impact of arbitrary delay for weight gain remains unclear. Studies have shown minimal weight gain in the weeks prior to cardiac surgery, and infants have a lower mortality rate when surgery is done as soon as is feasible [3, 6, 13]. Other studies have shown that delay for weight gain does not impact survival [14], and that weight is not an independent risk factor for mortality among *postoperative* patients [15, 16].

At our center, surgery is deferred in the setting of physiologic instability or worsening non-cardiac conditions. This explains why the interval to death in those who died prior to any surgery was longer than the interval to surgery in those who proceeded to surgical intervention. Infants who were assessed to be reasonable candidates for surgery showed signs of stability within the first 1–2 weeks. Among the patients who died without surgery, many infants died following multisystem clinical deterioration leading to redirection of care. For infants like these, the determination that continued aggressive care is futile is made on a case-by-case basis. Systematic study to determine when it is most appropriate for a trial of intensive care to be deemed unsuccessful is warranted to reduce unnecessary and potentially unjust practice variation, as well as provision of ultimately futile interventions.

Our primary outcome was survival to initial hospital discharge. Many of the survivors, however, are likely to require further hospitalizations and cardiac interventions. Although we did not assess longer-term morbidity and mortality for this group, we did evaluate the non-cardiac disease burden of surviving patients at discharge, which was quite minimal. This suggests that at initial hospital discharge, surviving premature babies with CHD are not disproportionately burdened with morbidity compared with surviving premature infants without CHD.

Our study has a number of limitations. First, in regard to the effect that extra-cardiac anomalies (ECA) play on the outcomes of preterm infants with CHD, we were unable to discern what impact the presence of ECA had on medical decision making, before or after birth. Second, our study was limited by virtue of examining patients at a single center, limiting generalizability and imparting a small sample size, which may be the reason that we did not

Table 2 Univariate analysis of characteristics of survivors versus non-survivors

Univariate analysis	Survivors $n = 25$	(%)	Non-survivors $n = 27$	(%)	p value
Maternal age (mean years)	30.3		28.4		0.341[a]
GA (mean weeks)	31 6/7		30 3/7		0.014[a]
GA < 32 weeks	9	36	19	70	0.025[b]
BW (mean g)	1775		1466		0.082[a]
BW < 1500 g	7	28	18	67	0.022[b]
Male gender	10	40	14	52	0.419[b]
Critical CHD[c]	17	68	21	78	0.536[b]
Extra-cardiac anomalies	9	36	19	70	0.025[b]
PPROM/ chorioamnionitis	6	24	11	41	0.372[b]
Prenatally diagnosed	16	64	20	74	0.551[b]
Hydrops fetalis	2	8	5	19	0.422[b]
Multiple gestation	8	32	5	19	0.343[b]
Antenatal steroids	16	64	22	81	0.439[b]
SGA/IUGR	5	20	7	26	1[b]

There was a significant difference in the survivors' mean GA, the percentage born prior to 32 weeks, the percentage with BW < 1500 g, and the presence of ECA of survivors compared to non-survivors. There was no significant difference in the other variables shown

[a] Student's t test

[b] Fisher's exact test

[c] Critical CHD versus moderately severe CHD. IUGR-intrauterine growth restriction as indicated in maternal record. PPROM-premature, prolonged (>18 h) rupture of the membranes. SGA-small for gestational age, <10th percentile for gestational age

Table 3 Multivariate logistic regression analysis of characteristics that were significant in univariate analysis and/or are likely to be known at the time of delivery thus could be used to predict survival in the perinatal period

Multivariate logistic regression	Odds of survival (95 % CI)	p value
No extra-cardiac anomalies	11.7 (1.6–81.7)	0.013
Increasing gestational age	1.7 (1.1–2.7)	0.019
No PPROM/chorioamnionitis	2.3 (0.5–10.7)	0.305
No hydrops fetalis	1.5 (0.2–12.5)	0.721
Singleton gestation	0.57 (0.1–3.1)	0.521
Moderate versus critical lesion	3.4 (0.6–17.7)	0.147
Female	1.6 (0.4–6.9)	0.527

The presence of ECA and younger GA both decrease the odds of survival while holding all other variables constant

identify intrauterine growth restriction, hydrops fetalis, or chorioamnionitis as independent risk factors for mortality. We were also not able to detect lesion-specific trends in mortality, which would have value in prenatal consultation. This was a retrospective observational study, which imparts additional limitations—we are unable to capture pregnancies that were not carried to term, and unable to account for bias in decisions about whether and when cardiac surgery would be performed. Finally, this study did not assess longer-term outcomes such as respiratory or neurologic morbidity; complete prenatal counseling for parents planning for the birth of premature infants with congenital heart disease would be supported by knowledge of these outcomes.

Conclusions

Our study suggests that there are identifiable risk factors for mortality in the perinatal period that can be utilized in antenatal counseling and decision making regarding resuscitation and initiation of intensive care of premature infants with critical or moderately severe CHD. These include GA, especially <32 weeks, BW, specifically

VLBW infants, and the presence of an ECA. In our cohort, most of the infants who died did so within the first month of life despite aggressive intensive care, whereas the infants who survived to their first cardiac intervention were assessed to be reasonable candidates for cardiac intervention within the first few weeks of life. Consideration of this early declaration of mortality prior to surgical intervention may support a trial of intensive care in premature infants with CHD to identify the best candidates for surgery, while still avoiding unnecessary, burdensome interventions.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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