Outcomes of Preterm Infants With Congenital Heart Defects After Early Surgery: Defining Risk Factors at Different Time Points During Hospitalization

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Background: Compared with those born at term gestation, infants with complex congenital heart defects (CCHD) who were delivered before 37 weeks gestational age and received neonatal open-heart surgery (OHS) have poorer neurodevelopmental outcomes in early childhood. We aimed to describe the growth, disability, functional, and neurodevelopmental outcomes in early childhood of preterm infants with CCHD after neonatal OHS. Prediction models were evaluated at various timepoints during hospitalization which could be useful in the management of these infants.

Study Design: We studied all preterm infants with CCHD who received OHS within 6 weeks of corrected age between 1996 and 2016. The Western Canadian Complex Pediatric Therapies Follow-up Program completed multidisciplinary comprehensive neurodevelopmental assessments at 2-year corrected age at the referral-site follow-up clinics. We collected demographic and acute-care clinical data, standardized age-appropriate outcome measures including physical growth with calculated z-scores; disabilities including cerebral palsy, visual impairment, permanent hearing loss; adaptive function ( Adaptive Behavior Assessment System-II); and cognitive, language, and motor skills (Bayley Scales of Infant and Toddler Development-II). Multiple variable logistic or linear regressions determined predictors displayed as Odds Ratio (OR) or Effect Size (ES) with 95% confidence intervals.

Results: Of 115 preterm infants (34 ± 2 weeks gestation, 2,339 ± 637 g, 64% males) with CCHD and OHS, there were 11(10%) deaths before first discharge and 21(18%) deaths by 2-years. Seven (6%) neonates had cerebral injuries, 7 had necrotizing enterocolitis; none had retinopathy of prematurity. Among 94 survivors, 9% had cerebral palsy and 6% had permanent hearing loss, with worse outcomes in those with syndromic diagnoses. Significant predictors of mortality included birth weight z-score [OR 0.28(0.11,0.72), P = 0.008], single-ventricle anatomy [OR 5.92(1.31,26.80), P = 0.021],...
INTRODUCTION

Infants with complex congenital heart defects (CCHD) who have open-heart surgery (OHS) during the neonatal period are at risk for mortality and neurodevelopmental morbidity (1, 2). Advancements in obstetric and neonatal care have improved the overall outcomes of preterm infants (born at <37 +0 weeks gestation) significantly with high survival rates without neurodevelopmental impairment in early childhood (3). However, when compared with term neonates, preterm infants generally have more adverse short- and long-term neurodevelopmental outcomes depending on the degree of prematurity (3, 4). It has been shown that delivery before 39–40 weeks of gestational age (GA) is associated with higher mortality and worse neurodevelopmental outcomes for those infants with CCHD having cardiac surgery (5–12).

Despite the adverse outcome compared with that of term infants, there is little information available regarding “gestation-related details” and predictors of outcomes in early childhood of preterm neonates with CCHD and early OHS at “different time points during hospitalization.” This information is important for management of the infants, parental counseling and informing the decision-making process. We therefore aimed to describe the growth, disability, functional, and neurodevelopmental outcomes in early childhood of preterm infants with CCHD who had OHS with cardiopulmonary bypass (CPB) by 6 weeks corrected age. The secondary aims of the study included the identification of risk factors for mortality and adverse functional outcomes at each of five time points that we believe are important moments of clinical decision-making and family counseling: (i) before and at birth, (ii) pre-operative, (iii) day 1 post-operatively, (iv) post-operatively day 5, and (v) at first hospital discharge.

METHODS

We studied all preterm infants with CCHD who received OHS with CPB at 6 weeks of corrected age or less at the Stollery Children’s Hospital in Edmonton, Alberta, Canada, between 1996 and 2016. Demographic, clinical and outcomes data were obtained from the Western Canadian Complex Pediatric Therapies Follow-up Program. This program maintains a prospectively collected registry and database including demographic, acute-care clinical and long-term neurodevelopmental outcomes in all infants who have complex cardiac surgery (CCS) at 6 weeks of age or less (13). The clinical information includes pre-operative, intra-operative, and post-operative data of these infants during the first hospital stay when the OHS was performed. Details of the methodology of this program have been previously published (13, 14). All neonates had standard genetic testing and geneticist assessment as appropriate. As per neuroimaging study protocol in these preterm infants, all had pre-operative cranial ultrasound examination with magnetic resonance imaging as indicated by clinical and neurologic findings. The occurrence of necrotizing enterocolitis and retinopathy of prematurity for this project was obtained by retrospective chart review. Consents were obtained from the patient’s legal guardian. The study was approved by institutional ethics boards at all six follow-up sites.

Outcomes

Disability and developmental assessments at a corrected age of 2 years were completed by multidisciplinary teams at the follow-up referral sites, of Winnipeg, Manitoba; Regina and Saskatoon, Saskatchewan; Calgary, Alberta; Vancouver, British Columbia, and the Glenrose Rehabilitation Hospital, Edmonton, Alberta, Canada. Standardized age-appropriate outcome measures included physical growth with calculated z-scores (15, 16), a functional measure (17) and a neurodevelopmental test of cognitive, language, and motor skills (18). Pediatricians experienced in developmental follow-up examined each child for evidence of cerebral palsy (defined as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain).

Abbreviations: ABAS-II, Adaptive Behavior Assessment System, second edition; CCHD, complex congenital heart defects; CI, confidence interval; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ES, effect size; GA, gestational age; GAC, General Adaptive Composite; IQR, interquartile range; OHS, open heart surgery; OR, odds ratio; SD, standard deviation.

Conclusions: Our findings suggest preterm neonates with CCHD and early OHS had significant mortality and morbidity at 2-years and were at risk for cerebral palsy and adverse neurodevelopment. This information may be important for management, parental counseling and the decision-making process.

Keywords: prediction model, neurodevelopmental outcome, mortality, prematurity, cardiac surgery
Objective 1: First, we conducted a descriptive analysis to explore the distribution of mortality and each neurodevelopmental outcome using mean, SD, median, and interquartile range (IQR). Student t, Fisher’s Exact and Chi-square tests were used to compare groups.

Objective 2: To determine potential predictors of adverse outcomes [mortality, and ABAS-II GAC scores], we used univariate and multiple variable regression analyses.

a. Univariate analyses: Using logistic regression, we compared the demographic and clinical variables at each time point between the surviving and non-surviving groups of infants during the first hospital stay for OHS. Using linear regression, we analyzed predictors of the ABAS-II GAC scores as a continuous variable. Following these comparisons, risk factors with \( P < 0.1 \) were selected for the multiple variable regression models.

b. Multiple variable analyses: The effect of risk factors for mortality and ABAS-II GAC scores was further examined in multiple variable models using five clinical time points for analyses. We chose these five periods as they are important time points informing clinical management decisions and family counseling. The five time points were: (i) before and at birth, (ii) pre-operative, (iii) post-operative day 1, (iv) post-operative day 5, and (v) before hospital discharge. Predictive analyses were performed at each time point with the retention of risk factors which had \( P < 0.1 \) in the previous clinical period. Because of the large association of chromosomal abnormalities with adverse outcome, the prediction of the ABAS-II GAC scores was further completed with the non-syndromic 76 children. Only potential predictor variables that occurred in 10% of more of the total population were entered in the regressions. In view of the small number of infants in some GAs, we also analyzed the effects of GA on outcomes using three different categorical bands (28–31, 32–34, and 35–37 weeks).

Continuous variables were tested for the normality of their distribution and are presented as means (SD) or medians (IQR). Odds Ratio (OR) and Effect Size (ES) are reported with 95% confidence intervals [CI]. Significance was determined as \( P \leq 0.05 \). Data analyses were performed using R software V3.6.1 (21).

RESULTS

General Description

From September 1996 to December 2016, all 115 preterm infants with CCHD who received OHS at \( \leq 6 \) weeks corrected age at the Stollery Children’s Hospital were registered. These 115 children made up 10.7% of all children at age 6 weeks and under having complex cardiac surgery with CPB at this institution during this time. The demographic and clinical characteristics are shown in Table 1. Of these infants, 11 (9.6%) and 21 (18.3%) died before first hospital discharge and by the age of 2 years corrected age, respectively. The reasons for death before first discharge included multiple organ dysfunction (9), brain hemorrhage (1) and septic shock (1). The causes of additional deaths included cardiac failure with chronic illness (5), thromboembolic event (1), probable non-accidental injury (1), sepsis (1) and unknown (2). Prior to the first surgery, 7 (6.1%) neonates had cerebral injuries known to be risk factors for disability [including
Cheung et al. Outcome of Preemies After Cardiac Surgery

| Time periods            | All preterm infants (n = 115) | Survivors at 2-years corrected age (n = 94) | Non-survivors at 2-years corrected age (n = 21) | P-value* |
|-------------------------|-------------------------------|---------------------------------------------|-------------------------------------------------|----------|
| **Before or at birth**  |                               |                                             |                                                 |          |
| Year of birth           | 2008.4(5.5) 2010(2004, 2013)   | 2008.4(5.6)                                 | 2007.9(5.3)                                     | 0.610    |
| Gestational age, weeks  | 34.4(1.9) 34 [34, 36]          | 34.4(2.0)                                   | 34.4(1.7)                                       | 0.994    |
| Gestational age groups  |                               |                                             |                                                 |          |
| < = 32 weeks            | 20(17%)                        | 16(17%)                                     | 4(19%)                                          | 0.464    |
| 33-34 weeks             | 22(19%)                        | 20(21%)                                     | 2(10%)                                          |          |
| 35-36 weeks             | 73(63%)                        | 58(62%)                                     | 15(71%)                                         |          |
| Birthweight, grams      | 2,339(637) 2,340 [1,960, 2,690] | 2,397(638)                                  | 2,079(587)                                      | 0.038    |
| Birthweight, z-score    | −0.01(1.1) −0.08 [−0.74, 0.54]  | 0.12(1.1)                                   | −0.61(0.98)                                     | 0.005    |
| Small for gestational age| 11(10%)                        | 7(7%)                                       | 4(19%)                                          | 0.221    |
| Head circumference, cm  | 31.6(2.4) 32 [30, 33.5]        | 31.7(2.4)                                   | 31.3(2.6)                                       | 0.489    |
| Head circumference, z-score| 0.29(1.1) 0.47 [−0.42, 0.92]   | 0.33(1.1)                                   | 0.13(1.2)                                       | 0.460    |
| Sex, male               | 74(64%)                        | 60(64%)                                     | 14(67%)                                         | 0.999    |
| 5-min Apgar score       | 7.7 (1.5) 8 [7, 9]             | 7.7 (1.5)                                   | 7.8(1.5)                                        | 0.871    |
| Multiple birth          | 19(17%)                        | 15(16%)                                     | 4(19%)                                          | 0.984    |
| Chromosomal/syndromic diagnoses | 21(18%)           | 18(19%)                                     | 3(14%)                                          | 0.834    |
|                        | 9-del22q11 2-Trisomy 21 3-VACTERL 3-CHARGE 2-Turner 1-17p13.3del 1-3 duplication, optic nerve hypoplasia | 8-del22q11 2-Trisomy 21 3-VACTERL 3-CHARGE 2-Turner 1-17p13.3del 1-3 duplication, optic nerve hypoplasia | 3(14%) | 0.834 |
| Cardiac defect, single ventricle | 31(27%) | 18(19%) | 13(62%) | <0.001 |
| **Pre-operative**       |                               |                                             |                                                 |          |
| Antenatal diagnosis     | 62(54%)                        | 49(52%)                                     | 13(62%)                                         | 0.568    |
| Highest plasma lactate, mmol/L | 3.5(3.2) 2.5 [1.5, 42] 3.3(3.4) | 3.3(3.4)                                   | 4.4(2.4)                                        | 0.07     |
| Lowest arterial pH      | 7.2(0.12) 7.31 [7.20, 7.35]    | 7.29(0.13)                                  | 7.22(0.09)                                      | 0.001    |
| Lowest PaO$_2$, mmHg    | 37.9(13.2) 38 [30, 44]         | 39.6(13.4)                                  | 30.6(9.5)                                       | 0.001    |
| Lowest base deficit, mmol/L | −4.8(4.9) −4 [−7, −1]         | −4.15(2)                                    | −6.7(2.9)                                       | 0.003    |
| Highest inotrope score$^b$ | 6.5(16.8) 0 [0, 8]             | 4.8(14.8)                                   | 13.8(22.8)                                      | 0.097    |
| Highest serum creatinine, umol/L | 63.2(30.5) 56 [41, 85]        | 58.3(28.1)                                  | 84.9(32.3)                                      | <0.001   |
| Brain insults (by imaging) considered high risk for adverse outcome | 7(6%) | 6(6%) | 1(5%) | 0.899 |
| Ventilation, days       | 8.6(14.4) 5 [0,10]             | 7.5(13.1)                                   | 13.4(18.8)                                      | 0.184    |

(Continued)
TABLE 1 | Continued

| Time periods                        | All preterm infants (n = 115) | Survivors at 2-years corrected age (n = 94) | Non-survivors at 2-years corrected age (n = 21) | P-valuea |
|-------------------------------------|-------------------------------|---------------------------------------------|------------------------------------------------|----------|
| **Operative, post-operative day 1** |                               |                                             |                                                |          |
| Postnatal age, days                 | 23.5(23.4) 14 [9, 33]         | 24.1(23.9)                                  | 20.8(21.4)                                      | 0.528    |
| Post-conceptual age, days           | 261.8(27.7) 261 [255, 271]    | 261.8(29.6)                                  | 262.1(16.9)                                     | 0.945    |
| CPB time, min                       | 117.6(41.1) 111 [90, 142]     | 115.3(42.7)                                  | 128.2(49.4)                                     | 0.274    |
| Cross clamp time, min               | 62.1(27.4) 66 [46, 78]        | 62.8(27.9)                                  | 58.9(25.4)                                      | 0.537    |
| DHCA, used                          | 80(70%)                       | 60(64%)                                     | 20(95%)                                        | 0.010    |
| Highest plasma lactate, mmol/L      | 6.2(3.9) 4.9 [3.5, 5.8]       | 5.5(3.3)                                    | 9.3(4.8)                                       | 0.002    |
| Lowest arterial pH                  | 7.27(0.08) 7.28 [7.22, 7.32]  | 7.28(0.07)                                  | 7.21(0.11)                                     | 0.009    |
| Lowest PaO₂, mmHg                   | 54.1(19.6) 54 [35, 68]        | 57.3(18.8)                                  | 39.6(16.6)                                     | <0.001   |
| Lowest base deficit, mmol/L         | −3.5(4.7) −3 [−5, −1]        | −3.0(4.3)                                   | −5.7(6.0)                                      | 0.065    |
| Highest inotrope scoreb             | 12.5(11.5) 10 [6, 16]         | 11.0(8.0)                                   | 19.0(19.9)                                     | 0.087    |
| Highest serum creatinine, umol/L    | 56.0(21.1) 59 [45, 89]        | 54.9(20.9)                                  | 61.3(21.7)                                     | 0.224    |
| **Post-operative day 2–5**          |                               |                                             |                                                |          |
| Highest plasma lactate, mmol/L      | 3.63(3.2) 2.5 [1.7, 4.5]      | 3.0(2.0)                                    | 6.2(5.9)                                       | 0.025    |
| Lowest arterial pH                  | 7.28(0.07) 7.29 [7.24, 7.32]  | 7.29(0.06)                                  | 7.24(0.10)                                     | 0.020    |
| Lowest PaO₂, mmHg                   | 53.7(17.0) 54 [38, 64]        | 55.9(16.1)                                  | 43.6(18.0)                                     | 0.007    |
| Lowest base deficit, mmol/L         | −3.6(4.3) −3 [−6, −1]        | −3.2(3.9)                                   | −5.5(5.4)                                      | 0.068    |
| Highest inotrope scoreb             | 12.6(15.7) 10 [4, 15]         | 10.2(8.1)                                   | 23.7(30.6)                                     | 0.058    |
| Highest serum creatinine, umol/L    | 68.9(32.8) 59 [45, 89]        | 66.7(33.0)                                  | 78.8(30.5)                                     | 0.115    |
| **Before discharge**                |                               |                                             |                                                |          |
| Post-operative ventilation, days     | 16.5(24.1) 10 [6, 15]         | 11.3(10.1)                                  | 39.4(46.5)                                     | 0.012    |
| Post-operative ICU, days            | 24.2(22.9) 18 [10, 31]        | 19.9(14.2)                                  | 44.4(37.2)                                     | 0.007    |
| CPR                                 | 13(11%)                       | 3(3%)                                       | 10(48%)                                        | <0.001   |
| Sepsisc                             | 28(24%)                       | 20(21%)                                     | 8(38%)                                         | 0.157    |
| ECMO                                | 14(12%)                       | 5(5%)                                       | 9(43%)                                         | <0.001   |
| Open sternum, days                  | 4.4(7.0) 4 [0, 6]             | 2.8(3.2)                                    | 11.4(13.0)                                     | 0.007    |

Data are presented in mean(SD), median [IQR], n(%).
CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; ICU, intensive care unit; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation.
a Students t test, chi-square or Fisher’s Exact test.
b Inotrope score (22) = dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 100 × epinephrine (μg/kg/min).
c Definition of sepsis (23).

infarction (3), periventricular leukomalacia (2), and grade 3–4 intraventricular hemorrhage (2). In addition, 7 (6.1%) preterm infants had necrotizing enterocolitis. None had retinopathy of prematurity.

Mortality Prediction

Following the five different time points when important parental counseling sessions may occur, Table 2 shows that among the risk factors studied at the before and at birth time point, birthweight z-scores and primary cardiac defect of single ventricle were associated with death and these factors remained significant when including variables from all time points. Other risk factors included the lowest arterial pH at the pre-operative time point, lowest arterial pH and highest lactate level post-operatively, and cardiopulmonary resuscitation (CPR) and days of post-operative ventilation before discharge. GA, postnatal age and the post-conceptual age of surgery were not statistically significantly different between survivors and non-survivors (Table 1).

Growth, Disability, and Neurodevelopmental Outcomes

All 94 (100%) surviving infants received neurodevelopmental evaluation at 2 years corrected age. The demographic and clinical characteristics of these surviving preterm infants with (n = 18, 19.1%) and without (n = 76, 80.9%) syndromic diagnoses are shown in the Table 3. The physical growth and neurodevelopmental outcomes are shown in Table 4. Although growth, functional, and neurodevelopmental parameters of survivors are within the population normative range, the means are shifted to the left of population norms. Family socioeconomic
| Time points | Univariate regression | Multiple logistic regression |
|-------------|-----------------------|-----------------------------|
| 1. Before or at birth | | |
| Birthweight, grams | 1.00(1.00, 1.00) | 1.00(1.00, 1.00) |
| Birthweight groups | | |
| ≤1,499 g | 2.92(0.77, 11.11) | 2.92(0.77, 11.11) |
| 1,500–1,999 g | 0.50(0.09, 2.69) | 0.50(0.09, 2.69) |
| 2,000–2,499 g | 0.41(0.10, 1.88) | 0.41(0.10, 1.88) |
| ≥2,500 g | 0.22(0.05, 1.09) | 0.22(0.05, 1.09) |
| Birthweight, z-score | 0.42(0.23, 0.76) | 0.42(0.23, 0.76) |
| Cardiac defect, single ventricle | 4.37(1.26, 15.18) | 4.37(1.26, 15.18) |
| 2. Pre-operative | | |
| Lowest arterial pH | 0.008(0.00, 0.28) | 0.008(0.00, 0.28) |
| Lowest PaO2, mmHg | 0.91(0.86, 0.97) | 0.91(0.86, 0.97) |
| Lowest base deficit, mmol/L | 0.90(0.82, 0.99) | 0.90(0.82, 0.99) |
| Highest inotrope scorea | 1.02(1.06) | 1.02(1.06) |
| Highest serum creatinine, umol/L | 1.03(1.01, 1.05) | 1.03(1.01, 1.05) |
| 3. Operative, post-operative day 1 | | |
| DHCA, used | 11.33(1.46, 88.21) | 11.33(1.46, 88.21) |
| Highest plasma lactate, mmol/L | 1.25(1.11, 1.43) | 1.25(1.11, 1.43) |
| Lowest arterial pH | 0.00(0.00, 0.021) | 0.00(0.00, 0.021) |
| Lowest PaO2, mmHg | 0.94(0.91, 0.97) | 0.94(0.91, 0.97) |
| Lowest base deficit, mmol/L | 0.90(0.81, 0.99) | 0.90(0.81, 0.99) |
| Highest inotrope scorea | 1.06(1.01, 1.12) | 1.06(1.01, 1.12) |
| 4. Post-operative day 2–5 | | |
| Highest plasma lactate, mmol/L | 1.31(1.12, 1.59) | 1.31(1.12, 1.59) |
| Lowest arterial pH | 0.00(0.00, 0.02) | 0.00(0.00, 0.02) |
| Lowest PaO2, mmHg | 0.95(0.925, 0.98) | 0.95(0.925, 0.98) |

(Continued)
TABLE 2 | Continued

| Time points | Univariate regression | Multiple logistic regression |
|-------------|-----------------------|-----------------------------|

| Time points | Time point 1, before and at birth | Time points 1–2, up to before first operation | Time points 1–3, up to end of day 1 post-operatively | Time points 1–4, up to day 5 post-operatively | Time points 1–5, for all time periods up to hospital discharge |
|-------------|----------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Lowest base deficit, mmol/L | 0.88(0.78, 0.98) | \(P = 0.025\) | \(P = 0.003\) | \(P = 0.001\) | \(P = 0.003\) |
| Highest inotrope score \(a\) | 1.05(1.02, 1.10) | \(P = 0.010\) | \(P < 0.001\) | \(P < 0.001\) | \(P = 0.003\) |

5. Before discharge

| Time points | Univariate regression | Multiple logistic regression |
|-------------|-----------------------|-----------------------------|

| Time points | Time point 1, before and at birth | Time points 1–2, up to before first operation | Time points 1–3, up to end of day 1 post-operatively | Time points 1–4, up to day 5 post-operatively | Time points 1–5, for all time periods up to hospital discharge |
|-------------|----------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Post-operative ventilation, days | 1.05(1.02, 1.10) | \(P = 0.003\) | \(P = 0.001\) | \(P = 0.001\) | \(P = 0.003\) |
| Post-operative ICU, days | 1.05(1.02, 1.07) | \(P < 0.001\) | \(P < 0.001\) | \(P = 0.007\) | \(P = 0.007\) |
| CPR | 27.58(7.25, 138.04) | \(P < 0.001\) | \(P < 0.001\) | \(P < 0.001\) | \(P < 0.001\) |
| ECMO | 13.35(3.97, 50.17) | \(P < 0.001\) | \(P < 0.001\) | \(P < 0.001\) | \(P < 0.001\) |
| Open sternum, days | 1.34(1.17, 1.57) | \(P < 0.001\) | \(P < 0.001\) | \(P < 0.001\) | \(P < 0.001\) |

Odds ratio (OR) with 95% confidence intervals (CI) by univariate regression (variables with \(P < 0.10\) included) and multiple logistic regression at 5 different time points.

CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; ICU, intensive care unit; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; OR, odds ratio; CI, confidence interval.

\(a\) Inotrope score \((22) = dopamine (\mu g/kg/min) + dobutamine (\mu g/kg/min) + 100 \times epinephrine (\mu g/kg/min).

status, years of mother's schooling, as well as 2-year growth, did not differ between those with and without syndromes (Table 4). Eight (10.5%) of the 76 survivors without identified syndromic diagnoses had spastic cerebral palsy; of these, three had pre-operative brain insult with risk for motor disability. Visual impairment occurred equally in each group: in the syndromic group one child had bilateral optic nerve colobomata; in the non-syndromic group one child had cortical visual impairment. Of the five infants with permanent sensorineural hearing loss, only one had a syndromic abnormality. Those infants with syndromic diagnoses had worse functional and cognitive outcomes compared with those without syndromes (Table 4).

Functional Outcome Prediction

As there was a significant contribution of chromosomal/syndromic diagnoses to ABAS-II GAC at 2 years corrected age in the 94 surviving preterm infants \([ES(95\% CI) = 13.8(−22.5, −5.1)]\), we sought possible predictors of outcome including only the 76 infants without syndromic abnormalities (Table 5). We did not evaluate the effects of pre-operative brain injury because of the small number of infants affected \((n = 6)\). Of the birthweight groups, those with a weight of 2,000–2,499 g \((n = 26)\) had ABAS-II GAC scores significantly below the others \((n = 50)\), \(76.9 \pm 13.7 \text{ vs.} 90.5 \pm 16.6, t = 3.593, P = 0.001\). This birth weight of 2,000–2,499 g was associated with the ABAS-II GAC at each of the 5 different time points. The adjusted \(R^2\) of the variance in ABAS-II GAC scores at 2 years accounted for in the multiple logistic models was 0.263 before discharge from the hospital (Table 5). The explained variance was 0.137 at birth with the predictor birthweight of 2,000–2,499 g alone. Other statistically significant predictive risk factors also included post-conceptual age of surgery, lowest arterial pH on day 2–5 post-operatively, and sepsis. GA, birthweight z-scores and postnatal age of surgery were not found to be independent variables associated with functional outcome.

DISCUSSION

This study adds “gestation-related information” to the mortality and developmental outcome information of preterm neonates with CCHD \((5–12, 24, 25)\), and may be useful for the in-hospital management of patients and families including but not limited to (a) the timing of surgical correction, (b) the identification and correction of risk factors that are associated with adverse neurodevelopmental outcomes, (c) parental counseling on the course, care plan, possible outcomes, and importance of follow-up and early interventions, and (d) informing decision-making so clinicians have a better understanding of the course and outcome of these critically-ill preterm neonates.

The preterm neonates of this study with CCHD (mean GA of 34.4 weeks; mean birthweight of 2,339 g), show a high mortality (18.3%) at 2 years of corrected age. When compared with preterm infants of lower GA (31–32 weeks) in the Canadian Neonatal
### TABLE 3 | Clinical characteristics of 94 surviving preterm infants after open heart surgery at 6 weeks or less corrected postnatal age from September 1996 to December 2016.

| Time periods                  | All surviving preterm infants (n = 94) | Survivors without chromosomal or syndromic diagnoses (n = 76) | Survivors with chromosomal or syndromic diagnoses (n = 18) | P-value* |
|-------------------------------|----------------------------------------|---------------------------------------------------------------|----------------------------------------------------------|----------|
| **Before or at birth**        |                                        |                                                               |                                                          |          |
| Year of birth                 | 2008(4.5) [2004, 2013]                 | 2008.7(5.5)                                                   | 2007.8(6.1)                                                | 0.523    |
| Gestational age, weeks        | 34.4(2.0) [34, 36]                    | 34.5(1.8)                                                   | 34.2(2.8)                                                 | 0.715    |
| Gestational age groups        |                                        |                                                               |                                                          |          |
| ≤32 weeks                     | 16(17%)                                | 13(17%)                                                     | 3(17%)                                                   | 0.855    |
| 33-34 weeks                   | 20(21%)                                | 17(22%)                                                     | 3(17%)                                                   |          |
| 35-36 weeks                   | 58(62%)                                | 46(61%)                                                     | 12(67%)                                                  |          |
| Birthweight, grams            | 2,397(838) [2,007, 2,706]              | 2,429(624)                                                   | 2,261(696)                                                | 0.316    |
| Birthweight groups            |                                        |                                                               |                                                          |          |
| ≤1,499 g                      | 7(7%)                                  | 5(7%)                                                       | 2(11%)                                                   | 0.707    |
| 1,500–1,999 g                 | 14(15%)                                | 12(16%)                                                     | 8(44%)                                                   |          |
| 2,000–2,499 g                 | 34(36%)                                | 26(34%)                                                     | 12(67%)                                                  |          |
| ≥2,500 g                      | 39(41%)                                | 33(43%)                                                     | 6(33%)                                                   |          |
| Birthweight, z-score          | 0.12(1.1) [−0.61, 0.65]               | 0.18(1.1)                                                   | −0.13(0.91)                                               | 0.219    |
| Small for gestational age     | 7(7%)                                  | 4(5%)                                                       | 3(17%)                                                   | 0.247    |
| Head circumference, cm        | 31.7(2.4) [30.5, 33.5]                | 31.7(2.2)                                                   | 31.8(3.2)                                                 | 0.930    |
| Head circumference, z-score   | 0.33(1.4) [−0.29, 0.93]               | 0.29(1.1)                                                   | 0.52(1.1)                                                 | 0.439    |
| Sex, male                     | 60(64%)                                | 49(64%)                                                     | 11(61%)                                                  | 0.999    |
| 5-min Apgar score             | 7.7(1.5) [7, 9]                        | 7.6(1.5)                                                    | 7.9(1.9)                                                  | 0.512    |
| Multiple birth                | 15(16%)                                | 15(20%)                                                     | 0(0%)                                                    | 0.089    |
| Cardiac defect, Single ventricle | 18(19.1%)                      | 17(22.4%)                                                   | 16(8%)                                                   | 0.180    |
| **Pre-operative**             |                                        |                                                               |                                                          |          |
| Antenatal diagnosis           | 49(52%)                                | 40(53%)                                                     | 9(50%)                                                   | 0.999    |
| Highest plasma lactate, mmol/L| 3.3(3.4) [2.1, 3.3]                   | 3.5(3.7)                                                    | 2.2(1.1)                                                  | 0.010    |
| Lowest arterial pH            | 7.29(0.13) [7.22, 7.37]               | 7.28(0.13)                                                  | 7.30(0.09)                                                | 0.388    |
| Lowest PaO₂, mmHg             | 39.6(13.4) [32, 45]                   | 37.3(10.23)                                                 | 49.1(20.0)                                                | 0.026    |
| Lowest base deficit, mmol/L   | −4.1(5.2) [−7, −1]                    | −4.2(5.4)                                                   | −3(4.2)                                                   | 0.825    |
| Highest inotrope scoreb       | 4.8(14.8) [0, 6]                      | 5.2(16.2)                                                   | 3.1(5.3)                                                  | 0.346    |
| Highest serum creatinine, umol/L| 58.3(28.1) [35, 78]                | 59.6(28.9)                                                  | 52.5(23.8)                                                | 0.334    |
| Brain insults (by imaging)    | 6(6%)                                  | 6(6%)                                                       | 0(0%)                                                    | 0.592    |
| Ventilation, days             | 7.5(13.1) [5, 10]                     | 6.9(8.1)                                                    | 10.3(25.1)                                                | 0.570    |
| **Operative, post-operative day 1** |                                      |                                                               |                                                          |          |
| Postnatal age, days           | 24.1(23.9) [14, 34]                   | 21.5(19.6)                                                  | 35.2(35.8)                                                | 0.134    |
| Post-conceptual age, days     | 261.8(29.6) [255, 271]                | 260.1(31.5)                                                 | 269(18.9)                                                 | 0.126    |
| CPB time, min                 | 115.3(42.7) [90, 138]                  | 118.2(45.1)                                                 | 102.9(28.6)                                               | 0.079    |
| Cross clamp time, min         | 62.8(27.9) [46, 77]                   | 64.5(30.1)                                                  | 55.4(13.4)                                                | 0.056    |
| DHCA, used                    | 60(64%)                                | 51(67%)                                                     | 9(50%)                                                   | 0.278    |
| Highest plasma lactate, mmol/L| 5.5(3.3) [3.4, 7.1]                   | 5.6(3.4)                                                    | 5.6(2.8)                                                  | 0.860    |
| Lowest arterial pH            | 7.28(0.07) [7.23, 7.33]               | 7.27(0.07)                                                  | 7.30(0.06)                                                | 0.074    |
| Lowest PaO₂, mmHg             | 57.3(18.8) [40.8, 74.3]               | 56.3(18.3)                                                  | 61.7(20.9)                                                | 0.324    |

(Continued)
Network, those with CCHD have more neonatal short-term complications including brain injuries (6.1% vs. 1–2% of PVL and parenchymal lesions) and necrotizing enterocolitis (6.1 vs. 1%), but not of retinopathy of prematurity (0 vs. 0% of Stage 3/4/5) (26). The prevalence of cerebral injuries with known association with disability in this group of moderate-late preterm and modestly low birthweight infants was high, 7 (6.1%). Chronic lung disease and patent ductus arteriosus were not examined in this cohort because the respective conditions were difficult to diagnose in surviving neonates with co-morbid cardiopulmonary condition of CCHD after OHS. Growth of these 2-year-old infants was within normal ranges, although skewed to the left of population norms. Consistent with previous reports (13, 27, 28), we have shown the primary cardiac defect of single ventricle and the peri-operative risk factor of CPR are important determinants of mortality. While GA and body weight did not predict death, the intra-uterine growth of the fetus as reflected by low birthweight z-scores was critical for this prediction. As part of the consideration of termination of pregnancy for a fetus with CCHD, it is important to examine fetal growth rather than GA alone, in addition to the compounding effect of CCHD. Postnatal age and post-conceptual age of surgery were not related to mortality. This finding should be interpreted with caution because of the small study population. We speculate that postnatal transition of cardiopulmonary systems may affect the tolerance of OHS, a pathophysiological phenomenon which is similar to the delay of surgery in infants with congenital diaphragmatic hernia (29). Therefore, based on the relation between outcome and postnatal and post-conceptual age, we suggest the OHS should be postponed to the time after feto-neonatal transition with the stabilization of cardiopulmonary status. This study provides information about the early childhood outcomes that may be useful for counseling parents of preterm neonates with CCHD. Dysmaturation and dysregulation of cortical neuronal development due to reduced cerebral oxygenation in CCHD might be responsible for neurodevelopmental adversity (30, 31). Cerebral palsy was found in 10.5% for those without syndromic diagnoses; this higher rates of cerebral palsy than for preterm survivors of the same GA without CCHD (32, 33) and higher than those of mostly term infants with CCHD (34). This study also suggests that sensorineural hearing loss was higher than that for preterm infants without CCHD (35, 36) and similar to term infants with CCHD (37). Vision loss was not increased for these preterm children over other preterm rates (35, 36). This study did not compare CCHD children with and without prematurity, however, mean scores for functional and neurodevelopmental outcomes of preterm neonates with CCHD in this study tend to be within the lower range of published results for preterm neonates (33, 35, 36). Particularly, low scores for self-care skills...
TABLE 4 | Growth and neurodevelopmental outcomes at 2-years corrected age for 94 surviving preterm infants after early open heart surgery from September 1996 to December 2016.

| Family background | All surviving preterm infants (n = 94) | Survivors without chromosomal or syndromic diagnoses (n = 76) | Survivors with chromosomal or syndromic diagnoses (n = 18) | P-value* |
|-------------------|---------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------|
| Socio-economic index | 44.6 (13.7) 43 [34, 54] | 44.5 (13.9) | 44.9 (13.1) | 0.902 |
| Mother’s schooling, years | 13.4 (3.2) 13 [12, 16] | 13.5 (3.4) | 12.9 (2.1) | 0.367 |
| **Growth** | | | | 0.867 |
| Weight, z-score | −0.71 (1.33) −0.66 [−1.73, 0.00] | −0.70 (1.31) | −0.75 (1.43) | 0.256 |
| Length, z-score | −0.96 (1.44) −0.97 [−1.95, 0.00] | −0.88 (1.43) | −1.31 (1.52) | 0.782 |
| Head circumference, z-score | −0.39 (1.36) −0.60 [−1.45, 0.22] | −0.41 (1.37) | −0.31 (1.38) | |
| **Disability** | | | | |
| Cerebral palsy (19) | 8 (9%) | 8 (11%) | 0 (0%) | 0.346 |
| Cerebral palsy types, all spastic | 5- hemiplegia; 1-quadruplegia; 1-triplegia; 1-monoplegia | | | |
| Visual impairment | 2 (2%) | 1 (1%) | 1 (6%) | Not applicable |
| Hearing loss | 6 (6%) | 4 (5%) | 2 (11%) | 0.323 |
| Hearing loss types | 3-bilateral sensorineural; 1-unilateral sensorineural | 1-bilateral sensorineural; 1-permanent conductive | |
| **Functional scores (ABAS-II) (17)** | | | | |
| General adaptive composite | 83.7 (18.1) 85 [70, 92] | 86.2 (17.8) | 73.7 (14.1) | 0.004 |
| Conceptual composite: | | | | 0.060 |
| -Communication | 88.3 (17.1) | 89.7 (17.0) | 76.9 (12.5) | | |
| -Functional pre-academics | 8.4 (3.4) | 8.6 (3.5) | 6.6 (2.2) | 0.137 |
| -Self-direction | 8.3 (2.9) | 8.4 (2.9) | 7.4 (2.9) | 0.403 |
| Practical composite: | | | | 0.062 |
| -Home living | 84.9 (17.5) | 86.5 (17.3) | 72.1 (14.1) | 0.039 |
| -Health and safety | 9.0 (3.2) | 9.2 (3.2) | 7.7 (3.0) | 0.268 |
| -Community use | 8.2 (3.5) | 8.5 (3.5) | 5.7 (2.4) | 0.045 |
| -Self-care | 8.3 (3.1) | 9.2 (3.0) | 6.9 (2.9) | 0.053 |
| Social composite: | | | | 0.065 |
| -Leisure | 8.4 (3.1) | 8.5 (3.3) | 6.4 (2.4) | 0.063 |
| -Social | 8.7 (3.4) | 8.9 (3.4) | 7.1 (2.5) | 0.207 |
| Motor skill | 8.3 (3.9) | 8.4 (3.9) | 7.1 (3.9) | 0.381 |

**Neurodevelopment scores (Bayley-III) (18), n = 71**

| Cognitive | 87.6 (15.4) 90 [80, 100] | 90.2 (13.6) (n = 54) | 80.1 (17.1) (n = 17) | 0.018 |
| Language | 82.4 (17.1) 83 [71, 94] | 84.1 (17.1) (n = 54) | 74.9 (17.3) (n = 17) | 0.055 |
| Motor | 86.1 (16.4) 85 [75, 94] | 87.1 (15.7) (n = 54) | 78.7 (17.4) (n = 17) | 0.062 |

Data are presented in mean (SD), median [IQR], n(%).
*Students t test or Fisher’s Exact test.
**Blishen Index (20).
## Predictive factors of General Adaptive Composite (ABAS-GAC) at 2-years of corrected age for 76 preterm infants without chromosomal/syndromic abnormalities with complex congenital heart defects who had early open heart surgery from September 1996 to December 2016.

### Time points

| Time points | Univariate regression | Multiple linear regression |
|-------------|-----------------------|---------------------------|
|             | Time point 1, before and at birth | Time points 1–2, up to before first operation | Time points 1–3, up to end of day 1 post-operatively | Time points 1–4, up to day 5 post-operatively | Time points 1–5, for all time periods up to hospital discharge |
| **1. Before or at birth** | | | | | |
| Year of birth | 0.66 (−0.03, 1.36) | | | | |
|  | | | | | |
| Gestational age groups | | | | | |
| < 32 weeks | 9.70 (−0.36, 19.76) | | | | |
|  | | | | | |
| Birthweight groups | | | | | |
| 2,000–2,499 g | −13.61 (−21.16, −6.08) | −12.74 (−20.16, −5.32) | −11.88 (−18.93, −4.83) | −11.60 (−18.67, −4.53) | |
|  | | | | | |
| Head circumference, z-score | 2.92 (−0.54, 6.38) | | | | |
|  | | | | | |
| **2. Pre-operative** | | | | | |
| Highest plasma lactate, mmol/L | −0.11 (−2.11, −0.04) | | | | |
|  | | | | | |
| Lowest arterial pH | 3.26 (0.52, 6.20) | 2.86 (0.19, 5.53) | 2.86 (0.19, 5.53) | 3.01 (0.48, 5.54) | |
|  | | | | | |
| Lowest PaO₂, mmHg | 0.32 (−0.05, 0.70) | | | | |
|  | | | | | |
| Lowest base deficit, mmol/L | 0.66 (−0.05, 1.37) | | | | |
|  | | | | | |
| Highest Inotrope score² | −0.26 (−0.49, −0.02) | | | | |
|  | | | | | |
| Highest serum creatinine, umol/L | −0.17 (−0.30, −0.05) | | | | |
|  | | | | | |
| **3. Operative, post-operative day 1** | | | | | |
| Post-conceptual age | −0.11 (−0.23, 0.02) | −0.11 (−0.22, −0.01) | −0.11 (−0.22, −0.00) | | |
|  | | | | | |
| Highest Inotrope score² | −0.58 (−1.05, −0.10) | | | | |
|  | | | | | |
| **4. Post-operative day 2–5** | | | | | |
| Lowest arterial pH | 7.18 (0.98, 13.37) | 7.14 (1.63, 12.63) | 6.75 (1.25, 12.25) | | |
|  | | | | | |
| Highest Inotrope score² | −0.41 (−0.86, −0.04) | | | | |
|  | | | | | |
| **5. Before discharge** | | | | | |
| Post-operative ventilation, days | −0.36 (−0.70, −0.01) | | | | |
|  | | | | | |
| Post-operative ICU, days | −0.27 (−0.55, 0.01) | | | | |

(Continued)
TABLE 5 | Continued

| Time points | Univariate regression | Multiple linear regression |
|-------------|-----------------------|---------------------------|
|             | Time point 1,         | Time points 1–2, up to    | Time points 1–3, up to end  | Time points 1–4, up to day 5 | Time points 1–5, for all time periods up to hospital discharge |
|             | before and at         | before first operation    | of day 1 post-operatively   | post-operatively             |                                                              |
|             | birth                  |                           |                            |                             |                                                              |
| Sepsis\(^b\) | \(-12.10\) (\(-20.98,\)   | \(-9.70\) (\(-17.74,\)   | \(-1.66\)                                                              |
|             | \(-4.53\)              | \(-1.66\)                 | \(P = 0.008\)               |
| Open sternum, days | \(-1.33\) (\(-2.51,\)  | \(-0.16\)                 | \(P = 0.027\)               |
| Total explained variance in each time point | 13.7%   | 17.7%   | 17.7%   | 26.2%   | 26.3% |

Coefficient, Effect Size (ES) with 95% confidence intervals (CI), by univariate linear regression (variables with \(P < 0.10\) included) and multiple linear regression at 5 different time points.

CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; ES, effect size; CI, confidence interval.

\(^b\) Inotrope score (\(Z\)) = dopamine (\(\mu g/\text{kg/min}\)) + dobutamine (\(\mu g/\text{kg/min}\)) + 100 \times \text{epinephrine (\(\mu g/\text{kg/min}\)).}

and language abilities indicate the need for early developmental testing and appropriate interventions for these children (38–40).

Among the predictive factors, the presence of syndromic diagnoses adversely affected neurodevelopmental outcome, as previously reported (41). Within birthweight subgroups, a birthweight of 2,000–2,499 g had a negative (unexpected) correlation with ABAS-II GAC in 76 preterm neonates without syndromic abnormalities. While Dimmick et al. (42) observed that low birthweight was associated with adverse outcomes in infants with CCHD, we do not know the exact reason to explain this relationship, which warrants replication to determine its importance. Due to the retrospective study design and small sample size, risk factors including CPR, inotrope scores, GA, birthweight z-scores and postnatal age of surgery had modest or no effects on the ABAS-II-GAC. Older post-conceptual age, low post-operative pH and sepsis added to the prediction. We have previously shown the significant effect of sepsis on adverse outcomes after early cardiac surgery (23). Using multiple variable analyses for prediction of ABAS-II GAC at 2 years corrected age, the cumulative variance explained was 26.3% in preterm infants without syndromic diagnoses. This highlights the possible importance of post-discharge risk factors in subsequent neurodevelopment, in addition to possible risk factors during pregnancy and hospitalization that we did not study.

Our study has several limitations. The research objective was retrospectively determined. Single center study and changes in clinical practice and surgical interventions over a span of 25 years, some antenatal risk factors were missed. This includes but limits to the study of cardiovascular and cerebrovascular state. Small sample size limited us from finding statistically significant relationships. In particular, there were only 6 infants with brain injuries identified in the pre-operative period and thus we could not study its predictive role in neurodevelopment in the multiple variable model. However, information on brain injury before surgery would be helpful in counseling. We did not have detailed information of the maternal conditions associated with the preterm births. Future investigations should address if these conditions may have impact on in utero growth or adverse post-natal effects on the infants which are independent of the gestational age. Given these limitations, our findings should be interpreted with caution and generalization to other centers. The use in parental counseling may be limited. Further multicenter prospective study will be needed to confirm our findings. Strengths of this study include the prospective inception cohort design with most data collected prospectively, and the detailed neurodevelopmental and functional outcomes determined prospectively without any loss to follow-up of survivors. Of note, the infants who did not survive were sicker than the survivors. While it may be interesting to study the prediction of a combined group of adverse outcomes including non-survivors and disabled survivors, the current study design was to study the prediction of mortality and neurodevelopmental outcomes in a separate manner.

CONCLUSIONS

Preterm neonates with CCHD and early OHS had significant mortality and morbidity. Early outcomes suggest more cerebral palsy and lower functional and neurodevelopmental scores than occurring with prematurity alone. In this preterm group, predictive factors for mortality included birthweight z-scores, cardiac lesion of single ventricle, prolonged post-operative ventilation and the need for CPR. In addition to syndromic diagnoses, predictive factors for adverse functional outcome
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AUTHOR CONTRIBUTIONS

P-YC conceptualized and designed the study, drafted the initial manuscript, reviewed, and revised the manuscript. CR designed the data collection instruments, conceptualized and designed the study, supervised data collection, critically reviewed, and revised the manuscript. MH and ID carried out the statistical analyses, and critically reviewed and revised the manuscript. HS and AJ conceptualized and designed the study, supervised data collection, and critically reviewed the manuscript for important intellectual content. GB conceptualized and designed the study, coordinated data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional ethics boards at all six follow-up sites (University of British Columbia, University of Alberta, University of Calgary, University of Regina, University of Saskatchewan, and University of Manitoba). Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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