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Early Developmental Outcome in Children with Hypoplastic Left Heart Syndrome and Related Anomalies: The Single Ventricle Reconstruction Trial

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Abstract

Background—Survivors of the Norwood procedure may suffer neurodevelopmental impairment. Clinical trials to improve outcomes have focused primarily on methods of vital organ support during cardiopulmonary bypass.

Methods—In the Single Ventricle Reconstruction trial of the Norwood procedure with modified Blalock-Taussig shunt vs. right-ventricle-to-pulmonary-artery shunt, 14-month neurodevelopmental outcome was assessed using the Psychomotor Development Index (PDI) and Mental Development Index (MDI) of the Bayley Scales of Infant Development®-II. We used multivariable regression to identify risk factors for adverse outcome.

Results—Among 373 transplant-free survivors, 321 (86%) returned at age 14.3±1.1 (mean±SD) months. Mean PDI (74±19) and MDI (89±18) scores were lower than normative means (each P<.001). Neither PDI or MDI score was associated with type of Norwood shunt. Independent

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predictors of lower PDI score ($R^2 = 26\%$) were clinical center ($P = .003$), birth weight < 2.5 kg ($P = .023$), longer Norwood hospitalization ($P < .001$), and more complications between Norwood procedure discharge and age 12 months ($P < .001$). Independent risk factors for lower MDI score ($R^2 = 34\%$) included center ($P < .001$), birth weight < 2.5 kg ($P = .04$), genetic syndrome/anomalies ($P = .04$), lower maternal education ($P = .04$), longer mechanical ventilation after the Norwood procedure ($P < .001$), and more complications after Norwood discharge to age 12 months ($P < .001$). We found no significant relationship of PDI or MDI score to, perfusion type, other aspects of vital organ support (e.g. hematocrit, pH strategy), or cardiac anatomy.

Conclusion—Neurodevelopmental impairment in Norwood survivors is more highly associated with innate patient factors and overall morbidity in the first year than with intraoperative management strategies. Improved outcomes are likely to require interventions that occur outside the operating room.

INTRODUCTION

Survival to adulthood is becoming a reality for patients with hypoplastic left heart syndrome (HLHS) and other single right ventricle (RV) anomalies treated with staged repair from the Norwood operation to the Fontan procedure. This remarkable progress has exposed a high prevalence of neurodevelopmental impairment in survivors,^{1–5} affecting their educational achievement, employability, and quality of life.^{6, 7} Potential risk factors for adverse neurodevelopmental outcome in this population include patient and environmental factors,^{8–12} management practices,^{13–22} and medical course.^{23, 24}

The Single Ventricle Reconstruction (SVR) trial compared outcomes in subjects with HLHS or related anomalies palliated using the Norwood procedure with either a modified Blalock-Taussig (MBT) shunt or the right-ventricular-to-pulmonary-artery (RV-to-PA) shunt. The primary outcome was freedom from death or cardiac transplantation by 12 months post-randomization.²⁵ In this manuscript, we report an important pre-specified secondary trial outcome, neurodevelopment assessed by in-person evaluation at 14 months after randomization. We evaluated the influence of shunt type on neurodevelopmental outcome based on the hypothesis that the RV-to-PA shunt group would have better neurodevelopment because of its potential advantage of reducing the aortic diastolic run-off and hence improving cerebral blood supply in the early postoperative period. As a secondary analysis, multivariable regression was used to identify other risk factors for adverse neurodevelopmental outcome. The SVR trial is the largest prospective study of children undergoing the Norwood procedure. Developmental testing at age 14 months in this cohort provides an unparalleled opportunity to explore the correlates of neurodevelopment, and to identify potential modifiable factors.

METHODS

Subjects

Details of the SVR trial design have been published.²⁶ Patients were recruited from 15 centers in North America participating in the NHLBI-funded Pediatric Heart Network between May 2005 and July 2008. Inclusion criteria consisted of a diagnosis of HLHS or other single, morphologic RV anomaly and planned Norwood procedure. Exclusion criteria included preoperative identification of anatomy rendering either a MBT shunt or a RV-to-PA shunt technically impossible and any major congenital or acquired extra-cardiac abnormality that could independently affect the likelihood of the subject meeting the primary outcome of transplant-free survival at 12 months post-randomization. The protocol was approved by the Institutional Review Board at each center, and written informed consent was obtained from a parent/guardian prior to randomization.

Neurodevelopmental Assessment

The primary measure of neurodevelopment was the Bayley Scales of Infant Development®-Second Edition (BSID-II).²⁷ Every examiner participated in conference calls in which the study protocol, the certification process, and data reporting procedures were discussed. Each submitted two videotaped assessments of children similar in age to trial subjects in order to be certified by a single expert (D.C.B.) prior to administering the BSID-II to a trial subject. These tapes, and the associated examiner record forms, were reviewed to ensure that appropriate administration and scoring procedures were followed. Throughout the study, the examiner record form for each trial subject was reviewed by D.C.B. for completeness and accuracy. The BSID-II was only administered in English or Spanish and it was administered in the dominant language spoken in the home. Testing personnel were blinded to the treatment assignment of the subjects.

The BSID-II offers a standardized assessment of cognitive and motor development for children ages 1 month through 42 months.²⁷ It yields two scores: the Psychomotor Development Index (PDI) and the Mental Development Index (MDI). The mean±standard deviation (SD) for PDI and MDI scores in the normative population is 100±15.

Study Design and Measurements

Subjects were randomly assigned to either a MBT shunt or a RV-to-PA shunt within strata defined by the presence or absence of aortic atresia and of obstructed pulmonary venous return, with dynamic balancing within surgeon. In all other respects, they were managed according to the usual practices at their clinical centers. A complete list of variables that were recorded and analyzed is provided in the Supplemental Table. In brief, prior to the Norwood procedure, we recorded demographic and preoperative medical history, including pregnancy history, fetal diagnosis, birth weight, race, gender, gestational age, Apgar scores, clinical status and anatomic diagnosis at presentation, occurrence of important preoperative complications, and age at operation.²⁶ We recorded intra-operative variables at the time of the Norwood procedure, the stage II procedure, and any additional cardiac operations, including total support time, total bypass time, and durations of deep hypothermic circulatory arrest (DHCA) and regional cerebral perfusion (RCP) times; details of bypass (e.g., lowest temperature, use of modified ultrafiltration, use of alpha blockade); and shunt type. The perfusion method during vital organ support was classified as deep hypothermic circulatory arrest (DHCA), regional cerebral perfusion (RCP), or DHCA+RCP. Patients who received RCP with < 10 minutes of DHCA, usually to allow for repositioning of cannulae, were classified in the RCP group. Shunt type was defined as the shunt in place at the end of the Norwood procedure, which differed from the randomly assigned shunt for 22 (7%) of subjects with a Bayley score. Postoperative data during the admissions for the Norwood and stage II operations were prospectively collected by daily review, and included procedures and events. Twelve months after randomization, we recorded vital status and interim medical history. At the in-person evaluation 14 months after randomization, we performed neurodevelopmental testing and collected data on height, weight, head circumference, interim medical history, and socioeconomic status. In addition to genetic evaluations performed during routine clinical care, an optional research genetic evaluation was offered to families. Patients were classified with regard to whether they had 1) a specific genetic syndrome, or 2) other anomalies (i.e., not identified with a syndrome). Growth data were converted into age-adjusted z-scores based on World Health Organization standards.²⁸

Statistical Methods

Descriptive statistics include median with interquartile range for skewed variables, mean ±SD for other continuous variables, and frequency with percentage for categorical variables. The frequency distributions of duration of mechanical ventilation and hospital stay were

nonlinearly related to outcome; thus we used a natural logarithmic transformation. We used median imputation for highest lactate level with values specific to pre-intubation status (101 subjects) and mean imputation for Apgar scores (20 subjects). For the Bayley scores, interactions between each candidate predictor and four pre-specified variables were examined: 1) birth weight <2.5 kg vs. ≥2.5 kg; 2) gestational age <37 weeks vs. ≥37 weeks; 3) Pre-Norwood head circumference z-score <−1 vs. ≥−1; and 4) presence vs. absence vs. unknown status of a genetic syndrome or other abnormality. We used simple linear regression and regressions adjusted for site to obtain initial estimates of association of each candidate predictor with PDI and MDI scores. All variables with unadjusted $P < 0.20$ were used as candidate predictors for multivariable modeling. Interaction terms were allowed to enter the multivariable model only in hierarchical fashion. Stepwise linear regression was employed to develop multivariable models, in conjunction with bootstrapping (1000 samples) to obtain reliability estimates for each of the predictors. We required that all terms in the final multivariable model have a reliability >50% and $P < .05$. All analyses were conducted using SAS version 9.2 (Statistical Analysis System, SAS Institute, Inc., Cary, NC) and SAS macros for bootstrapping estimates of reliability.

RESULTS

A flow chart of SVR trial subjects from randomization to neurodevelopmental follow-up is shown in Figure 1. The follow-up rate for the BSID-II examination among transplant-free survivors was 86%. The mean (\pm SD) age at follow-up was 14.3 ± 1.1 months (range 12.2–19.5 months). The 314 patients who completed the examination were less likely to be of black or other race ($P < .001$). However, the groups did not differ in their socioeconomic class or level of highest maternal education. The mean time interval between the Norwood and stage II procedures was 5.2 ± 1.9 months (median 5.0 months). Ten (3%) subjects in the cohort were not discharged between stage I and II surgery.

At 14 months, children had impaired growth: mean weight, height, and head circumference z-scores-for-age were -0.7 ± 1.1 , -1.3 ± 1.7 , and -0.4 ± 1.4 , respectively. Among the 296 subjects for whom a parent history was available, 47% had received developmental support in the first year of life: 39% with physical therapy, 26% with speech/language therapy, 10% with early intervention, and 4% with other forms of support. Genetic syndromes or other anomalies were detected in 25% of the cohort and were absent in 57%; the remaining 18% were not evaluated by a geneticist. Subjects with confirmed genetic syndrome and other anomalies had longer hospitalization (median 28 days [IQR 20–43 days] vs. 22 days [IQR 16–35 days] and 24 days [IQR 17–38 days] for no and unknown syndrome status, $P = .01$). Birth weight tended to be lower in the patients with confirmed genetic syndromes (3.0 ± 0.6 vs. 3.2 ± 0.5 or 3.2 ± 0.5 kg in the no and unknown groups, $P = .06$).

Distributions of PDI and MDI scores are depicted in Figure 2. Tables 1 and 2 summarize the significant univariate associations ($P < .05$) of PDI or MDI score with patient factors, management practices, and medical course.

For the overall cohort, PDI scores were profoundly lower than in the normative population (Figure 2): scores were < 85 (>1 SD below expected mean) in 65% of subjects, and < 70 (>2 SD below expected mean) in 44% of subjects. The subgroup of subjects with no genetic syndrome and birth weight of ≥2.5 kg had the highest PDI and MDI scores (each $P < .001$) and also had shorter Norwood hospital length of stay ($P = .033$). Subjects who received the MBT shunt and RV-to-PA shunt had similar PDI scores (75 ± 19 vs. 74 ± 20 , respectively, $P = 0.48$; Supplemental Figure). In multivariable linear regression modeling (Table 3), independent predictors of lower PDI scores were clinical center where the Norwood procedure was performed ($P = .003$), birth weight <2.5 kg ($P = .02$), longer log-transformed

days of Norwood hospitalization ($P<.001$), and greater number of complications between the time of discharge after the Norwood procedure and age 12 months ($P<.001$). The percentage of variance explained by the model (adjusted R^2) was 26%. Mean PDI score dropped approximately 13 points for every three extra days of hospital stay during the Norwood hospitalization. Presence of a genetic syndrome or other anomaly did not achieve statistical significance ($P=.07$).

MDI scores were also much lower than in the normative population (Figure 2): scores were < 85 (>1 SD below normal mean) in 36% of subjects, and <70 (>2 SD below normal mean) in 16% of subjects. Within subject, MDI scores were higher than PDI scores ($P<.001$). Mean MDI scores did not differ significantly between patients who received the MBT shunt vs. the RV-to-PA shunt (89 ± 17 vs. 88 ± 18 , respectively, $P=.55$; eFigure 1). In multivariable regression analysis (Table 3), independent predictors of lower MDI score included the clinical center where the Norwood procedure was performed ($P<.001$), birth weight <2.5 kg ($P=.04$), the presence of a genetic syndrome or other anomalies ($P=.04$), lower maternal education level ($P=.04$), longer log days on the ventilator after the Norwood procedure ($P<.001$), and a greater number of complications between the time of hospital discharge after the Norwood procedure and age 12 months ($P<.001$). The percentage of variance explained by the model (adjusted R^2) was 34%. Birth weight percentile for gestational age was a less significant predictor for PDI and MDI scores than raw birth weight.

Early intervention in the first year of life was not included in our original multivariable models, because it was considered to be a correlate of adverse outcome. However, the percentage of subjects who received early intervention varied significantly by center, ranging from 0% to 23% ($p=0.02$) for early intervention administered for the indication of a cognitive disorder and from 0% to 78% for receipt of any form of early intervention (e.g., physical therapy, occupational therapy). We therefore explored whether center differences in the percentages of children receiving either early intervention for a cognitive disorder or any form of early intervention in the first year of life could explain the center effect on outcomes. Mean PDI and MDI scores were significantly lower on average by 11 points in those who received early intervention for a cognitive disorder compared to those who did not (PDI, 66.4 ± 18.0 vs. 75.5 ± 19.3 , $P=.014$; MDI, 78.7 ± 20.7 vs. 90.1 ± 17.0 , $P<.001$). Similarly, children who received any form of early intervention in the first year of life (e.g., physical therapy, occupational therapy) fared worse than those who received no form of early intervention (PDI, 67.8 ± 18.3 vs. 81.5 ± 17.9 , $P<.001$; MDI, 84.1 ± 19.0 vs. 93.9 ± 14.7 , $P<.001$). However, adjustment for either of these intervention terms in the final multivariable models for MDI and PDI did not appreciably alter the effects of center on developmental scores. Similarly, we could find no other center characteristics, such as center volume or surgeon volume, which had a significant effect on PDI or MDI score in multivariable analysis. Finally, we explored whether the center effect could be related to an outlier; when eliminating centers one at a time from the multivariable models; study inferences were similar.

Some variables that had been hypothesized to predict developmental outcome were notable for their lack of association with either PDI or MDI scores. Perfusion type examined both as a categorical variable (DHCA, RCP, or DHCA together with RCP), and as total minutes of DHCA during Norwood surgery was not associated with PDI score in univariate analyses. MDI scores differed ($P<.001$) in univariate analysis among patients who underwent vital organ support during the Norwood procedure using DHCA, RCP, or a combination of DHCA and RCP (mean scores 85.1, 93.4, and 92.0, respectively, $P<.001$). As noted above, perfusion type was not an independent predictor of MDI in multivariable analysis. Because the final multivariable model included clinical center, we further explored whether perfusion type would become an independent predictor of MDI if site were not considered. Even then,

perfusion strategy did not meet the criteria for inclusion because of low reliability by bootstrapping (40%). In addition, we found no significant relationship of PDI or MDI score to other aspects of vital organ support, such as hematocrit or pH strategy during core cooling or to patient factors such as diameter of the ascending aorta or cardiac anatomy.

Finally, we assessed whether the strength of the candidate predictors varied according to four pre-specified patient factors (see Methods) related to birth weight, preterm status, pre-Norwood head circumference z-score, and presence of a genetic syndrome or other anomalies. The lack of effect of shunt type on PDI and MDI scores was consistent across the predetermined subgroups. The association of other candidate predictors with outcome also did not vary according to these pre-specified patient factors. None of the interaction terms entered the final multivariable models for either MDI or PDI.

DISCUSSION

We found a high prevalence of neurodevelopmental impairment in patients with HLHS syndrome and other single right ventricle anomalies, discouragingly similar to that described in patients who underwent Norwood surgery from 1998 to 2003.⁵ Lower BSID-II scores at age 14 months were predicted by both innate patient factors and measures of greater severity of illness. Patient factors that portended greater risk included the presence of genetic syndromes or other anomalies, lower maternal education, and lower birth weight. Consistent with previous reports,^{23, 24} patients in our study with a more complicated postoperative course following the Norwood procedure also had worse outcomes, as indicated by independent risk factors of longer postoperative mechanical ventilation or hospital stay. These measures of longer recovery likely integrate the effects of many other factors during the Norwood hospitalization, including adverse events, low cardiac output, poor feeding, or comorbidities. Between Norwood discharge and age 12 months, a greater number of complications were also associated with worse development, a novel finding that highlights ongoing brain vulnerability and opportunities for intervention. Subjects whose Norwood procedure was performed using the recently popularized RV-to-PA shunt scored no better on the BSID-II than those receiving a MBT shunt, even though they had better early survival.²⁵ Thus, patient characteristics and indices of greater severity of illness were more highly associated with later neurodevelopmental outcome than specific operative management strategies.

Methods of vital organ support during infant heart surgery are among the best studied and most easily modified potential risk factors for brain injury. Previous studies have suggested that longer duration of DHCA may have adverse effects on neurodevelopmental outcomes.^{2, 29} An alternative to DHCA, RCP involves low-flow perfusion to the brain during aortic arch reconstruction and has been hypothesized to be potentially neuroprotective relative to DHCA. A single-center randomized trial comparing DHCA to RCP during Norwood surgery found no evidence that RCP improves infant development at age one year.³⁰ Nonetheless, half of surgeons who responded to a survey on support techniques recently reported routine or exclusive use of RCP.³¹ In our study, neither longer DHCA duration nor use of a predominant DHCA strategy during the Norwood procedure emerged as an independent risk factor for any developmental outcome. No other perfusion techniques used during cardiopulmonary bypass emerged as independent risk factors for worse developmental outcomes despite a wide range of practices among participating centers.

Most patient factors are not modifiable, but birth weight might be improved by postponing the time of elective delivery to 39–40 weeks, as recommended by the American College of Obstetricians and Gynecologists.^{32, 33} In a recent large series, 26% of neonates with critical

congenital heart disease were delivered electively at 37–38 weeks gestation,³⁴ a percentage that is similar to national statistics.³²

The modest percentage of variance in outcomes explained by postnatal factors in our study is consistent with growing evidence that risk for adverse neurodevelopmental outcomes begins prenatally. Patients with HLHS have a high rate of cerebral dysgenesis and microcephaly,^{35, 36} suggesting that genetic factors and epigenetic insults contribute to abnormalities in brain development.¹² Furthermore, abnormal fetal cerebral hemodynamics could adversely affect brain development. Compared to normal third-trimester fetuses, those with HLHS and other congenital heart lesions have progressively smaller gestational age- and weight-adjusted brain volume, as well as perturbed neuroaxonal development and metabolism on fetal brain MRI.⁹ On histopathological examination, the HLHS fetus already has chronic diffuse white matter injury.¹² Preoperatively, abnormalities of brain metabolism and microstructure, suggestive of brain immaturity, are present in a high percentage of infants with single-ventricle lesions and D-transposition of the great arteries (D-TGA).³⁷ Indeed, brain maturation in neonates with HLHS and D-TGA is delayed by approximately one month compared to a normative sample.¹¹ Moreover, Andropoulos et al.¹⁰ showed that low brain maturity score by MRI is associated with greater brain injury in both the preoperative and postoperative periods. Thus, preoperative condition could increase brain vulnerability to perioperative hemodynamic instability and intraoperative hypoxia-ischemic injury.

The results of this study must be viewed in light of its limitations. We are uncertain why the clinical center at which the Norwood procedure was performed emerged as an independent predictor of both PDI and MDI scores in final multivariable models. We prospectively recorded data on many potential risk factors, including details of perfusion techniques. Nonetheless, it is possible that differences in developmental scores according to site reflect residual confounding from unmeasured variables in patient characteristics or perioperative management. For example, neurotoxicity of anesthetic agents in the developing brain has been an area of increasing concern, but the types and quantities of anesthesia were not recorded in the Single Ventricle Reconstruction trial.^{38–40} It is also possible that differences in site scores were related to subjective differences in psychologist's scoring at the centers. However, the test administration technique of all psychologists was standardized centrally prior to their testing of study subjects, and there was drift in scores over time at only one site. Furthermore, study inferences were similar when centers were eliminated from the multivariable models one at a time. Of note, the examiners were blinded to treatment group, and shunt types were balanced within surgeon and thus, within clinical center, so that the treatment group comparison should not be biased.

We performed developmental testing at the oldest possible age within the design of the SVR trial, for which 14-month development was a secondary outcome. It is difficult to assess developmental skills such as visual perception, perceptual-motor integration, early number concepts and or pre-writing skills before age two years. Bayley scores at 14 months are poorly predictive of later neurodevelopment in normally-developing children, but their predictive validity is better in samples of at-risk infants,⁴¹ including children with congenital heart disease.⁴² The specificity and negative predictive value of low scores for later cognitive function are relatively high;^{42, 43} children who score well in infancy tend to score well later on. However, sensitivity and positive predictive value tend to be lower, indicating that only a subset of children who score poorly in infancy will score poorly later on. This may reflect many factors, including the benefits of early intervention and the influence of intercurrent medical and psychosocial events. Poor PDI scores are, however, predictive of later motor function, with strong tracking of motor proficiency from the 18-month PDI score to the prepubertal period.⁴⁴ Furthermore, the Bayley Scales at 14 months have good

concurrent validity and reliability; because assessment of infants with congenital heart disease has commonly been performed using the Bayley Scales at age one year, its use in the current study allows comparison with previously published data.

We were unable to perform brain MRIs on study subjects because this would have required general anesthesia in medically fragile children, posing a controversial risk-to-benefit ratio. Neurologic examination also was not incorporated in the study protocol and would have been challenging to standardize among 15 centers. Many variables were highly associated with each other. We did not adjust for multiple comparisons in our analyses. However, the P-values for the predictors in the final models were highly statistically significant. We used bootstrapping to assess the reliability of variables that were selected in our multivariable models, providing reassurance about their robustness. Intraoperative variables did not emerge as independent predictors of neurodevelopmental outcomes, but adjustment for postoperative events in the causal pathway may have diminished their statistical significance. Finally, our study design allowed us to identify many of the variables associated with adverse neurodevelopmental outcome, but not to determine causality.

In summary, in the largest multi-center prospective study to date of children with HLHS and other single right ventricle anomalies undergoing staged reconstruction, we found that neurodevelopmental impairment was most highly associated with innate patient factors and general medical morbidity in the first year of life. Substantial improvement in neurodevelopmental outcome in this vulnerable population is likely to require interventions that occur outside the operating room, such as discouraging elective deliveries before 39 weeks, protecting the brain during preoperative and postoperative hemodynamic instability, and optimizing developmental support after Norwood discharge. While single ventricle lesions and their management are unusually complex, they constitute an important model for considering universal effects of critical congenital defects (both cardiac and non-cardiac) requiring complex interventions in the newborn period.³⁹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007; 115(2):163–172. [PubMed: 17210844]
2. Goldberg CS, Schwartz EM, Brunberg JA, et al. Neurodevelopmental outcome of patients after the Fontan operation: A comparison between children with hypoplastic left heart syndrome and other functional single ventricle lesions. *J Pediatr*. 2000; 137(5):646–652. [PubMed: 11060530]
3. Mahle WT, Clancy RR, Moss EM, Gerdes M, Jobes DR, Wernovsky G. Neurodevelopmental outcome and lifestyle assessment in school-aged and adolescent children with hypoplastic left heart syndrome. *Pediatr*. 2000; 105(5):1082–1089.
4. McCrindle BW, Williams RV, Mitchell PD, et al. Relationship of patient and medical characteristics to health status in children and adolescents after the Fontan procedure. *Circulation*. 2006; 113(8): 1123–1129. [PubMed: 16490823]

5. Tabbutt S, Nord AS, Jarvik GP, et al. Neurodevelopmental outcomes after staged palliation for hypoplastic left heart syndrome. *Pediatr*. 2008; 121(3):476–483.
6. Azakie T, Merklinger SL, McCrindle BW, et al. Evolving strategies and improving outcomes of the modified Norwood procedure: a 10-year single-institution experience. *Ann Thorac Surg*. 2001; 72(4):1349–1353. [PubMed: 11603459]
7. Wernovsky G, Newburger J. Neurologic and developmental morbidity in children with complex congenital heart disease. *J Pediatr*. 2003; 142(1):6–8. [PubMed: 12520246]
8. Glauser TA, Rorke LB, Weinberg PM, Clancy RR. Congenital brain anomalies associated with the hypoplastic left heart syndrome. *Pediatr*. 1990; 85:984–990.
9. Limperopoulos C, Tworetzky W, McElhinney DB, et al. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation*. 2010; 121(1):26–33. [PubMed: 20026783]
10. Andropoulos DB, Hunter JV, Nelson DP, et al. Brain immaturity is associated with brain injury before and after neonatal cardiac surgery with high-flow bypass and cerebral oxygenation monitoring. *J Thorac Cardiovasc Surg*. 2010; 139(3):543–556. [PubMed: 19909994]
11. Licht DJ, Shera DM, Clancy RR, et al. Brain maturation is delayed in infants with complex congenital heart defects. *J Thorac Cardiovasc Surg*. 2009; 137(3):529–536. [PubMed: 19258059]
12. Hinton RB, Andelfinger G, Sekar P, et al. Prenatal head growth and white matter injury in hypoplastic left heart syndrome. *Pediatr Res*. 2008; 64(4):364–369. [PubMed: 18552707]
13. Kurth CD, Steven JL, Montenegro LM, et al. Cerebral oxygen saturation before congenital heart surgery. *Ann Thorac Surg*. 2001; 72(1):187–192. [PubMed: 11465176]
14. Ferry PC. Neurologic sequelae of cardiac surgery in children. *Am J Dis Child*. 1987; 141:309–312. [PubMed: 3544810]
15. Wypij D, Newburger JW, Rappaport LA, et al. The effect of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment: the Boston Circulatory Arrest Trial. *J Thorac Cardiovasc Surg*. 2003; 126(5):1397–1403. [PubMed: 14666011]
16. Schell RM, Stanley T, Croughwell N, et al. Temperature during cardiopulmonary bypass and neuropsychologic outcome. *Anesth*. 1992; 77:A119.
17. Bellinger DC, Wernovsky G, Rappaport LA, et al. Cognitive development of children following early repair of transposition of the great arteries using deep hypothermic circulatory arrest. *Pediatr*. 1991; 87:701–707.
18. du Plessis AJ, Jonas RA, Wypij D, et al. Perioperative effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. *J Thorac Cardiovasc Surg*. 1997; 114:991–1001. [PubMed: 9434694]
19. Bellinger DC, Wypij D, du Plessis AJ, et al. Developmental and neurologic effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. [see comments.] [erratum appears in *J Thorac Cardiovasc Surg* 2001 May;121(5):893.]. *Journal of Thoracic & Cardiovascular Surgery*. 2001; 121(2):374–383. [PubMed: 11174744]
20. Jonas RA, Wypij D, Roth SJ, et al. The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: results of a randomized trial in infants. *J Thorac Cardiovasc Surg*. 2003; 126(6):1765–1774. [PubMed: 14688685]
21. Jonas, RA. Problems of deep hypothermic circulatory arrest and low-flow perfusion. With particular reference to the paediatric population. In: Smith, P.; Taylor, K., editors. *Cardiac Surgery and the Brain*. 1 ed. London: Edward Arnold; 1993. p. 95-107.
22. Jonas RA. Neurological protection during cardiopulmonary bypass/deep hypothermia. *Pediatr Cardiol*. 1998; 19:321–330. [PubMed: 9636257]
23. Newburger JW, Wypij D, Bellinger DC, et al. Length of stay after infant heart surgery is related to cognitive outcome at age 8 years. *J Pediatr*. 2003; 143(1):67–73. [PubMed: 12915826]
24. Limperopoulos C, Majnemer A, Shevell MI, et al. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. *J Pediatr*. 2002; 141(1):51–58. [PubMed: 12091851]
25. Ohye RG, Sleeper LA, Mahony L, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med*. 2010; 362(21):1980–1992. [PubMed: 20505177]

26. Ohye RG, Gaynor JW, Ghanayem NS, et al. Design and rationale of a randomized trial comparing the Blalock-Taussig and right ventricle-pulmonary artery shunts in the Norwood procedure. *J Thorac Cardiovasc Surg.* 2008; 136(4):968–975. [PubMed: 18954638]
27. Bayley, N. *Bayley Scales of Infant Development, Second Edition.* Second Edition ed. San Antonio, TX: The Psychological Corporation; 1993.
28. de OM, Garza C, Onyango AW, Borghi E. Comparison of the WHO child growth standards and the CDC 2000 growth charts. *J Nutr.* 2007; 137(1):144–148. [PubMed: 17182816]
29. Newburger JW, Jonas RA, Wernovsky G, et al. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. *N Engl J Med.* 1993; 329:1057–1064. [PubMed: 8371727]
30. Goldberg CS, Bove EL, Devaney EJ, et al. A randomized clinical trial of regional cerebral perfusion versus deep hypothermic circulatory arrest: outcomes for infants with functional single ventricle. *J Thorac Cardiovasc Surg.* 2007; 133(4):880–887. [PubMed: 17382619]
31. Ohye RG, Goldberg CS, Donohue J, et al. The quest to optimize neurodevelopmental outcomes in neonatal arch reconstruction: the perfusion techniques we use and why we believe in them. *J Thorac Cardiovasc Surg.* 2009; 137(4):803–806. [PubMed: 19327499]
32. Ashton DM. Elective delivery at less than 39 weeks. *Curr Opin Obstet Gynecol.* 2010; 22(6):506–510. [PubMed: 20978440]
33. ACOG Committee Opinion No. 394, December 2007. Cesarean delivery on maternal request. *Obstet Gynecol.* 2007; 110(6):1501. [PubMed: 18055756]
34. Costello JM, Polito A, Brown DW, et al. Birth before 39 weeks' gestation is associated with worse outcomes in neonates with heart disease. *Pediatr.* 2010; 126(2):277–284.
35. Glauser T, Rorke L, Weinberg P, Clancy R. Congenital brain anomalies associated with hypoplastic left heart syndrome. *Pediatr.* 1990; 85(6):984–990.
36. Shillingford AJ, Ittenbach RF, Marino BS, et al. Aortic morphometry and microcephaly in hypoplastic left heart syndrome. *Cardiol Young.* 2007; 17(2):189–195. [PubMed: 17338838]
37. Miller SP, McQuillen PS, Hamrick S, et al. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med.* 2007; 357(19):1928–1938. [PubMed: 17989385]
38. Vutskits L. Anesthetic-Related Neurotoxicity and the Developing Brain: Shall We Change Practice? *Paediatr Drugs.* 2011; 14(1):13–21. [PubMed: 22149549]
39. Stratmann G. Review article: Neurotoxicity of anesthetic drugs in the developing brain. *Anesth Analg.* 2011; 113(5):1170–1179. [PubMed: 21965351]
40. Wise-Faberowski L, Loepke A. Anesthesia during surgical repair for congenital heart disease and the developing brain: neurotoxic or neuroprotective? *Paediatr Anaesth.* 2011; 21(5):554–559. [PubMed: 21481079]
41. Kopp, C.; McCall, R. Predicting later mental performance for normal, at risk, and handicapped infants. In: Baltes, P.; Brim, O., editors. *Life-span development and behavior.* New York: Academic Press; 1982. p. 33
42. McGrath E, Wypij D, Rappaport LA, Newburger JW, Bellinger DC. Prediction of IQ and achievement at age 8 years from neurodevelopmental status at age 1 year in children with D-transposition of the great arteries. *Pediatr.* 2004; 114(5):e572–e576.
43. Hack M, Taylor HG, Drotar D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. *Pediatr.* 2005; 116(2):333–341.
44. MacCobb S, Greene S, Nugent K, O'Mahony P. Measurement and prediction of motor proficiency in children using Bayley infant scales and the Bruininks-Oseretsky test. *Phys Occup Ther Pediatr.* 2005; 25(1–2):59–79. [PubMed: 15760824]

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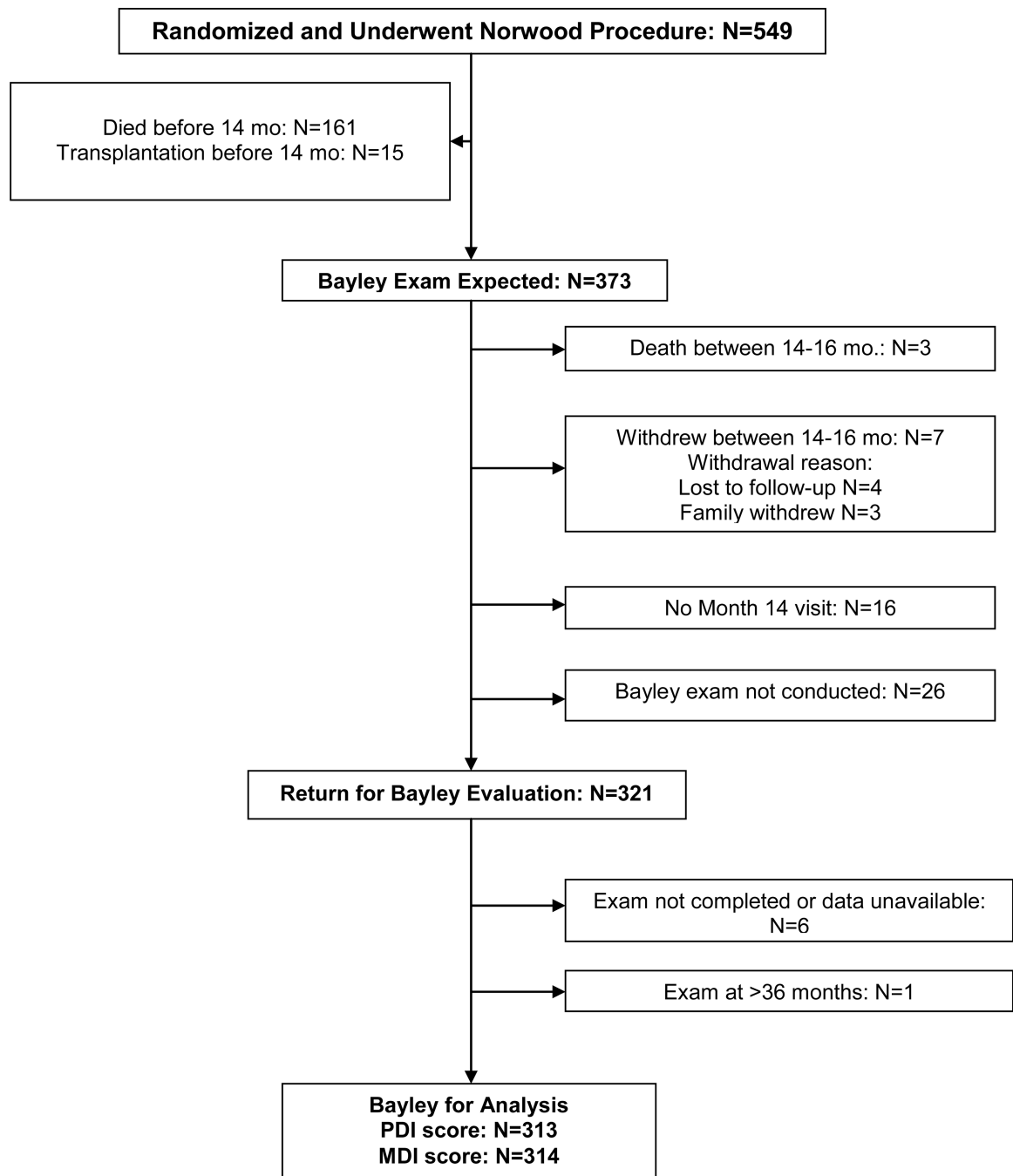


Figure 1.
Flow chart of SVR trial subjects from randomization to neurodevelopmental follow-up.

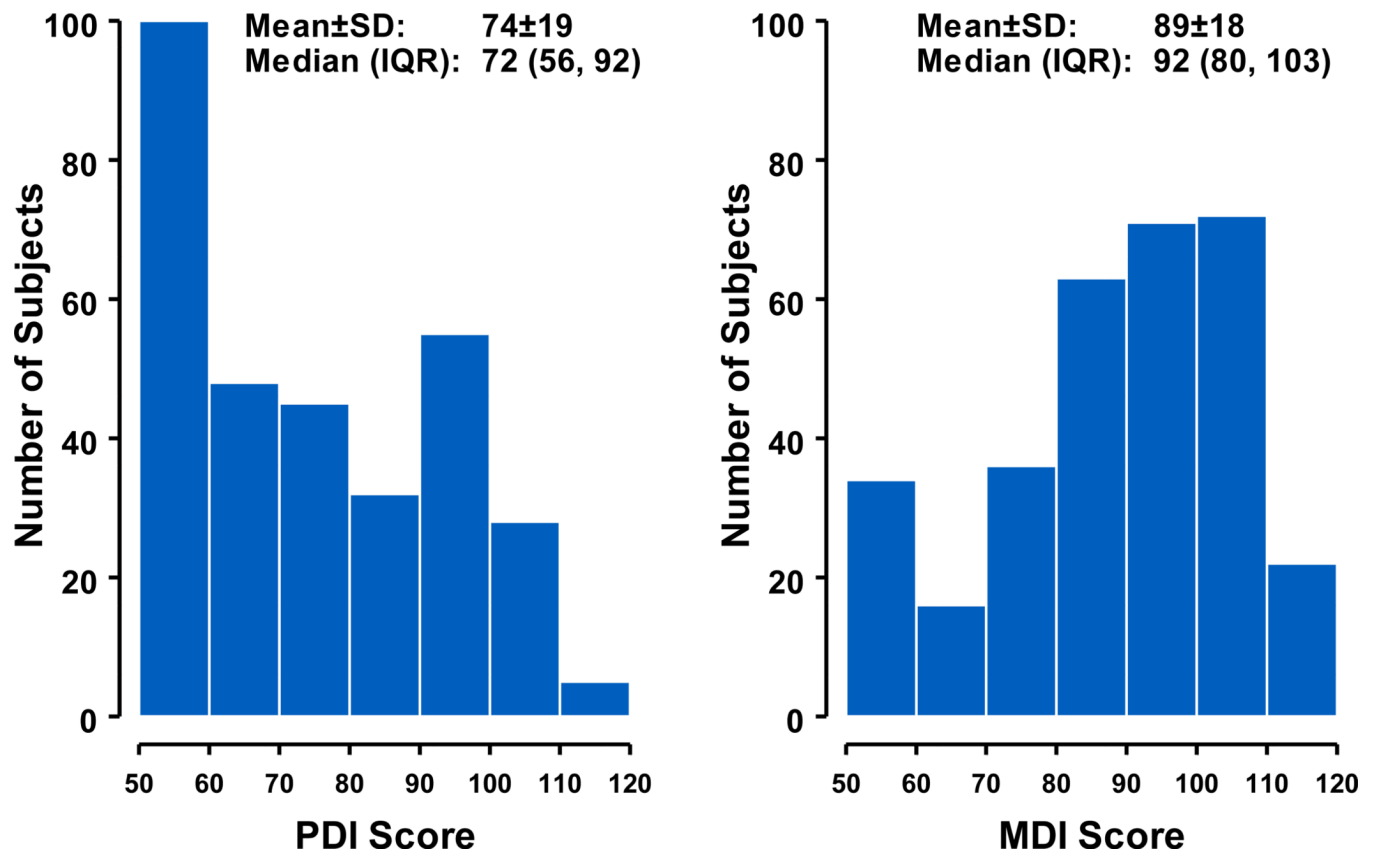


Figure 2. Histogram depicting the number of subjects according to scores on the Psychomotor Development Index (PDI, left panel) and Mental Development Index (MDI, right panel) of the Bayley Scales of Infant Development®—Second Edition.

Univariate Regressions using Predictors from Birth to Norwood Preoperative Period. Factors with $P < .05$ for either the PDI or MDI score shown.

Table 1

Variable	Bayley PDI Score		Bayley MDI Score	
	Mean±SD or %	Slope or Mean	p-value	Slope or Mean
Site			.006	<.001
Birth				
Gestational age, wk	38.4±1.4	1.00	.19	1.52
Gestational age<37 wk			.03	.06
Yes	7.3%	65.9		82.0
No	92.7%	75.1		89.2
Birth weight, g	3157±512	0.005	.01	0.008
Birth weight percentile for gestational age	38.3±27.3	0.07	.07	0.11
Birth weight <2500 g			.01	.006
Yes	9.2%	65.6		80.2
No	90.8%	75.3		89.6
Pre-Norwood HC-for-age z	-0.6±1.4	1.09	.19	2.29
Multiple birth				.002
Yes	3.8%	61.2	.02	78.4
No	96.2%	96.2		89.1
Demographics				
Maternal education			.03	<.001
Elementary	3%	66.1		70.7
Junior high	2%	52.8		61.6
Partial high	8%	79.2		89.7
Graduate high	19%	73.0		88.4
Partial college	30%	72.6		88.5
College graduate	27%	77.7		90.8
Post graduate	11%	76.9		92.4
Genetic and other anomalies				
Genetic syndrome			.004	<.001
Yes	3.8%	58.2		65.3

Variable	Bayley PDI Score		Bayley MDI Score	
	Mean±SD or %	Slope or Mean	p-value	Slope or Mean
No	77.4%	75.9		89.9
Unknown	18.8%	71.6		88.6
Other anomaly			.002	.006
Yes	23.2%	68.7		83.1
No	58.3%	77.5		90.8
Unknown	18.5%	71.9		89.1
Pre-operative				
Age at Norwood admission, days	1.0±2.3	0.98	.04	0.93
Mechanical ventilation			.11	
Yes	42.2%	72.4		86.0
No	57.8%	76.1		90.7
Pre-Norwood respiratory failure			.11	
Yes	10.9%	69.5		82.6
No	89.1%	75.0		89.4
Pre-Norwood metabolic acidosis			.90	
Yes	5.4%	73.9		80.4
No	94.6%	74.5		89.2
Cardiac catheterization intervention			.45	
Yes	4.5%	70.6		77.6
No	95.5%	74.6		89.2
No. of complications			.51	
0	77.4%	75.0		90.2
1	14.0%	71.3		80.3
2	8.6%	74.3		88.3

HC=head circumference; LOS=length of stay; z=z-score

Birth weight percentile for gestational age could be calculated for gestational ages between 35 to 41 weeks. Because 8 subjects were born at <35 weeks and 1 subject was born at 42 weeks, the percentile for birth weight for gestational age was set to missing for 9 subjects.

Table 2

Univariate Regressions Using Predictors from Norwood Operation to 14 months. Factors with $P < .05$ for either the PDI or MDI score shown.

Variable	Bayley PDI score		Bayley MDI Score	
	Mean±SD or %	Slope or Mean	Slope or Mean	p-value
Stage 1 Surgery				
Perfusion type			.70	<.001
DHCA only	52.6%	73.7	85.0	
RCP with DHCA 10 min	26.9%	75.0	93.4	
RCP and DHCA	20.5%	76.1	92.3	
DHCA time, min	29.8±22.1	-0.04	-0.16	<.001
RCP time, min	24.6±29.6	0.01	0.11	.001
Alpha-stat vs. pH-stat during cooling:				
PH-stat	75.5%	74.0	89.8	.04
α-stat	24.5%	75.7	85.2	
Hematocrit, %	30.1±5.1	-0.50	-0.20	.31
Open sternum				
Yes	75.2%	72.7	87.6	.06
No	24.8%	79.7	91.9	
α-blockade				
Yes	48.7%	76.3	91.6	.004
No	51.3%	72.7	85.9	
Post-Norwood to Norwood hospital discharge				
CPR				
Yes	7.0%	68.6	80.5	.02
No	93.0%	74.8	89.3	
ECMO				
Yes	4.1%	66.5	78.7	.04
No	95.9%	74.7	89.1	
No. of cardiac surgeries	1.4±1.3	-3.67	-3.11	<.001
No. of complications	2.2±2.6	-1.97	-1.75	<.001
Duration of ventilation, days	10.4±21.3	-0.18	-0.22	<.001

Variable	Bayley PDI score			Bayley MDI Score		
	Mean±SD or %	Slope or Mean	p-value	Slope or Mean	p-value	p-value
Post-operative LOS, days	32.4±30.1	-0.22	<.001	-0.18	<.001	<.001
Norwood discharge to age 12 months						
Stage II surgery LOS, days	13.1±16.5	-0.42	<.001	-0.29	<.001	<.001
No. of complications	2.4±2.5	-2.07	<.001	-2.13	<.001	<.001
No. of cardiac catheterization interventions	0.7±1.2	-2.17	.014	-0.93		.25
From Norwood to age 12 months						
No. of episodes of DHCA (linear fit)	1.0±0.7	-1.14	.48	-4.41		.002
No. of episodes of DHCA			.74			.006
0	25.2%	75.2		93.8		
1	53.8%	74.8		87.6		
2	21.0%	72.8		85.2		
Cumulative duration of DHCA, min	37.3±29.7	-0.05	.22	-0.13		<.001
No. of SAEs (linear fit)	0.2±0.5	-7.51	<.001	-6.75		<.001
No. of SAEs			.002			.002
0	78.7%	76.4		90.5		
1	18.2%	67.7		81.9		
2	3.2%	63.7		82.2		
Somatic growth						
Pre-Stage II minus Pre-Norwood						
Weight-for-age z	-1.4±1.1	2.49	.01	-0.04		.96
HC-for-age z	-0.9±1.7	2.69	<.001	2.06		.001
Month 14 minus Pre-Norwood						
Weight-for-age z	-0.3±1.3	1.73	.04	-0.15		.84
Height-for-age z	-0.9±1.7	1.27	.05	0.26		.65
Month 14 minus Pre-Stage II						
HC-for-age-z	1.2±1.6	-2.32	.001	-1.86		.004

HC=head circumference; LOS=length of stay; z=z-score; DHCA=deep hypothermic circulatory arrest; RCP=regional cerebral perfusion; CPR=cardiopulmonary resuscitation; SAE=serious adverse event

Table 3

Multivariable Regression Models for Bayley Summary Scores

PDI Score Multivariable Model (N = 313, Adjusted R ² = .26)	Estimate	Covariate -adjusted mean	p- value	Partial R ²	Multivariable bootstrapping reliability (%)
Site			.003	10%	55
Low birth weight (<2500 g)			.02	2%	80
Yes	-7.70	69.5			
No	Ref	77.2			
Log length of Norwood hospitalization, days	-11.53		<.001	13%	77
No. of complications post-Norwood discharge up to 12 months	-1.60		<.001	5%	85
MDI Score Multivariable Model (N = 311, Adjusted R ² = .034)	Estimate	Covariate -adjusted mean	p- value	Partial R ²	Multivariable bootstrapping reliability (%)
Site			<.001	13%	68
Low birth weight (<2500 g)			.04	2%	66
Yes	-6.16	81.8			
No	Ref	88.0			
Genetic syndrome and/ other anomalies			.04	2%	53
Yes	-7.19	80.9			
No	-2.25	85.8			
Unknown	Ref	88.1			
Maternal education level			.045	4%	70
Elementary	-14.51	77.2			
Junior high	-21.60	70.1			
Partial high	-2.49	89.2			
Graduate high	-3.93	87.8			
Partial college	-3.02	88.7			
College graduate	-1.97	89.7			
Post graduate	Ref	91.7			
Log days on ventilator post-Norwood during hospitalization	-7.48		<.001	10%	59
No. of complications post-Norwood discharge up to 12 months	-1.47		<.001	5%	78

* Model selection rule required $p < .05$ for all terms in the model and a reliability estimate of $> 50\%$

Ref = reference group