Infants less than or equal to 2.5 kg have increased mortality and worse motor neurodevelopmental outcomes at 2 years of age after Norwood–Sano palliation

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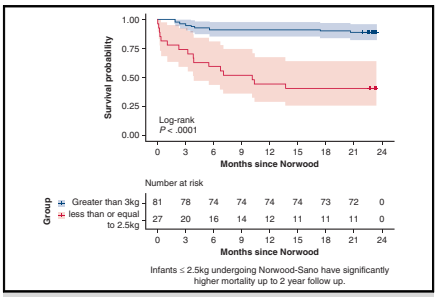
ABSTRACT

Objectives: In infants with single-ventricle congenital heart disease, prematurity and low weight at the time of the Norwood operation are risk factors for mortality. Reports assessing outcomes (including neurodevelopment) post Norwood palliation in infants ≤2.5 kg are limited.

Methods: All infants who underwent a Norwood–Sano procedure between 2004 and 2019 were identified. Infants ≤2.5 kg at the time of the operation (cases) were matched 3:1 with infants >3.0 kg (comparisons) for year of surgery and cardiac diagnosis. Demographic and perioperative characteristics, survival, and functional and neurodevelopmental outcomes were compared.

Results: Twenty-seven cases (mean ± standard deviation: weight 2.2 ± 0.3 kg and age 15.6 ± 14.1 days at surgery) and 81 comparisons (3.5 ± 0.4 kg and age 10.9 ± 7.9 days at surgery) were identified. Post-Norwood, cases had a longer time to lactate ≤2 mmol/L (33.1 ± 27.5 vs 17.9 ± 12.2 hours, $P < .001$), longer duration of ventilation (30.5 ± 24.5 vs 18.6 ± 17.5 days, $P = .005$), greater need for dialysis (48.1% vs 19.8%, $P = .007$), and greater need for extracorporeal membrane oxygenation support (29.6% vs 12.3%, $P = .004$). Cases had significantly greater postoperative (in-hospital) (25.9% vs 1.2%, $P < .001$) and 2-year (59.2% vs 11.1%, $P < .001$) mortality. Neurodevelopmental assessment showed the following for cases versus comparisons, respectively: cognitive delay (18.2% vs 7.9%, $P = .272$), language delay (18.2% vs 11.1%, $P = .505$), and motor delay (27.3% vs 14.3%, $P = .013$).

Conclusions: Infants ≤2.5 kg at Norwood–Sano palliation have significantly increased postoperative morbidity and mortality up to 2-year follow-up. Neurodevelopmental motor outcomes were worse in these infants. Additional studies are warranted to assess the outcome of alternative medical and interventional treatment plans in this patient population. (JTCVS Open 2023;14:417-25)



Infants ≤2.5 kg undergoing Norwood–Sano have greater mortality up to 2-year follow up.

CENTRAL MESSAGE

Infants ≤2.5 kg at Norwood–Sano palliation have significantly increased postoperative morbidity and mortality and worse neurodevelopmental scores up to 2-year follow-up.

PERSPECTIVE

Infants ≤2.5 kg with single-ventricle congenital heart disease requiring Norwood-type palliation represent one of the greatest-risk patient populations. Given the high mortality and morbidity associated with early Norwood–Sano palliation, alternative palliative strategies should be considered to improve outcomes.

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Abbreviations and Acronyms

Bayley-III = Bayley Scales of Infant and Toddler Development III
BCPA = bidirectional cavopulmonary anastomosis
LWB = low birth weight
RV = right ventricle
SV-CHD = single-ventricle congenital heart disease

Survival after repair of congenital heart defects has improved significantly over the last few decades.[1,2] Prematurity and low birth weight (LBW, typically defined as ≤2.5 kg) at time of definitive repair or initial palliation may predispose infants to greater postoperative morbidity and mortality.[3-6] In addition, both prematurity and LBW are known risk factors for worse neurodevelopmental outcomes in those with[7-10] and without[11,12] congenital heart disease. Infants who are born premature and/or with LBW with single-ventricle congenital heart disease (SV-CHD) undergoing Norwood palliation are arguably the greatest-risk cohort for adverse outcomes, including morbidity, mortality, and significant developmental delay.[13-15] To date, studies assessing perioperative and long-term outcomes of Norwood palliation in infants ≤2.5 kg have been limited by confounding factors and have generally not assessed differences in neurodevelopmental outcomes. The primary outcome of our study was to compare transplant-free survival to hospital discharge of infants ≤2.5 kg compared with infants >3.0 kg at the time of the Norwood operation using a matched case–comparison study design. Secondary outcomes included comparison of morbidity and perioperative outcomes post-Norwood and bidirectional cavopulmonary anastomosis (BCPA); transplant-free survival to BCPA and Fontan; and neurodevelopmental outcomes at 20 to 24 months.

METHODS

Patients

All infants who underwent the Norwood–Sano procedure between 2004 and 2019 at the Stollery Children's Hospital in Edmonton, Alberta, Canada were identified. The Stollery is the main Western Canadian surgical referral program. All infants were followed by the Western Canadian Complex Pediatric Therapies Follow-up Program, and none were lost to follow-up. Details of the program's methodology and database created from prospective data collection have been previously published.[16,17] Informed written consent was attained from the patient's parents or legal guardian. Approval for this study was obtained from each institution's ethics board (University of Alberta Institutional Review Board Approval Number Pro00001030, September 1, 2022).

All infants were intended to undergo 3-stage surgical palliation with a Norwood procedure, a BCPA, and a Fontan procedure, performed at the Stollery Children's Hospital. For the Norwood procedure, a right ventricle (RV)-to-pulmonary artery shunt has been the institutional preference for all patients since 2002.[14] All cases were discussed at combined cardiosurgical conference before surgical planning, as per the institution and program standards. Timing for each surgery was guided by published clinical standards and the patient's clinical status. Our institution's historical approach has been to complete the Norwood operation at a patient weight of ≥2.5 kg; however, this is performed at a smaller weight if clinically indicated in cases in which there is considerable pulmonary over circulation and inadequate systemic blood flow or pulmonary congestion due to a restrictive atrial septum.

Chromosomal abnormalities were identified with laboratory testing using G-banding karyotype, molecular analysis for 22q deletion, and microarray. Infants weighing ≤2.5 kg at the time of the Norwood operation (cases) were matched 3:1 with infants weighing >3.0 kg (comparisons) for year of surgery and cardiac diagnosis. During the study period, 189 patients underwent the Norwood operation with a weight at surgery of 2.5 to 3.0 kg. These patients were excluded from this analysis to facilitate case-matching and to isolate the impact of low surgical weight as an outcome. Demographic and perioperative characteristics, survival, functional, and neurodevelopmental outcomes were compared.

Developmental Assessment

Birth and 2-year somatic data (head circumference and length and weight z scores) were collected at routine follow-up. The Blishen index was used to assess socioeconomic status with maternal education determined by years of schooling.[18] Bayley Scales of Infant and Toddler Development III (Bayley-III), administered by or under the supervision of certified pediatric psychologists, were used to assess 2-year cognitive, language, and motor neurodevelopmental outcomes, with delay defined as a score of <70. The methodology of this program has been previously published.[16,19] The Bayley-III is a standardized, validated, and widely accepted tool used in follow-up clinics to measure domains of infant and toddler development by comparing individual scores to predetermined US normative age-matched values (population norm score of mean ± 1 standard deviation is 100 ± 15). For infants born prematurely <37 weeks of gestation, corrected gestational age was used up to 2 years, as per standard recommendations. The results of a parent-completed questionnaire, the General Adaptive Composite from the Adaptive-Behavioral Assessment System, second edition, were used to assess functional outcomes.[20,21]

Variables and Outcomes

Collected data included baseline demographics, perinatal, perioperative (Norwood, BCPA and Fontan), and cumulative variables for post-Norwood and post-BCPA (eg, overall hospitalization days, overall ventilations days, sepsis). As previously reported, sepsis was defined as a positive blood culture that was treated for at least 5 days with intravenous antibiotics.[22] All variables examined in this study are included in Table 1. Inotrope scores were calculated using the modified inotrope score formula.[23] Cardiac and noncardiac hospitalization, the use of cardiac and pulmonary medications, as well as the number of noncardiac medical specialists being seen were ascertained at the time of the follow-up. The hospitalizations included all admissions to any hospital between discharge from the initial hospitalization and the time of the neurodevelopmental assessment at 20 to 24 months of age. The medications included those being regularly taken at the time of the follow-up assessment. The number of specialists included those giving care at the time of the assessment. Outcome variables included postoperative and overall survival, and neurodevelopmental and functional outcomes. Mortality was ascertained by direct contact with the families and primary physician. Postoperative deaths were defined as within 30 days after surgery or before hospital discharge.

Statistical Analysis

Demographic and perioperative variables for infants undergoing BCPA and Norwood procedures and 2-year outcomes after early palliative cardiac surgery were compared between cases and comparison groups using

conditional logistic regression. Unadjusted Kaplan–Meier curves were generated to compare the survival of BCPA and survival of 2-years of age between cases and comparisons followed by a log-rank test to compare the difference in the survival between the 2 groups. For survival to BCPA, person-months were calculated as difference between age at first surgery and death (before BCPA), BCPA, or loss to follow-up, whichever occurred first. For 2-year survival, person-months were calculated from age at first surgery to death within 2 years, loss to follow-up, or end of study, whichever occurred first. In addition, we used stratified Cox proportional hazard regression model to estimate the hazard ratios (95% confidence intervals) between the 2 groups for BCPA and for 2-year survival. Data analyses were performed using R, version 4.0.4 (R Foundation for Statistical Computing).

RESULTS

A total of 27 cases (≤2.5 kg at the time of the Norwood) were matched with 81 comparisons (>3.0 kg at the time of the Norwood). The detailed demographic and perioperative variables of the 2 groups are summarized in Table 1 (Norwood procedure) and Table 2 (BCPA procedure). In the entire cohort, 64 infants (59%) had hypoplastic left heart syndrome (16 cases, 53 comparisons). The remainder of the cases included 5 double-outlet right ventricle, 2 unbalanced atrioventricular septal defects, 2 critical aortic stenosis, and 2 double-inlet left ventricle. The remainder of the comparisons included 7 double-outlet right ventricle and 1 with a hypoplastic RV, 5 unbalanced atrioventricular septal defects, 5 critical aortic stenosis, 4 double-inlet left ventricle, 3 tricuspid atresia, 2 isomerism with a hypoplastic ventricle, and one each for transposition of the great arteries with a hypoplastic RV and corrected transposition of the great arteries with a hypoplastic RV. Overall, 93% of cases and 86% of comparisons had a dominant right ventricle. There was no baseline difference between the 2 groups, including the presence of a chromosomal abnormality or prenatal diagnosis. At the time of Norwood surgery, cases were older (15.6 ± 14.1 vs 10.9 ± 7.9 days, $P = .030$) and, as expected, weighed less (2.2 ± 0.25 vs 3.5 ± 0.36 kg, $P < .001$) than comparisons. Surgical characteristics, including cardiopulmonary bypass, antegrade cerebral perfusion, and deep hypothermic circulatory arrest time, were not different between the 2 groups.

In the post-Norwood period, cases were sicker than comparisons, with a greater peak serum lactate (8.4 ± 3.2 vs 6.6 ± 3.0 mmol/L, $P = .007$), greater time to lactate ≤2.0 mmol/L (33.1 ± 27.5 vs 17.9 ± 12.2 hours, $P < .001$), longer ventilation time (30.5 ± 24.5 vs 18.6 ± 17.5 days, $P = .005$), more frequent use of dialysis (48.1 vs 19.8%, $P = .007$), and greater need for cardiopulmonary resuscitation (29.6 vs 9.9%, $P = .018$) and extracorporeal membrane oxygenation (40.7 vs 12.3%, $P = .004$). The overall hospitalization duration was not different between the 2 groups. At the time of stage 2 palliation, cases had a lower operative weight and a longer postoperative ventilation duration but otherwise had a similar postoperative course to comparisons (Table 2).

Survival

Of 108 total infants who underwent Norwood–Sano palliation, 8 died (7%) in-hospital during the postoperative period, with an additional 10 dying before stage 2 palliation (overall interstage mortality 16.7%). Total interstage mortality was significantly greater in cases (41%) compared with controls (9%), with a hazard ratio of 26.1 (95% confidence interval, 3.3-206.0, $P = .002$). At 2-year follow-up, the mortality difference was 16 total deaths among cases (59%) and 9 among the comparison group (11%). Kaplan–Meier survival curves are shown in Figures 1-3. There were no additional deaths to stage 3 (Fontan) completion, with an overall survival to Fontan completion of 77% (41% for cases vs 89% for the comparison group).

Clinical and Neurodevelopmental/Functional Outcomes

Clinical and neurodevelopmental/functional outcomes are summarized in Table 3. A total of 11 cases and 63 comparison infants underwent assessment at 2 years. Cases had lower length z scores (–2.4 ± 1.2 vs −0.81 ± 1.3, $P < .001$), weight z scores (–2.2 ± 0.99 vs –0.52 ± 1.23, $P < .001$), and lower motor score (73.6 ± 10.5 vs 87.3 ± 17.2, $P = .013$) compared with the comparison group. There was no statistically significant difference in cognitive, language, and functional scores or the presence of disability.

DISCUSSION

In this single-center case–comparison study, we sought to compare morbidity and mortality between infants with SV-CHD who were ≤2.5 kg (cases) and >3.0 kg (comparisons) at the time of Norwood–Sano palliation. We found that cases had significantly greater interstage and 2-year mortality. Furthermore, we found that cases were significantly sicker in the post-Norwood period, with higher lactates, longer ventilation times, more need for dialysis, and more frequent need for cardiopulmonary resuscitation and extracorporeal membrane oxygenation. Cases also had worse motor neurodevelopmental outcomes at 2-year assessment. Our study is the first to compare the impact of patient size on mortality, morbidity, and medium-term neurodevelopmental outcomes after Norwood palliation using a case–comparison approach.

Despite improvements in operative and perioperative care, neonates born with LBW and/or premature with various forms of CHD undergoing congenital heart surgery have a greater risk of mortality and morbidity.[3,24-26] The overall early mortality has been reported to be as high as 15%, but these studies report on heterogeneous groups of congenital heart defects with a wide range of complexity, and it is likely that the impact of LBW on outcomes is more pronounced in more complex forms of CHD. Indeed, in the largest analysis assessing the impact of

TABLE 1. Demographic and perioperative variables for patients undergoing Norwood procedure

Variables	Cases, ≤2.5 kg (n = 27)	Comparisons, >3 kg (n = 81)	*P* value*
Demographics			
Gestational age, wk	35.8 (2.1)	39.2 (1.2)	**<.001**
Birth weight, g	2179.4 (327)	3481.2 (327)	**<.001**
Small for GA	8 (29.6%)	3 (3.7%)	**.002**
Birth weight, z score	–0.977 (0.882)	0.228 (0.8)	**<.001**
Birth length, z score	–0.699 (1.23)	0.46 (0.61)	**<.001**
Birth head circumference, z score	–0.708 (1)	0.239 (0.913)	**<.001**
Male sex	15 (55.6%)	56 (69.1%)	.214
Chromosomal abnormality	2 (7.4%)	10 (12.3%)	.485
Prenatal diagnosis	24 (88.9%)	61 (75.3%)	.141
Preoperative			
Highest serum lactate, mmol/L	3.5 (1.7)	2.9 (1.8)	.103
Lowest arterial pH	7.24 (1.09)	7.31 (0.08)	**.001**
Lowest Pao_2	33.8 (7.5)	39.2 (8.5)	**.004**
Lowest base deficit, mmol/L	–5.39 (3.4)	–3.87 (3.8)	**.042**
Highest inotrope score	4.9 (6.1)	5.7 (9.5)	.678
Ventilation time, d	9.9 (10.8)	6.1 (8.2)	**.024**
CPR	0	0	
ECMO	0	0	
Operative			
Age at surgery, d	15.6 (14.1)	10.9 (7.9)	**.030**
Age at surgery >14 d	11 (40.7%)	14 (17.3%)	**.014**
Weight, kg	2.2 (0.25)	3.5 (0.36)	**<.001**
Year of surgery	2011.6 (4.5)	2011.0 (4.7)	.067
CPB, min	140.7 (65.6)	121.3 (42.3)	.068
ACP, min	54.8 (28.9)	50.8 (23.2)	.459
DHCA, min	18.7 (14.2)	15.9 (13.1)	.398
Postoperative day 1			
Highest serum lactate, mmol/L	8.4 (3.2)	6.6 (3)	**.007**
Lactate time to <2 mmol/L, h	33.1 (27.5)	17.9 (12.2)	**<.001**
Lowest arterial pH	7.23 (0.12)	7.27 (0.09)	.056
Lowest PaO_2	35.3 (5.6)	34.3 (5.2)	.407
Lowest base deficit, mmol/L	–6.56 (6.4)	–3.18 (4.7)	**.005**
Highest inotrope score	15.3 (14.9)	11.6 (6.8)	.077
Postoperative days 2-5			
Highest serum lactate, mmol/L	5.5 (4.4)	3.2 (2.5)	**<.001**
Lowest arterial pH	7.25 (0.09)	7.31 (0.07)	**<.001**
Lowest Pao_2	38.5 (16.2)	37.5 (15.7)	.781
Lowest base deficit, mmol/L	–5.61 (6.35)	–1.33 (5.27)	**.001**
Highest inotrope score	11.5 (10.5)	8.8 (5.8)	.098
Postoperative days 1-30			
Ventilation time, d	19.1 (22.8)	12.1 (13)	**.049**
ICU stay, d	31.4 (23.2)	29.8 (58.0)	.883
Open sternum, d	9 (6.9)	5 (3)	**<.001**
Convulsion (patients)	2 (7.4%)	2 (2.5%)	.272
CPR (patients)	8 (29.6%)	8 (9.9%)	**.018**
ECMO (patients)	11 (40.7%)	10 (12.3%)	**.004**
Overall hospitalization			
Ventilation time, d	30.5 (24.5)	18.6 (17.5)	**.005**
Hospitalization, d	53.3 (48.9)	48.5 (63.5)	.721
Convulsion (patients)	3 (11.1%)	3 (3.7%)	.178
CPR (patients)	8 (29.6%)	8 (9.9%)	**.018**
Dialysis (patients)	13 (48.1%)	16 (19.8%)	**.007**
Sepsis (patients)	9 (33.3%)	22 (27.2%)	.523

P values in bold are statistically significant. *GA*, Gestational age; *Pao_2*, arterial oxygen tension; *CPR*, cardiopulmonary resuscitation; *ECMO*, extracorporeal membrane oxygenation; *CPB*, cardiopulmonary bypass; *ACP*, antegrade cerebral perfusion; *DHCA*, deep hypothermic circulatory arrest; *ICU*, intensive care unit. **P* values < .001 remain significant after multiple comparison adjustment.

TABLE 2. Demographic and perioperative variables for patients undergoing a BCPA procedure

Variables	Cases, ≤2.5 kg (n = 13)	Comparisons, >3 kg (n = 70)	*P* value*
Operative			
Age at surgery, mo	6.8 (2.5)	5.4 (1.4)	**.006**
Weight at surgery, kg	5.2 (0.63)	6.3 (1.1)	**<.001**
CPB, min	84.9 (60.9)	68.4 (34.4)	.171
Postoperative day 1			
Highest serum lactate, mmol/L	2.7 (2.4)	2.1 (1.5)	**.04**
Lowest arterial pH	7.26 (0.08)	7.28 (0.05)	.152
Lowest Pao_2	42.6 (5.6)	40.1 (5.4)	.132
Highest serum creatinine, μmol/L	40.1 (5.4)	40.3 (11.9)	.839
Postoperative days 1-30			
Ventilation time, d	4.7 (6.6)	2.2 (2.9)	**.035**
ICU, d	9.3 (9.3)	6.2 (9.3)	.27
CPR (patients)	2 (15.4%)	0	-
ECMO	2 (15.4%)	1 (1.4%)	-
All hospital days	43.3 (69.4)	21.3 (36.9)	.096

P values in bold are statistically significant. *CPB*, Cardiopulmonary bypass; *Pao_2*, arterial oxygen tension; *ICU*, intensive care unit; *CPR*, cardiopulmonary resuscitation; *ECMO*, extracorporeal membrane oxygenation; *BCPA*, bidirectional cavopulmonary anastomosis. **P* values < .001 remain significant after multiple comparison adjustment.

operative weight (<2.5 kg vs 2.5-4.0 kg) on surgical outcomes using the Society of Thoracic Surgeons Congenital Heart Surgery Database, Curzon and colleagues reported that mortality for patients undergoing repair of total anomalous pulmonary venous connection was 29.2 versus 9.9%, whereas for coarctation of the aorta it was 7.1 versus 2.7%.

Infants with SV-CHD undergoing Norwood–Sano palliation are arguably among the greatest risk for adverse outcomes. There is conflicting data regarding mortality after the Norwood operation performed in infants weighing ≤2.5 kg. Curzon and colleagues[3] reported a mortality rate of 30% for infants weighing ≤2.5 kg, whereas earlier reports suggested an even greater mortality rate.[3,27-29] More recently, Kalfa and colleagues[30] reported a much lower single-center hospital mortality of 10.7% in 28 infants ≤2.5 kg undergoing Norwood palliation while also commenting that LBW (as a continuous variable) was associated with a greater risk of early mortality. Alsoufi and colleagues[15,31] identified lower weight at time of Norwood operation as a risk factor for interstage mortality, and infants with a weight <2.5 kg had high mortality out to second-stage BCPA palliation. Using a case–comparison approach, our data seem to support that a weight of ≤2.5 kg at the time of the Norwood operation predisposes infants to greater mortality in the short and medium term.

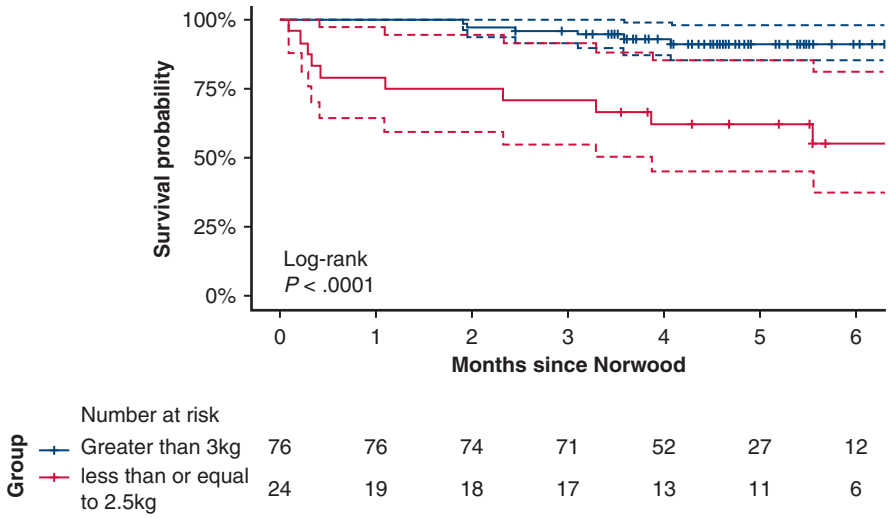

FIGURE 1. Kaplan–Meier plot demonstrating comparison of survival to bidirectional cavopulmonary anastomosis between cases (≤2.5 kg, *red*) and controls (>3.0 kg, *blue*). *Dotted lines* show the 95% confidence intervals for survival probability. The x-axis was truncated to include time points with at least 10 individuals at risk.

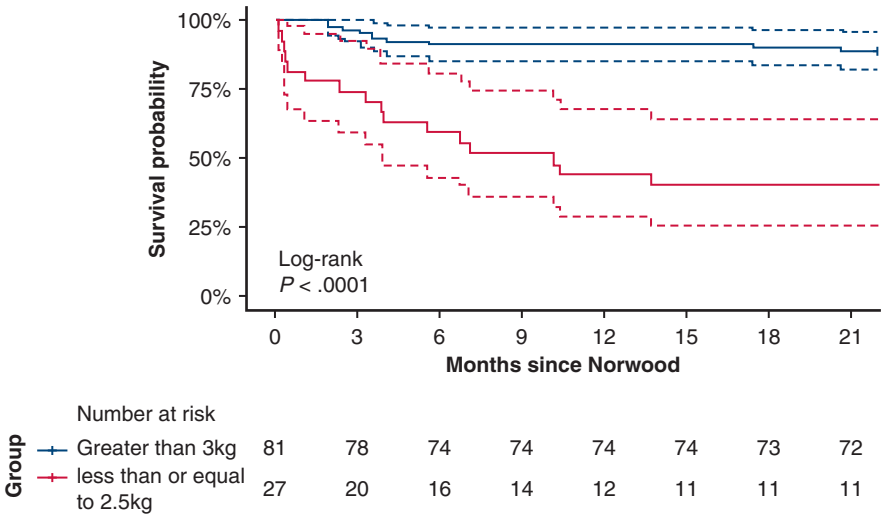

FIGURE 2. Kaplan–Meier plot demonstrating comparison of survival to 2 years of age between cases (≤2.5 kg, *red*) and controls (>3.0 kg, *blue*). *Dotted lines* show the 95% confidence intervals for survival probability. The x-axis was truncated to include time points with at least 10 individuals at risk.

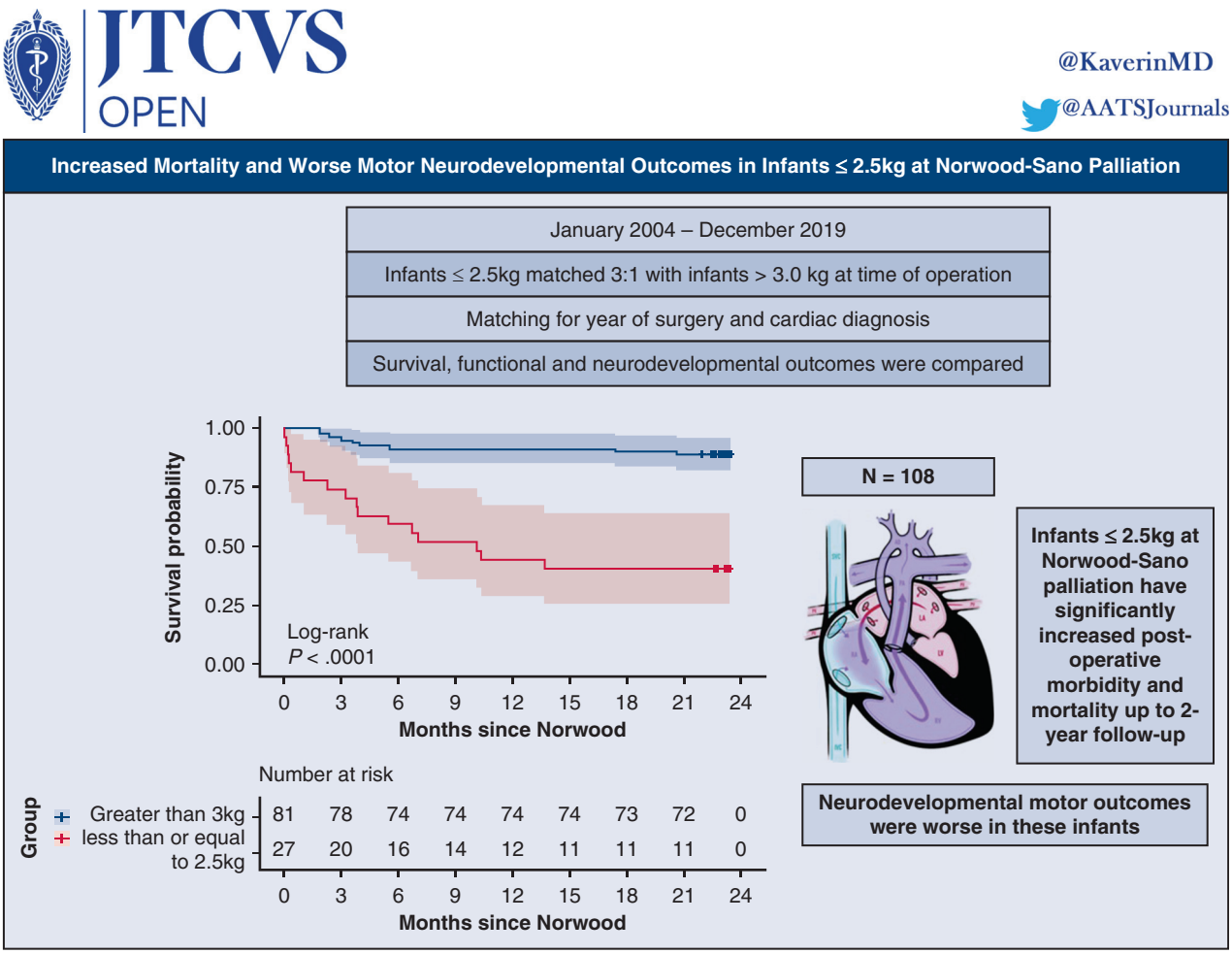

FIGURE 3. Kaplan–Meier plot demonstrating increased mortality in infants ≤2.5 kg at Norwood–Sano palliation compared with those who were >3.0 kg at time of operation. These infants had worse motor neurodevelopmental outcomes at 2 years of follow-up.

TABLE 3. Comparison of 2-year outcomes after early palliative cardiac surgery in relation to body weight at surgery

Variables	Cases, ≤2.5 kg (n = 11)	Comparisons, >3 kg (n = 63)	*P* value*
Demographic			
Blishen index of socioeconomic status	41.7 (9.8)	44.9 (13.1)	.316
Mother's years of schooling	12.9 (1.8)	14 (2.2)	.127
Assessment age, mo	23.4 (6.6)	22.1 (3.6)	.406
Disability			
Motor, cerebral palsy	1 (9.1%)	7 (11.1%)	.809
Visual impairment	0	1	
Permanent hearing loss	2 (18.2%)	4 (6.3%)	.804
Convulsive disorder	1	0	
Growth			
Length, z score	–2.4 (1.2)	–0.81 (1.3)	**<.001**
Weight, z score	–2.2 (0.99)	–0.52 (1.23)	**<.001**
Head circumference, z score	–0.77 (1.9)	–0.14 (1.57)	.093
Health			
Hospitalizations–not cardiac reasons	1.8 (3.4)	0.95 (1.5)	.161
Hospitalizations–cardiac reasons	1.7 (1.6)	1 (1)	.055
Medical specialists–noncardiology	3.6 (2.5)	2.3 (1.9)	.057
Gastrostomy–before age 2 y	5 (45.5%)	22 (34.9%)	.688
Pulmonary medications at age 2 y	1 (9.1%)	4 (6.3%)	.529
Cardiac medications at age 2 y	10 (90.9%)	59 (93.7%)	.918
Neurodevelopmental and functional test results			
Cognitive standard score	86.9 (13.3)	91 (13.9)	.363
Cognitive <70	2 (18.2%)	5 (7.9%)	.272
Language standard score	84.9 (14.2)	88.2 (14.7)	.494
Language <70	2 (18.2%)	7 (11.1%)	.505
Motor standard score	73.6 (10.5)	87.3 (17.2)	**.013**
Motor <70	3 (27.3%)	9 (14.3%)	.099
ABAS-GAC Composite	78.7 (17.2)	85.9 (17.9)	.218
ABAS-GAC, <70	4 (36.4%)	10 (15.9%)	.243

P values in bold are statistically significant. *ABAS-GAC*, Adaptive Behavior Assessment System-General Adaptive Composite. **P* values < .001 remain significant after multiple comparison adjustment.

In our study, cases had significantly greater morbidity in the postoperative period, but this was not clearly explained by differences in intraoperative parameters (ie, cardiopulmonary bypass, deep hypothermic circulatory arrest, and antegrade cerebral circulation) or patient-specific factors other than operative weight (ie, chromosomal abnormalities or need for inotropic support) between the 2 groups. This greater incidence of postoperative morbidity in infants ≤2.5 kg undergoing single-ventricle palliation has been previously demonstrated and may be related to prematurity and its sequalae.[31]

Multiple studies have demonstrated that neurodevelopmental outcomes are abnormal in a portion of patients with single-ventricle physiology who have undergone palliation to a Fontan circulation.[14,19,32] Our report is the first to systematically assess the impact of patient weight at time of operation on medium-term neurodevelopmental and functional outcomes. We found that cases had worse 2-year motor neurodevelopmental scores but not cognitive, language, and functional scores. When assessing 6-year neurodevelopmental outcomes in children with hypoplastic left heart syndrome, Sananes and colleagues[32] reported that many children who exhibit deficits at 6 years were not identified based on assessments at an earlier age. The high mortality rate and the small number of cases in our series may have led to under-recognition of suboptimal neurodevelopmental outcomes.

In an analysis of the single-ventricle reconstruction trial, Newburger and colleagues[33] identified innate patient factors (including birth weight <2.5 kg) and overall morbidity in the first year of life as primary drivers of neurodevelopmental impairment. There is also evidence that infants with CHD have ongoing brain maturation after birth.[34] Although our data do not identify the exact contributors to neurodevelopmental delays experienced by infants undergoing Norwood palliation, it does stand to reason that optimization of postoperative hemodynamics could allow for better brain maturation and potentially improved longer term neurodevelopmental outcomes. These results may also raise intrigue about the longer-

term neurodevelopmental and cognitive outcomes of cases and controls. However, neurodevelopmental measures such as the Bayley-III scores are, in general, not shown to have a reliable correlation with cognitive IQ scores at an older age and are therefore not used to predict long-term outcomes.

These data can help to inform family counseling and prenatal decision-making with regards to continuation of pregnancy and postnatal treatment strategies. It is still unclear what the best approach to management of patients with LBW and SV-CHD is, with both primary repair (ie, Norwood palliation) and less-invasive strategies (ie, hybrid/modified hybrid) involving different risks. Recent published data suggest that short-term outcomes in high-risk neonates requiring Norwood palliation may be better using the hybrid approach as a bridge to delayed Norwood palliation or comprehensive stage II; however, the impact on longer-term survival and neurodevelopmental outcomes remains unknown.[35] Based partially on the data presented here, our center's practice has shifted with a bias toward hybrid palliation rather than early Norwood. Further research is needed to define optimal early management strategies that will result in the best long-term survival and neurodevelopmental outcomes.

Limitations

The results of this study are limited by its nonrandomized design and use of patients from a single surgical center. However, a matched design was used to mitigate certain confounders. The number of cases in this report is small, limiting the statistical power to detect small differences. The neurodevelopmental follow-up was limited to a single assessment, so it is possible with longer-term follow-up, further evidence of neurodevelopmental delays would be detected.

CONCLUSIONS

Infants $\leq$2.5 kg with SV-CHD undergoing Norwood–Sano palliation have greater mortality, post-Norwood morbidity, and worse motor outcomes compared with infants >3.0 kg. Further research should focus on the impact of weight on longer-term neurodevelopmental outcomes and whether alternative approaches to the Norwood procedure provide a survival and neurodevelopmental benefit.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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References

1. Spector LG, Menk JS, Knight JH, McCracken C, Thomas AS, Vinocur JM, et al. Trends in long-term mortality after congenital heart surgery. *J Am Coll Cardiol*. 2018;71:2434-46.
2. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics*. 2013;131:e1502-8.
3. Curzon CL, Milford-Beland S, Li JS, O'Brien SM, Jacobs JP, Jacobs ML, et al. Cardiac surgery in infants with low birth weight is associated with increased mortality: analysis of the Society of Thoracic Surgeons Congenital Heart Database. *J Thorac Cardiovasc Surg*. 2008;135:546-51.
4. Kansy A, Tobota Z, Maruszewski P, Maruszewski B. Analysis of 14,843 neonatal congenital heart surgical procedures in the European Association for Cardiothoracic Surgery Congenital Database. *Ann Thorac Surg*. 2010;89:1255-9.
5. Ades AM, Dominguez TE, Nicolson SC, Gaynor JW, Spray TL, Wernovsky G, et al. Morbidity and mortality after surgery for congenital cardiac disease in the infant born with low weight. *Cardiol Young*. 2010;20:8-17.
6. Azakie A, Johnson NC, Anagnostopoulos PV, Egrie GD, Lavrsen MJ, Sapru A. Cardiac surgery in low birth weight infants: current outcomes. *Interact Cardiovasc Thorac Surg*. 2011;12:409-14.
7. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. *N Engl J Med*. 2000;343:378-84.
8. Perlman JM. Neurobehavioral deficits in premature graduates of intensive care—potential medical and neonatal environmental risk factors. *Pediatrics*. 2001;108:1339-48.
9. Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics*. 2009;124:717-28.
10. Hack M, Taylor HG. Perinatal brain injury in preterm infants and later neurobehavioral function. *JAMA*. 2000;284:1973-4.
11. Fuller S, Nord AS, Gerdes M, Wernovsky G, Jarvik GP, Bernbaum J, et al. Predictors of impaired neurodevelopmental outcomes at one year of age after infant cardiac surgery. *Eur J Cardio Thorac Surg*. 2009;36:40-8.
12. Gaynor JW, Wernovsky G, Jarvik GP, Bernbaum J, Gerdes M, Zackai E, et al. Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. *J Thorac Cardiovasc Surg*. 2007;133:1344-53.e3.
13. Tabbutt S, Nord AS, Jarvik GP, Bernbaum J, Wernovsky G, Gerdes M, et al. Neurodevelopmental outcomes after staged palliation for hypoplastic left heart syndrome. *Pediatrics*. 2008;121:476-83.
14. Atallah J, Dinu I, Joffe A, Robertson C, Sauve R, Dyck J, et al; tWestern Canadian Complex Pediatric Therapies Follow-Up Group. Two-year survival and mental and psychomotor outcomes after the Norwood procedure: an analysis of the modified Blalock-Taussig shunt and right ventricle-to-pulmonary artery shunt surgical eras. *Circulation*. 2008;118:1410-8.
15. Alsoufi B, McCracken C, Kochilas LK, Clabby M, Kanter K. Factors associated with interstage mortality following neonatal single ventricle palliation. *World J Pediatr Congenit Heart Surg*. 2018;9:616-23.
16. Robertson CM, Sauve RS, Joffe AR, Alton GY, Moddemann DM, Blakley PM, et al. The registry and follow-up of complex pediatric therapies program of Western Canada: a mechanism for service, audit, and research after life-saving therapies for young children. *Cardiol Res Pract*. 2011;2011:965740.
17. Robertson CM, Joffe AR, Sauve RS, Rebeyka IM, Phillipos EZ, Dyck JD, et al. Outcomes from an interprovincial program of newborn open heart surgery. *J Pediatr*. 2004;144:86-92.
18. Blishen BR, Carroll WK, Moore C. The 1981 socioeconomic index for occupations in Canada. *Can Rev Sociol*. 1987;24:465-88.
19. Martin B-J, Jonker IDV, Joffe AR, Bond GY, Acton BV, Ross DB, et al. Hypoplastic left heart syndrome is not associated with worse clinical or neurodevelopmental outcomes than other cardiac pathologies after the Norwood–Sano operation. *Pediatr Cardiol*. 2017;38:922-31.
20. Bayley N, Infant S. *Bayley Scales of Infant and Toddler Development–Third Edition: Technical Manual*. Accessed April 11, 2023. https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft14978-000
21. Harrison P, Oakland T. *Manual of the Adaptive Behaviour Assessment System II*. Psychological Corp: Harcourt Assessment Company; 2003.

22. Sidhu N, Joffe AR, Doughty P, Vatanpour S, Dinu I, Alton G, et al. Sepsis after cardiac surgery early in infancy and adverse 4.5-year neurocognitive outcomes. *J Am Heart Assoc*. 2015;4:e001954.
23. Wernovsky G, Wypij D, Jonas RA, Mayer JE Jr, Hanley FL, Hickey PR, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation*. 1995;92:2226-35.
24. Padley JR, Cole AD, Pye VE, Chard RB, Nicholson IA, Jacobe S, et al. Five-year analysis of operative mortality and neonatal outcomes in congenital heart disease. *Heart Lung Circ*. 2011;20:460-7.
25. Swenson A, Dechert R, Schumacher R, Attar M. The effect of late preterm birth on mortality of infants with major congenital heart defects. *J Perinatol*. 2012;32:51-4.
26. Lechner E, Wiesinger-Eidenberger G, Weissensteiner M, Hofer A, Tulzer G, Sames-Dolzer E, et al. Open-heart surgery in premature and low-birth-weight infants—a single-centre experience. *Eur J Cardio Thorac Surg*. 2009;36:986-91.
27. Pizarro C, Davis DA, Galantowicz ME, Munro H, Gidding SS, Norwood WI. Stage I palliation for hypoplastic left heart syndrome in low birth weight neonates: can we justify it? *Eur J Cardio Thorac Surg*. 2002;21:716-20.
28. Gelehrter S, Fifer CG, Armstrong A, Hirsch J, Gajarski R. Outcomes of hypoplastic left heart syndrome in low-birth-weight patients. *Pediatr Cardiol*. 2011;32:1175-81.
29. Weinstein S, Gaynor JW, Bridges ND, Wernovsky G, Montenegro LM, Godinez RI, et al. Early survival of infants weighing 2.5 kilograms or less undergoing first-stage reconstruction for hypoplastic left heart syndrome. *Circulation*. 1999;100:II167-70.
30. Kalfa D, Krishnamurthy G, Levasseur S, Najjar M, Chai P, Chen J, et al. Norwood stage I palliation in patients less than or equal to 2.5 kg: outcomes and risk analysis. *Ann Thorac Surg*. 2015;100:167-73.
31. Alsoufi B, McCracken C, Ehrlich A, Mahle WT, Kogon B, Border W, et al. Single ventricle palliation in low weight patients is associated with worse early and midterm outcomes. *Ann Thorac Surg*. 2015;99:668-76.
32. Sananes R, Goldberg CS, Newburger JW, Hu C, Trachtenberg F, Gaynor JW, et al. Six-year neurodevelopmental outcomes for children with single-ventricle physiology. *Pediatrics*. 2021;147:e2020014589.
33. Newburger JW, Sleeper LA, Bellinger DC, Goldberg CS, Tabbutt S, Lu M, et al. Early developmental outcome in children with hypoplastic left heart syndrome and related anomalies: the single ventricle reconstruction trial. *Circulation*. 2012;125:2081-91.
34. Hottinger SJ, Liamlahi R, Feldmann M, Knirsch W, Latal B, Hagmann CF, et al. Postoperative improvement of brain maturation in infants with congenital heart disease. *Semin Thorac Cardiovasc Surg*. 2020;34:251-9.
35. Ceneri NM, Desai MH, Tongut A, Ozturk M, Ramakrishnan K, Staffa SJ, et al. Hybrid strategy in neonates with ductal-dependent systemic circulation and multiple risk factors. *J Thorac Cardiovasc Surg*. 2022;164:1291-303.e6.

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