Impact of preoperative risk factors on outcomes after Norwood palliation for hypoplastic left heart syndrome

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Background: Infants with hypoplastic left heart syndrome (HLHS) are susceptible to pre-Norwood comorbidities (PCs) and complications. This study aimed to describe the effect of PCs on timing and survival of Norwood palliation (NP).

Methods: A single-center, retrospective review of infants with HLHS who underwent initial NP between 2003 and 2010 was performed. PCs included intact atrial septum, $\geq$ moderate atrioventricular regurgitation (AVVR), no antenatal diagnosis, mitral stenosis/aortic atresia subtype, genetic abnormality, and prematurity. Complications included pre-NP mechanical ventilation, inotropic support, infection, arrhythmia, and end-organ injury. The primary outcome measure was survival after NP.

Results: 113 patients were included with 78 (69%) patients having at least one PC and 61 (78%) of those patients having at least one complication. Patients with PCs underwent NP later than those without PCs (7 vs 6 days, $P = .036$) as well as when associated with a complication (8 vs 5 days, $P < .001$). Patients with PCs had similar post-Norwood hospital length of stay ($P = .116$) except when the PC occurred in conjunction with a complication (28 vs 21 days; $P = .015$). In-hospital mortality post-NP was 10% and interstage mortality was 15%. On multivariable analysis, $\geq$ moderate AVVR was associated with increased overall mortality (OR 2.8, 95% CI 1.3-6.2). Age at NP was not associated with mortality ($P = .638$).

Conclusions: Although PCs are common in infants with HLHS, only $\geq$ moderate AVVR was associated with increased mortality in this single-center experience. Older age at NP was not a significant risk factor for interstage mortality. (J Thorac Cardiovasc Surg 2014;147:897-901)

Infants born with hypoplastic left heart syndrome (HLHS) are vulnerable to significant comorbidities and complications during the preoperative period before Norwood palliation (NP).^{1,2} These pre-Norwood comorbidities (PCs) and complications have been implicated in both survival and developmental outcomes in multiple single-center and multi-center reports.^{1,3-8} Most recently, results from the Single Ventricle Reconstruction trial demonstrated several anatomic considerations, such as the degree of atrioventricular valve regurgitation (AVVR) and ascending aorta diameter, and patient considerations, such as prematurity and chromosomal abnormalities, that were associated with increased post-Norwood morbidity and mortality.^{7,8} Fortunately, continued advancement in antenatal diagnosis of HLHS by fetal echocardiography has helped decrease the incidence of some PCs and complications.⁹⁻¹¹ However, the survival benefit from antenatal diagnosis remains unclear.^{10,12,13}

Advancements in surgical technique and perioperative care have improved survival in this population.^{14,15} Nevertheless, even the most recent reports demonstrate that early post-Norwood and interstage mortality continue to plague these infants.^{16,17} The timing of NP, a potential modifiable risk factor, has been the topic of prior study and has yielded mixed results. Although several reports have demonstrated decreased survival in infants undergoing NP at older ages,^{2,6,14,18} others have reported either no difference in mortality or even improved survival with older age at NP.^{1,7,19} Ultimately, the age at NP is somewhat an institutionally dependent factor reliant on surgical availability and referral patterns.

The objective of this study was to assess how the presence of PCs and complications affect early and interstage mortality in infants with HLHS in a single, tertiary care pediatric cardiac center. Secondly, we sought to examine the effect of PCs on the timing of surgery and implications on mortality.

METHODS

Patient Selection

A retrospective review of the pediatric cardiovascular surgery database was performed to identify all infants with HLHS who underwent NP at our institution between January 2003 and December 2010. All infants with HLHS who underwent NP as their initial surgical procedure during the study period were reviewed, including those who required atrial septal or other catheter-based interventions in the pre-Norwood period. Infants with variants of this condition such as double-outlet right ventricle with mitral atresia as well as patients requiring initial operations other than the

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Abbreviations and Acronyms

AVVR	=	atrioventricular valvular regurgitation
CI	=	confidence interval
HLHS	=	hypoplastic left heart syndrome
IQR	=	interquartile range
LOS	=	length of stay
NP	=	Norwood palliation
OR	=	odds ratio
PCs	=	pre-Norwood comorbidities

Norwood operation were excluded. Given the study objective, patients with HLHS who were not palliated surgically were not included. The cohort of patients was subsequently assigned into 2 groups on the basis of the presence of PCs.

All available medical records, laboratory and imaging results, and applicable surgical reports were reviewed. We recorded the presence of PCs (defined below), pre-Norwood complications (defined below), age at NP, post-Norwood length of stay (LOS), and mortality. Patient data were recorded through stage II palliation. The study was approved by the Baylor College of Medicine Institutional Review Board.

Definitions

PCs included intact atrial septum, $\geq$ moderate AVVR, the lack of antenatal diagnosis, mitral stenosis–aortic atresia HLHS subtype, genetic abnormality, and prematurity. Intact atrial septum was defined as the absence of any atrium-level communication. Genetic anomalies were determined by chromosomal microarray analysis, genetic consult, or presence of dysmorphisms. Prematurity was defined as gestational age <37 weeks. The patient cohort was divided into the group with ≥ 1 PC (PC group) and the group who had no-PC (no-PC group).

Preoperative complications included mechanical ventilation, inotropic support, arrhythmia, end-organ damage, and infection. Mechanical ventilation was defined as ventilation for ≥ 24 hours that was not associated with elective intubation for transport. End-organ damage included neurologic (preoperative seizure or brain injury documented by imaging), hepatic (defined as elevation of transaminase $>$ twice normal values and either persistent coagulopathy or hyperbilirubinemia), or renal injury (defined as $\geq$ pRIFLE I* classification²⁰). Infection was defined as documented preoperative bacterial infection based on identified organism or presumptive infection treated with intravenous antibiotics for ≥ 7 days.

Infancy was defined as age <12 months and the pre-Norwood period included the time from birth or transfer to our institution to the time of NP. Our study evaluated both the inpatient and interstage periods between Norwood and stage II palliation. The inpatient period was defined as either the time from NP to hospital discharge, from NP to stage II if the patient required continued hospitalization, or from NP to time of death if mortality occurred before hospital discharge. The interstage period was defined as the time after hospital discharge after the Norwood procedure but before stage II palliation.

Data Collection and Statistics

The data were not normally distributed. Descriptive statistics are reported using median and interquartile range for scale variables and proportions for categorical variables. Univariable analysis of categorical variables was performed by the Pearson χ^2 or Fisher exact test, whereas continuous variables were analyzed using the Mann-Whitney *U* test. Univariable and multivariable Cox regression analyses were used to determine risk factors

for mortality and are expressed as hazard ratios and 95% confidence intervals (CIs). Univariable factors found to be associated with mortality with a *P* value $< .100$ were included in the multivariable analysis. Survival functions were estimated using Kaplan-Meier analysis with log rank test of significance. Two-tailed test of significance was used in all statistical analyses. Statistics were performed using SPSS version 19.0 (IBM Corp, Armonk, NY).

RESULTS**Patient Population**

Of 117 patients identified with HLHS, 113 patients met inclusion criteria and were included in the data analysis. Four patients with HLHS did not undergo initial NP and were excluded from data analysis. These patients included 1 patient who underwent initial bilateral pulmonary artery banding who died in the interstage period, 2 patients with intact atrial septum who received comfort care, and 1 patient who underwent hybrid palliation as a bridge to successful cardiac transplantation owing to coronary artery–left ventricle fistulas.

A total of 78 (69%) patients had at least 1 PC. Patient demographics and frequency of PCs are listed in Table 1. Among patients with PCs, 36 (46.1%) patients had 1 PC, 36 (46.1%) had 2 PCs, 5 (6.4%) had 3 PCs, and 1 (1.3%) had 4 PCs. Of the 78 patients with a PC, 61 (78.2%) had a pre-Norwood complication. Patients with PCs had more frequent preoperative complications than those without PCs as demonstrated by higher rates of inotropic support (57.7% vs 28.6%; *P* = .004), mechanical ventilation (44.9% vs 22.9%; *P* = .026), and infection (11.5% vs 0%; *P* = .036). There was no significant intergroup difference in the rate of arrhythmia (1.3% vs 8.6%; *P* = .053). The presence of pre-Norwood complications by PC is listed in Table 2.

Despite similar rates of antenatal diagnosis in nonwhite versus white patients (62.3% vs 48.3%; *P* = .138), non-white patients were more likely to be born outside of our institution (odds ratio [OR], 3.0; 95% CI, 1.4-6.6). However, the frequency of PC did not differ between nonwhite versus white patients (55.1% vs 48.6%; *P* = .518). With regard to pre-Norwood complications, patients with no antenatal diagnosis were more likely to have a complication than those with antenatal diagnosis (OR, 8.3; 95% CI, 3.6-19.3). The use of a modified Blalock-Taussig shunt versus a Sano conduit was similar between the PC and no-PC groups (76.9% vs 88.6%; *P* = .148).

The overall survival to stage II palliation for the cohort was 75.2% (85 patients). Among the 28 patients who died, 11 (9.7%) patients died during the inpatient period and 17 (15.1%) died during the interstage period. On univariable analysis of PCs, intact atrial septum and $\geq$ moderate AVVR were associated with increased overall mortality (Table 3). Likewise, mechanical ventilation before the NP was found to be associated with increased mortality (*P* = .010). On multivariable analysis, only $\geq$ moderate

* RIFLE = Risk, Injury, Failure, Loss, and End-stage kidney disease.

TABLE 1. Patient demographics

Demographic	Value (n = 113)
Male sex, n (%)	65 (57.5)
Ethnicity, n (%)	
Asian	1 (0.9)
African American	13 (11.5)
Hispanic	46 (40.7)
White	53 (46.9)
HLHS subtype, n (%)	
MA, AA	57 (50.4)
MA, AS	9 (8.0)
MS, AS	26 (23.0)
MS, AA*	21 (18.6)
Birth weight Z-score, median (IQR)	−0.4 (−1.0 to 0.0)
No antenatal diagnosis,* n (%)	51 (45.1)
≥ Moderate AVVR,* n (%)	21 (18.6)
Genetic abnormality,* n (%)	17 (15.0)
Prematurity,* n (%)	13 (11.5)
Intact atrial septum,* n (%)	4 (3.5)
Modified BTS (vs Sano), n (%)	91 (80.5)

HLHS, Hypoplastic left heart syndrome; AA, aortic atresia; MA, mitral atresia; AS, aortic stenosis; MS, mitral stenosis; IQR, interquartile range; AVVR, atrioventricular valve regurgitation; BTS, Blalock-Taussig shunt; Sano, Sano conduit. *Demographic considered as a preoperative comorbidity.

AVVR was independently associated with increased mortality in this cohort. Although mechanical ventilation was associated with increased mortality on univariable analysis, no preoperative complication was associated with mortality on multivariable analysis.

The median age at time of NP for the entire cohort was 7 (interquartile range [IQR], 4-8) days, with 64.6% of patients being ≤7 days of age. Median age at time of NP was older in the PC group than in the no-PC group (7 [IQR, 5-9] vs 6 [IQR, 4-7] days; $P = .036$). However, when the lack of antenatal diagnosis was excluded as a PC, the presence of any other PC was not associated with age at NP ($P = .422$). Patients with PC who had a pre-Norwood complication did have a higher median age at time of NP (8 [IQR, 5-12] vs 5 [IQR, 4-7] days; $P < .001$). Patient age at NP was unaffected by race ($P = .817$). When survival after NP was assessed by timing of the Norwood palliation, older age at palliation (age ≥7days) was not associated with mortality when compared with NP at <7 days of age (log rank $P = .638$, Figure 1).

Postoperatively, patients in the PC group had a median post-Norwood hospital LOS similar to that of the no-PC group ($P = .116$) except when the PC occurred in conjunction with a preoperative complication (28 [IQR, 19-49] days vs 21 [IQR, 14-32] days; $P = .015$). Continued admission through to stage II palliation and interstage readmission were not statistically different between the 2 groups ($P = .324$ and $P = .084$, respectively).

DISCUSSION

This retrospective study of 113 infants with HLHS demonstrates that PCs are very common in infants with HLHS and are associated with a significant delay in the timing of NP. The effects of timing of NP on patient outcomes have been the focus of prior investigations, although the evidence in the literature is mixed. Although older age at time of NP was initially thought to be associated with better outcomes,^{1,19} more recent data have demonstrated either worse outcomes^{2,6,14,17,18} or no difference in outcomes after NP.⁷ Our study is unique in that we assessed the impact of PCs both on the timing of NP and on early and interstage mortality.

PCs were present in > two thirds of the cohort, and > three quarters of those patients had concomitant pre-Norwood complications. Among the complications analyzed in this study, the need for mechanical ventilation and inotropic support were most common. Prior studies have reported that the need for mechanical ventilation is associated with poorer neurodevelopmental outcomes^{3,5} and increased postoperative mortality.¹ Similar to those findings, we demonstrated a significant association between mechanical ventilation and overall mortality. However, on multivariable analysis, mechanical ventilation did not reach statistical significance when placed in a model with well-established risk factors for mortality. Unlike previous reports,^{4,8,21} our study failed to find an association between prematurity or genetic anomalies and mortality, although this may be due to small sample size.

Neither the presence of PCs, PCs with complications, nor delayed NP (independent of PCs) was associated with diminished inpatient or interstage survival on multivariable analysis. This suggests that NP can be successfully achieved in an infant with a complicated pre-Norwood course if the patient's condition can be adequately stabilized. Although

TABLE 2. Presence of preoperative complication by preoperative comorbidity

Complication	Preoperative comorbidity					
	≥ Moderate AVVR	No antenatal diagnosis	MS-AA subtype	Prematurity	Genetic abnormality	IAS
Inotropic support	3.3 (1.2-9.1)*	2.9 (1.3-6.1)*	1.2 (0.5-3.1)	0.9 (0.3-2.8)	0.9 (0.3-2.6)	1.1 (1.0-1.2)
Mechanical ventilation	3.4 (1.3-9.0)*	2.8 (1.3-6.0)*	1.0 (0.4-2.7)	0.7 (0.2-2.4)	0.9 (0.3-2.6)	1.1 (1.0-1.2)
Infection	4.1 (0.9-16.8)	4.8 (0.9-24.1)	1.3 (0.2-6.6)	2.4 (0.4-13.1)	0.8 (0.8-0.9)	1.0 (0.9-1.0)
Arrhythmia	0.8 (0.7-0.9)	0.5 (0.4-0.6)	1.5 (0.1-15.0)	0.9 (0.8-0.9)	1.9 (0.2-19.8)	1.0 (0.9-1.0)

All data are presented as odds ratio (95% confidence interval). AVVR, Atrioventricular regurgitation; MS-AA, mitral stenosis–aortic atresia; IAS, intact atrial septum. *Significant association.

TABLE 3. Risk factors for overall mortality before stage II palliation

Risk factor	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Female sex	1.4	0.7-2.9	—	—
Nonwhite ethnicity	1.7	0.8-3.7	—	—
Pre-Norwood comorbidity				
HLHS subtype				
MA, AA	Reference		—	—
MA, AS	1.3	0.5-3.5	—	—
MS, AS	1.4	0.3-5.8	—	—
MS, AA	0.5	0.1-1.9	—	—
No antenatal diagnosis	0.8	0.4-1.6	—	—
Intact atrial septum	3.6	1.1-11.9	2.1	0.6-7.5
Moderate-Severe AVVR	3.6	1.7-7.7	2.8	1.3-6.2
Genetic disorder	1.7	0.7-4.3	—	—
Prematurity	0.6	0.1-2.3	—	—
Pre-Norwood complication				
Mechanical ventilation	2.7	1.2-5.9	2.0	0.9-4.6
Infection	1.6	0.5-5.4	—	—
Inotrope requirement	1.2	0.6-2.5	—	—
End organ damage	1.1	0.5-2.6	—	—
Arrhythmia	1.0	0.1-6.8	—	—

HR, Hazard ratio; CI, confidence interval; HLHS, hypoplastic left heart syndrome; MA, mitral atresia; AA, aortic atresia; AS, aortic stenosis; MS, mitral stenosis; AVVR, atrioventricular valve regurgitation.

our findings suggest that infants may undergo NP safely at an age of ≥ 7 days, it is important to recognize that 65% of patients underwent NP by day 7 after birth in our cohort and that 95% underwent NP by 10 days after birth. Ultimately, established risk factors, such as intact atrial septum or severe AVVR,^{2,7,8,22,23} are more likely to be stronger determinants of post-Norwood mortality as suggested by our data.

Advances in fetal echocardiography have improved the ability and availability to diagnose HLHS prenatally. Although several studies have shown little to no survival benefit with antenatal diagnosis, there are other data that indicate that antenatal diagnosis may minimize the risk of preoperative morbidity and improve long-term outcomes.^{10,11,13} In the current study, infants who received an antenatal diagnosis of HLHS were less likely to experience multiple preoperative comorbidities. Moreover, they underwent NP considerably earlier than those without antenatal diagnosis. These differences in outcomes are most likely explained by heightened perinatal awareness, including parental prenatal counseling, delivery within a pediatric surgical center, or prompt transfer to a surgical center. Yet, despite this heightened awareness, we found that antenatal diagnosis was not associated with significant improvement in postoperative mortality. It should be noted, however, that mortality may be too coarse an end point to detect the impact of delayed NP on long-term single ventricle physiology, the health of the pulmonary vascular bed, ventricular performance, and even on neurodevelopment.

FIGURE 1. Kaplan-Meier survival function by the timing of Norwood palliation at < 7 and ≥ 7 days of age.

The presence of a PC significantly prolonged time to NP and lengthened postoperative hospital LOS when occurring in conjunction with a pre-Norwood complication. These findings are important in consideration of health care use and efforts to reduce medical costs. Recent reports have demonstrated increasing health care costs in infants undergoing staged palliation for HLHS.²⁴ Given the economic burden that prolonged hospitalization places on the health care system and the families of these affected infants, our findings suggest that attention should be focused on maximizing antenatal diagnosis to better identify PCs whenever possible, reduce complication rates, and implement organized discharge planning early on in their hospital course. Additionally, although the precise cause of delayed timing could not be ascertained owing to study design, it is conceivable that a longer pre-Norwood course may lead to a higher risk of complications. Thus, completing the initial palliative surgery in a prompt manner may play a role in both reducing likelihood of pre-Norwood complications and LOS after the Norwood procedure.

We found that nonwhite ethnicity was associated with a higher incidence of birth outside of our tertiary, surgical referral center, which mirrors other reports demonstrating racial disparities among children with congenital heart disease.²⁵ Interestingly, our study showed that rates of antenatal diagnosis were similar between races and that the presence of PCs was not affected by race. It is conceivable, however, that a difference in need for hospital transfer versus direct access to a surgical center may translate into increased risk for the development of pre-Norwood complications in the neonatal period, although this was not seen in our study.

Limitations

Our current study is limited by its single-center, retrospective design of a relatively small number of patients. Although all available data were used in all statistical analyses, negative associations described in this study

may be a result of a lack of statistical power. Therefore, it is difficult to exclude the possibility of a type II error, and further study with a greater number of patients would be required to establish negative associations. The potential for selection bias exists as a function of the study design. Only infants who underwent NP as their initial surgical procedure were included, and some infants who were small for gestational age or premature may have been excluded.

CONCLUSIONS

PCs are common in infants with HLHS and are associated with pre-Norwood complications. When occurring concomitantly with a pre-Norwood complication, PCs are significantly associated with delayed NP and longer post-Norwood hospital LOS. Prenatal diagnosis appears to be beneficial in minimizing the risk of pre-Norwood complications and expediting the timing of NP. Mortality was affected by the presence of $\geq$ moderate AVVR in this cohort and not the presence of any pre-Norwood complication or older age at NP. With successful antenatal diagnosis and medical management of infants with PCs, post-Norwood outcomes are likely to parallel those without preoperative complications.

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