Intermediate-term mortality and cardiac transplantation in infants with single-ventricle lesions: Risk factors and their interaction with shunt type

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Objective: The study objective was to identify factors associated with death and cardiac transplantation in infants undergoing the Norwood procedure and to determine differences in associations that might favor the modified Blalock–Taussig shunt or a right ventricle-to-pulmonary artery shunt.

Methods: We used competing risks methodology to analyze death without transplantation, cardiac transplantation, and survival without transplantation. Parametric time-to-event modeling and bootstrapping were used to identify independent predictors.

Results: Data from 549 subjects (follow-up, 2.7 ± 0.9 years) were analyzed. Mortality risk was characterized by early and constant phases; transplant was characterized by only a constant phase. Early phase factors associated with death included lower socioeconomic status ($P = .01$), obstructed pulmonary venous return ($P < .001$), smaller ascending aorta ($P = .02$), and anatomic subtype. Constant phase factors associated with death included genetic syndrome ($P < .001$) and lower gestational age ($P < .001$). The right ventricle-to-pulmonary artery shunt demonstrated better survival in the 51% of subjects who were full term with aortic atresia ($P < .001$). The modified Blalock–Taussig shunt was better among the 4% of subjects who were preterm with a patent aortic valve ($P = .003$). Lower pre-Norwood right ventricular fractional area change, pre-Norwood surgery, and anatomy other than hypoplastic left heart syndrome were independently associated with transplantation (all $P < .03$), but shunt type was not ($P = .43$).

Conclusions: Independent risk factors for intermediate-term mortality include lower socioeconomic status, anatomy, genetic syndrome, and lower gestational age. Term infants with aortic atresia benefited from a right ventricle-to-pulmonary artery shunt, and preterm infants with a patent aortic valve benefited from a modified Blalock–Taussig shunt. Right ventricular function and anatomy, but not shunt type, were associated with transplantation. (J Thorac Cardiovasc Surg 2012;144:152-9)

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The risk of mortality after the Norwood procedure for hypoplastic left heart syndrome (HLHS) and other single right ventricle anomalies with arch obstruction remains significant. Risk factors for death and transplantation after the Norwood procedure may be thought of as occurring in 2 categories: factors intrinsic to the patient that are traditionally considered nonmodifiable, such as anatomic subtype, weight, gestational age, and pulmonary venous obstruction, and modifiable factors that may be subject to practice variation, such as perioperative management, timing of surgery, technique, and perfusion strategies. The Pediatric Heart Network Single Ventricle Reconstruction (PHN SVR) trial prospectively collected preoperative, operative, and postoperative multi-institutional data from more than 500

Abbreviations and Acronyms

AA	= aortic atresia
AS	= aortic stenosis
HLHS	= hypoplastic left heart syndrome
HR	= hazard ratio
MA	= mitral atresia
MBTS	= modified Blalock–Taussig shunt
MS	= mitral stenosis
OPVR	= obstructed pulmonary venous return
PHN	= Pediatric Heart Network Single
SVR	Ventricle Reconstruction
RVPAS	= right ventricle-to-pulmonary artery shunt
SES	= socioeconomic status

newborns with HLHS and related single right ventricle anomalies. This trial demonstrated that a Norwood procedure with a right ventricle-to-pulmonary artery shunt (RVPAS), compared with a modified Blalock–Taussig shunt (MBTS), was associated with better transplant-free survival 12 months after randomization.¹ By using all available follow-up (2.7 ± 0.9 years in event-free subjects), we analyzed the PHN SVR dataset to achieve the following goals: to estimate the cumulative incidence of death and cardiac transplantation in subjects who have undergone the Norwood procedure, to determine the association of traditionally nonmodifiable factors with outcomes using parametric regression modeling, and to determine the interaction of shunt type with these factors. We also sought to use this information to develop an algorithm to tailor shunt type to the patient profile.

MATERIALS AND METHODS**Study Design**

The SVR trial has been described in detail in earlier reports.^{1,2} Enrollment occurred between May 2005 and July 2008 at 15 centers in the United States and Canada. Briefly, subjects with single right ventricle anomalies with systemic outflow obstruction were randomly assigned to receive an MBTS or RVPAS during the Norwood procedure. Randomization was stratified by the presence versus absence of aortic atresia (AA) and obstructed pulmonary venous return (OPVR), with dynamic balancing within surgeon. The primary trial end point was death or cardiac transplantation at 1 year post-randomization. In addition, an end-of-trial contact was completed in summer 2009 to obtain maximal follow-up on all subjects. A key secondary end point was time to death or cardiac transplantation at the time of last follow-up and is the focus of this report.

The trial protocol was approved by the institutional review board or ethics committee of all institutions, and a parent or legal guardian of each subject provided written informed consent.

Patient Sample

There were 555 neonates randomized in the trial. The analysis cohort included 549 subjects. We excluded 5 subjects who did not undergo

a Norwood procedure and 1 subject who withdrew from the trial in the first week after randomization, and for whom no additional data were collected.

Data Collection

This report is based on an analysis of early and nonmodifiable patient factors. Detailed information on birth characteristics, patient demographics, and pre-Norwood procedure medical history was collected on standardized forms. Socioeconomic status (SES) was assigned using a US census–based score derived from 6 measures related to income, housing, and occupational-related features of the subject's census block tract³ at the time of randomization. Cause of death was assigned by a 5-member panel who arrived at consensus decision on each event after independent review by each member.⁴ The panel consisted of the SVR Study Chair, a pediatric cardiologist, a pediatric cardiac intensivist, and 2 pediatric cardiac surgeons.

Two-dimensional and Doppler echocardiographic data from a standardized echocardiogram obtained before the Norwood procedure were used in this analysis. All echocardiograms were interpreted centrally at a core laboratory (Medical College of Wisconsin). Variables used in this report include right ventricular fractional area change, presence versus absence of antegrade flow in the aorta (patent vs atretic aortic valve), and no/mild versus moderate/severe valve regurgitation (aortic, mitral, tricuspid).

Definitions

The type of shunt used in the Norwood procedure (MBTS or RVPAS) was defined as the shunt in place at the end of the Norwood procedure, which differed from the randomly assigned shunt for 48 subjects (9%). Pre-term was defined as gestational age less than 37 weeks. OPVR was defined as the use of postnatal intervention directed at the atrial septum, including balloon septostomy, open atrial septectomy, and urgent Norwood procedure.²

Statistical Methods

The primary end point of the SVR trial was a composite of the earliest occurrence of death or transplant. However, we hypothesized that the hazard functions for death and transplant might differ, as well as the factors associated with those end points. Therefore, outcomes at the time of last follow-up were examined using a competing risks framework. In addition, we hypothesized that the factors associated with these outcomes might differ according to time domain. Parametric regression modeling methodology allowed us to fit early, constant, and late phase hazard functions and to test their significance.

Summary statistics are reported as mean $\pm$ standard deviation or median and interquartile range. Mean or median imputation was used; 2% or less data were missing in variables on which imputation was performed, with the exception of highest lactate (18%) and fractional area change (8%). Genetic syndrome and nonsyndromic abnormalities were analyzed with an explicit category for unknown status. All outcomes were measured as time since randomization. The following independent and mutually exclusive states were defined for analysis: death, cardiac transplantation, and transplant-free survival (ie, no transition to another state). Nonparametric Kaplan–Meier estimates of freedom from death and transplantation were obtained and used to inform starting values for parametric model estimation of the hazard functions for each state and the number of phases. Competing risks cumulative incidence event rate estimation was used. Univariate (Table E1) and multivariable modeling were conducted using the parametric regression model.⁵ Bootstrap resampling was used to estimate the reliability of each factor selected by stepwise regression for the multivariable model.^{6,7} We retained main effects in the model if the term had reliability of 50% or more and a *P* value less than .05. In addition to the identification of independent associated factors, the interaction of shunt type with each candidate factor was examined unless there were insufficient events to achieve model convergence. The final multivariable

FIGURE 1. Proportion of subjects in each of 3 competing mutually exclusive end states: death, transplant, and alive without transplant for all 549 subjects (solid curves). Dashed curves represent the pointwise 68% (1 standard error) confidence bands based on the parametric fit. The squares and associated error bars represent the nonparametric estimates ± 1 standard error.

model was also solved to predict the time-related probability of each state for selected combinations of associated factors representing plausible patient profiles. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC) and SAS macros from the Cleveland Clinic.⁵

RESULTS

The analytic cohort included 549 subjects (MBTS 268, RVPAS 281). The mean follow-up in subjects who survived and did not undergo cardiac transplant was 2.7 ± 0.9 years, with a maximum follow-up of 4.4 years. There were 178 deaths: 100 in the MBTS group and 78 in the RVPAS group. More than one third (39%) were of cardiovascular cause,

25% had unknown cause, 10% were due to multisystem organ failure, 7% were due to infection, 7% were of pulmonary cause, 5% were due to surgical complications, and 7% were due to other causes. There were 19 transplants: 7 in the MBTS group (all occurring within 1 year of randomization) and 12 in the RVPAS group (half occurring within 1 year of randomization). A genetic syndrome, diagnosed at a median age of 0.5 (interquartile range, 0.1–9.0) months, was present in 26 subjects (5%), including 8 with CHARGE association; 5 with Turner syndrome; 4 with Kabuki syndrome; 1 each with DiGeorge, Alagille, Goldenhar, Down, or Thode-Leonard syndrome; and 4 others with unspecified syndromes.

Figure 1 displays competing risk time-related prevalence for the 3 states (death, transplant, survival without transplant). For the entire cohort, the 1- and 3-year mortality rates were 29% and 33%. The transplant prevalence at 1 and 3 years was 2.5% and 3.6%, respectively. The parametric curves provide an accurate estimate of the event rates derived from nonparametric modeling (shown by the point estimates). This concordance indicates that the parametric regression model provides a suitable fit to the data and is appropriate for identifying factors associated with each state.

The multivariable model for death included several independent factors and 2 interactions with shunt type (Table 1). The hazard for death was characterized by an early phase and a constant phase that when combined describe the pattern of mortality over time. Clinical factors associated with the constant phase contribute to the likelihood of death equally across the entire time period of analysis. Although early and constant phase factors contribute in varying degrees to the hazard of death across the entire time spectrum,

TABLE 1. Multivariable model for mortality (total n = 549, 178 deaths)

	Hazard ratio	95% CI	P value	Reliability
Early phase				
OPVR vs no OPVR	4.75	(2.65–8.52)	<.001	88%
No HLHS vs HLHS with AS/MS	4.00	(1.91–8.37)	<.001	
No HLHS vs HLHS with AA/MS	1.75	(0.98–3.13)	.06	64%
No HLHS vs HLHS with AS/MA	1.28	(0.46–1.56)	.63	
No HLHS vs HLHS with AA/MA	2.07	(1.12–3.82)	.021	63%
Lower SES score (per 5-point decrease)	1.28	(1.06–1.56)	.012	
Smaller ascending aorta diameter, per mm	1.23	(1.04–1.45)	.013	56%, 55%
RVPAS vs MBTS				
Term, aortic valve not patent	0.36	(0.22–0.60)	<.001	50%
Term, aortic valve patent	0.57	(0.49–1.47)	.52	
Preterm, aortic valve not patent	1.25	(0.66–2.38)	.49	55%
Preterm, aortic valve patent	2.97	(1.43–6.19)	.004	
Constant phase				
Lower gestational age, per wk	1.56	(1.28–1.90)	<.001	78%
Genetic syndrome present vs none	9.34	(3.07–28.40)	<.001	
Genetic syndrome unknown vs none	4.74	(2.10–10.72)	<.001	78%
RVPAS vs MBTS*	1.10	(0.43–2.83)	.85	

AA, Aortic atresia; AS, aortic stenosis; HLHS, hypoplastic left heart syndrome; MA, mitral atresia; MBTS, modified Blalock–Taussig shunt; RVPAS, right ventricle-to-pulmonary artery shunt; MS, mitral stenosis; OPVR, obstructed pulmonary venous return; SES, socioeconomic score. *Shunt type forced into model.

TABLE 2. Additional pairwise anatomic diagnosis comparisons from multivariable model for death in Table 1

Comparison	Hazard ratio	95% CI	P value
AS/MS vs			
AA/MA	0.52	(0.23–1.15)	.11
AA/MS	0.44	(0.20–0.95)	.04
AS/MA	0.32	(0.10–1.00)	.05
AA/MA vs			
AA/MS	0.84	(0.54–1.31)	.46
AS/MA	0.62	(0.23–1.67)	.35
AA/MS vs AS/MA	0.73	(0.27–1.98)	.54

AA, Aortic atresia; AS, aortic stenosis; MA, mitral atresia; MS, mitral stenosis.

the early phase factors characterized the hazard predominantly in the first year after the Norwood procedure. After this time, the hazard of death up to 4.4 years was predominantly attributable to constant phase factors. Early phase factors associated with death included lower SES score (hazard ratio [HR] = 1.28 per 5-point decrease, a decrement approximately comparing subjects from 2 adjacent SES quartiles, $P = .012$), a smaller ascending aorta diameter (HR = 1.23 per 1 mm decrease, $P = .014$), the presence of OPVR, and certain subtypes of cardiac anatomy (Tables 1 and 2). Subjects with HLHS-aortic stenosis (AS)/mitral atresia (MA), HLHS-AA/mitral stenosis (MS), and a diagnosis other than HLHS were at highest risk of death and had similar mortality. Among subjects with HLHS and AA, there was no difference in mortality among those with MA compared with those with MS (HR = 0.85, $P = .46$). Mortality was lowest in subjects with HLHS-AS/MS (Table 1). Two factors were associated with a constant hazard of death (both $P < .001$): the presence of a genetic syndrome (12/26 subjects with a genetic syndrome died) and lower gestational age (HR = 1.56 per decreasing week).

In the multivariable model for death, there were 2 significant 2-way interactions. Shunt type had a significant interaction with preterm status ($P = .029$) and aortic valve patency ($P = .018$). Four subgroups resulted from these 2 factors: term infants with an atretic aortic valve (51% of subjects), term infants with a patent aortic valve (38% of subjects), preterm infants with an atretic aortic valve (7% of subjects), and preterm infants with a patent aortic valve (4% of subjects). We found no significant benefit of either shunt type for term infants with a patent aortic valve ($P = .57$) or for preterm infants with an atretic aortic valve ($P = .49$); this represents approximately half the cohort (45%). The RVPAS was associated with lower mortality for term infants with an atretic aortic valve (RVPAS vs MBTS HR = 0.36, $P < .001$), which represent the other half of the cohort. The MBTS was associated with lower mortality for the small subgroup of preterm infants with a patent aortic valve (RVPAS vs MBTS HR = 2.97, $P = .004$).

We used the parametric regression model to generate predicted cumulative incidence of death by cardiac anatomy and shunt type for low-risk subjects (Figure 2, A and B). The predicted mortality for any patient profile can be obtained from the model. Figure 2, C and D, shows selected scenarios of poor outcome in those with HLHS and AA/MS: Subjects with OPVR who are preterm and have a smaller than average ascending aortic diameter have less than a 20% chance of survival to 1 year, regardless of shunt type. Because OPVR is a risk factor associated with the early phase of the hazard for death, mortality occurs rapidly (by 6–8 months, usually before the stage II procedure). Subjects with no OPVR, but who have a genetic syndrome, are preterm, and have a small aortic diameter, also have less than a 20% chance of survival at 4 years, but the mortality occurs over time, because genetic syndrome is a risk factor associated with the underlying constant (rather than early) hazard of death. Conversely, Figure 2, E and F, shows selected scenarios of good outcome. These profiles are for subjects with HLHS with AS/MS (Figure 2, E) or AA/MA (Figure 2, F) with other characteristics fixed at SES at the third quartile, no OPVR, term status, and an above-average ascending aorta diameter. For these subjects, all have survival more than 70% at 4 years, regardless of shunt type.

Eight variables were associated with an increased risk of transplant at the P less than .10 level (Table E2). We found no significant interactions of shunt type and other variables. The multivariable model for transplant (Table 3) had 3 independent factors: lower right ventricle fractional area change from the pre-Norwood echocardiogram, a diagnosis other than HLHS, and a larger number of pre-Norwood surgeries (Table E2 shows the procedure listing). Shunt type was not associated with transplant (RVPAS vs MBTS HR = 1.46, 95% CI, 0.57–3.70, $P = .43$). The presence of moderate/severe tricuspid regurgitation was also clinically significant (HR = 2.61), but was not statistically significant ($P = .07$) because of its correlation with cardiac anatomy and number of prior surgeries. Figure 3 shows the cumulative incidence of transplant for 8 patient profiles. For example, 11% of infants with 35% fractional area change on pre-Norwood echocardiogram and no pre-Norwood surgery are predicted to undergo transplant by 3 years regardless of anatomy, whereas 27% to 36% of infants with HLHS, 25% fractional area change, and 1 pre-Norwood surgery will undergo transplantation by that time. One high-risk scenario is an infant with a diagnosis other than HLHS, 25% fractional area change, and 1 pre-Norwood surgery (62%–76% 3-year probability of transplant).

DISCUSSION

The goal of this analysis of the PHN SVR trial dataset was to identify patient and preoperative factors associated with the intermediate-term occurrence of death and cardiac

FIGURE 2. A, Parametric survival curve by anatomic subtype of subjects undergoing RVPAS. B, Parametric survival curve by anatomic subtype of subjects undergoing MBTS. C, Parametric survival curve for higher-risk subjects, showing the impact of OPVR on survival among subjects undergoing the Norwood procedure with MBTS versus RVPAS. D, Parametric survival curve for higher-risk subjects showing the impact of a genetic syndrome on survival among subjects undergoing the Norwood procedure with MBTS versus RVPAS. E, Parametric survival curve for lower-risk subjects, showing the impact of shunt type, SES, and aortic diameter on survival of subjects with HLHS-AA/MA. F, Parametric survival curve for lower-risk subjects, showing the impact of shunt type, SES, and aortic diameter on survival of subjects with HLHS-AS/MS. *RVPA*, Right ventricle-to-pulmonary artery; *SES*, socioeconomic status; *GA*, gestational age; *OPVR*, obstructed pulmonary venous return; *Ao*, aorta; *diam*, diameter; *MS*, mitral stenosis; *MBT*, modified Blalock–Taussig; *HLHS*, hypoplastic left heart syndrome; *AA*, aortic atresia; *MA*, mitral atresia.

transplant in infants with single right ventricle anomalies undergoing staged palliation. The candidate factors chosen for this analysis include those with little or no potential for modification before surgery. Because these characteristics

are unique to each patient at the time of diagnosis, they are the factors the teams caring for these neonates must use to formulate decisions before surgical intervention. Primarily nonmodifiable factors were chosen with the additional goal of identifying those patient-specific factors that might allow better assignment to an MBTS or RVPAS for the Norwood procedure.

By using parametric regression, we characterized the hazard of death as having a constant phase and an early phase. Many of these risk factors, specifically OPVR, shunt type, smaller ascending aorta, non-HLHS anatomy, genetic syndromes, and lower gestational age, have been identified in previous retrospective and prospective studies.^{1,8-12}

Although a genetic syndrome was present in only 5% of the cohort, it had a strong negative association with

TABLE 3. Multivariable model for cardiac transplantation

Variable	Hazard ratio	95% CI	P value	Reliability
RVPAS vs MBTS*	1.46	(0.57–3.70)	.43	—
Lower pre-Norwood RV fractional area change, %	1.49†	(1.12–1.97)	.006	60%
HLHS vs other diagnosis	0.32	(0.11–0.89)	.029	51%
No. of pre-Norwood surgeries	5.64	(1.69–18.77)	.005	54%

HLHS, Hypoplastic left heart syndrome; *MBTS*, Modified Blalock–Taussig shunt; *RV*, right ventricle; *RVPAS*, right ventricle-to-pulmonary artery shunt. *Shunt type was forced into the model. †Per 5-unit decrease.

FIGURE 3. Predicted probability of freedom from transplant for subjects with differing cardiac anatomy, right ventricle function, and numbers of pre-Norwood surgeries. *HLHS*, Hypoplastic left heart syndrome; *RV*, right ventricle; *MBTS*, modified Blalock-Taussig shunt; *RVPAS*, right ventricle-to-pulmonary artery shunt; *Nwd*, Norwood.

survival. Only 14 of 26 subjects with an identified genetic syndrome were alive at last follow-up. In a recent analysis of the Society of Thoracic Surgeons and Congenital Heart Surgeons' Society databases, the risk of death after the Norwood procedure among patients with chromosomal defects, the majority of which were Turner syndrome, was increased and found to be greatest within the first year of the Norwood procedure.¹³ Likewise, we found that 10 of the 12 deaths occurring in subjects with a genetic syndrome occurred in the first year. The specific mechanism of increased risk of mortality is unknown but is likely due to abnormalities of organ system function specific to each genetic syndrome.^{12,13} The poor survival of this group is important to consider during prenatal and preoperative counseling.

The presence of OPVR also had a high impact on mortality. This condition is associated with profound hypoxia and the need for an emergency Norwood procedure or a pre-Norwood intervention. Although creation of an unrestrictive atrial septal communication can usually be accomplished at the time of surgery, these patients frequently have persistent abnormalities of the pulmonary vasculature. The wall of the pulmonary veins can be thickened by the presence of multiple elastic lamina, normally not seen in pulmonary veins.^{14,15} Despite anatomic decompression of the left atrium, these patients have ongoing hypoxia with a pulmonary vascular bed unsuitable for subsequent single ventricle palliation. Although we have confirmed the profound risk associated with OPVR, effective treatment remains elusive. Attempts at prenatal intervention are promising but as yet have not resulted in significantly improved outcomes.¹⁵

There were important differences in survival with respect to anatomic subtype. Consistent with single-center reports, subjects with a non-HLHS diagnosis, such as unbalanced atrioventricular canal defect, double-outlet right ventricle

with MA, or heterotaxy syndrome, had poorer survival.¹⁰ The superior survival among subjects with AS/MS was observed even after adjustment for ascending aortic diameter but may be due in part to the presence of antegrade flow with more reliable coronary circulation and possibly a larger aortic root and arch, simplifying the Norwood procedure. Furthermore, the presence of even a small left ventricle that can contribute to cardiac output may be helpful. Two large single-center retrospective studies have suggested that patients with AA/MS may be at higher risk for death after stage 1 palliation, possibly because of the higher prevalence of coronary artery fistulas.^{16,17} In this analysis, there was no significant difference in mortality between subjects with AA and MA and those with AA and MS. Our data do not provide justification for alternative strategies in this group of patients.

We found an important interaction between shunt type and aortic valve patency, as well as between shunt type and prematurity, in association with early phase mortality. Specifically, term infants with an atretic aortic valve had better survival if they underwent an RVPAS compared with an MBTS. The benefit of the RVPAS at 12 months, as previously reported for the SVR trial, seems to be confined, based on a mean follow-up of 2.7 ± 0.9 years, to this group of 272 subjects (51% of the total cohort).¹ The risk of mortality for a term patient with an atretic aortic valve undergoing an RVPAS was one third that of a similar patient undergoing an MBTS. In contrast, among 21 preterm infants (4% of the cohort) with a patent aortic valve, survival was better with an MBTS. For the 45% of the subjects outside of these 2 groups (ie, term patients with a patent aortic valve and preterm patients with AA), we were unable to demonstrate a significant association between shunt type and mortality. Among the postulated benefits of the RVPAS is improved coronary artery perfusion.¹⁸⁻²⁰ The RVPAS results in a higher diastolic pressure, and thus a higher coronary artery driving pressure, which may provide an important benefit to the patient with AA. In contrast with patients with a patent aortic valve, patients with AA are more likely to have coronary artery anomalies including fistulas.^{21,22} Furthermore, patients with an atretic aortic valve are more likely to have a smaller ascending aorta, making surgical construction of an unobstructed connection between the ascending aorta and the main pulmonary artery more technically challenging. Indeed, obstruction in this connection, which can impair coronary artery blood flow in the presence of AA, has been cited as a cause of death among patients undergoing the Norwood procedure.²³ The more favorable hemodynamics of the RVPAS may ameliorate mild obstruction that could otherwise result in critical coronary artery insufficiency, myocardial ischemia, and death among similar patients with an MBTS. Therefore, the benefit of the RVPAS over the MBTS in term newborns with AA may be explained by

better coronary artery blood flow. Why an MBTS would be favorable among preterm subjects with a patent aortic valve is less clear. Perhaps the ventriculotomy in a small heart is less well tolerated and overwhelms other risk factors. It must be emphasized that only 11% of the subjects in this trial were preterm.

This analysis studied factors that are known about the newborn with HLHS before surgical intervention and that are the basis for decision-making by the teams caring for the patient with HLHS. They are generally considered non-modifiable, but in fact 2 of the factors, gestational age and SES, might be modifiable. This study and single-center studies of outcome have identified the importance of gestational age as a risk factor for mortality, as well as for neurodevelopmental outcome.⁹⁻¹² Although some early deliveries are inevitable, the increased risk of mortality should be taken into consideration if earlier elective delivery is considered. In the case of SES, the impact on survival is thought to be due to limited access to health care resources.²⁴ Therefore, provision of services to compensate for the challenges associated with low SES may positively affect outcome.

Given the high mortality of subjects after the Norwood procedure, it seems at first surprising that there was such a low use of transplantation. Although the decision-making process concerning the use of transplantation in this group is beyond the scope of this study, it is noteworthy that many of the factors associated with mortality, such as OPVR and a genetic syndrome, are often considered contraindications for transplant.²⁵ Furthermore, multiorgan dysfunction that occurs as a consequence of inadequate cardiac output after the Norwood procedure may also preclude the use of transplantation as salvage therapy. The relative lack of donor availability also limits use of this therapy. These data suggest that transplantation may be an alternative for only a small fraction of patients at risk for mortality after the Norwood procedure.

Study Limitations

This analysis has several limitations. We had limited power to detect interactions of shunt type and patient subgroup when subgroup sizes were small and to detect differences in mortality for selected subgroups regardless of shunt. For example, the difference in mortality between patients with HLHS with AA/MA versus those with AS/MS was 2-fold, clinically significant, but of marginal statistical significance. There was also low power to identify statistically significant risk factors for transplantation because of the small number of such events. Nevertheless, the risk models developed for both mortality and transplantation included multiple independent factors and have clinical relevance. Finally, the presence versus absence of a genetic syndrome was unknown for one third of subjects, and the increased HR for death relative to

subjects without a genetic syndrome reflects in part mortality that occurred before a genetic evaluation could be performed.

CONCLUSIONS

These data suggest that term patients with AA have better outcomes with an RVPAS and that preterm infants with a patent aortic valve may have better outcomes with an MBTS. For slightly less than half of the cohort, non-modifiable factors did not aid in shunt selection. Lower gestational age and SES, as well as the presence of a genetic syndrome, are also independent predictors of mortality. Transplant was used in only 3% of subjects after the Norwood procedure. Right ventricular function and anatomy, but not shunt type, were associated with transplantation. Patient-specific factors associated with mortality after the Norwood procedure are frequently contraindications to transplantation. Effective alternative therapies for the highest-risk Norwood candidates remain elusive.

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APPENDIX

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TABLE E1. Patient characteristics and association with mortality by phase

Variable	Mean $\pm$ SD or %	Early phase		Constant phase	
		HR	P value	HR	P value
RVPAS vs MBTS	51% vs 49%	0.58	.002	1.64	.32
Prenatal					
Prenatal diagnosis	77%	.87	.45	1.89	.38
Fetal intervention	2.7%	—	—	—	—
Birth					
Gestational age, wk	38.2 $\pm$ 1.6	.89	.030	0.65	<.001
Gestational age < 37 wk	12%	2.31	<.001	3.61	.028
Apgar at 1 min	7.6 $\pm$ 1.6	0.94	.21	0.997	.94
Apgar at 5 min	8.6 $\pm$ 0.8	.85	.07	0.89	.61
Birth weight, kg	3.10 $\pm$ 5.41	0.59	.001	0.69	.42
Birth weight < 2.5 kg	14%	2.10	<.001	2.13	.21
Birth weight < 1.5 kg	0.4%	2.96	.29	18.4	.006
Demographic					
Male	62%	0.81	.22	2.04	.25
Hispanic	19%	1.06	.88	0.58	.68
White race	80%	0.80	.27	0.68	.50
SES score, US census (HR per 5-point decrease)	0.05 $\pm$ 5.08	1.27	.006	0.88	.57
Anatomy					
HLHS	88%	0.60	.019	1.90	.54
AA, MA	38%	0.93	.69	1.14	.81
AA, MS	25%	1.22	.49	0.44	.40
AS, MS	12%	0.32	.008	2.22	.19
Any AA	62%	1.07	.70	0.53	.25
Obstructed PV drainage	3.5%	4.30	<.001	Not estimable	
Total anomalous pulmonary venous return	1.6%	2.09	.33	8.25	.27
Ascending aorta diameter, mm	3.15 $\pm$ 1.75	0.87	.018	1.07	.56
Genetic syndrome					
Yes vs no	5%	1.48	.45	7.91	.001
Unknown vs no	32%	3.30	<.001	2.78	.049
Non-syndromic abnormality					
Yes vs no	19%	0.77	.43	2.02	.22
Unknown vs no	32%	3.00	<.001	2.89	.05
Pre-Norwood echocardiography					
Patent aortic valve	42%	0.88	.35	1.66	.28
ASD mean Doppler gradient, mm Hg	5.0 $\pm$ 3.0	1.02	.55	0.97	.69
RV fractional area change	0.35 $\pm$ 0.09	2.07	.49	0.63	.91
LV present	69%	0.95	.77	1.26	.68
Moderate/severe tricuspid regurgitation	12%	1.24	.42	2.54	.13
Moderate/severe mitral regurgitation	4%	0.41	.29	.008	.58
Moderate/severe aortic valve regurgitation	0.8%	0.10	.54	~0	.40
Preoperative					
Median highest lactate, mmol/L (IQR)	3.1 (2.5, 4.5)	1.06	.018	0.84	.26
Mechanical ventilation	48%	1.73	.002	0.97	.95
Pre-Norwood apnea	14%	1.34	.18	0.94	.89
Pre-Norwood shock	2.6%	—	—	—	—
Pre-Norwood respiratory failure	13%	1.09	.76	3.02	.045
Pre-Norwood metabolic acidosis	5.7%	1.05	.99	0.69	.97
Pre-Norwood catheter intervention	5.1%	2.24	.005	0	.95
No. of pre-Norwood catheter intervention (median [IQR])	0.07 $\pm$ 0.32 (0 [0–0])	2.24	.005	~0	.95
Pre-Norwood noncardiac surgery	1.5%	0.53	.69	4.55	.19
Pre-Norwood any surgery	2.0%	—	—	—	—
No. of pre-Norwood total surgeries (median [IQR])	0.02 $\pm$ 0.17 (0 [0–0])	1.21	.61	1.42	.75

(Continued)

TABLE E1. Continued

Variable	Mean $\pm$ SD or %	Early phase		Constant phase	
		HR	P value	HR	P value
Pre-Norwood complications	28%	1.57	.011	1.14	.80
No. of pre-Norwood complications (median [IQR])	0.58 $\pm$ 1.23 (0 [0–1])	1.16	.003	0.91	.71

SD, Standard deviation; HR, hazard ratio; RVPAS, right ventricle-to-pulmonary artery shunt; MBTS, modified Blalock–Taussig shunt; SES, socioeconomic status; HLHS, hypoplastic left heart syndrome; ASD, atrial septal defect; IQR, interquartile range; LV, left ventricle.

TABLE E2. Results summary for cardiac transplant risk factors with univariate P value less than .2 and for shunt type

Variable	Transplant	No transplant	Hazard ratio	95% CI	P value
	Mean $\pm$ SD or % (n)	Mean $\pm$ SD or % (n)			
N	19	530			
RVPAS vs MBTS	63% (12)	51% (269)	1.43	(0.56–3.63)	.45
Male vs female	42% (8)	63% (332)	0.42	(0.17–1.04)	.06
Percentage in census tract below federal poverty level	7.6 $\pm$ 7.2	13.1 $\pm$ 12.4	1.31 per 5% increase	(0.96–1.80)	.09
HLHS	74% (14)	88% (467)	0.33	(0.19–0.55)	.03
HLHS with AS/MS	5% (1)	21% (109)	0.18	(0.02–1.36)	.10
HLHS with AS/MA	11% (2)	3% (15)	4.05	(0.94–17.5)	.06
Total anomalous pulmonary venous connection	5% (1)	2% (8)	6.03	(0.80–45.6)	.08
Pre-Norwood moderate/severe tricuspid regurgitation	32% (6)	11% (59)	3.86	(2.29–6.18)	.006
Pre-Norwood RV fractional area change	0.30 $\pm$ 0.09	0.35 $\pm$ 0.08	1.43 per 5-unit decrease	(1.09–1.85)	.009
Total No. of pre-Norwood surgeries*	0.11 $\pm$ 0.46	0.02 $\pm$ 0.15	4.21	(1.30–13.7)	.017

AS, Aortic stenosis; CI, confidence interval; HLHS, hypoplastic left heart syndrome; MA, mitral atresia; MBTS, modified Blalock–Taussig shunt; MS, mitral stenosis; RV, right ventricular; RVPAS, right ventricle-to-pulmonary artery shunt; SD, standard deviation. *Includes 1 subject with atrial septectomy and bilateral pulmonary artery bands, 2 subjects with bowel surgery, 1 subject with extracorporeal membrane oxygenation, 1 subject with exploratory laparotomy, 1 subject with choanal atresia and stent placement, and 1 subject with tracheoesophageal fistula repair