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Risk factors for hospital morbidity and mortality after the Norwood procedure: A report from the Pediatric Heart Network Single Ventricle Reconstruction trial

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Abstract

Objectives—We sought to identify risk factors for mortality and morbidity during the Norwood hospitalization in newborn infants with hypoplastic left heart syndrome and other single right ventricle anomalies enrolled in the Single Ventricle Reconstruction trial.

Methods—Potential predictors for outcome included patient- and procedure-related variables and center volume and surgeon volume. Outcome variables occurring during the Norwood procedure and before hospital discharge or stage II procedure included mortality, end-organ complications, length of ventilation, and hospital length of stay. Univariate and multivariable Cox regression analyses were performed with bootstrapping to estimate reliability for mortality.

Results—Analysis included 549 subjects prospectively enrolled from 15 centers; 30-day and hospital mortality were 11.5% (63/549) and 16.0% (88/549), respectively. Independent risk factors for both 30-day and hospital mortality included lower birth weight, genetic abnormality, extracorporeal membrane oxygenation (ECMO) and open sternum on the day of the Norwood procedure. In addition, longer duration of deep hypothermic circulatory arrest was a risk factor for 30-day mortality. Shunt type at the end of the Norwood procedure was not a significant risk factor for 30-day or hospital mortality. Independent risk factors for postoperative renal failure (n = 46), sepsis (n = 93), increased length of ventilation, and hospital length of stay among survivors included genetic abnormality, lower center/surgeon volume, open sternum, and post-Norwood operations.

Conclusions—Innate patient factors, ECMO, open sternum, and lower center/surgeon volume are important risk factors for postoperative mortality and/or morbidity during the Norwood hospitalization.

Risk factors for hospital morbidity and mortality after the Norwood procedure for patients with hypoplastic left heart syndrome (HLHS) have been reported from single centers and multicenter databases. Many centers report low birth weight, genetic abnormalities, restrictive atrial septum, duration of cardiopulmonary bypass (CPB), and extracorporeal membrane oxygenation (ECMO) as risk factors for mortality.[1–14] Multicenter reports have shown higher mortality at smaller volume centers.[2,15,16]

The Pediatric Heart Network Single Ventricle Reconstruction (SVR) trial provides a unique opportunity to analyze prospectively collected preoperative, operative, and postoperative data in the largest cohort of newborn infants with HLHS and other single right ventricle anomalies to date. Primary results of the SVR trial reported differences in outcome between subjects undergoing the Norwood procedure with a right ventricular–pulmonary artery shunt (RVPAS) versus a modified Blalock-Taussig shunt (MBTS).[17] The initial report focused solely on the comparative outcomes relative to shunt type. The primary aim of this prespecified secondary analysis was to examine the associations of patient-related risk factors and perioperative management variables on morbidity and mortality during the Norwood hospitalization. To facilitate comparisons with previous reports of surgical morality for the Norwood procedure, we analyzed both 30-day and hospital mortality. Our

secondary aim was to explore associations with shunt type on longer-term transplant-free survival in subjects requiring cardiopulmonary resuscitation (CPR) and/or ECMO.

METHODS

Study Design

Details of the SVR trial design have been previously published.[17,18] In brief, inclusion criteria consisted of a diagnosis of HLHS or other single right ventricle anomaly and a planned Norwood procedure. Patients were excluded if the preoperative cardiac anatomy rendered either the MBTS or RVPAS technically impossible or if they had any major congenital or acquired extracardiac abnormality that could independently decrease the likelihood of transplant-free survival at 1 year of age. Subjects were randomly assigned to receive either the MBTS or the RVPAS. The institutional review board at each center approved the protocol. Written informed consent was obtained from a parent/guardian before randomization. Other than the type of shunt placed, the remainder of the perioperative care was per institutional standard. For the purposes of this analysis, subjects were categorized by the shunt in place at the end of the Norwood procedure.

Data Collection and Definitions

Data were prospectively collected. The 16 outcome variables are defined in Appendix Table 1. Other than 30-day mortality, outcomes were recorded if they occurred before hospital discharge or before stage II procedure for subjects not discharged. ECMO initiated after the Norwood procedure was considered an outcome variable. The 42 potential risk factors are defined in Appendix Table 2. Subjects underwent genetic evaluations when indicated by clinical suspicion of a genetic abnormality. In addition, a research option for a genetic evaluation was offered. Preoperative shock was defined as a composite of hepatic failure (Appendix Table 1), renal failure (Appendix Table 1), lactate greater than 10 mmol/L, or intubation for shock. Perfusion strategies included deep hypothermic circulatory arrest (DHCA) alone or regional cerebral perfusion (RCP) with or without DHCA. Open sternum included all subjects with an open sternum on the day of the Norwood procedure. These subjects were categorized as those at a “routine” center where sternums of all patients were left open at the end of the Norwood procedure or those at an “elective” center where the surgeon selectively decided to leave the patient’s sternum open. ECMO for failure to separate from CPB was examined as a potential risk factor. The day of Norwood procedure was defined as day 1.

The longer-term outcome of patients requiring CPR (defined as receiving chest compressions) and/or ECMO was examined in further detail. Subjects were characterized as follows: CPR alone (CPR), ECMO alone (ECMO), ECMO required to restore circulation during CPR (E-CPR), and neither CPR nor ECMO (“none”). For the subanalysis of these 4 groups, only CPR, ECMO, or E-CPR occurring within 30 days of Norwood procedure were included. Subjects requiring ECMO for failure to separate from CPB were included in the ECMO group.

Statistical Methods

Summary statistics include mean ± standard deviation, median, and range. We analyzed 2 mortality outcomes: (1) time to death up to discharge from the Norwood hospitalization, using Kaplan-Meier estimation and Cox proportional hazards regression, with censoring at dates of cardiac transplant and at time of stage II procedure (for those not discharged) and (2) a dichotomous 30-day post-Norwood procedure mortality indicator, using logistic regression. We analyzed 4 continuous outcomes using linear regression: post-Norwood right ventricular fractional area change, log-transformed time to initial extubation, log-transformed total days ventilated, and log-transformed hospital length of stay. Subjects who died or underwent cardiac transplant during the hospitalization were excluded from analysis of the extubation, ventilation, and length of stay outcomes. We analyzed 10 dichotomous morbidity outcomes using logistic regression; for 3 of these (necrotizing enterocolitis, liver failure, mediastinitis), only univariate analyses were conducted owing to the low event rate. For construction of multivariable models, variables with a P value ≤ .2 in univariate analysis were used as candidate predictors in regression modeling. The R^2 and maximum rescaled R^2 values are reported for linear and logistic regression models, respectively. In addition, generalized additive modeling was used to identify nonlinear associations between outcomes and continuous candidate predictors. Variables with a nonlinearity P value < .05 were considered in the multivariable selection procedure. Bootstrap resampling was used to estimate the reliability of each factor selected by stepwise regression for the multivariable mortality model.[19,20]We retained a term in the model if it had reliability greater than 50% and a P value of less than .05.

We used analysis of variance and the Kruskal-Wallis test for comparison of the distributions of baseline characteristics across the 4 ECMO/CPR groups. To account for potential survival bias in this secondary analysis of CPR with or without ECMO subjects, we used Cox proportional hazards regression with a time-dependent group indicator to model time to death or transplant, using all available follow-up data. A test of interaction between subject group and shunt type was used to assess differential treatment effect by group.

RESULTS

Between May 2005 and July 2008 there were 549 evaluable SVR subjects: 268 with an MBTS and 281 with an RVPAS.

Mortality

Mortality during the Norwood hospitalization was 16% (88/549). Deaths occurred at a median of 16 days, (range, 1–149 days). The 30-day mortality was 12% (63/549). Figure 1 shows the Kaplan-Meier survival curve for all subjects during the Norwood hospitalization. Included among the survivors were 9 subjects who underwent cardiac transplantation before discharge; median time to transplant was 51 days after the Norwood procedure (range, 9–270 days). There were 22 subjects who remained in the hospital until the stage II procedure; median time to stage II procedure was 116 days (range, 49–271 days).

Significant risk factors by univariate analysis for 30-day mortality included the following: lower birth weight, lower gestational age, genetic abnormality, duration of DHCA, duration of total support time, ECMO for failure to separate from CPB, open sternum at the Norwood procedure, and surgeon Norwood volume. Additional risk factors by univariate analysis for Norwood hospital mortality included preoperative intervention on the atrial septum and younger age at surgery. Significant risk factors by multivariable analysis, for 30-day and hospital mortality, are shown in Table 1. Shunt type was not a significant risk factor for mortality. ECMO and open sternum on the day of the Norwood procedure were the strongest risk factors for mortality. ECMO was initiated during the Norwood procedure in 8% of subjects with open sternum and 1% of subjects with closed sternum ($P = .002$). Open sternum remained a significant risk factor for mortality with ECMO included in the multivariable model. Sternums were routinely left open in all patients at 7 centers (median hospital mortality, 18%; range, 2%–39%) and sternums were electively left open at 8 centers (median hospital mortality, 13%; range, 0%–30%). The 7 routine open sternum centers represented 59% (244/415) of the subjects with open sternum. The mortality risk of open sternum did not differ significantly between routine and elective centers. For the open sternum cohort, reliability by bootstrapping methodology for hospital mortality was high at 90%. Although subjects with the anatomic subtype of mitral stenosis with aortic atresia were more likely to require ECMO during the Norwood procedure (13% vs 4%; $P < .001$), mitral stenosis with aortic atresia was not an independent risk factor for 30-day ($P = .23$) or hospital (hazard ratio, 1.48; 95% confidence interval, 0.92–2.36; $P = .1$) mortality.

Morbidity

Results of multivariable analyses for the morbidity outcomes are shown in Table 2. Shunt type was only an independent risk factor for CPR (odds ratio, 2.02; $P = .005$) and decreased ventricular function as measured by postoperative echocardiographic fractional area change (odds ratio, −3.59; $P < .001$) with the MBTS compared with the RVPAS. Genetic abnormality, center volume, surgeon volume, open sternum, and post-Norwood operations were the most common independent risk factors for post-Norwood morbidities.

Less frequent morbidities were explored by univariate analyses. Hepatic failure occurred in 16 subjects at a median of 22 days (range, 2–159 days) after the Norwood procedure. Fifty percent (8/16) of the subjects with hepatic failure died before discharge. Significant risk factors for hepatic failure included lower birth weight ($P = .02$), aortic atresia ($P = .03$), MBTS ($P = .04$), longer support time ($P = .05$), and heart block on the day of the Norwood procedure ($P = .02$). Mediastinitis occurred in 15 subjects at a median of 8 days (range, 3–35 days) after the Norwood procedure. Significant risk factors for mediastinitis included preoperative intubation for apnea or transport ($P = .04$), RVPAS ($P = .04$), and heart block on the day of the Norwood procedure ($P = .02$). Open sternum was not a risk factor for mediastinitis. Necrotizing enterocolitis occurred in 14 subjects at a median of 22.5 days (range, 2–66 days) after the Norwood procedure. No significant risk factors were identified.

ECMO and CPR

Of the 549 evaluable subjects, 22% (122/549) received CPR (n = 37), ECMO (n = 49), or E-CPR (n = 36) within the first 30 days after the Norwood procedure and 78% (427/549) did

not require these interventions (“none”). Important baseline characteristics among the 4 groups are shown in Table 3. Within the ECMO, CPR, and E-CPR groups, there was no difference in the number of subjects according to shunt type. After the Norwood procedure, the mean time to initiation of CPR was 3.1 ± 1.4 days, ECMO was 1.1 ± 1.7 days, and E-CPR was 4.7 ± 5.9 days. Within the ECMO subjects, 71% (35/49) required ECMO for failure to separate from CPB. Low birth weight was more common in the CPR and E-CPR groups ($P < .001$).

Longer-term survival for these subjects was examined with a mean follow-up of 2.7 ± 0.9 years. Subjects receiving CPR, ECMO, or E-CPR had a lower transplant-free survival ($P < .0001$; Figure 2). The 2-year transplant-free survival was 35% for CPR, 26% for ECMO, 30% for E-CPR, and 75% for the “none” group. The impact of shunt type on transplant-free survival within the 4 groups is shown in Table 4. Subjects who did not require CPR or ECMO had better survival with an RVPAS. After adjustment for surgeon and birth weight, subjects with an MBTS had a better outcome after E-CPR or ECMO relative to subjects with an RVPAS compared with those subjects in the “none” group. This differential effect of shunt type was not observed for the CPR group in comparison with the “none” group.

DISCUSSION

The primary outcome of the SVR trial demonstrated a transplant-free survival benefit for subjects receiving an RVPAS, which was statistically significant at 12 months of age but no longer significant at longer follow-up (32 ± 11 months).[17] This prespecified secondary analysis reports the most extensive evaluation of risk factors for morbidity and mortality during the Norwood hospitalization in a multicenter cohort of newborn infants with HLHS and other single right ventricular anomalies to date. Multivariable analysis showed that only birth weight, genetic abnormality, ECMO, and open sternum at the Norwood procedure were independent risk factors for 30-day and hospital mortality, and the duration of DHCA was an independent risk factor for 30-day mortality.

Early outcomes for patients with HLHS have improved substantially over the past 3 decades. Reports of early postoperative mortality are predominantly from centers achieving excellent outcomes with reported surgical survivals of 81% to 93%.[3,4,7–13] Results from multiple centers have been limited to database extraction with lower survivals of 72% to 78%.[2,15,16] Reported risk factors for early mortality after the Norwood procedure differ among centers and include *patient-related* factors such as prematurity,[10] lower birth weight,[2–4,7] and presence of genetic or noncardiac abnormalities[3,10]; *anatomic* factors such as mitral stenosis/aortic atresia,[14] smaller ascending aorta,[2] restrictive atrial septum, or significant tricuspid regurgitation[4,7]; *preoperative* factors such as shock[7] and ECMO[10]; *operative* factors such as older age at surgery,[2] shunt type,[11] longer DHCA,[2] CPB, or total support time[4,14]; and *postoperative* factors such as ECMO[1,4,6,14] and low mixed venous saturation.[13] An earlier surgical era[13] and lower center surgical volume[2,15,16] have also been associated with early mortality. Differences in reported risk factors between centers may reflect variation among centers, variation in patient populations, or studies with small patient populations.

Of the independent risk factors that we identified for hospital mortality after the Norwood procedure, lower birth weight, genetic abnormality, longer duration of DHCA, and ECMO have been previously reported. We did not find the type of shunt by non–intention-to-treat analysis to be a significant risk factor for either 30-day or Norwood hospital mortality. These findings are consistent with the initial SVR trial report in which using intention-to-treat analysis, death, or transplant occurred within 30 days of the Norwood procedure in 10% (28/274) of subjects with an RVPAS compared with 14% (38/275) with an MBTS.[17] We did not find aortic atresia, size of the ascending aorta, or preoperative shock significant by univariate analysis. Prematurity, restrictive atrial septum requiring intervention, mitral stenosis/aortic atresia, moderate/severe tricuspid regurgitation, younger age at surgery, longer total support time, and lower center HLHS or surgeon Norwood volume were significant or marginally significant by univariate analysis in our study; however, they were not found to be risk factors for early mortality on multivariable analysis.

Open sternum remained significantly associated with hospital and 30-day mortality after adjusting for other important independent risk factors including ECMO for failure to separate from CPB. Open sternum remained a significant risk factor for mortality independent of the center's strategy (elective vs routine sternal closure). Few conflicting reports address open sternum as a risk factor for mortality.[7,21] Examination of the Society of Thoracic Surgeons Congenital Database (n = 1283, 45 centers) found 74% of patients undergoing Norwood procedure for HLHS were managed with an open sternum.[22] Surgical mortality did not differ between centers with a high versus a low proportion of patients with an open sternum. In addition to mortality, we found open sternum to be an independent risk factor for postoperative renal failure, moderate to severe tricuspid regurgitation, longer time to first extubation, and duration of ventilation. We found the duration of open sternum to be a risk factor for sepsis, although importantly, not for mediastinitis. The practice of elective sternal closure is subject to selection bias; the patients chosen to have the sternum closed at the Norwood procedure were likely considered to be at lower risk for a poor outcome. In addition, the practice of open sternum may serve as a surrogate for variability in center clinical practices, which were not measured in this study. The decision to close the sternum in this trial was influenced by multiple factors, including the center's preference, the surgeon's assessment, and the use of ECMO with transthoracic cannulation. Thus, it is not possible to infer causality between open sternum and mortality. However, the significantly lower mortality among patients who had their chest closed at the conclusion of the Norwood procedure suggests that sternal closure can be performed safely in selected patients.

Although many centers have reported risk factors for surgical or hospital mortality after the Norwood procedure, analysis of risk factors for less frequent morbidities has been challenging owing to small sample sizes. We found a low (<3%) incidence of necrotizing enterocolitis, hepatic failure, and mediastinitis. Central nervous system injury, renal failure, ECMO, and CPR occurred early with the median time to event less than 1 week after surgery. Hepatic failure, necrotizing enterocolitis, catheter intervention, and sepsis tended to occur later in the postoperative course.

The impact of center volume on mortality after the Norwood procedure has been reported.[15,16] However, this study is the first multicenter report to include both center and

surgeon volumes in the risk analysis. Using the Kids' Inpatient Database (2003, n = 624 patients, 60 centers), lower institutional HLHS volume was shown to be a significant risk factor for Norwood hospital mortality.[15] Confounding variables included in the analysis were limited. More recently, using the Society of Thoracic Surgeons Congenital Heart Surgery Database (2011, n = 2557, 53 centers), lower center Norwood procedure volume was associated with higher hospital mortality.[16] We did not find center HLHS or surgeon Norwood volume to be risk factors for 30-day or hospital mortality. This may reflect the different variables included in each analysis. In our analysis, if the operative variable of open sternum is not divided into elective and routine centers, then center volume remains in the model as an independent risk factor for hospital mortality. We did find volume to be a significant risk factor for several important morbidities. Lower surgeon Norwood volume was a risk factor for renal failure, longer time to first extubation, and duration of ventilation; lower center HLHS volume was a risk factor for sepsis, longer time to first extubation, duration of ventilation, and hospital length of stay.

Innate patient variables made up a majority of the independent risk factors we identified for morbidity and mortality with a few risk factors potentially modifiable. Perhaps designating a regional HLHS center could increase center/surgeon volume. Routine preoperative intubation for transport and apnea may be unnecessary and can potentially be avoided with a lower dose of prostaglandin. Lower gestational age may be avoided by discouraging elective delivery before 39 weeks.[23]

The need for CPR[24] and ECMO[1,4,6] is a serious morbidity for infants with HLHS. Most commonly, ECMO is reserved for extremely low cardiac output, profound hypoxemia, or inability to regain spontaneous circulation with CPR. Early survival after ECMO in newborn infants with HLHS is reported at 17% to 54%.[1,6,13,25] We found a low transplant-free survival for subjects requiring ECMO, CPR, and E-CPR with attrition continuing for months after Norwood procedure. Of note, the survival of subjects requiring E-CPR did not differ from that of subjects placed on ECMO for either failure to separate from bypass or clinical deterioration without CPR. Our data did not enable us to report the subset of patients placed on ECMO for acute shunt failure, a subgroup reported to have better survival (83%–100%).[1,6] Similar to previous reports, we found improved survival after CPR alone for the RVPAS subjects.[24] In contrast, we found that in subjects requiring ECMO or E-CPR, the MBTS was associated with a more favorable outcome.

Limitations

As study participation was limited to 15 participating centers, performing 5 or more Norwood procedures annually, the inferences cannot be generalized to centers with smaller case volumes. The only variable randomly assigned was shunt type. Patients with a potentially higher risk of mortality independent of a planned Norwood procedure may be excluded by study criteria. Some subjects died before postoperative echocardiography, which could bias these outcome measures. Formal genetic evaluation was not obtained for all subjects, weakening the potential strength of this candidate predictor. Genetic abnormality was the only significant risk factor for central nervous system injury, which could reflect ascertainment bias in as much as these subjects were more likely to undergo

cranial imaging. Finally, we did not examine interactions between all possible risk factors. There may be selected subgroups with higher or lower risk for Norwood mortality or certain morbidities that were not identified.

CONCLUSIONS

In a large, multicenter prospective cohort of newborn infants with HLHS and related right ventricular anomalies undergoing the Norwood procedure as subjects of the SVR trial, we found lower birth weight, genetic abnormality, ECMO for failure to separate from CPB, and open sternum to be independent risk factors for 30-day and hospital mortality. Longer duration of DHCA was an independent risk factor for 30-day mortality. Shunt type was not found to be an independent risk factor for Norwood hospital mortality or morbidity outcomes with the exception that subjects with an MBTS had decreased ventricular function on postoperative echocardiography and increased odds of CPR. Patients requiring CPR and/or ECMO after the Norwood procedure have significantly lower transplant-free survival and remain at risk for attrition remote from the initial event. Although most risk factors were innate patient variables, potentially modifiable risk factors might include preoperative intubation, lower gestational age, elective open sternum, and center/surgeon volume.

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Abbreviations and Acronyms

CPB	cardiopulmonary bypass
CPR	cardiopulmonary resuscitation
DHCA	deep hypothermic circulatory arrest
ECMO	extracorporeal membrane oxygenation
E-CPR	ECMO required to restore circulation during CPR
HLHS	hypoplastic left heart syndrome
MBTS	modified Blalock-Taussig shunt
RCP	regional cerebral perfusion
RVPAS	right ventricular–pulmonary artery shunt
SVR	Single Ventricle Reconstruction

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Appendix

APPENDIX TABLE 1

Outcome variables after the Norwood procedure

Outcome	N	n	Definition/comment
Mortality, 30 day	549	63	Includes 4 subjects who died after discharge
Hospital mortality	549	88	Mortality during or after the Norwood procedure until discharge or stage II operation
Necrotizing enterocolitis	549	14	Defined as pneumatosis intestinalis or free air
Hepatic failure	549	16	AST, ALT, GGT >500 units
Mediastinitis	549	15	Deep sternal wound infection demonstrating sternal instability or requiring surgical incision and drainage
Catheter intervention	549	38	Transcatheter interventions (38 subjects) included: balloon dilation and/or stent of shunt (14), balloon dilation and/or stent of branch pulmonary artery (5), balloon dilation of the aorta (2), balloon dilation of the aortic valve (1), atrial radiofrequency ablation (1), innominate artery stent (3), device placed (1) and multiple interventions (11)
Central nervous system injury	549	47	Defined as intracranial bleed or stroke confirmed by imaging, clinical or EEG seizure. Imaging was per clinical team
Renal failure	549	46	Creatinine >1.5 mg/dL, tripling of creatinine over <7 days or dialysis
Sepsis	549	93	Confirmed positive blood culture
ECMO after Norwood procedure	549	56	Postoperative ECMO, excluding patients placed on ECMO during Norwood procedure
CPR	549	97	Postoperative CPR (defined as chest compressions), excluding CPR during Norwood procedure
Fractional area change	452		Predischarge ECHO
TR ≥2.5 mm	471	112	Predischarge ECHO showing TR jet ≥2.5 mm on one of two views
Log time to first extubation, d	447		Deaths (88) and transplants (9) were excluded. Five subjects had insufficient data. Log transformed data was used for analyses
Log length of ventilation, d	451		Deaths (88) and transplants (9) were excluded. One subject had insufficient data. Log transformed data was used for analyses

Outcome	N	n	Definition/comment
Log hospital length of stay, d	452		Discharge includes subjects transferred to other institutions. Subjects who died (88) or were transplanted (9) were excluded. Log transformed data was used for analyses.

N, Number of patients in analysis; *n*, number of patients with outcome; *AST*, aspartate aminotransferase; *ALT*, alanine transaminase; *GGT*, gamma-glutamyl transpeptidase; *EEG*, electroencephalogram; *ECMO*, extracorporeal membrane oxygenation; *CPR*, cardiopulmonary resuscitation; *ECHO*, echocardiogram; *TR*, tricuspid regurgitation.

APPENDIX TABLE 2

Candidate predictors

Candidate predictor	N	n	Mean ± SD	Definition/comment
Patient characteristics				
Prenatal diagnosis	549	421		
Birth weight, kg	549		3.1 ± 0.5	
Birth weight <2.5 kg	549	76		
Gestational age, wk	549		38 ± 1.6	
Gestational age <37 wk	549	64		
Genetic abnormality	549			
Yes		29		Yes, abnormal chromosomes only (3), genetic syndrome only (21), genetic syndrome and abnormal chromosomes (5)
No		344		No, normal chromosomes and formal genetic evaluation found no syndrome
Unknown		176		Unknown, subjects without chromosomes or genetic evaluation
Nonsyndromic anomalies	374	268		None
		38		1
		25		2
		43		≥3
Genetic abnormality and/or nonsyndromic anomalies	549			
Yes		120		
No		253		
Unknown		176		
		176		
Preoperative				
Preoperative intubation, any	547	263		Intubation, for any reason
Preoperative intubation for apnea/transport	547	101		
Preoperative intubation for shock	547	117		Intubation for shock, respiratory failure or acidosis
Preoperative left atrial decompression	549	21		Intervention on atrial septum for obstructed pulmonary venous return
Preoperative surgical intervention	549	8		Non-cardiac surgical interventions: bowel surgery (2), chest tube (2), other (4)
Preoperative bloodstream infection	549	8		
Preoperative central nervous system injury	549	14		Defined as seizure, stroke or intracranial bleed confirmed by imaging

Candidate predictor	N	n	Mean ± SD	Definition/comment
Preoperative shock	547	38		See Appendix Table 2. Hepatic failure (6), renal failure (10), elevated lactate (23), or intubation for shock (14)
Preoperative echocardiogram				
Left ventricular cavity present	359	254		
Fractional area change preoperatively, %	503		35 ± 8.6	RV fractional area change
TR ≥2.5 mm preoperatively	506	471		Width of the tricuspid regurgitation jet ≥2.5 mm in either AP or lateral view
Aortic stenosis	537	226		Flow through aortic valve
Anatomy				
Aortic atresia	549	345		
MS/AA	549	138		Mitral stenosis, aortic atresia. Mortality analyses only
MS/AS/IVS	549	45		Mitral stenosis, aortic stenosis with intact ventricular septum
MS/AS/VSD	549	11		Mitral stenosis, aortic stenosis with ventricular septal defect
Anomalous pulmonary venous return	549	11		
Ascending aorta diameter, observed, cm	534		0.32 ± 0.17	Surgeon observed
Ascending aorta diameter, echocardiogram, cm	534		0.36 ± 0.18	
Operative				
Age at Norwood procedure, d	549		5.8 ± 4.1	
Shunt	549			Shunt in place at the end of the Norwood procedure. MBTS 268, RVPAS 281
Regional cerebral perfusion	544			Perfusion strategy unknown (5)
Yes		247		RCP alone (36), with DHCA (211)
No		297		
Duration of DHCA, min	544		31.7 ± 23.2	Subjects managed with no DHCA were included as 0 minutes
Duration of DHCA >10 min	414		40.4 ± 19.5	Duration of DHCA: DHCA alone (297) RCP with DHCA (117)
Duration of regional cerebral perfusion, min	546		23.7 ± 29.2	Subjects managed with DHCA (297) alone were included as 0 minutes.
Duration of RCP, excluding DHCA alone, min	249		51.9 ± 20.1	
Total support time, min	549		143 ± 54.1	Inclusive of CPB, DHCA, and RCP
ECMO at Norwood procedure	549	35		ECMO during Norwood procedure for failure to separate from bypass
Perioperative				
Heart block	549	13		Second- or third-degree heart block in ICU on day of Norwood procedure
Open sternum	544			Open sternum on day of Norwood procedure
Yes, routine site		244		All sternums left open at routine site
Yes, elective site		171		Elective site with selective decision to leave sternum open
No, elective site		129		Elective site with selective decision to close sternum

Candidate predictor	N	n	Mean ± SD	Definition/comment
Duration of open sternum, d	549	538	4.7 ± 6.4	Thirty-four subjects died with open sternum and date of death was used. Subjects with closed sternum were included as 0. Eleven had missing data
Operations after Norwood procedure	549	429		Subjects with additional surgical procedures (cardiac or other) after the Norwood procedure and before discharge
Volume				
Center volume	549			Patients with single RV screened per center per year
≤15		93		
16 to ≤20		109		
21 to ≤30		176		
>30		171		
Surgeon Norwood volume	549			Patients with single RV scheduled for Norwood procedure screened per surgeon per year
≤5		108		
6 to ≤10		113		
11 to ≤15		239		
>15		89		

N, Number of subjects for which the data were available; *n*, number of subjects with a predictor or number of subjects in each category; *SD*, standard deviation; *RV*, right ventricle (ventricular); *AP*, anteroposterior; *MBTS*, modified Blalock-Taussig shunt; *RVPAS*, right ventricular–pulmonary artery shunt; *RCP*, regional cerebral perfusion; *DHCA*, deep hypothermic circulatory arrest; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit.

APPENDIX TABLE 3

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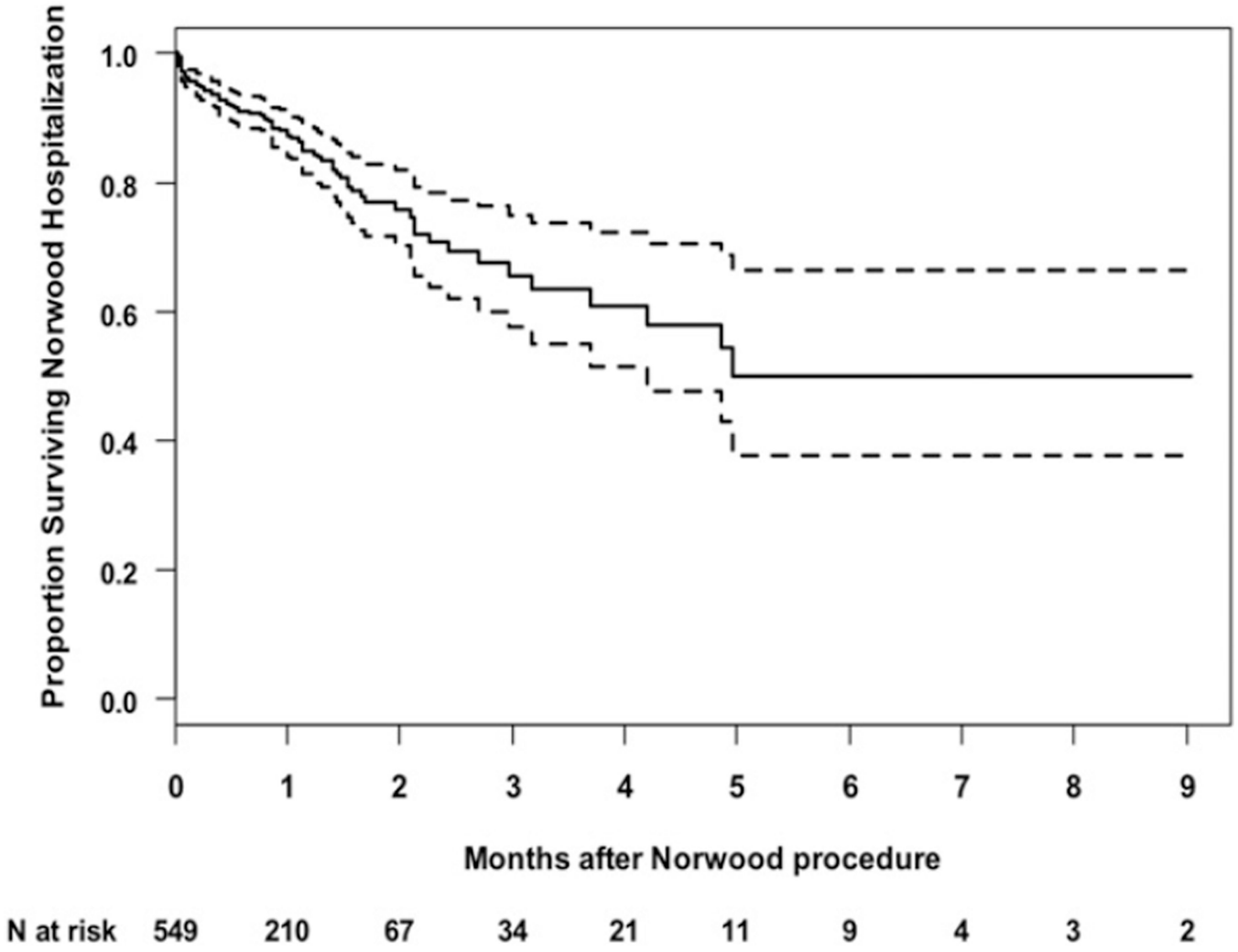

FIGURE 1.

Kaplan-Meier estimates and pointwise 95% confidence bands for hospital survival after the Norwood procedure (N = 549). Patients were censored when they were transplanted (n = 9) or discharged (n = 430).

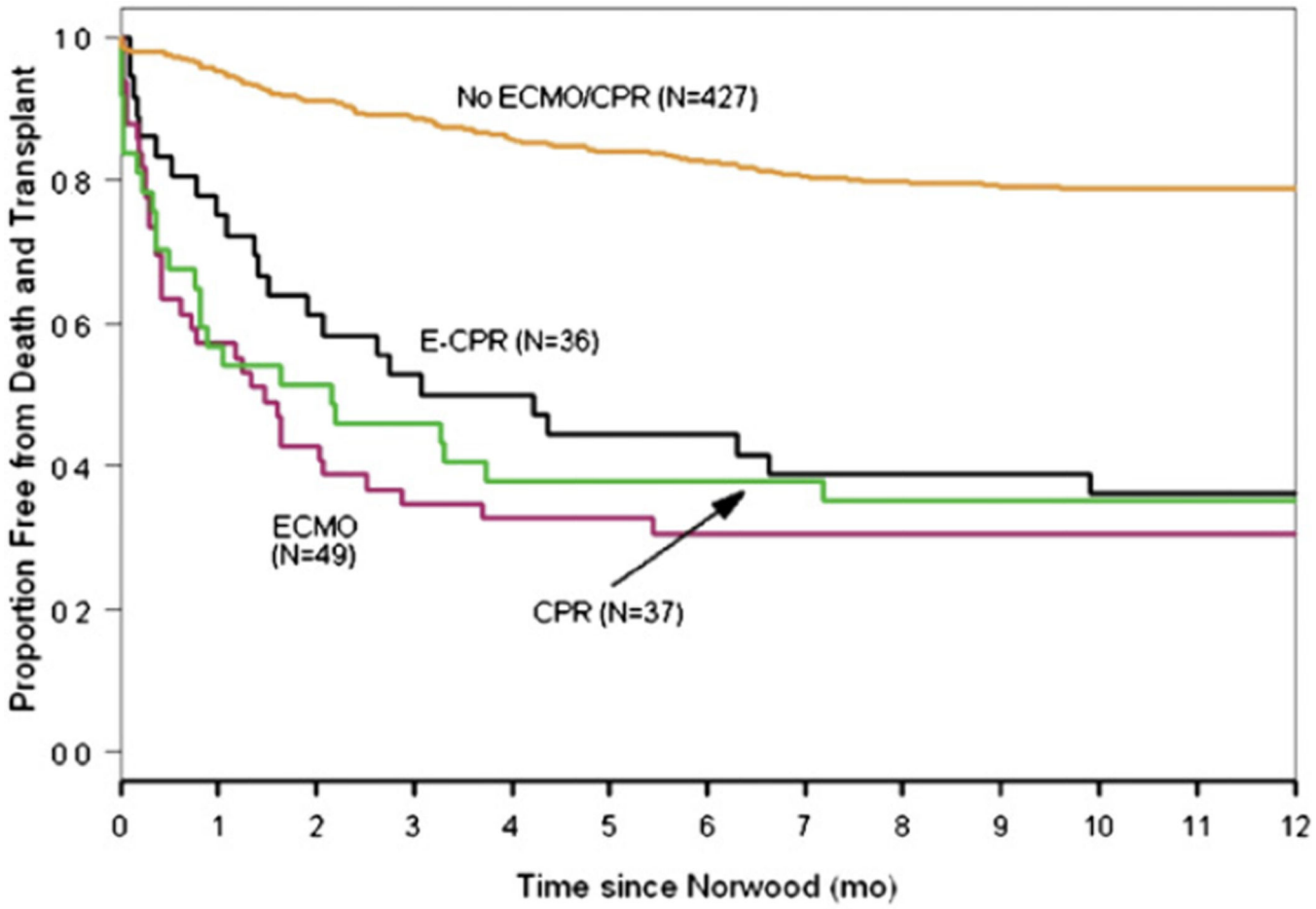

FIGURE 2.

Kaplan-Meier estimates for transplant-free survival after the Norwood procedure using all available follow-up (mean, 2.7 ± 0.9 years for survivors). Group classification is according to extracorporeal membrane oxygenation *(ECMO)*, cardiopulmonary resuscitation *(CPR)*, ECMO required to restore circulation during CPR *(E-CPR)*, and none of these interventions *(none)* within the first 30 days after the Norwood procedure.

TABLE 1

Independent risk factors for 30-day and hospital mortality after the Norwood procedure

	Thirty-day mortality			Hospital mortality			
Candidate predictor	**Odds ratio**	**95% CI**	***P***	**Hazard ratio**	**95% CI**	***P***	**Reliability**
Birth weight, kg	0.52	(0.29, 0.94)	.03	0.62	(0.41, 0.93)	.02	63%
Genetic abnormality			<.001			<.001	81%
Yes	2.93	(0.78, 10.9)		2.89	(1.21, 6.9)		
No	Ref			Ref			
Unknown	13.6	(6.23, 29.5)		6.42	(3.67, 11.2)		
DHCA duration, min	1.10	(1.03, 1.19)	.01				
ECMO at Norwood procedure	4.38	(1.76, 10.9)	.002	3.41	(1.94, 5.98)	<.001	69%
Open sternum			<.001			.002	90%
Yes, routine site	18.1	(5.17, 63.4)		5.87	(2.22,15.6)		
Yes, elective site	5.81	(1.75, 19.3)		4.25	(1.65, 10.6)		
No, elective site	Ref			Ref			

CI, Confidence interval; *DHCA*, deep hypothermic circulatory arrest; *ECMO*, extracorporeal membrane oxygenation; *Ref*, reference group.

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TABLE 2

Multivariable models for morbidity outcomes after the Norwood procedure

Outcome	No. of subjects with event	Time to event, days; median (range)	Odds ratio	95% CI	*P*
Catheter intervention (R^2 = 7%)	27	27 (2–129)			
Preoperative intubation for apnea/transport			0.23	(0.05, 0.97)	.05
Left atrial decompression			4.02	(1.19, 13.6)	.03
Regional cerebral perfusion			2.11	(1.04, 4.29)	.04
Central nervous system injury (R^2 = 4%)	38	5 (1–157)			
Genetic abnormality					.01
Yes			2.84	(1.29, 6.28)	
No			Ref		
Unknown			2.68	(1.27, 5.64)	
Renal failure (R^2 = 26%)	46	3 (1–77)			
Anomalous pulmonary venous return			10.2	(2.43, 42.4)	.002
Preoperative intubation for apnea/transport			3.46	(1.66, 7.21)	<.001
Heart block			18.8	(5.05, 70)	<.001
Open sternum					.02
Yes, routine site			7.61	(1.86, 31.2)	
Yes, elective site			6.72	(1.62, 27.9)	
No, elective site			Ref		
Surgeon Norwood volume					.006
≤5/y			0.31	(0.09, 1.09)	
6 to ≤10/y			0.90	(0.28, 2.91)	
11 to ≤15/y			0.20	(0.06, 0.61)	
>15/y			Ref		
Center volume					.02
≤15/y			1.55	(0.53, 4.58)	
16 to ≤20/y			0.44	(0.14, 1.45)	
21 to ≤15/y			0.32	(0.11, 0.91)	
>30/y			Ref		
Sepsis (R^2 = 16%)	93	19 (1–133)			

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Outcome	No. of subjects with event	Time to event, days; median (range)	Odds ratio	95% CI	*P*
Gestational age, wk			0.79	(0.68, 0.92)	.002
AS/MS/VSD			3.81	(1.05, 13.9)	.04
Duration of DHCA, min			1.07	(1.004, 1.13)	.04
Open sternum duration, d			1.08	(1.05, 1.12)	<.001
Center volume					.003
≤15/y			2.28	(1.17, 4.47)	
16 to ≤20/y			0.94	(0.40, 2.19)	
21 to ≤30/y			0.64	(0.33, 1.26)	
>30/y			Ref		
ECMO after Norwood procedure (R^2 = 40%)	56	2 (1–149)			
Birth weight <2.5 kg					.04
Yes			2.38	(1.04, 5.44)	
No			Ref		
Age at Norwood procedure, d			0.87	(0.78, 0.98)	.02
Operations after Norwood procedure			2.23	(1.84, 2.69)	<.01
CPR (R^2 = 25%)	97	5 (1–149)			
Birth weight, kg			0.54	(0.34, 0.85)	.008
Genetic abnormality					<.001
Yes			0.32	(0.17, 0.62)	
No			0.28	(0.16, 0.49)	
Unknown			Ref		
Shunt					.005
MBTS			2.02	(1.23, 3.32)	
RVPAS			Ref		
Operations after Norwood procedure			1.51	(1.32, 1.73)	<.001
TR (≥2.5 mm) (R^2 = 11%)	112	NA			
TR (≥2.5 mm) preoperative			2.92	(1.55, 5.49)	.001
Open sternum					.003
Yes, routine site			2.11	(1.12, 3.96)	
Yes, elective site			3.21	(1.66, 6.23)	
No, elective site			Ref		

Outcome	No. of subjects with event	Time to event, days; median (range)	Odds ratio	95% CI	*P*
Heart block			5.29	(1.41, 19.85)	.01

Outcome	N	Median (range)	Slope or mean diff	Adjusted mean	*P*
Fractional area change, % (R^2 = 13%)	452	36 (12–63)			
Fractional area change preoperatively, %			0.23		<.001
Shunt					<.001
MBTS			−3.59	32.2	
RVPAS				35.8	
ECMO at Norwood procedure					.007
Yes			−5.34	31.4	
No				36.7	
Log time to first extubation, d (R^2 = 59%)	447	5.1 (0.6–109)			
Gestational age, wk			−0.06		<.001
Left atrial decompression					.01
Yes			0.46	5.50	
No			Ref	5.04	
TR (≥2.5 mm) preoperatively					.03
Yes			0.15	5.34	
No			Ref	5.20	
Duration of regional cerebral perfusion, min			−0.0002		.04
ECMO at Norwood procedure					.001
Yes			0.50	5.52	
No			Ref	5.02	
Open sternum					<.001
Yes, routine site			0.55	5.49	
Yes, elective site			0.45	5.38	
No, elective site			Ref	4.93	
Duration of open sternum, d			0.02		.03
Operations after Norwood procedure			0.15		<.001
Center volume					<.001
≤15/y			−0.06	5.09	

Outcome	N	Median (range)	Slope or mean diff	Adjusted mean	*P*
16 to ≤20/y			0.31	5.46	
21 to ≤30/y			0.21	5.36	
>30/y			Ref	5.15	
Surgeon Norwood volume					<.001
≤5/y			0.54	5.44	
6 to ≤10/y			0.54	5.44	
11 to ≤15/y			0.40	5.30	
>16/y			Ref	4.90	
Log, length of ventilation, d (R^2 = 59%)	447	7 (1–270)			
Gestational age, wk			−0.06		<.001
Genetic abnormality					<.001
Yes			0.44	2.82	
No			Ref	2.55	
Unknown			0.16	2.38	
Preoperative intubation for any reason					.001
Yes			0.19	2.68	
No			Ref	2.49	
Left atrial decompression					.02
Yes			0.49	2.83	
No			Ref	2.34	
Preoperative shock					.02
Yes			0.27	2.72	
No			Ref	2.45	
TR (≥2.5 mm) preoperatively					.004
Yes			0.24	2.70	
No			Ref	2.47	
Age at Norwood procedure, d			−0.02		.02
Open sternum					.006
Yes, routine site			0.25	2.69	
Yes, elective site			0.20	2.63	
No, elective site			Ref	2.43	
Operations after Norwood procedure			0.34		<.001

Outcome	N	Median (range)	Slope or mean diff	Adjusted mean	*P*
Center volume					.005
≤15/y			0.004	2.49	
16 to ≤20/y			0.26	2.75	
21 to ≤30/y			0.12	2.61	
>30/y			Ref	2.49	
Surgeon Norwood volume					.008
≤5/y			0.33	2.71	
6 to ≤10/y			0.27	2.65	
11 to ≤15/y			0.21	2.59	
>16/y			Ref	2.38	
Log, hospital length of stay, d (R^2 = 49%)	452	24 (6–270)			
Birth weight, kg			−0.01		.03
Genetic abnormality					.007
Yes			0.33	3.78	
No			Ref	3.44	
Unknown			0.06	3.5	
Preoperative intubation for shock					.009
Yes			0.15	3.66	
No			Ref	3.5	
TR (≥2.5 mm) preoperative					.04
Yes			0.15	3.65	
No			Ref	3.5	
Duration of DHCA, min					.003
≤45 min			−0.017	3.49	
>45 min			Ref	3.66	
Operations after Norwood procedure			0.27		<.001
Center volume					<.001
≤15/y			0.16	3.62	
16 to ≤20/y			0.34	3.8	
21 to ≤30/y			−0.03	3.43	
>30/y			Ref	3.46	

CI, Confidence interval; *Ref*, reference group; *AS/MS/VSD*, aortic stenosis, mitral stenosis, ventricular septal defect; *DHCA*, deep hypothermic circulatory arrest; *ECMO*, extracorporeal membrane oxygenation; *CPR*, cardiopulmonary resuscitation; *MBTS*, modified Blalock-Taussig; *RVPAS*, right ventricle–pulmonary artery shunt; *TR*, tricuspid regurgitation; *NA*, not available; *Diff*, difference.

TABLE 3

Baseline characteristics of subjects requiring ECMO, CPR, E-CPR, or neither interventions (none) within the first 30 days after Norwood procedure

Variable	CPR (37)	ECMO (49)	E-CPR (36)	None (427)	*P*
Birth weight, kg	2.89 ± .7	3.12 ± .6	2.95 ± .6	3.13 ± .5	.09
Birth weight <2.5 kg	10 (27%)	9 (18%)	11 (31%)	46 (11%)	<.001
Gestational age, wk	37.6 ± 2.1	38.2 ± 1.7	37.9 ± 1.5	38.2 ± 1.6	.20
Age at Norwood procedure, d	6.2 ± 3.6	5.0 ± 3.0	4.8 ± 2.8	5.9 ± 4.3	.11
Ascending aorta, mm*	3.1 ± 1.4	2.8 ± 1.5	2.9 ± 1.8	3.2 ± 1.8	.27
TR ≥2.5 mm, preoperative%†	3 (9%)	3(6%)	4 (13%)	25 (6%)	.47
Fractional area change, preoperative, %‡	49 ± 11	46 ± 8	47 ± 8	46 ± 9	.34
Incidence of event within shunt type					
MBTS (268)	23 (9%)	27 (10%)	22 (8%)	196 (73%)	
RVPAS (281)	14 (5%)	22 (8%)	14 (5%)	231 (82%)	
P	.13	.37	.17		

ECMO, Extracorporeal membrane oxygenation; *CPR*, cardiopulmonary resuscitation; *E-CPR*, ECMO required to restore circulation during CPR; *TR*, tricuspid regurgitation; *MBTS*, modified Blalock Taussig shunt; *RVPAS*, right ventricular to pulmonary artery shunt.

*Ascending aorta size by surgeon observation.

†Sample sizes for TR are CPR, 31; ECMO, 48; E-CPR, 35; None, 392.

‡Sample sizes for fractional area change are CPR, 30; ECMO, 45; E-CPR, 34; None, 394.

TABLE 4

Association of shunt type with transplant-free survival within the 4 groups: CPR, ECMO, E-CPR and neither intervention (none)

	Hazard ratio	95% CI	*P*	Interaction *P**
Without adjustment				
MBTS vs RVPAS				
CPR	1.28	(0.89, 1.84)	.94	.48
ECMO	0.82	(0.43, 1.58)	.55	.15
E-CPR	0.62	(0.28, 1.36)	.23	.06
None	1.42	(0.98, 2.06)	.07	
Adjustment for birth weight and surgeon				
MBTS vs RVPAS				
CPR	1.3	(0.54, 3.16)	.56	.74
ECMO	0.67	(0.33, 1.36)	.26	.05
E-CPR	0.48	(0.21, 1.11)	.09	.01
None	1.54	(1.04, 2.28)	.03	

ECMO, Extracorporeal membrane oxygenation; *CPR*, cardiopulmonary resuscitation; *E-CPR*, ECMO required to restore circulation during CPR; *CI*, confidence interval; *MBTS*, modified Blalock-Taussig shunt; *RVPAS*, right ventricle–pulmonary artery shunt.

* *P* value from test of interaction of shunt type and therapy group versus none.