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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Risk Factors for Death or Transplant After Stage 2 Palliation for Single Ventricle Heart Disease

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ABSTRACT

BACKGROUND For infants with single ventricle heart disease, the time after stage 2 procedure (S2P) is believed to be a lower risk period compared with the interstage period; however, significant morbidity and mortality still occur.

OBJECTIVES This study aimed to identify risk factors for mortality or transplantation referral between S2P surgery and the first birthday.

METHODS Retrospective cohort analysis of infants in the National Pediatric Cardiology Quality Improvement Collaborative who underwent staged single ventricle palliation from 2016 to 2022 and survived to S2P. Multivariable logistic regression and classification and regression trees were performed to identify risk factors for mortality and transplantation referral after S2P.

RESULTS Of the 1,455 patients in the cohort who survived to S2P, 5.2% died and 2.3% were referred for transplant. Overall event rates at 30 and 100 days after S2P were 2% and 5%, respectively. Independent risk factors for mortality and transplantation referral included the presence of a known genetic syndrome, shunt type at stage 1 procedure (S1P), tricuspid valve repair at S1P, longer time to extubation and reintubation after S1P, ≥ moderate tricuspid regurgitation prior to S2P, younger age at S2P, and the risk groups identified in the classification and regression tree analysis (extracorporeal membrane oxygenation after S1P and longer S2P cardiopulmonary bypass time without extracorporeal membrane oxygenation).

CONCLUSIONS Mortality and transplantation referral rates after S2P to 1 year of age remain high ~7%. Many of the identified risk factors after S2P are similar to those established for interstage factors around the S1P, whereas others may be unique to the period after S2P. (JACC Adv 2024;3:100934) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CART = classification and regression trees

CPB = cardiopulmonary bypass

ECMO = extracorporeal membrane oxygenation

mBTTS = modified Blalock-Taussig-Thomas shunt

NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative

RVPAS = right ventricle-to-pulmonary artery shunt

S1P = stage 1 procedure

S2P = stage 2 procedure

SVHD = single ventricle heart disease

TR = tricuspid regurgitation

Infants born with single ventricle heart disease (SVHD) have the highest morbidity and mortality of all patients with congenital heart disease.[1,2] Staged palliation for these children usually consists of the Stage 1 procedure (S1P) at the time of birth, a superior cavopulmonary anastomosis (Stage 2 or Glenn procedure [S2P]) at 4 to 6 months of age, and a Fontan procedure at 2 to 4 years of age. Although recent improvements in surgical technique and perioperative care have led to dramatic reductions in interstage mortality between S1P and S2P, few survival gains have been observed after S2P.[3-7] Between the Single Ventricle Reconstruction trial (2005-2008) to the present-day National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) registry, rates of interstage mortality and transplantation fell from 27% to 9%.[7-9] In contrast, mortality and transplantation rates after S2P through the first year of life have remained stagnant at ~7% suggesting an opportunity for improvement.

Most research to-date has focused on characterizing risk factors for mortality during the interstage period.[4,8-13] For example, the NEONATE score was developed using data from the NPC-QIC registry to identify patients who are at highest risk of mortality or transplantation during the interstage period,[9] and similar analyses have been conducted using data from the Single Ventricle Reconstruction trial.[4] In contrast, little is known about risk factors for adverse outcomes after S2P when there are significant changes in cardiovascular anatomy and physiology.[14]

Accordingly, the aims of this study were to characterize mortality and referral for transplantation after S2P up to 1 year of age and to identify risk factors during this period. Using data from a large

TABLE 1 Sociodemographic and Anatomic Characteristics of the Sample

	Total Cohort (N = 1,455)	Death or Transplant (n = 110)	Event-Free at First Birthday (n = 1,345)	*P* Value
Gestational age, y	39.0 (38.0-39.3)	39.0 (37.7-39.2)	39.0 (38.0-39.3)	0.05
Birth weight, kg	3.2 ± 0.5	3.1 ± 0.5	3.2 ± 0.5	0.28
Female, %	37.7	38.2	37.7	0.92
Race, %				**0.036**
White	68.2	63.6	68.6	
Black	15.1	10.9	15.4	
Other	16.8	25.5	16.1	
Hispanic ethnicity, %	14.7	18.2	14.4	0.29
Child Opportunity Index				
Overall	49.2 ± 27.4	46.9 ± 28.5	49.4 ± 27.3	0.58
Education subscore	48.1 ± 27.0	46.7 ± 26.5	48.2 ± 27.1	0.45
Health subscore	49.1 ± 28.3	47.1 ± 29.1	49.3 ± 28.3	0.38
Social/economic subscore	49.9 ± 27.9	47.7 ± 29.3	50.1 ± 27.8	0.36
Insurance status, %				0.37
Government	50.2	58.7	49.6	
Commercial	45.1	38.5	45.6	
Non-U.S. (Canada and UK)	0.6	1.0	0.5	
None/self	1.3	1.0	1.3	
Unknown	2.8	1.0	3.0	
Fetal diagnosis, %	86.7	86.5	86.8	0.90
Anatomic diagnosis, %				0.55
HLHS	72.7	73.6	72.6	
Single ventricle[a]	16.6	12.7	17.0	
Unbalanced AV canal	5.2	6.4	5.1	
Other	5.5	7.3	5.4	
Major extracardiac anomalies[b] %	5.2	9.1	4.8	0.056
Genetic syndrome, %[c]	8.7	14.5	8.3	**0.027**

Values are median (IQR), mean ± SD, or %. [a]Single ventricle diagnoses include double inlet left ventricle, single double outlet right ventricle, mitral atresia, and tricuspid atresia. [b]Extracardiac anomalies include major abnormalities of the brain, gastrointestinal system, genitourinary tract, upper and lower respiratory tracts, lungs, and spine. [c]Genetic anomalies include 22q11 microdeletion syndrome (DiGeorge), CHARGE association, heterotaxy syndrome, Turner syndrome, Jacobsen syndrome, VACTERL syndrome, and others (free text).

AV = atrioventricular; HLHS = hypoplastic left heart syndrome.

multicenter registry of infants with SVHD, we investigated a broad range of potential risk factors including sociodemographic, birth, anatomic, physiologic, growth and nutrition, surgical, and postoperative characteristics. Understanding which patients are at greatest risk for adverse outcomes after S2P may lead to targets for quality improvement efforts and allow physicians to better risk stratify patients after S2P.

METHODS

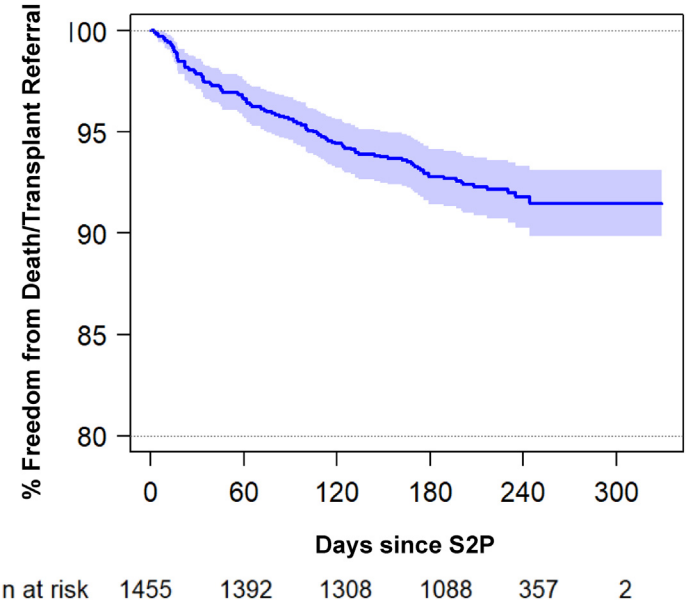
STUDY SAMPLE. We used data from the NPC-QIC phase II registry for patients born between January 2016 and January 2022. Details of the NPC-QIC registry have been previously published.[5] In brief, the NPC-QIC is an international learning collaborative of 69 surgical sites across the United States, Canada, and the United Kingdom which aims to reduce mortality and improve quality of life for infants with SVHD. The registry includes neonates diagnosed with SVHD and aortic arch obstruction who require a S1P. It represents an extensive database that includes deidentified demographic data, procedural and postoperative data from the S1P and S2P hospitalizations, outpatient visits, and hospital readmissions up to 1 year of age. Data are abstracted from patient charts by participating centers and entered into a secured Research Electronic Data Capture (REDCap, Nashville, Tennessee). Participating centers have all received local Institutional Review Board approval, and parental consent is obtained for participation in the NPC-QIC database.

For this analysis, we included all infants who underwent S2P. We excluded patients who were lost to follow-up or withdrew before 1 year of age (n = 35), patients who were switched to a biventricular conversion strategy (n = 1), patients who underwent delayed S2P at >14 months (n = 5), and patients for whom we lacked any follow-up information after S2P (n = 244). Primary insurance type differed between patients who were included (n = 1455) versus excluded (n = 285) from the analytic cohort with a higher percentage of excluded patients insured by government insurance (P = 0.011) (Supplemental Table 1). Other demographic and anatomic characteristics did not differ between included and excluded patients.

STUDY DESIGN AND STATISTICAL ANALYSIS. The primary outcome was a composite endpoint of death or transplantation referral after S2P up to 1 year of age. Causes of death were summarized. In the NPC-QIC database, patients who are listed for transplantation are considered "transplantation referrals," with the date of listing corresponding to the date of exit from the database. To identify potential risk factors for mortality and transplantation referral, we compared sociodemographic and clinical characteristics by death/transplantation referral status using chi-square tests for categorical variables and Student's t-test or Mann Whitney U tests for continuous variables. Candidate variables are listed in Supplemental Table 2 and included 88 variables collected from the time of birth through S2P. Socioeconomic status was defined using the Child Opportunity Index, which is zip code level measure of child-specific resources available within a community. Higher scores indicate greater opportunity. When continuous variables were not normally distributed, they were also evaluated as categorical variables using either established cutoff values or tertiles. A 2-tailed P value <0.05 was considered statistically significant.

To identify important interactions between candidate variables that may not have been appreciated in advance, we performed a classification and regression tree (CART) analysis. CART identifies the variables most strongly associated with a particular outcome and identifies variable splits or branches within these variables that may be considered as interaction terms in multivariable regression models. All candidate variables were included in the CART analysis

FIGURE 1 Freedom From Death or Transplantation Since Stage 2 Procedure



Kaplan-Meier curve illustrating freedom from death or transplantation referral by time (days) since the Stage 2 procedure for the full cohort. S2P = stage 2 procedure.

TABLE 2 Comparison of Stage 1 Preoperative, Perioperative, and Postoperative Characteristics by Composite Outcome

	Total Cohort (N = 1,455)	Death or Transplant (n = 110)	Event-Free at First Birthday (n = 1,345)	*P* Value
Pre-S1P clinical course				
Born at stage 1 site, %	58.2	56.4	58.4	0.68
S1P delayed, %	9.7	7.3	9.9	0.38
Pre-S1P adverse events,[a] %	43.4	52.7	42.7	**0.042**
Pre-S1P pulmonary artery band, %	8.6	15.5	8.1	**0.009**
Pre-S1P catheterization, %	9.3	14.7	8.8	**0.046**
S1P operative characteristics				
Age at S1P (days)	9.3 ± 14.9	9.5 ± 14.2	9.3 ± 15.0	0.88
Weight at procedure (kg)	3.3 ± 0.6	3.2 ± 0.6	3.3 ± 0.6	0.19
Type of S1P, %				**0.003**
BTT shunt	27.3	19.1	28.0	
RVPA shunt	57.4	60.9	57.1	
Hybrid	6.2	13.6	5.6	
Other	9.1	6.4	9.4	
Additional cardiac procedures, %	19.7	23.6	19.3	0.28
Tricuspid valve repair, %	2.5	6.4	2.2	**0.012**
Pulmonary vein repair, %	0.8	1.8	0.7	0.20
Other repair, %	15.6	16.3	15.5	0.82
CPB time (min)	152 (122-189)	152 (127-192)	152 (122-189)	0.63
Cerebral perfusion, %	58.4	50.9	59.0	0.10
Cerebral perfusion time (min)	64.6 ± 27.1	66.2 ± 32.1	64.5 ± 26.8	0.66
Circulatory arrest, %	63.4	55.5	64.1	0.072
Circulatory arrest time (min)	22.7 ± 23.1	22.6 ± 31.1	22.7 ± 22.5	0.97
Cross clamp, %	87.2	84.5	87.4	0.38
Cross clamp time (min)	71.0 ± 31.8	74.9 ± 27.8	70.6 ± 32.1	0.22
Circulatory bypass, %	6.5	9.1	6.3	0.26
Intraoperative ECMO, %	3.0	6.4	2.8	**0.039**

Continued on the next page

modeling the presence or absence of the composite outcome. To avoid overfitting, the CART was pruned using a complexity parameter threshold of 0.012.

Multivariable Cox proportional hazards regression was performed to determine factors associated with death or transplantation referral after S2P. All univariate variables and interactions identified by CART were included as candidate variables for the multivariable analysis except for S1P discharge variables because they were not applicable to patients who remain in the hospital between S1P and S2P. Models were built using stepwise selection with a significance level of 0.15 for entry into the model and a significance level of 0.05 for retention. In cases of missing covariate data, mean imputation was used for continuous variables when the degree of missingness <5%, and an unknown category was created for categorical variables.

Because patients who remain inpatient during the interstage period represent a particularly high-risk group, we performed a separate subgroup analysis of these patients. All analyses were performed using SAS, version 9.4 (SAS Institute) and R, version 3.4.2 (R Foundation for Statistical Computing).

RESULTS

Of the 1,455 patients included in the study sample, 38% were female, 15% were of Hispanic ethnicity, 68% were White, 15% were Black, and 17% identified as a different race (Table 1). The majority of patients were diagnosed prenatally (87%), and most patients (72%) had an anatomic diagnosis of hypoplastic left heart syndrome. Only 5% of the sample had other extracardiac anomalies and 9% had a known genetic syndrome.

There were 76 deaths and 34 transplant referrals during follow-up. Overall mortality or transplantation referral was 7.5% between the time of the S2P and the first birthday. Median follow-up among event-free patients was 220 (IQR: 189-241) days and among those who died or were referred for transplantation was 71 (IQR: 25-125) days. Overall event rates at 30 and 100 days after stage 2 were 2% and 5%, respectively (Figure 1). Causes for the 76 deaths are listed in Supplemental Table 3 with low cardiac output and multi-organ system failure being the most common (18% and 17%, respectively).

TABLE 2 Continued

	Total Cohort (N = 1,455)	Death or Transplant (n = 110)	Event-Free at First Birthday (n = 1,345)	*P* Value
Post-S1P clinical course				
Days to initial extubation	7.7 ± 11.3	11.5 ± 11.2	7.4 ± 11.2	0.006
Reintubation, %	13.3	24.8	12.4	**<0.001**
Any post-S1P ECMO, %	9.2	26.6	7.8	**<0.001**
Delayed sternal closure, %	71.9	73.6	71.7	0.67
Post-S1P complication overall, %	69.2	81.8	68.2	**0.003**
Arrhythmia	1.0	0.9	1.0	0.95
Necrotizing enterocolitis	0.1	0	0.1	0.78
Neurologic deficit or stroke	0.3	2.7	0.1	**<0.001**
Diaphragm paresis	3.6	6.4	3.3	0.10
Pleural effusion	8.7	14.5	8.3	**0.025**
Pneumonia	1.6	7.3	1.1	**<0.001**
Pneumothorax	3.0	7.3	2.7	**0.007**
Seizure	6.3	14.5	5.7	**<0.001**
Sepsis	6.3	15.5	5.6	**<0.001**
Vocal cord dysfunction	16.6	17.3	16.5	0.84
Wound infection	6.3	9.1	6.0	0.20
Post-S1P cardiac arrest, %	7.9	19.6	6.9	**<0.001**
Post-S1P arrhythmia, %	33.4	39.1	32.9	0.19
Post-S1P catheterization, %	25.8	46.4	24.2	**<0.001**
Post-S1P reoperation, %	17.6	29.1	16.7	**0.001**
Other post-S1P procedure,[b] %	49.1	60.0	48.2	**0.018**
G-tube placement	20.3	19.1	20.4	0.81
Tracheostomy	1.0	2.7	0.9	0.098
Off inotropes/vasoactives in ≤5 days, %	31.0	20.0	31.9	**0.011**
S1P discharge characteristics				
S1P disposition, %				**<0.001**
Discharged	85.6	61.8	87.6	
Transferred	1.1	0.9	1.1	
Remained inpatient until S2P	13.3	37.3	11.3	
Age at discharge (days)	46.2 ± 28.9	54.5 ± 31.0	45.8 ± 28.8	**0.018**
Weight at discharge (kg)	3.8 ± 0.7	3.9 ± 0.8	3.8 ± 0.7	0.10
Length at discharge (cm)	52.3 ± 4.1	52.2 ± 4.6	52.4 ± 4.0	0.79
O2 saturation, %	82.6 ± 5.1	83.4 ± 5.2	82.6 ± 5.1	0.21
Route of nutrition, % (not exclusive)				
G/GJ tube	19.0	17.3	19.1	0.64
NG/NJ tube	36.0	30.9	36.4	0.25
Oral (breast)	13.8	6.4	14.4	**0.023**
Oral (bottle)	59.2	32.7	61.4	**<0.001**
Oral feeding (breast or bottle) %	72.5	53.6	73.6	**<0.001**
Type of nutrition, %				0.25
Breast milk	10.0	5.8	10.2	
Formula	35.3	43.5	34.8	
Combination	54.8	50.7	55.0	
Home monitoring program, %	98.7	98.5	98.7	0.88

Values are %, mean ± SD, or median (IQR). [a]Pre-S1P adverse events included arterial pH <7.2, creatinine >2, inotrope infusion at the time of surgery, lactate >3, mechanical ventilation to treat cardiorespiratory failure, necrotizing enterocolitis requiring medical or surgical treatment, preoperative neurological deficit, preoperative circulatory support, seizure, sepsis, shock, and need for tracheostomy. [b]Other post-S1P procedures included bedside laryngoscopy, bronchoscopy, cardioversion, dialysis, diaphragm plication, fundoplication, G-tube placement, pericardiocentesis, thoracic duct ligation, and tracheostomy.

BTT = Blalock-Taussig-Thomas; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; GJ = gastrostomy-jejunostomy; IQR = interquartile range; NG = nasogastric; NJ = nasojejunal; RVPA = right ventricle-to-pulmonary artery; S1P = stage 1 procedure; S2P = stage 2 procedure; SD = standard deviation.

Bivariate associations between patient socio-demographic, anatomic, S1P and S2P characteristics with death or transplant referral status are provided in Tables 1 to 3. A greater percentage of patients who died or were referred for transplantation had a known genetic syndrome (15% vs 8%, $P = 0.027$), and more of these patients identified as being of a race other than White or Black (26% vs 16%, $P = 0.036$) (Table 1).

Prior to S1P, there was a higher rate of adverse events (53% vs 43%, $P = 0.042$), pulmonary artery banding procedures (16% vs 8%, $P = 0.009$), and preoperative catheterization procedures (15% vs 9%, $P = 0.046$) among patients who died or were referred for transplantation compared to those who survived event free (**Table 2**). More patients who died or were referred for transplantation underwent hybrid initial palliation procedures (14% vs 6%, $P = 0.003$). Patients with a known genetic syndrome were more likely to undergo a hybrid procedure (10.2% vs 5.8%, $P = 0.011$), required tricuspid valve repair during S1P (6% vs 2%, $P = 0.012$), and required extracorporeal membrane oxygenation (ECMO) postoperatively (27% vs 8%, $P < 0.001$) compared with those who survived without transplantation. Rates of S1P postoperative complications (82% vs 68%, $P = 0.003$), cardiac arrest (20% vs 7%, $P < 0.001$), reintubation (24% vs 8%, $P < 0.001$), catheterization (46% vs 24%, $P = 0.001$), and reoperation (29% vs 17%, $P = 0.001$) were also higher in those who died or were referred for transplantation compared with those who did not. Specifically, children who died or were referred for transplantation had higher rates of neurologic deficits or stroke, pleural effusions, pneumonia, pneumothorax, seizures, and sepsis after S1P (**Table 2**).

Approximately 37% of patients who ultimately died or were referred for transplantation after S1P remained inpatient during the interstage period compared with only 11% of those who survived without transplant ($P < 0.001$) (**Table 2**). At the time of discharge from the S1P, oral feeding (breast or bottle) was more prevalent in children who survived after S2P without transplantation than those who did not (74% vs 54%, $P < 0.001$).

Although most children were readmitted during the interstage period, readmissions were more common in children who survived event free compared with those who did not (72% vs 58%, $P = 0.002$) (**Table 3**). Growth parameters prior to S2P including weight and length were higher, on average, in survivors compared with those who died or were referred for transplantation. More children who died or were referred for transplantation had ≥ moderate right ventricular dysfunction (10% vs 3%, $P = 0.002$) and ≥ moderate tricuspid regurgitation (TR) (29% vs 16%, $P = 0.002$) prior to S2P compared with those who survived transplant free. Only 2 children underwent tricuspid valve repair at the time of S2P. Longer S2P cardiopulmonary bypass (CPB) and cross clamp times were associated with the composite outcome in bivariate comparisons ($P < 0.001$ and $P = 0.023$, respectively).

A CART analysis was also performed to identify potential interactions among variables that define particularly high- or low-risk subgroups that should be considered in the development of a multivariable model for death/transplantation referral (**Figure 2**). The CART identified a potential interaction between receipt of ECMO after S1P and the S2P CPB time ≤ or >2.6 hours. This finding suggests that longer CPB times (>2.6 hours) were associated with the primary outcome only among infants who did not require ECMO after S1P.

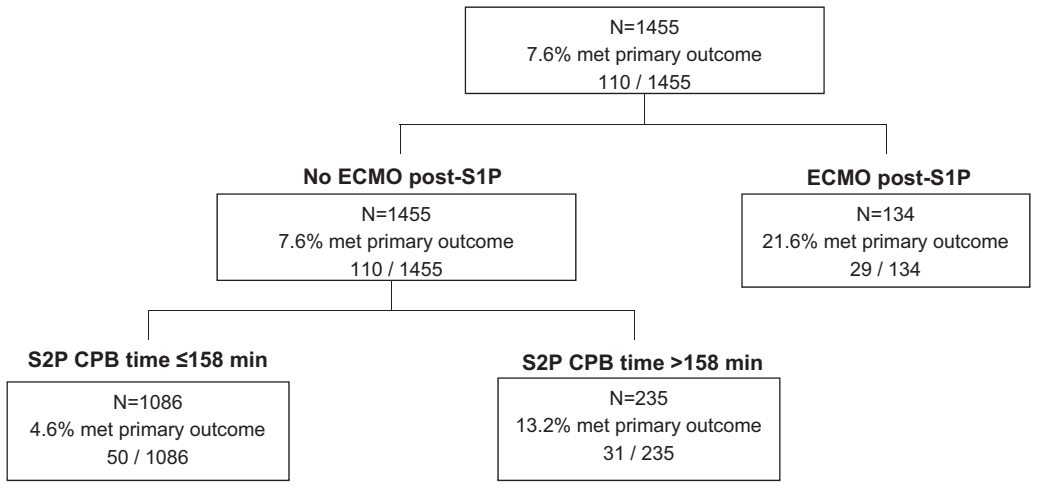
The results of the multivariable Cox proportional hazards regression model are shown in **Figure 3**. Factors independently associated with death or transplantation referral after S2P to the first birthday were the presence of a known genetic syndrome, type of S1P, tricuspid valve repair at S1P, longer time (days) to initial extubation after S1P, reintubation after S1P, ≥ moderate TR prior to S2P, younger age at S2P (≤130 days old), and the risk groups identified in the CART analysis (ECMO after S1P and longer S2P CPB time without ECMO after S1P). The factors most strongly associated with death or transplantation referral were the receipt of ECMO after S1P (HR: 4.42 [95% CI: 2.61-7.49]) and initial hybrid approach during S1P (HR: 4.02 [95% CI: 1.87-8.61]). The Harrell's C-index for the model was 0.75. Notably, neither patient race nor Childhood Opportunity Index were independently associated with mortality or transplantation referral.

In subgroup analyses, patients who remained inpatient during the interstage period (n = 193) were more likely to have a genetic syndrome (13.5% vs 8.0%, $P = 0.012$) or major extracardiac anomalies (10.4% vs 4.0%, $P < 0.001$) and were more likely to experience adverse events before the S1P (55.4% vs 41.5%, $P < 0.001$). These patients were also more likely to require additional cardiac procedures during S1P (28.5% vs 18.4%, $P = 0.001$) and to experience complications after the S1P (89.6% vs 66.1%, $P < 0.001$). Within this subgroup, patients who died or were referred for transplantation (n = 41, 21%) were more likely to have a genetic syndrome (29.3% vs 9.2%, $P = 0.003$) and were more likely to have a hybrid procedure or right ventricle-to-pulmonary artery shunt (RVPAS) rather than a modified Blalock-Taussig-Thomas shunt (mBTTS) ($P = 0.043$) (Supplemental Table 4).

DISCUSSION

Using data from the largest longitudinal international registry of infant patients with SVHD, we found that mortality and transplantation referral rates after the

FIGURE 2 CART Analysis



Results of CART analysis demonstrating an interaction between receipt of ECMO During Stage 1 procedure and longer durations of cardiopulmonary bypass during Stage 2 procedure. CART = classification and regression trees; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; S1P = stage 1 procedure; S2P = stage 2 procedure.

S2P to 1 year of age remain high at ~7% with approximately one-third of deaths occurring in the first 30 days after the S2P. We identified factors associated with mortality or transplantation referral during this period which included both S1P and S2P risk factors. The variables most strongly associated with mortality or transplantation referral were undergoing a hybrid procedure at S1P (HR: 4.0, 95% CI: 1.9-8.6) and requiring ECMO after S1P (HR: 4.4, 95% CI: 2.6-7.5). Other variables independently associated with death or transplantation referral after S2P included the presence of a known genetic syndrome, having undergone a hybrid procedure or RVPAS at the time of S1P rather than a mBTTS, tricuspid valve repair at S1P, days to initial extubation and need for reintubation after S1P, ≥ moderate TR prior to S2P, younger age at S2P, and longer S2P CPB time (**Central Illustration**).

Many of the risk factors for mortality and transplantation referral after S2P identified in this analysis overlap with those previously identified to be risk factors during the interstage period. Specifically, using data from the NPC-QIC, Ahmed et al found that S1P type, postoperative ECMO, and ≥ moderate TR were risk factors for poor clinical outcomes during the interstage period.[9] Over the longer term, Newburger et al identified obstructed pulmonary venous drainage, the presence of a genetic syndrome, ≥ moderate TR prior to S1P, open sternum after S1P, use of ECMO during S1P, annual surgeon S1P volume, and lower birthweight as predictors of 3-year mortality and transplantation;[14] however, this study only investigated factors prior to and during the S1P and did not consider post-S1P course or S2P characteristics. Unlike our study, other studies have also identified sociodemographic characteristics such as Hispanic ethnicity and lower neighborhood socioeconomic status as predictors of short-term mortality and transplantation.[4,15-17] These differences may be due to differences in study populations between the NPC-QIC and the Single Ventricle Reconstruction (SVR) trial or approach (eg, evaluation of transplantation and mortality as a composite outcome, evaluation of interactions using CART analysis, targeted evaluation of the period of time between S2P and first birthday). Alternatively, it may be that sociodemographic factors are more important at times of very high risk (eg, interstage period) compared to times of moderate risk (eg, post-S2P). Indeed, a separate analysis of the SVR trial demonstrated that the effect of low neighborhood socioeconomic status on the risk of mortality or transplantation was greatest in the first 30 days after the S1P.[15]

Patients who remain inpatient during the interstage period represent a particularly high-risk population with nearly a 3-fold higher risk of death/transplantation compared to those who are discharged. Nevertheless, many of the risk factors (eg, genetic syndrome and type of S1P) were predictive of death/transplantation in this cohort as in the overall cohort.

TABLE 3 Comparison of Interstage and Stage 2 Procedure Characteristics by Composite Outcome

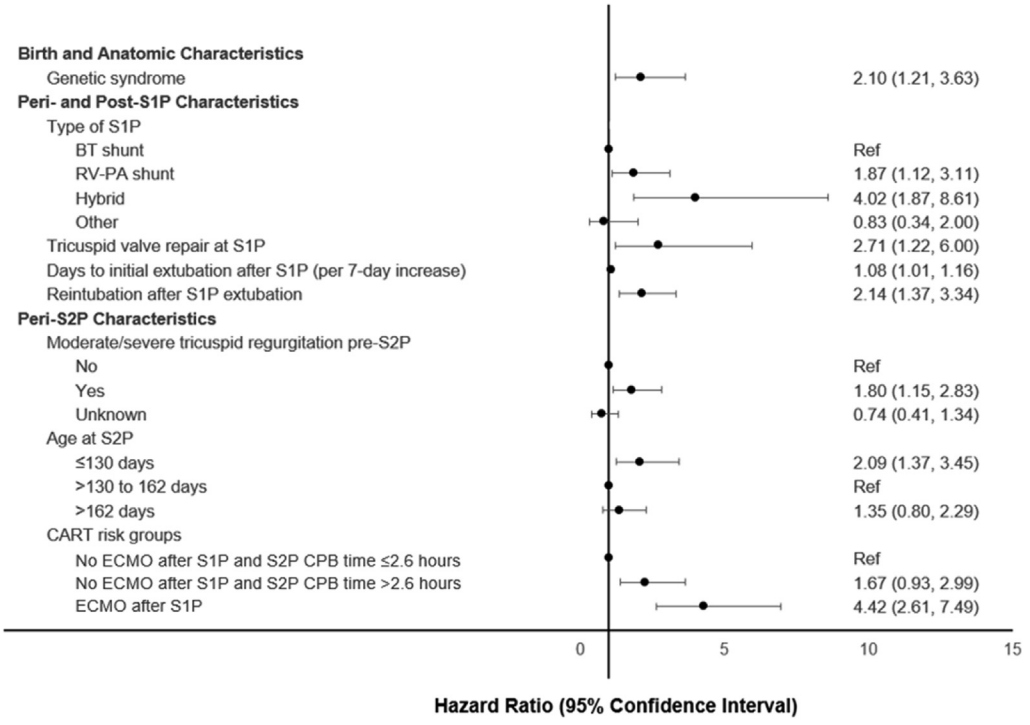
	Total Cohort (N = 1,455)	Death or Transplant (n = 110)	Event-Free at First Birthday (n = 1,345)	*P* Value
Interstage				
Readmission during interstage period, %	71.3	58.2	72.3	**0.002**
Major adverse event overall, %	3.3	4.5	3.2	0.45
Aspiration	0.6	1.8	0.5	0.14
Cardiac arrest	0.2	0.9	0.1	0.21
Infection requiring IV antibiotics	1.7	0.9	1.8	1.00
Shunt occlusion	0.5	0	0.5	1.00
Life-threatening arrhythmia requiring DC-cardioversion	0.1	0.9	0	0.076
Seizure	0.5	1.8	0.4	0.093
Stroke	0.1	0	0.1	1.00
Unanticipated catheterization, %	20.1	22.7	19.9	0.47
Cardiac operation, %	11.6	14.5	11.4	0.32
Pre-S2P characteristics				
Age at S2P (days)	145 (123-176)	140 (111-172)	145 (124-176)	0.044
S2P weight (kg)	6.1 (5.5-6.7)	5.8 (5.2-6.2)	6.1 (5.6-6.8)	**<0.001**
S2P length (cm)	62.0 (59.0-64.5)	59.5 (57.5-62.0)	62.0 (59.5-64.8)	**<0.001**
Moderate/severe RV dysfunction, %	4.0	10.3	3.4	**0.002**
Moderate/severe tricuspid valve regurgitation, %	17.4	28.9	16.3	**0.002**
Restrictive atrial communication, %	4.4	8.3	4.1	0.073
Distal aortic arch obstruction, %	4.3	2.9	4.4	0.57
S2P operative characteristics				
Type of S2P, % (not exclusive)				
Unilateral BDG	65.4	68.2	65.1	0.52
Bilateral BDG	21.5	20.0	21.6	0.69
Comprehensive S2P	5.4	10.9	5.0	0.010
Hemi-Fontan	8.0	3.6	8.3	0.090
Kawashima	1.9	0.9	1.9	0.46
Additional procedures, % (not exclusive)				
Tricuspid valve repair	0.2	0.9	0.1	0.14
Tricuspid valve replacement	0	0	0	n/a
Pulmonary vein repair	0	0	0	n/a
Other procedure	3.0	6.4	2.8	**0.04**
CPB time (min)	91 (60-133)	110 (71-176)	90 (58-130)	**<0.001**
Cerebral perfusion, %	5.8	9.1	5.6	0.14
Cerebral perfusion (min)	52.8 ± 43.2	54.2 ± 25.5	52.6 ± 45.2	0.91
Circulatory arrest, %	12.6	15.5	12.3	0.35
Circulatory arrest (min)	31.5 ± 20.1	24.5 ± 21.4	32.2 ± 19.9	0.14
Cross clamp, %	30.7	42.7	29.7	**0.005**
Cross clamp time (min)	49.4 ± 35.0	60.6 ± 43.2	48.1 ± 33.7	**0.023**

Values are %, median (IQR), or mean ± SD.
BDG = bidirectional Glenn; CPB = cardiopulmonary bypass; DC = direct current; IV = intravenous; RV = right ventricular; S2P = stage 2 procedure; SD = standard deviation.

Although several studies have reported on risk factors for interstage mortality, relatively few have characterized outcomes after S2P. In general, these studies have been retrospective reviews at single centers and have investigated a small number of patient characteristics. For example, 2 separate single center analyses reported attrition (death or transplantation) rates of 12% between S2P and Fontan surgeries and identified the presence of moderate or severe TR as being the strongest predictor of a poor outcome.[18,19] The present analysis adds to this literature by expanding the list of candidate variables to include both S1P and S2P characteristics and by pooling patients across centers for a more robust analysis.

This contemporary NPC-QIC cohort benefited tremendously from the findings of the SVR trial in terms of identifying and standardizing surgical and clinical practice patterns in single ventricle palliation.[20] As such, the overall mortality and

FIGURE 3 Risk Factors for Death or Transplantation After Stage 2 Procedure



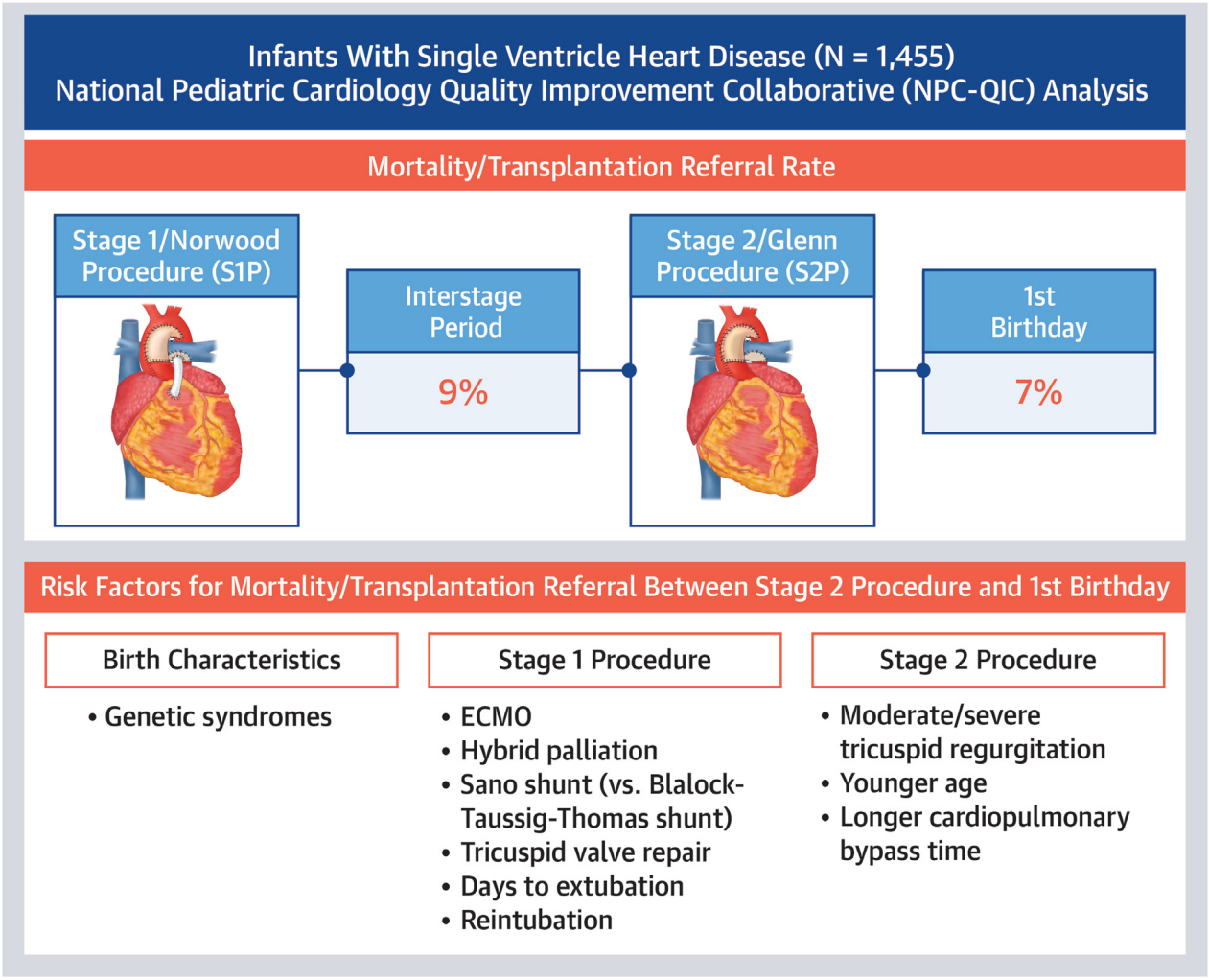
Forest plot showing results of multivariable cox proportional hazards regression model identifying risk factors for death or transplantation referral after Stage 2 procedure. CART = classification and regression trees; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; RVPA = right ventricle-to-pulmonary artery; S1P = stage 1 procedure; S2P = stage 2 procedure.

transplantation referral rates in this cohort from the time of Norwood to 12 months are substantially lower than those reported by the initial SVR trial (~16% vs 31%, respectively).[7] Most of the improvement in transplant-free survival rates has been witnessed in the interstage period with changes in perioperative care and the widespread implementation of home monitoring programs. Mortality and transplantation rates from S2P to 12 months, the focus of this study, have remained stagnant between the original SVR cohort and the NPC-QIC cohort (6% vs 7%, respectively), suggesting ongoing room for improvement.[7]

We also found that patients who had an RVPAS placed at the time of the S1P were at increased risk of mortality or transplantation referral after S2P relative to those who had an mBTTS placed (HR: 1.87, 95% CI: 1.12-3.11). These findings differ from those in the interstage period where receipt of an RVPAS appears to have a survival advantage; however, they are consistent with the 1-year findings of the SVR trial. Specifically, the SVR trial found that mortality and transplantation events were lower in the randomized RVPAS group between S1P and S2P compared with the mBTTS group (21% vs 33%, respectively), but the RVPAS group had slightly higher event rates from S2P to 12 months of age (7% vs 5%, respectively). Subsequent analyses of the SVR trial employing interaction terms between shunt type and time have found that the survival benefit observed with an RVPAS is only present during the interstage period.[21]

Our findings also highlight the association of TR with adverse outcomes. Both tricuspid valve repair at the time of S1P and the presence of ≥ moderate TR prior to S2P were independent risk factors for mortality or transplantation referral after S2P. Early surgical repair of TR often proves challenging due to the inherent friability of neonatal valve tissue and exposes patients to longer CPB times, which may place patients at risk for ventricular dysfunction after the S1P. In a recent analysis, only 58% of neonates undergoing concomitant tricuspid valve repair at the time of S1P had improvement in the TR grade postoperatively.[22] In addition, this study found that only certain mechanisms of TR may be amenable to repair

CENTRAL ILLUSTRATION **Risk Factors for Mortality and Transplantation Referral From Stage 2/Glenn Palliation to First Birthday in Infants With Single Ventricle Heart Disease**



Bucholz EM, et al. JACC Adv. 2024;3(5):100934.

ECMO = extracorporeal membrane oxygenation.

at the time of S1P. As such, patients who develop TR early may be at risk for needing repeat tricuspid valve interventions throughout staged palliation.[23] TR has been identified as a risk factor for poor clinical outcomes in almost every analysis of patients with SVHD.[4,9,21]

Other risk factors for mortality or transplantation referral after S2P included duration of intubation after S1P and reintubation. These factors may be proxies for poor lung development in the setting of a restrictive atrial septum or perioperative injury, poor ventricular systolic or diastolic function, prolonged low cardiac output state, or increased pulmonary arterial pressures which may predispose patients to poor outcomes after S2P. Similarly, earlier age at S2P may be a surrogate for children who are struggling through the interstage period due to inadequate or excessive pulmonary blood flow, significant TR, or ventricular dysfunction. Prior studies using data from the SVR trial have suggested that the optimal time for S2P is between 3 and 6 months and that earlier S2P does not rescue

patients with greater risk factor burdens.[24] The data from this study would suggest that later timing of S2P (>4 months) may be associated with greater transplant-free survival after S2P in a contemporary cohort although it is important to note that the cutpoint of 130 days was defined using tertiles rather than data-driven approaches.

Finally, we identified an interaction between receipt of ECMO after S1P and longer length of CPB time during S2P. Among patients who did not receive ECMO after S1P, a longer CPB time >158 minutes during S2P was associated with a 1.7-fold higher hazards of death or referral for transplantation compared to a shorter CPB time. Patients with longer CPB times during S2P may have been those who underwent hybrid palliation during S1P and thus required a comprehensive S2P or those who required additional procedures such as tricuspid valve repair or repeat aortic arch reconstructions. Patients who received ECMO after S1P had the highest hazards of death after S2P, similar to prior studies demonstrating a strong association between ECMO after S1P and interstage mortality; 22% of patients who received ECMO after S1P died or were referred for transplantation after S2P. While not a modifiable risk factor for the individual patient, this nevertheless helps identify a higher risk population for which increased clinical surveillance during the period from S2P to first birthday is warranted.

Although several of the risk factors identified in this analysis are not modifiable, there may be opportunities for risk factor modification or standardization of practices across sites to improve outcomes after S2P. For example, further research into which patients should qualify for hybrid procedures or tricuspid valve repair at S1P or S2P may help establish uniform recommendations or decision support tools to be shared across centers. Similarly, additional research is warranted as to the optimal timing of S2P and which clinical factors should warrant earlier or delayed procedures to optimize outcomes.

STUDY LIMITATIONS. This analysis has several limitations. First, the NPC-QIC registry includes 69 sites which have varying practice patterns with regard to surgical approach, standards of postoperative care, and interstage management. As such, there may be important site-level effects that are not accounted for in a global analysis. In addition, some of the covariates associated with mortality or transplantation referral may reflect differences in site-specific practices (eg, type of S1P, timing of S2P) rather than independent risk factors. Second, echocardiographic and catheterization data were collected by the individual sites and thus may be subject to differences in interpretation. Given the large number of contributing sites and collaborative nature of the registry for quality improvement, a core imaging laboratory was not feasible. Third, approximately 16% of enrolled patients were excluded from the analytic cohort with the most common reason being loss to follow-up (n = 244). No additional information on reasons for losses to follow-up was captured by participating sites; however, it is possible that these patients transferred care to other centers, obtained follow-up through local cardiologists, or died. Additionally, no data are available in the database on subsequent outcomes for those patients listed for heart transplantation, as listing constituted an exit from the study database. Finally, the NPC-QIC registry did not capture information on patients with failing physiology who were deemed not to be transplant candidates. As such, some high-risk patients with limited life expectancy may have been captured as transplant-free survivors.

CONCLUSIONS

In summary, we found that mortality and transplantation referral rates after S2P to 1 year of age remain high in patients with SVHD. Some of the risk factors identified have been shown to also be associated with interstage mortality, whereas others may be unique to the period after S2P. Further research is needed to understand whether risk factor modification or standardization of practice patterns across sites results in improved transplant-free survival.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Using data from the NPC-QIC, the largest longitudinal cohort of infants with SVHD, we showed that mortality and transplantation rates after S2P until the first year of age remain high (~7%) despite reductions in interstage mortality. The strongest risk factors for mortality or transplantation referral after S2P were undergoing a hybrid procedure and requiring ECMO after S1P. Other independent risk factors included genetic syndromes, receipt of an RVPAS at S1P, tricuspid valve repair during S1P, days to extubation and need for reintubation following S1P, ≥ moderate TR prior to S2P, younger age at S2P, and longer S2P CPB time.

TRANSLATIONAL OUTLOOK: Families of patients with SVHD should be counseled that the risk of mortality and transplantation remains high following S2P. Providers should consider following high-risk patients with the risk factors identified above more closely as outpatients or via home monitoring programs to identify points of intervention. Standardized practice patterns through learning registries like the NPC-QIC may be beneficial for improving S2P outcomes across institutions.

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KEY WORDS single ventricle heart disease, hypoplastic left heart syndrome, Glenn palliation, outcome prediction

APPENDIX For supplemental tables, please see the online version of this paper.