Development of a validated risk score for interstage death or transplant after stage I palliation for single-ventricle heart disease

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ABSTRACT

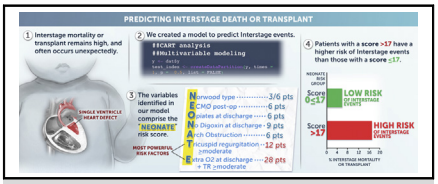
Objective: To develop a risk score to predict mortality or transplant in the interstage period.

Background: The "interstage" period between the stage 1 and stage 2 palliation is a time of high morbidity and mortality for infants with single-ventricle congenital heart disease.

Methods: This was an analysis of patients with single-ventricle congenital heart disease requiring arch reconstruction who were enrolled in the National Pediatric Cardiology Quality Improvement Collaborative registry from 2008 to 2015. The primary composite endpoint was interstage mortality or transplant. Multivariable logistic regression and classification and regression tree analysis were performed on two-thirds of the patients ("learning cohort") to build a risk score for the composite endpoint, that was validated in the remaining patients ("validation cohort").

Results: In the 2128 patients analyzed in the registry, the overall event rate was 9% (153 [7%] deaths, 42 [2%] transplants). In the learning cohort, factors independently associated with the composite endpoint were (1) type of *N*orwood; (2) postoperative *E*CMO; (3) discharge with *O*piates; (4) *N*o Digoxin at discharge; (5) postoperative *A*rch obstruction, (6) moderate-to-severe *T*ricuspid regurgitation without an oxygen requirement, and (7) *E*xtra Oxygen required at discharge in patients with moderate-to-severe tricuspid regurgitation. This model was used to create a weighted risk score ("NEONATE" score; 0-76 points), with >75% accuracy in the learning and validation cohorts. In the validation cohort, the event rate in patients with a score >17 was nearly three times those with a score ≤17.

Conclusions: We introduce a risk score that can be used post-stage 1 palliation to predict freedom from interstage mortality or transplant. (J Thorac Cardiovasc Surg 2020;160:1021-30)



The NEONATE risk score for patients with single-ventricle congenital heart disease.

CENTRAL MESSAGE

We introduce a novel, validated risk score to be used before discharge following S1P to assess the risk of interstage death/transplant—greatest for patients with TR and a supplemental O_2 requirement.

PERSPECTIVE

Interstage mortality is poorly understood and remains a high-risk period for patients with SVCHD. We present a validated risk score to predict interstage mortality that identified moderate or greater TR and a persistent supplemental O_2 requirement as the greatest risk subgroup. Interstage mortality may be impacted by intensifying surveillance for this group and modifying risk factors identified by our model.

See Commentaries on pages 1031 and 1033.

Patients with complex congenital cardiac anomalies resulting in single-ventricle congenital heart disease (SVCHD) with aortic arch obstruction typically undergo a 3-stage series of palliative open-heart surgeries, culminating in a total cavopulmonary anastomosis.[1] During the "interstage" period, or the time between hospital discharge following the stage 1 palliation (S1P) and the time of the stage 2 palliation (S2P), the single ventricle pumps simultaneously to parallel

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Abbreviations and Acronyms

CART = classification and regression tree
ECMO = extracorporeal membrane oxygenation
HLHS = hypoplastic left heart syndrome
IM = interstage mortality
mBTS = modified Blalock–Taussig shunt
NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative
RV-PAC = right ventricle-to-pulmonary artery conduit
S1P = stage 1 palliation
S2P = stage 2 palliation
SVCHD = single-ventricle congenital heart disease
SVR = single ventricle reconstruction
TR = tricuspid regurgitation

systemic and pulmonary circulations, with the balance of flow through the 2 circulations dependent on dynamic changes in relative vascular resistances. This circulation leaves infants particularly vulnerable to hemodynamic instability in the face of respiratory illness, fever, dehydration, vagal events, and other factors that are known to impact cardiac output and pulmonary and/or systemic vascular resistance.[2-5] Descriptive analyses of interstage mortality (IM) have revealed that among patients discharged home after S1P, most deaths occur unexpectedly at home or in the emergency department, with an unknown cause of death in approximately half of cases.[6-8]

We therefore sought to develop a risk-stratification tool that could quantitatively assess the risk of IM or transplant for patients with SVCHD who require an aortic arch intervention. We hypothesized that studying the characteristics of the patients who experienced IM would allow for the development of a scoring tool designed to risk stratify infants being discharged home in the interstage period.

METHODS

Study Setting and Population

This study was an analysis of data collected prospectively on patients enrolled in the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) registry between 2008 and 2015, as part of a national learning collaborative of >60 surgical sites to reduce mortality, and improve quality of life, for infants with SVCHD. The methods of subject recruitment, and data acquisition and maintenance, have been described previously.[4] Subjects were included if (1) diagnosed with SVCHD and aortic arch obstruction requiring S1P with arch reconstruction and either a modified Blalock–Taussig shunt (mBTS), right ventricle-to-pulmonary artery conduit (RV-PAC), or hybrid approach; and (2) were discharged from the hospital before S2P or transplant. Subjects were excluded if lost to follow-up or transferred to a non-NPC-QIC site before undergoing S2P. Deidentified data were collected at fixed intervals and entered by each site into a Research Electronic Data Capture (REDCap) database, which was maintained by a central data management site (Cincinnati Children's Hospital). After verification of eligibility, informed consent was obtained, and multiple data elements were collected from the time of the patient's birth through discharge from their stage II operation or transplant. Site self-audits were performed every 6 months to demonstrate that >95% of eligible infants at participating centers had been enrolled, with data entered. Quality control was conducted using a combination of REDcap system programmed edit checks and Statistical Analysis System (SAS) reports.[4]

Echocardiograms were obtained by the institution at fixed time points, including (1) postnatally; (2) post-S1P, (3) predischarge, and (4) at clinic visits at the discretion of the institution. The images were read by the surgical institution, and the results of the official report were entered into the dataset. Images were not available for review. Neoaortic arch obstruction was defined as a peak instantaneous gradient was >10 mm Hg.

This study was performed according to a protocol approved by the institutional review board of each participating institution, including the Committee for Clinical Investigation at Boston Children's Hospital. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Study Design and Statistical Analysis

The primary outcome was a composite endpoint of death or transplant after initial hospital discharge post-S1P. The Student t test was used to compare normally distributed data of patients undergoing S2P versus death or transplant and is presented as mean ± standard deviation. A Wilcoxon rank sum test was used to evaluate the non-normally distributed variables, with data presented as median (interquartile range). Categorical unordered and ordered variables were analyzed with a Fisher exact test and Mantel–Haenszel test for linear trend, respectively, to assess association with IM. Two-tailed $P < .05$ was considered statistically significant.

To identify important interactions that would optimize goodness of fit of the logistic regression model for interstage death or transplant, a CART (Classification and Regression Tree) analysis was performed with R, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). The candidate predictor variables were all the demographic, surgical, hospitalization, and discharge factors collected in the NPC-QIC database. The response variable was the presence versus the absence of the composite outcome (interstage death/transplant). To avoid overfitting, the CART was pruned using a complexity parameter threshold of 0.012.

SAS (version 9.4; SAS Institute, Cary, NC) was used to randomly select 1596 patients (75% of the total cohort) to serve as the learning cohort. Univariate and multivariable logistic regression analyses were then performed to determine the variables that predicted freedom from IM. All univariate variables with a P value <.2, and the high-risk group identified by CART, were included as candidate predictors for the multivariable analysis. Generalized additive modeling was used to estimate the shape of relationship between continuous predictors and the outcome. A 2-tailed $P < .05$ was considered statistically significant.

Finally, the derived risk score was validated in the remaining patients (25% of the total cohort). The risk score was categorized according to tertiles as well as based on the results of receiver operating characteristic analysis. Sensitivity, specificity, false-positive rate, false-negative rate, positive predictive value, negative predictive value, and accuracy (true positive and true negative results) were calculated.

RESULTS

Patient Characteristics

A total of 2184 patients from 60 participating surgical centers met inclusion for the NPC-QIC registry during

TABLE 1. Preoperative patient characteristics of the total patient cohort

Characteristic	Total cohort (n = 2128)	S2P (n = 1933)	Death or transplant (n = 195)
Gestational age			
Median (interquartile range)	39 (38-39)	39 (38-39)	39 (38-39)
<38 wk, %	19	18	22
Birth weight	3.2 (2.9-3.5)	3.2 (2.9-3.5)	3.1 (2.8-3.5)
Female, %	37	37	44
White, %	82	82	79
Black, %	13	13	13
Hispanic, %	9	18	21
Prenatal diagnosis, %	80	80	79
Fetal intervention, %	2	2	2
Primary anatomical diagnosis, %			
Hypoplastic left heart syndrome	74	75	80
Mitral atresia, aortic atresia	34	33	34
Mitral stenosis, aortic atresia	20	19	29
Mitral atresia, aortic stenosis	3	3	5
Mitral stenosis, aortic stenosis	19	20	11
NOS	1	0	1
Double-inlet left ventricle	5	5	2
Unbalanced AV canal	6	6	7
DORV with left-sided hypoplasia	6	6	7
Other	7	8	7
Associated abnormalities, %			
Restrictive atrial septum	17	17	19
Pulmonary vein abnormality	3	2	5
Moderate or greater TR	3	3	4
Moderate or greater ventricular dysfunction	2	3	1
Major anomaly of another organ, %	11	11	11

S2P, Stage 2 palliation; *NOS*, not otherwise specified; *AV*, atrioventricular; *DORV*, double-outlet right ventricle; *TR*, tricuspid regurgitation.

the study period from 2008 to 2015. Of this cohort, 15 patients were lost to follow-up or transferred to a different, non–NPC-QIC facility and were excluded from the analysis. Forty-one patients were deemed not to be a candidate for an S2P but did not meet the composite outcome and were also excluded. The median gestational age of the remaining cohort (2128 subjects) was 39 weeks, with a median birth weight of 3.2 kg; 796 (37%) were female, and 1735 (82%) were white (Table 1). The most common native cardiac anatomy was a form of hypoplastic left heart syndrome (HLHS; n = 1622, 76%). Eleven and 17% had a major anomaly of at least one additional organ system and restrictive atrial septum, respectively. The prevalence of moderate or greater tricuspid regurgitation (TR; n = 69, 3%) or moderate or greater ventricular systolic dysfunction (n = 52, 2%) was low. Twenty, 30, and 50% of patients were at sites that enrolled <5, 5 to 10, and >10 patients per year, respectively, as a surrogate for center S1P volume. The overall composite outcome event rate was 9%, with 153 (7%) interstage deaths, and 42 (2%) orthotopic heart transplants.

Learning Cohort

The learning cohort comprised 1596 patients. The overall event rate (9%) in the learning cohort was the same as that of the total cohort, with 118 (7%) interstage deaths and 30 (2%) orthotopic heart transplants. Univariate logistic regression demonstrated that the patient characteristics associated with the composite endpoint were female sex, primary anatomical diagnosis of HLHS of the mitral stenosis/aortic atresia variant, HLHS not otherwise specified, or double-outlet right ventricle with left-sided hypoplasia, and pulmonary venous anomaly or obstruction—independent of the primary diagnosis (Table 2). The only surgical characteristic associated with IM or transplant was the type of Norwood procedure, with a 21%, 11%, and 7% rate of IM for patients who had undergone a hybrid procedure, mBTS, and RV-PAC, respectively. Postoperative and discharge characteristics are detailed in Table 3.

Classification and Regression Tree Analysis

A CART analysis was then performed to identify potential interactions among variables that define

TABLE 2. Univariate logistic regression model for interstage death/transplant in the "learning cohort"

Learning cohort	S2P (n = 1448)	Death/transplant (n = 148)	*P* value
Patient characteristics			
Gestational age, y, median (range)	39 (38-39)	39 (38-39)	.21
Birth weight, kg	**3.2 (2.9-3.5)**	**3.1 (2.8-3.5)**	**.15**
Female, %	**36**	**47**	**.005**
Race			.72
White, %	81	80	
Black, %	13	13	
Other	6	7	
Hispanic, %	17	20	.36
Prenatal diagnosis, %	79	81	.62
Fetal intervention, %	3	2	.66
Primary anatomical diagnosis, %			**.035**
Hypoplastic left heart syndrome			
Mitral atresia, aortic atresia	33	35	
Mitral stenosis, aortic atresia	19	28	
Mitral atresia, aortic stenosis	3	5	
Mitral stenosis, aortic stenosis	20	13	
NOS	1	1	
Double-inlet left ventricle	5	1	
Unbalanced AV canal	6	6	
DORV with left-sided hypoplasia	**5**	**8**	**.035**
Other	8	3	
Associated diagnoses, %			
Restrictive atrial septum	17	18	.84
Pulmonary vein abnormality	**2**	**5**	**.039**
Moderate or greater TR	4	5	.23
Moderate or greater ventricular dysfunction	**3**	**1**	**.15**
Major anomaly of another organ, %	11	8	.32
Stage 1 palliation characteristics			
Type of S1P			**<.001**
RV-PAC, %	58	43	
BT shunt, %	34	39	
Hybrid, %	7	17	
Age at procedure, d	6 (4,8)	6 (4,8)	.84
Weight at procedure, kg	3.3 (2.9-3.6)	3.3 (2.9-3.6)	.41
Bypass time, min	152 ± 58	146 ± 58	.27
Aortic crossclamp time, min	66 ± 32	65 ± 33	.77
Circulatory arrest time, min	22 ± 23	25 ± 52	.4
Intraoperative temperature nadir	**20 ± 5**	**21 ± 6**	**.07**
Use of regional perfusion, %	**69**	**64**	**.19**
Postoperative ECMO, %	**7**	**14**	**.001**
Predischarge VAD, %	**3**	**9**	**.001**
Reoperation for arch repair, %	**1**	**3**	**.011**
Reoperation for BTS revision, %	1	1	.84
Reoperation for RV-PAC, %	**2**	**3**	**.14**
Permanent PM implantation, %	**1**	**3**	**.02**
Postoperative catheterization, %	**19**	**31**	**<.001**
Postoperative G-tube, %	23	26	.41

Bold indicates $P < .2$. *S2P*, Stage 2 palliation; *NOS*, not otherwise specified; *AV*, atrioventricular; *DORV*, double-outlet right ventricle; *TR*, tricuspid regurgitation; *S1P*, stage 1 palliation; *RV-PAC*, right ventricle-to-pulmonary artery conduit; *BT*, Blalock–Taussig; *ECMO*, extracorporeal membrane oxygenation; *VAD*, ventricular assist device; *BTS*, Blalock–Taussig shunt; *PM*, pacemaker; *G-tube*, gastrostomy tube.

particularly high- or low-risk subgroups that should be considered in development of a multivariable model for interstage death/transplant. The CART indicated that the risk of interstage death/transplant in patients with moderate-to-severe TR (moderate or greater TR) on the predischarge echocardiogram was altered by a persistent requirement for supplemental oxygen at discharge (56% vs 20%) interstage death/transplant for patients with

TABLE 3. A univariate comparison of hospitalization and discharge characteristics according to interstage death/transplant status for patients in the learning cohort

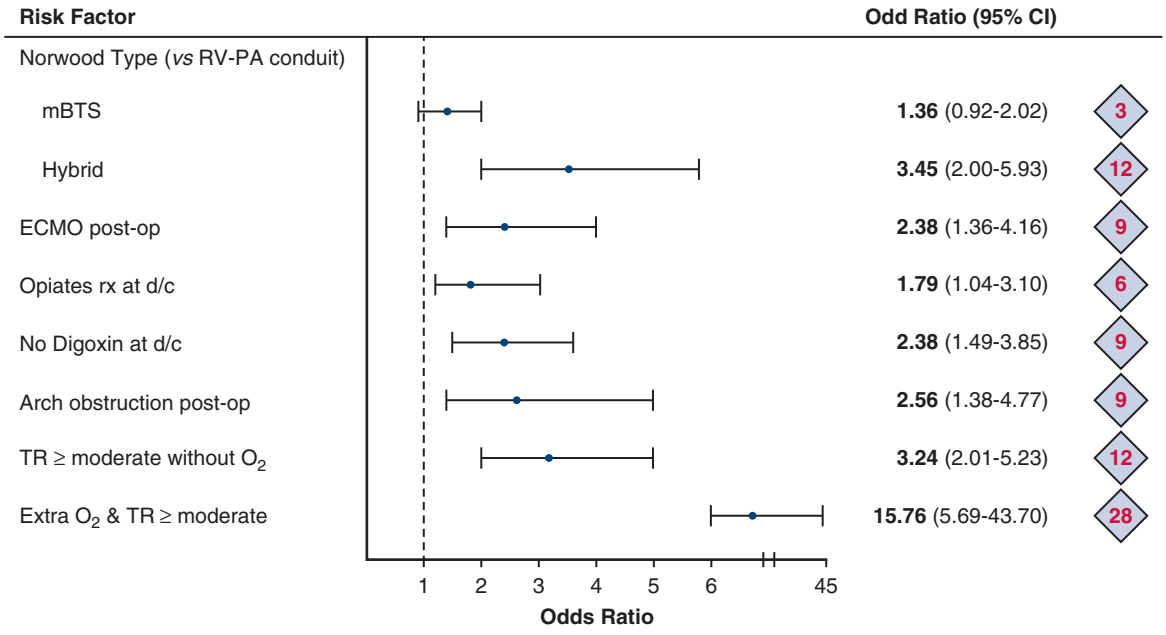
Learning cohort	S2P (n = 1448)	Death/transplant (n = 148)	*P* value
Hospitalization characteristics			
Mechanical ventilation >14 d, %	11	14	.43
Reintubation	**14**	**19**	**.1**
Age at final extubation, d	**13 (10-23)**	**16 (11-29)**	**.12**
Age at initiation of enteral feeds, d	**10 (8-15)**	**10 (8-16)**	**.11**
Age at full enteral feeds, d	19 (14-30)	21 (16-33)	.6
Age at initial transfer to wards, d	22 (15-35)	24 (17-38)	.97
Postoperative arrhythmia requiring tx, %	**71**	**64**	**.09**
Arrest, %	**6**	**14**	**.001**
Necrotizing enterocolitis	6	8	.37
Seizure(s)	6	7	.4
Chylothorax	10	8	.45
Discharge characteristics			
Age at initial hospital discharge, d	35 (25-54)	39 (28-54)	.27
Discharge weight	3.6 (3.2-4.1)	3.5 (3.3-4)	.55
Oxygen saturation at discharge, %	83 (80-86)	82 (79-85)	.24
Discharge with oxygen, %	**9**	**16**	**.005**
Discharge medications			
Number of medications	4 (3-5)	4 (3-5)	.22
ACE inhibitor, %	**38**	**43**	**.18**
Antiarrhythmic, %	**5**	**8**	**.13**
Aspirin, %	**91**	**95**	**.1**
Beta-blocker, %	**7**	**11**	**.06**
Benzodiazepines, %	**3**	**5**	**.13**
Clonidine, %	4	3	.65
Digoxin, %	30	20	**.009**
Diuretics, %	100	100	1
Enoxaparin, %	7	6	.64
Opiates, %	7	15	**.001**
Plavix, %	2	2	.79
Spironolactone, %	**9**	**13**	**.18**
Route of enteral intake			.66
Oral only, %	35	32	
NG or GT only, %	27	26	
PO/gavage, %	38	41	
Caloric density of feeds, kcal/oz	25 ± 3	25 ± 3	.54
Discharge with home health care, %	52	56	.4
Discharge with home surveillance, %	97	96	.7
Predischarge echocardiogram			
Moderate-to-severe TR, %	9	28	**<.01**
Arch obstruction, %	7	16	**<.01**
Moderate-to-severe dysfunction, %	4	2	.22
Restrictive ASD	2	1	.9

Bold indicates $P < .2$. *S2P*, Stage II palliation; *tx*, treatment; *ACE*, angiotensin-converting enzyme; *NG*, nasogastric; *GT*, gastrostomy tube; *PO*, per os; *TR*, tricuspid regurgitation; *ASD*, atrial septal defect.

moderate or greater TR with and without an oxygen requirement, respectively. The event rate was 8% in patients with less than moderate TR.

Multivariable Analysis

Independent predictors of death or transplant were *N*orwood type (using RV-PAC as the reference), postoperative extracorporeal membrane oxygenation (*E*CMO), *O*piates prescribed at discharge, Digoxin *N*ot prescribed at discharge, *A*rch obstruction postoperative, *T*ricuspid regurgitation that was moderate or greater on predischarge echocardiogram in patients who did not have a supplemental oxygen requirement at discharge, and *E*xtra oxygen required at discharge in addition to moderate or greater TR (NEONATE; Figure 1, *A*). The overall c-statistic for the model was 0.72.



A

Norwood Type (vs: RV-PAC)	
BTS	3
Hybrid	6
ECMO post-op	6
Opiates at discharge	6
No Digoxin at Discharge	9
Arch obstruction on pre-discharge echo	6
Tricuspid regurgitation ≥ moderate	12
Extra O2 at discharge + TR ≥ moderate	28

B

FIGURE 1. A, The variables included in the multivariable logistic regression model are noted on the *Y-axis*, with odds ratios on the *X-axis*. To the right of the odds ratios and error bars is noted the odds ratios (95% confidence intervals) for each variable, followed by the weighted point allocation for each variable within the diamond (based on the log odds parameter estimates). The reference group for the last 2 risk factors is patients with no or mild TR. These variables and their associated, weighted point allocations were used to create (B) the "NEONATE" risk score, for risk stratification of single-ventricle patients at the time of initial hospital discharge after undergoing a Stage I procedure. *CI*, Confidence intervals; *RV-PAC*, right ventricle-to-pulmonary artery conduit; *mBTS*, modified Blalock–Taussig shunt; *ECMO*, extracorporeal membrane oxygenation; *rx*, prescribed; *d/c*, discharge; *post-op*, postoperatively; *TR*, tricuspid regurgitation; *O2*, oxygen.

Derived Composite Outcome Risk Score

Using weights proportional to the log odds ratio parameter estimates from the multivariable model, we created a "NEONATE" scoring system that could be employed at discharge post-S1P to predict IM or transplant (Figure 1, *B*). The maximum possible score was 76 points. The median NEONATE score in the learning cohort was 14 (interquartile range 9-17), with a range of scores between 0 and 60 (Figure 2).

Validation Cohort

The validation cohort consisted of 532 patients. The composite outcome event rate (9%) in the validation cohort was identical to that of the learning cohort. Accordingly, comparability of the validation cohort with the learning cohort was also evidenced by the very similar median NEONATE score of 14 ± 8 (interquartile range 9-17).

For the purpose of risk stratification, patients were separated into low (NEONATE score ≤12), medium

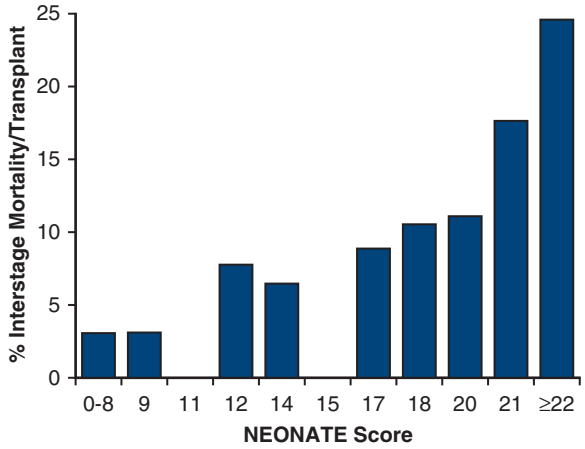


FIGURE 2. The distribution of "NEONATE" scores is shown on the X-axis, with the percent interstage mortality/transplant on the Y-axis, demonstrating that as the NEONATE score increase, the associated rate of interstage events also increases. *NEONATE*, Norwood type (using RV-PAC as the reference), postoperative extracorporeal membrane oxygenation (ECMO), Opiates prescribed at discharge, Digoxin Not prescribed at discharge, Arch obstruction postoperatively, Tricuspid regurgitation that was moderate or greater on predischarge echocardiogram in patients who did not have a supplemental oxygen requirement at discharge, and Extra oxygen required at discharge in addition to moderate or greater tricuspid regurgitation.

(NEONATE score 13-17), and high (NEONATE score >17) risk categories; thresholds for separation were obtained from tertiles of the risk score observed in the learning cohort. In addition, receiver operating characteristic analysis also identified a score of >17 as optimal for identifying patients with and without the outcome. The event rate in the high-risk subgroup (21% in the learning cohort, 17% in the validation cohort) was nearly 3 times that in the low (4% in the learning cohort, 6% in the validation cohort) and medium risk (7% in both cohorts) subgroups (Figure 3; learning cohort $P < .001$, validation cohort $P = .002$). Using a NEONATE score >17 as a primary stratification of risk predicted interstage death/transplant with 55% sensitivity, 78% specificity, and 76% accuracy in the learning cohort, with similar performance in the validation cohort (Figure 4). There was no threshold score above which all patients met the composite endpoint.

DISCUSSION

In this multicenter registry study, we developed and validated a novel risk stratification system that can be used at the time of initial hospital discharge post-S1P to predict freedom from IM or transplant with high specificity and accuracy. The strength of this model is particularly robust when using a NEONATE score cutoff of 17 points to stratify patients into dichotomous categories of low and high risk. The strongest independent predictor of an interstage event was the presence of moderate or greater TR on discharge echocardiogram—an effect that was compounded in patients with oxygen dependence at the time of discharge. Other independent predictors of interstage death or transplant included having undergone either a hybrid procedure or mBTS rather than an RV-PAC; postoperative need for ECMO; residual neoaortic arch obstruction at the time of discharge; and discharge with an opiate or without digoxin.

These data suggest that although surrogate markers of prolonged hospitalization, ie, postoperative ECMO use and discharge on opiates, remain important predictors of overall patient fragility, the greatest risk in the interstage period may arise from factors that exacerbate the inherent instability of the interstage physiology. TR creates a positive feedback loop of ventricular volume load and inefficient ventricular output, placing patients at an increased risk for ventricular arrhythmias, as well as acute pump failure during periods of stress that increase the systemic or pulmonary vascular resistance. The risks of neoaortic arch obstruction are similar but are mediated instead by a chronic pressure load that creates a positive feedback loop of increased end-diastolic pressure, leading to decreased coronary perfusion pressure and increased pulmonary vascular congestion and resistance. Conversely, discharge home on digoxin may have been protective due to its known inotropic and parasympathetic effects, which improve cardiac output by increasing diastolic filling time and systemic vasodilation while simultaneously decreasing the risk of arrhythmias by modulating the atrioventricular nodal refractory period. Finally, discharging patients home on opiates may have been harmful due to the potential for accidental medication overdose, leading to respiratory suppression and death. In addition, it has been described that chemoreflex sensitivity is depressed in cyanotic congenital heart disease, which might make the more susceptible to sudden infant death syndrome at baseline, which may be compounded with the addition of opiates.[11]

Previous Studies

The Single Ventricle Reconstruction (SVR) trial is the major prospective, multicenter clinical trial examining mortality in patients with SVCHD. In a secondary analysis of 426 patients who survived to hospital discharge, the transplant-free mortality rate was 12%.[2] Independent predictors of IM included gestational age <37 weeks, Hispanic ethnicity, lower socioeconomic status, mitral atresia/aortic atresia variant of HLHS, having undergone a mBTS, and a greater number of post-Norwood complications. Other than mBTS, these variables differed from ours, possibly because the present study (1) broadened the study population by including hybrids; (2) includes surgical centers with lower surgical volume than those in the SVR

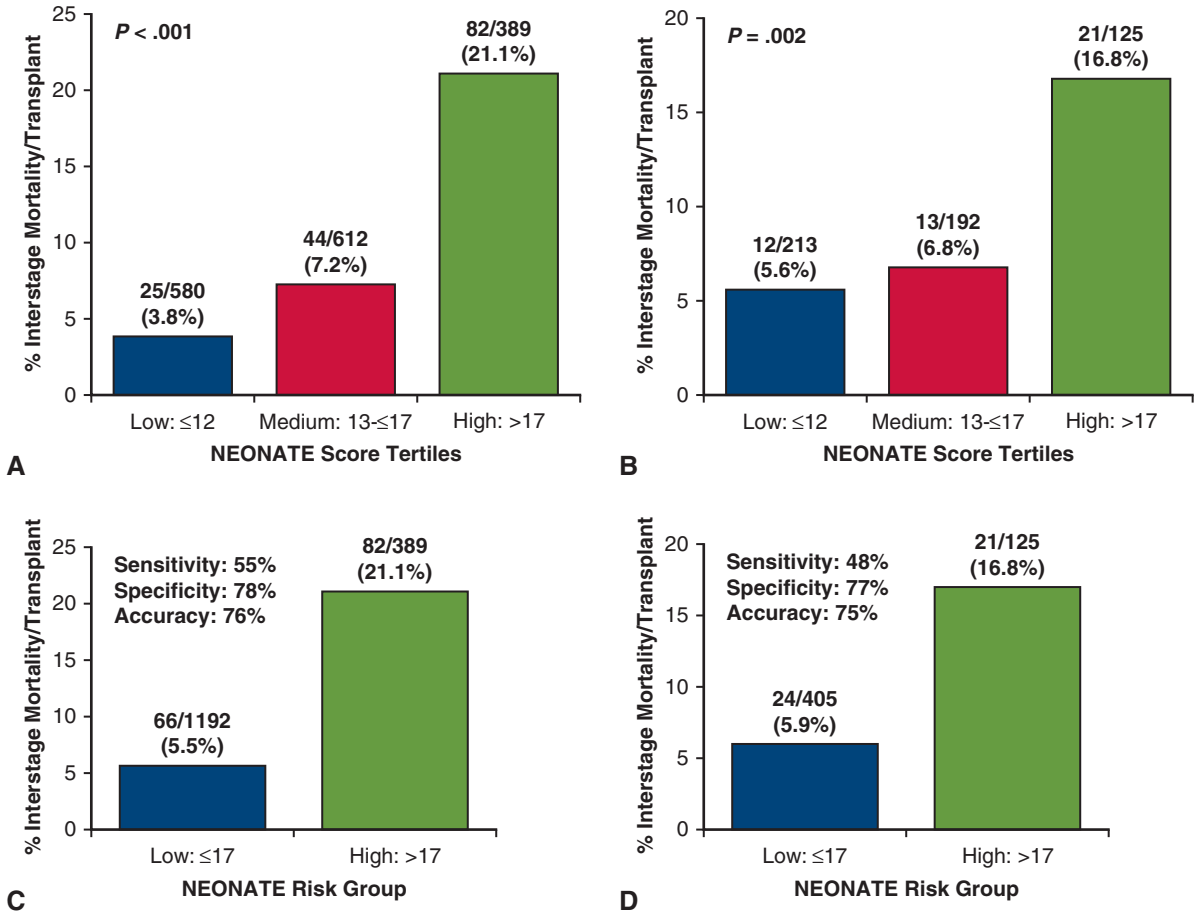


FIGURE 3. Rate of interstage mortality or transplant after hospital discharge, stratified by tertile of NEONATE score in the (A) learning and (B) validation cohorts, as well as the predictive performance of using a NEONATE score of 17 points as a primary stratification of risk in the (C) learning and (D) validation cohorts. *Blue*, *red*, and *green bars* indicate low-, medium-, and high-risk patient groups, respectively. *NEONATE*, Norwood type (using RV-PAC as the reference), postoperative extracorporeal membrane oxygenation (ECMO), Opiates prescribed at discharge, Digoxin Not prescribed at discharge, Arch obstruction postoperatively, Tricuspid regurgitation that was moderate or greater on predischarge echocardiogram in patients who did not have a supplemental oxygen requirement at discharge, and Extra oxygen required at discharge in addition to moderate or greater tricuspid regurgitation.

trial; (3) included transplant in the primary endpoint; (4) did not examine socioeconomic factors; and (5) allowed for the introduction of interactions (patient subgroups) identified by CART analysis—as opposed to the SVR trial analysis, which included only main effects in the model.

In a prospective analysis of 824 infants with variants of ductal-dependent HLHS, Meza and colleagues[12] identified reoperation post-S1P, lower birth weight, lower oxygen saturation post-S1P, MBTS, and a smaller baseline ascending aortic diameter as independent risk factors for death in the interstage period. These risk factors are similar to ours, aside from birth weight, which was not included in our model. This may be reflective of selection bias, as the NPC-QIC database excludes patients who don't survive to discharge, which may have excluded the lowest birth weights. In addition, differential risk assessment and prediction between studies must be understood and compared in the context of the outcome measure—ie, survival versus transplant-free survival.[13]

A report of IM revealed that 75% of deaths occurred suddenly and, unexpectedly, of these, more than one half occurred at home or in the emergency department. In the subset of patients for whom a postmortem autopsy was performed, there was no identifiable anatomic abnormality or other cause of death in most cases.[10] These findings are reflective of both a poor understanding of the acute trigger of interstage death, and the absence of patient-specific risk assessment tools to assist clinicians in objectively identifying the most vulnerable patients. Furthermore, given the sudden and unexpected nature of death in many of these patients, occult arrhythmia is a suspected, but difficult to prove, culprit.[9,10]

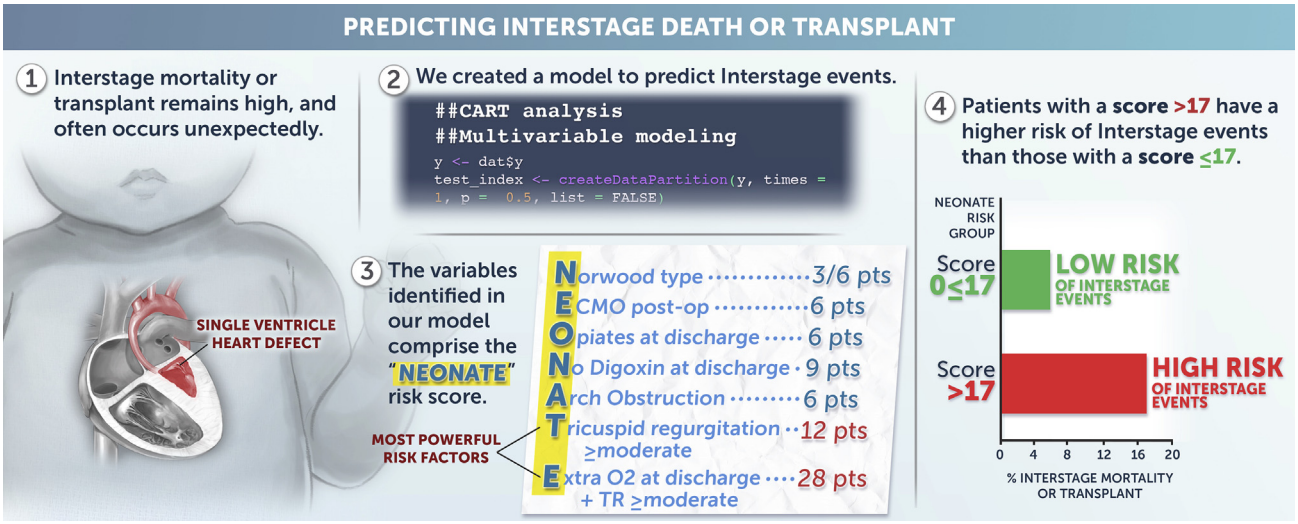


FIGURE 4. Predicting interstage mortality or transplant. We created a validated risk score for patients with single-ventricle congenital heart defects ready for discharge to home in the interstage period after stage I/Norwood palliation, designed to guide objective decision-making regarding the safety of patient discharge. Multivariate modeling identified the 7 variables comprising the NEONATE risk score that had good predictive ability across the diverse patient group represented in both the learning and validation cohorts of the National Pediatric Cardiology Quality Improvement Registry. Patients with a NEONATE score of ≤17 were at low risk of interstage death and transplant compared with those with NEONATE score >17. *CART*, Classification and regression tree; *ECMO*, extracorporeal membrane oxygenator; *O2*, oxygen; *TR*, tricuspid regurgitation.

Clinical Implications

We created the first validated risk score for patients with SVCHD in the interstage period, designed to guide clinicians and families in making objective decisions regarding the safety of patient discharge. The NEONATE risk score had good predictive ability across the diverse patient group represented in both the learning and validation cohorts of the NPC-QIC Registry, with a C-statistic of 0.72, similar to other models in routine practice.[14-16] Our data indicate that the patients at lowest risk for an interstage event are those with a NEONATE score ≤17 points at the time of discharge—IM or transplant occurred in 1 of 4 patients discharged home with moderate or greater TR, and in 1 of every 2 patients discharged home with moderate or greater TR + home oxygen. These findings highlight the association of TR with poor clinical outcomes. Although earlier surgical intervention for TR would be one option for addressing this major risk factor, the inherent friability of neonatal valve tissue makes such repairs technically challenging, and additional exposure to cardiac bypass comes at the expense of worsening ventricular systolic and diastolic function, which may then predispose to more TR. An alternative approach is continued inpatient hospitalization until the time of the S2P, and/or earlier listing for heart transplant.[14] For other patients with high NEONATE scores, IM may be reduced with a targeted, standardized, and more intensive home monitoring strategy. At present, home-monitoring strategies are in place for most of the centers included in the NPC-QIC registry, but the frequency and route of monitoring is quite variable across centers.[17]

Of importance, our model also identified other potentially modifiable risk factors, in addition to TR, that may be targeted in the future to further reduce IM. In the learning cohort, 127 (8%) patients were discharged home on opiates, and 1133 (71%) were not discharged with digoxin. The rate of IM or transplant for these patients was 17% and 11%, respectively. Given an overlap of only 2 patients between these groups, the modification of these 2 variables may result in a substantial reduction in the overall risk of a major event in the interstage period. Although performing a prospective randomized controlled trial would be the gold standard to definitively evaluate the effect of digoxin in the interstage period, a number of factors challenge the feasibility of this type of investigation, including the rarity of the disease, the short duration (generally less than 6 months) of the interstage period, the relative low frequency of the composite outcome, and thus the large number of patients who would need to be enrolled to detect differences in mortality. Furthermore, it may be unethical to withhold this medication in such a vulnerable population.[9] To examine the effect of opiates, one may alter practice to ensure that patients remain hospitalized until they have been weaned off of opiates. The rate of IM could then be reanalyzed after this change in practice has been instituted.

Limitations

This registry study should be viewed considering its limitations. As with all multicenter registries, it was not possible to account for inherent intra- and intercenter variability in operative technique and standards of

postoperative care. An important aspect of this is significant variability in which patients are discharged home at all in the interstage period. Given that the database only includes patients who were discharged home post-S1P, this may introduce significant exclusion and/or inclusion bias, by virtue of a subset of the sickest patients potentially being excluded from the analysis and derivation of the NEONATE score. However, this is somewhat minimized by the fact that the type of SVCHD, gestational age, surgical-site volume, length of intensive care unit stay or hospitalization, and method of feeding at discharge were not predictive of mortality in our model; furthermore, site enrollment/year as a surrogate for center surgical volume was not associated with the composite outcome. Some variables that may impact clinical outcomes, such as measures of socioeconomic status, are simply not collected in the database. In addition, full reports of diagnostic and interventional catheterizations were not available, and some of the variables collected in our dataset—particularly related to echocardiographic findings—included subjective measures of severity. This would have been mitigated by using a core imaging laboratory with a single reader, which was not employed in the NPCQIC registry. However, some bias was eliminated since all echocardiographic reports were completed before hospital discharge, thereby blinding readers to a patient's ultimate outcome.

CONCLUSIONS

We introduce a novel, validated risk score that can be used at the time of post-S1P discharge to assess risk of subsequent interstage death or transplant. Future studies are required both to corroborate this experience and to assess changes in mortality and transplantation rate with the modification of variables identified in this study.

Conflict of Interest Statement

Dr Lannon has a financial relationship with the American Academy of Pediatrics and the Children's Heart Association of Cincinnati. All authors have nothing to disclose with regard to commercial support.

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