A prognostic tool to predict outcomes in children undergoing the Norwood operation

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ABSTRACT

Objectives: To create and validate a prediction model to assess outcomes associated with the Norwood operation.

Methods: The public-use dataset from a multicenter, prospective, randomized single-ventricle reconstruction trial was used to create this novel prediction tool. A Bayesian lasso logistic regression model was used for variable selection. We used a hierarchical framework by representing discrete probability models with continuous latent variables that depended on the risk factors for a particular patient. Bayesian conditional probit regression and Markov chain Monte Carlo simulations were then used to estimate the effects of the predictors on the means of these latent variables to create a score function for each of the study outcomes. We also devised a method to calculate the risk of outcomes associated with the Norwood operation before the actual heart operation. The 2 study outcomes evaluated were in-hospital mortality and composite poor outcome.

Results: The training dataset used 520 patients to generate the prediction model. The model included patient demographics, baseline characteristics, cardiac diagnosis, operation details, site volume, and surgeon experience. An online calculator for the tool can be accessed at <https://soipredictiontool.shinyapps.io/NorwoodScoreApp/>. Model validation was performed on 520 observations using an internal 10-fold cross-validation approach. The prediction model had an area under the curve of 0.77 for mortality and 0.72 for composite poor outcome on the validation dataset.

Conclusions: Our new prognostic tool is a promising first step in creating real-time risk stratification in children undergoing a Norwood operation; this tool will be beneficial for the purposes of benchmarking, family counseling, and research. (J Thorac Cardiovasc Surg 2017;154:2030-7)

Receiver operating characteristic curves.

Central Message

We report a novel prognostic tool to predict real-time outcomes among children undergoing the Norwood operation. The tool can be used for benchmarking, family counseling, and research.

Perspective

Our novel prognostic tool is a first step in creating real-time risk stratification for children undergoing a Norwood operation. This tool provides efficient risk-adjustment by condensing 10 risk factors into 1 probability before the heart operation and condensing 18 risk factors into 1 probability after the operation; this prognostic tool predicts poor outcomes associated with the Norwood operation.

See Editorial Commentary page 2038.

Patients with single-ventricle lesions and systemic outflow obstruction undergo palliation with the Norwood operation. Unfortunately, this procedure is associated

with high morbidity and mortality.¹⁻⁴ There are published data that report the risk factors associated with poor outcomes after this high-risk heart operation^{1,5-7}; however, there is no prognostic scoring system that can predict outcomes for an individual patient after a Norwood operation. As clinical judgment alone can be imperfect, prognostic scoring systems can be used as adjuncts to clinical decision-making in the care of individual patients.^{8,9}

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Scanning this QR code will take you to the supplemental video and appendix for the article.

Abbreviations and Acronyms

ECMO	= extracorporeal membrane oxygenation
MBT	= modified Blalock–Taussig
MCMC	= Markov chain Monte Carlo
RVPA	= right ventricle–pulmonary artery
SVR	= Single-Ventricle Reconstruction

Therefore, we sought to create a prediction tool to assess outcomes associated with the Norwood operation both before and after the operation; to do this, we used advanced statistical models, such as Bayesian conditional probit regression models and Markov chain Monte Carlo (MCMC) simulations. The 2 specific outcomes evaluated in our study were in-hospital mortality and composite poor outcome (defined as mortality or heart transplantation or need for cardiopulmonary resuscitation or use of extracorporeal membrane oxygenation [ECMO] outside the operating room or prolonged mechanical ventilation or prolonged hospital length of stay). The purpose of creating this tool was to provide families and health care providers with realistic expectations both before and after the Norwood operation; this tool will also help with benchmarking, quality improvement, cost reduction, and observational research.

MATERIAL AND METHODS

Data Source

The Single Ventricle Reconstruction (SVR) Trial was a prospective study that compared outcomes between patients who underwent the Norwood operation. The subjects were randomized to a modified Blalock–Taussig (MBT) shunt or a right ventricle–pulmonary artery (RVPA) shunt at the time of the Norwood operation. Details of the trial design and primary results have been reported.^{10,11} The trial was performed at 15 centers in the United States and Canada between 2005 and 2009, and a public-use data set from the SVR trial became available in 2013. The 2 specific outcomes evaluated in our study were in-hospital mortality and composite poor outcome. The 75th percentile of the cohort data distribution was used to establish cutoff values for defining prolonged mechanical ventilation and prolonged hospital length of stay. This definition uses the same approach as Wernovsky and colleagues.¹² The University of Arkansas for Medical Sciences Institutional Review Board for the protection of human subjects reviewed the study protocol and determined that querying de-identified patient data does not fall under the jurisdiction of the Institutional Review Board oversight process.

Study Population

Patients undergoing Norwood operation for a diagnosis of hypoplastic left heart syndrome or a related single, morphologic right ventricular anomaly from the Pediatric Heart Network SVR trial public use dataset were included.^{10,11} No specific exclusion criteria were applied for the patients included in the SVR trial public-use dataset. The original dataset excluded patients with cardiac anatomy that would render either the MBT shunt or the RVPA shunt technically impossible; it also excluded patients with any major congenital or acquired extracardiac abnormality. Data collected included demographic information, baseline characteristics, anatomic diagnoses, interventions performed before Norwood operation, operation characteristics, and center data.

Analysis and Model Creation

The primary goal of this study was to use a model-based approach to create and validate a prediction tool for each of the 2 outcomes among patients undergoing the Norwood operation (both before and after the operation). Variables with missing data were imputed once by fully conditional specification before variable selection.

Variable selection. We used a Bayesian lasso logistic regression model to perform variable selection and regularization to create the prediction tool. Several candidate preoperative and operative predictors were used jointly to predict composite poor outcome in the variable selection model. For shrinkage, a lasso prior was used on the coefficients. The MCMC-based estimation for the Bayesian lasso logistic regression model was performed with the bayesreg package in R (R Core Team, Vienna, Austria).¹³ After MCMC simulations, we obtained posterior samples for each of the coefficients and constructed the middle 50% posterior credible sets. Predictors were considered to be significant only if corresponding credible sets did not include 0. Other predictors were selected for inclusion a priori due to clinical importance or based on the literature.

Prediction model. We used Bayesian conditional probit regression and MCMC simulations from the posterior distribution of the parameters to create a prediction tool for the study outcomes. To eliminate the effect of the scale of the continuous variables on the score, we standardized each continuous variable to a [0,1] range by subtracting the minimum value from each observation and then dividing by the actual range of that variable before entering them into the model. We used a 2-step conditional probit model to model the effect of the aforementioned variables on the outcomes. The parameter estimates from this model were then used to compute the predictive score for each outcome after the Norwood operation. Instead of modeling the probability of mortality and composite poor outcome separately, we approached this problem with a 2-step conditional probit model. We first used a bivariate (2-dimensional) outcome measure for each patient; we defined a bivariate random vector $Y = (Y_1, Y_2)$ such that they take the following values:

$$y = \begin{cases} (0, 0), & \text{Alive, No Morbidity} \\ (1, 0), & \text{Dead, No Morbidity} \\ (0, 1), & \text{Alive, Has Morbidity} \\ (1, 1), & \text{Dead, Has Morbidity} \end{cases}$$

Thus, Y_1 was the indicator variable for mortality or heart transplant (yes/no), and Y_2 was the indicator for morbidity, which was defined as the presence of at least 1 of the following 4 factors: (1) need for cardiopulmonary resuscitation after Norwood operation, (2) use of ECMO outside of the operating room, (3) prolonged mechanical ventilation, or (4) prolonged length of hospital stay. To model this bivariate outcome Y for each patient based on preoperative characteristics, we used a 2-step conditional probit regression model. We reparametrized the joint distribution of $Y = (Y_1, Y_2)$ using the marginal distribution of morbidity and the conditional distribution of mortality, given the patient does or does not have morbidity. This conditional probit model can be motivated with the 2 latent variables, Y_1^* and Y_2^* , as follows:

$$Y_k^* = \begin{cases} >0, & y_k = 1 \\ <0, & y_k = 0 \end{cases}$$

for $k=1, 2$. We modeled the prior probability distribution of these 2 latent variables with the patient characteristics identified previously. For each patient i , we set up the model such that:

$$\begin{aligned} Y_2^* &\sim N(x_i^T \beta_S, 1) \\ Y_{1i}^* | Y_{2i}^* > 0 &\sim N(x_i^T \beta_{M|S}, 1) \\ Y_{1i}^* | Y_{2i}^* < 0 &\sim N(x_i^T \beta_{M|NS}, 1) \end{aligned}$$

where each of β_S , $\beta_{M|S}$, $\beta_{M|NS}$ is a $p \times 1$ vector of regression coefficients (including intercept), x_i is a vector of patient i 's characteristics, and x_i^T indicates the transpose of the vector x_i . The coefficient vectors β_S , $\beta_{M|S}$, and

$\beta_{M/NS}$ pertain to the effect of covariates on the chance of the patient having morbidity, the chance of the patient dying given the patient has morbidity, and the chance of the patient dying given the patient does not have morbidity. Here, we allow that the chance of a patient dying when the patient has morbidity might be different than the chance of the patient dying when the patient does not have morbidity. With this model, the probabilities for the 4 combinations of the bivariate outcome Y were computed based on the equations to follow:

$$\begin{aligned} p_{00} &= P(Y_1 = 0, Y_2 = 0) = \Phi(-x_i^T \beta_S) \Phi(-x_i^T \beta_{M/NS}) \\ p_{01} &= P(Y_1 = 0, Y_2 = 1) = \Phi(x_i^T \beta_S) \Phi(-x_i^T \beta_{M/NS}) \\ p_{10} &= P(Y_1 = 1, Y_2 = 0) = \Phi(-x_i^T \beta_S) \Phi(x_i^T \beta_{M/NS}) \\ p_{11} &= P(Y_1 = 1, Y_2 = 1) = \Phi(x_i^T \beta_S) \Phi(x_i^T \beta_{M/NS}) \end{aligned}$$

where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution given by

$$\Phi(t) = \int_{-\infty}^t \frac{1}{\sqrt{2\pi}} e^{-z^2/2} dz$$

Thus, for each patient, the Norwood scores for each of the outcomes were calculated using the probabilities described previously as follows:

$$\begin{aligned} P(\text{Mortality}) &= p_{10} + p_{11} = \Phi(-x_i^T \beta_S) \Phi(x_i^T \beta_{M/NS}) + \Phi(x_i^T \beta_S) \Phi(x_i^T \beta_{M/NS}) \\ P(\text{Composite Poor Outcome}) &= p_{01} + p_{10} + p_{11} = 1 - p_{00} \\ &= 1 - \Phi(-x_i^T \beta_S) \Phi(-x_i^T \beta_{M/NS}) \end{aligned}$$

The MCMC algorithm used to estimate the parameter vectors β_S , $\beta_{M/NS}$, and $\beta_{M/NS}$ and to calculate the scores is described in detail in [Appendix E1](#). We also devised a method to calculate the risk of in-hospital mortality associated with the Norwood operation before the actual heart operation. Before the Norwood operation, a patient's demographic and pre-Norwood characteristics are known (and fixed), but the variables related to the heart operation are still unknown. To overcome this hurdle, we computed a weighted average of mortality scores, averaging all possible combinations of these variables coupled with a known set of preoperative characteristics. This was achieved via a kernel-density approach based on the variables related to the heart operation.¹⁴ Please refer to the [Appendix E1](#) for more details regarding the kernel density method.

Model validation. We used an internal 10-fold cross-validation approach to validate our prediction tool. Ten subsets (approximately 1/10th) of the data were created at random. The first subset was held out as the test sample, and the model was fitted on the remaining 9 subsets combined (training set). The resulting score developed from this training sample was used to predict outcomes in the test set. This process was repeated 10 times overall, holding each subsequent subset as a test sample and using the rest of the data as the training sample. To assess the accuracy of the prediction model, we calculated the area under the received operating characteristic curve for each outcome on the combined validation sample from the 10 rotations. Finally, we created a Web-based tool using R Shiny to allow users to calculate risk scores for individual patients.¹⁵ In general, 2-sided P values less than or equal to .05 were considered to be statistically significant.

RESULTS

In total, 549 patients qualified for inclusion. Of these, 241 patients (43.9%) were associated with composite poor outcome. In-hospital mortality was noted among 88 patients (16.0%), and cardiopulmonary resuscitation was required for 97 patients (17.6%) after heart operation. ECMO was deployed for 35 patients (6.4%) in the operating room and for 56 patients (10.3%) outside of the operating

room. The median duration of mechanical ventilation was 7 days (interquartile range 5, 13), and the median duration of hospital stay was 24 days (interquartile range 16, 41).

The characteristics of patients with and without composite poor outcomes are shown in [Table 1](#). The patients associated with composite poor outcomes were smaller in weight, associated with lower gestational age, more commonly associated with obstructed venous return, and were intubated more frequently before their Norwood operation. Operation characteristics such as longer cardiopulmonary bypass time, longer crossclamp time, open sternum after the heart operation, ECMO deployment at termination of heart operation in the operating room, and postoperative tricuspid valve regurgitation were associated more commonly with composite poor outcome. In addition, lower site volume and lower surgeon experience also were associated with a greater incidence of composite poor outcomes ([Table 1](#)).

We then used a Bayesian logistic lasso regression model to select variables for inclusion in the final model for creating the score. The training dataset used 520 patients to make the prediction model. The following variables were selected for inclusion by the variable selection model: birth weight, sex, gestational age, race, hypoplastic left heart syndrome, obstructed venous return, mechanical ventilation before Norwood operation, cardiopulmonary bypass time, crossclamp time, type of shunt (MBT shunt or RVPA shunt), other concomitant procedures performed at Norwood operation, ECMO deployment in the operating room, moderate/severe tricuspid valve regurgitation during Norwood operation, site volume, and surgeon experience. The following other variables were selected for inclusion in the model a priori because of their established clinical importance or on the basis of existing literature: aortic atresia, regional cerebral perfusion, and type of aortic arch reconstruction ([Table 2](#)).^{1-7,10} Overall, 90% of the variability among the latent variables was explained by the covariates in the final model used to create the prediction tool. An online calculator for the tool can be accessed at <https://soipredictiontool.shinyapps.io/NorwoodScoreApp/>. In addition to predicting outcomes after the Norwood operation, our model also predicts mortality before the heart operation.

We then validated the model with a 10-fold, internal cross-validation approach. Model validation was done on 520 observations. Our model predicted 92 deaths in our internal validation sample when the observed number of deaths was 88, and it predicted 240 patients with composite poor outcome when the observed number of patients with composite poor outcomes was 238 ([Table 3](#)). Overall, the area under the received operating characteristic curve on the internal validation sample was 0.77 for mortality and 0.72 for composite poor outcome, suggesting that the model has good discriminative ability for predicting outcomes ([Figure 1](#)).

TABLE 1. Patient and center characteristics

Variable	n	Composite poor outcome, n (%)	P
Age at Norwood, d			
<5	154	65 (42.2)	.64
5 to <7	159	67 (42.1)	
≥7	236	109 (46.2)	
Birth weight, g			
<2880	176	96 (54.6)	.002
2881 to <3334	186	77 (41.4)	
≥3334	187	68 (36.4)	
Sex			
Female	209	90 (43.1)	.75
Male	340	151 (44.1)	
Gestational age, wk			
<37	64	40 (62.5)	.001
≥37	485	201 (41.4)	
Prenatal diagnosis			
No	129	60 (46.5)	.49
Yes	420	181 (43.1)	
Race			
White	436	190 (43.6)	.29
African American	86	35 (40.7)	
Other	22	13 (59.1)	
Hispanic ethnicity			.65
No	438	193 (44.1)	
Yes	101	42 (41.6)	
Anatomic diagnosis			
HLHS			
No	75	40 (53.3)	.08
Yes	474	201 (42.4)	
Left ventricle present			
No	167	70 (41.9)	.61
Yes	375	166 (44.3)	
Aortic atresia			
No	206	95 (46.1)	.41
Yes	343	146 (42.6)	
Ascending aorta diameter, mm			
<2	114	48 (42.1)	.75
2 to <3.5	231	101 (43.7)	
≥3.5	190	88 (46.3)	
Obstructed venous return			
No	530	226 (42.6)	.001
Yes	19	15 (79.0)	
Baseline TV regurgitation			
No	167	70 (41.9)	.66
Yes (moderate/severe)	375	166 (44.3)	
Pre-Norwood interventions			
Fetal intervention			
No	406	175 (43.1)	.98
Yes	14	6 (42.9)	
Cardiac catheterization			
No	521	224 (43.0)	.06
Yes	28	17 (60.7)	

(Continued)

TABLE 1. Continued

Variable	n	Composite poor outcome, n (%)	P
Other surgical procedures			
No	541	234 (43.3)	.01
Yes	8	7 (87.5)	
Endotracheal intubation			
No	284	108 (38.0)	.003
Yes	263	133 (50.6%)	
Operation characteristics			
Total bypass time, min			
<114	180	65 (36.1)	.007
114 to <159	180	77 (42.8)	
≥159	189	99 (52.4)	
Total crossclamp time, min			
<43	176	66 (37.5)	.006
43 to <61	176	71 (40.3)	
≥61	197	104 (52.8)	
Shunt type			
RVPA	281	118 (42.0)	.35
Modified BT	268	123 (45.9)	
Classic aortic arch repair			
No	66	28 (42.4)	.80
Yes	479	211 (44.1)	
Other concomitant cardiac procedures			
No	488	208 (42.6)	.08
Yes	61	33 (54.1)	
Use of steroids			
No	51	20 (39.2)	.48
Yes	498	221 (44.4)	
Regional cerebral perfusion			
No	297	119 (40.1)	.04
Yes	252	122 (48.4)	
Ultrafiltration			
No	187	84 (44.9)	.72
Yes	362	157 (43.4)	
Open sternum			
No	118	23 (19.5)	<.001
Yes	426	213 (50.0)	
Post-Norwood TV regurgitation			
No	364	115 (31.6)	.002
Yes (moderate/severe)	116	59 (50.9)	
Post-Norwood neo-aortic valve regurgitation			
No	470	169 (36.0)	.51
Yes (moderate/severe)	11	5 (45.5)	
ECMO use in operating room			
No	514	212 (41.3)	<.001
Yes	35	29 (82.9)	
Site volume			
Annual single-ventricle volume, per y			
≤15	93	56 (60.2)	.002
16 to ≤20	109	57 (52.3)	
21 to ≤30	176	65 (36.9)	
>30	171	63 (36.8)	
Annual surgeon Norwood volume, per y			
≤5	108	62 (57.4)	.009

(Continued)

TABLE 1. Continued

Variable	n	Composite poor outcome, n (%)	P
6 to ≤10	113	57 (50.4)	
11 to ≤15	239	92 (38.5)	
>15	89	30 (33.7)	

HLHS, Hypoplastic left heart syndrome; TV, tricuspid valve; RVPA, right ventricle-pulmonary artery; BT, Blalock-Taussig; ECMO, extracorporeal membrane oxygenation.

DISCUSSION

We report a prognostic tool to predict poor outcomes both before and after a Norwood operation; the tool uses advanced modeling methods, such as Bayesian conditional probit regression models and MCMC simulations (Video 1). The newly proposed risk adjustment tool, composed of patient data, cardiac diagnosis, data related to heart operation, site volume, and surgeon experience, has a high degree of discrimination for predicting mortality and other outcomes among children undergoing a Norwood operation. This risk adjustment tool provides an efficient adjustment by condensing 10 risk factors into 1 probability before the heart operation and condensing 18 risk factors into 1 probability after the heart operation to predict poor outcomes.

To our knowledge, this is the first risk adjustment tool created to predict outcomes associated with this high-risk operation. Risk-stratifying patients before the heart operation will allow providers to deal with the technical, ethical, and financial issues inherent to this high-risk operation. This prognostic tool, which is unique to each patient, provides an opportunity for family counseling before and immediately after the heart operation. It also provides an opportunity to determine the probability of other poor outcomes related to the Norwood operation, including heart transplantation, the need for cardiopulmonary resuscitation, use of ECMO outside of the operating room, prolonged mechanical ventilation, or prolonged length of hospital stay.

Recently, Jeffries and colleagues¹⁶ developed a severity-of-illness score called the Pediatric Index of Cardiac Surgical Intensive Care Mortality score for children undergoing heart operations. However, this score was designed for use with surgical operations of all complexities, and it lacks important variables related to cardiac diagnoses, heart operation, surgeon experience, and site volume. We know from existing literature that these are all important risk factors for predicting morbidity and mortality among children undergoing a Norwood operation.^{1-7,17,18} Hence, including these factors may better predict outcomes in a uniform patient population than previous methods.

Our study uses advanced statistical tools to discover relationships between multiple variables and outcomes. The model developed in our study is more precise, accurate, and unbiased as compared with commonly used regression

models (such as logistic regression or probit regression models). Even though the logit and probit link functions are highly nonlinear, the traditional regression models use the point estimates of covariate effects. Treating the output as a point estimate of probability would result in significant approximation error. Our method does not rely on point estimates of covariate effects on outcomes. Our new model takes into account the effect of any such model uncertainty as it computes the entire probability distribution for the risk of outcome for any patient. The conditional probit approach also allows one to compute the conditional risk of any one outcome given the knowledge of other outcomes.

To determine the probability of mortality occurring before the Norwood operation is performed, we used a sophisticated model-based approach. We dealt with 2 probability distributions simultaneously: (1) the empirical distribution for the model coefficients in the probit-regression as determined through MCMC and (2) the distribution for the variables related to the heart operation that cannot be learned prior to the operation. For the latter distribution, we chose a nonparametric density estimation technique based on kernels so that our method does not rely on any assumption about the pattern of those variables in the historical clinical records only. The benefit of using this probability-based approach instead of relying on point-estimates is that it takes into account many possible real-world scenarios, weighted by the likelihood of their occurrence so that the final output adequately reflects the uncertainty in inference and decision-making.

Our study has several limitations. The retrospective nature of this study renders it susceptible to study design flaws and bias. The data used to create the prediction tool were collected during a period of time when surgical and postoperative practices might have been different than the current practices. Although we attempted to adjust for important patient- and center-level factors, our dataset lacked important variables (eg, underlying comorbidities, data on postoperative variables immediately after the heart operation, use of nitric oxide, data on inotropes, and data on mechanical ventilation) that could have impacted our analysis. We also could not account for team structure or night time in-house practitioner coverage for the intensive care unit that could have impacted the study outcomes.¹⁹

Another potential shortcoming of our study is that the dataset that was used to derive the prediction tool also was used to validate the same tool. Therefore, we recommend validating this tool in a different multi-institutional dataset from the current era. We believe there is an opportunity to improve the model discrimination with additional clinical data, and we recommend that our tool be validated over time for continued reproducibility. Like other prediction models, our tool could be subject to drift that may require frequent modifications. Because our tool was

TABLE 2. Bayesian lasso regression variable selection model

Variable	Level	Estimate	Lower 50%	Upper 50%	Selected
Age at Norwood, d	1 d	0.38	−0.01	0.86	No
Birth weight, g	1 g	−1.57	−2.05	−1.09	Yes
Sex	Male	0.11	0.01	0.22	Yes
Gestational age, wk	1 wk	−1.34	−1.92	−0.81	Yes
Prenatal diagnosis	Yes	0	−0.1	0.11	No
Race	AA	−0.11	−0.26	0.01	Yes
Race	Other	0.31	0.07	0.59	Yes
Hispanic ethnicity	Yes	0.01	−0.1	0.12	No
HLHS	Yes	−0.28	−0.46	−0.11	Yes
Left ventricle present	Yes	0.05	−0.04	0.16	No
Aortic atresia	Yes	−0.07	−0.19	0.03	No
Exterior diameter ascending aorta	1 mm	−0.1	−0.41	0.18	No
Obstructed venous return	Yes	0.84	0.43	1.27	Yes
Pre-Norwood ETT	Yes	0.2	0.08	0.33	Yes
Pre-Norwood cardiac catheterization	Yes	0.03	−0.2	0.26	No
Baseline TV regurgitation	Moderate/severe	0	−0.12	0.14	No
Operation bypass time	1 min	0.6	0.17	1.12	Yes
Operation cross clamp time	1 min	0.79	0.25	1.37	Yes
Use of steroids	Yes	0.14	−0.01	0.33	No
Regional cerebral perfusion	Yes	−0.06	−0.18	0.04	No
Ultrafiltration	Yes	0.02	−0.07	0.13	No
Shunt type	MBT shunt	0.12	0.02	0.24	Yes
Type of arch reconstruction	Classic	0.07	−0.06	0.22	No
Other concomitant cardiac procedures	Yes	0.22	0.06	0.41	Yes
ECMO use in operating room	Yes	1.18	0.87	1.48	Yes
Post-Norwood TV regurgitation	Moderate/severe	0.93	0.78	1.07	Yes
Post-Norwood neo-aortic valve regurgitation	Moderate/severe	0.21	−0.08	0.56	No
Site volume	>20	−0.61	−0.78	−0.44	Yes
Surgeon volume	>10	−0.22	−0.36	−0.1	Yes

AA, African-American; HLHS, hypoplastic left heart syndrome; ETT, endotracheal tube; TV, tricuspid valve; MBT, modified Blalock-Taussig; ECMO, extracorporeal membrane oxygenation.

derived from patients undergoing a Norwood operation, this tool should not be applied to patients undergoing other heart operations.

CONCLUSIONS

We report a novel prognostic tool to predict real-time outcomes among children undergoing a Norwood operation.

TABLE 3. Comparison of predicted with observed outcomes by quintile of predictive index for composite poor outcome

Quintile	n	New tool probability			Composite poor outcome		Incidence ratio O/E (95% CI)
		Minimum	Maximum	Average	O	E	
1	108	0.0899	0.2308	0.1731	28	18.7	1.49 (0.94-2.26)
2	108	0.2313	0.3393	0.2837	30	30.6	0.98 (0.63-1.46)
3	108	0.3410	0.4501	0.3965	42	42.8	0.98 (0.68-1.37)
4	108	0.4517	0.6376	0.5469	58	59.1	0.98 (0.73-1.30)
5	108	0.6427	0.9999	0.8226	80	88.8	0.91 (0.70-1.14)
Overall	540	0.0899	0.9999	0.4446	238	240.1	0.99 (0.86-1.13)

O, Observed; E, expected; CI, confidence interval.

FIGURE 1. Receiver operating characteristic curves. The *red line* depicts the AUC for composite poor outcome, and the *blue line* depicts the AUC for mortality or heart transplantation. AUC, Area under the curve.

This tool is a promising first step toward creating a risk-stratification for the purposes of benchmarking, family counseling, and research. In addition to providing prognostic information on mortality, this tool also provides information on other poor outcomes after the Norwood operation, such as heart transplantation, need for cardiopulmonary resuscitation, use of ECMO outside the operating

room, prolonged mechanical ventilation, or prolonged length of hospital stay. Future studies should seek external validation and improved discrimination for this prediction tool.

Conflicts of Interest Statement

Authors have nothing to disclose with regard to commercial support.

VIDEO 1. Study description by Dr Punkaj Gupta. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)31795-6/fulltext](http://www.jtcvsonline.org/article/S0022-5223(17)31795-6/fulltext).

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Key Words: Norwood operation, prediction tool, severity of illness, risk predictors—Bayesian, Markov chain Monte Carlo

APPENDIX E1.

Bayesian Markov Chain Monte Carlo (MCMC)

Algorithm to Estimate Parameters in the Conditional Probit Model

We estimated the parameters β_S , $\beta_{M|S}$, and $\beta_{M|NS}$ by Gibbs sampling, a MCMC technique to simulate a sequence of observations from the posterior distributions of the parameters when direct sampling is difficult.^{E1} Given any patient's outcome for morbidity and mortality, y_1^* and y_2^* for that patient are simulated from the aforementioned normal distributions but truncated to be positive (>0) or negative (<0), based on whether y_1 and y_2 are 1 or 0, respectively. Given draws of Y_1^* and Y_2^* for every patient, we generated MCMC samples from posterior distributions of β_S , $\beta_{M|S}$, $\beta_{M|NS}$ with the following steps:

1. Assigned multivariate normal prior distributions with a large variance to each of the parameter vectors β_S , $\beta_{M|S}$, and $\beta_{M|NS}$.
2. The multivariate posterior distributions of β_S , $\beta_{M|S}$, $\beta_{M|NS}$ were then derived based on the conjugate normal family.^{E2} For the first iteration, we started with initial parameter estimates of $\beta = (\beta_S, \beta_{M|S}, \beta_{M|NS})$.
3. For the t^{th} iteration, we generated $y_1^{*(t)} | \beta^{(t)}, X, y$ and $y_2^{*(t)} | \beta^{(t)}, X, y$ based on the truncated normal densities described previously.
4. Sampled $\beta^{(t+1)} | y_1^{*(t)}, y_2^{*(t)}, X, y$ from the posterior multivariate normal density derived in step 2.
5. Steps 3 to 5 were repeated 75,000 times.^{E3,E4} The first 25,000 were then discarded as "burn-in." The remaining 50,000 samples, taken to be approximate random samples from the posterior densities of the parameters, were thinned at every fifth draw (to further reduce any correlation among samples) to obtain the final 10,000 samples of β_S , $\beta_{M|S}$, and $\beta_{M|NS}$.
6. For each posterior sample of the parameters thus obtained, the scores for each outcome were computed with the formulae given previously.
7. The scores were then averaged over the 10,000 samples to obtain the final Norwood scores for each of the 3 outcomes.
8. For computing the risk of mortality or heart transplantation prior to the Norwood operation, we used 5000 MCMC samples from the posterior distribution for each weighted combination of the variables related to the heart operation.

Assessing Convergence of the MCMC Samples

We assessed convergence of the MCMC chain using Geweke's convergence diagnostic with the coda package in R.^{E5,E6} It computes a z score based on the difference between the first 10% and the last 50% of the posterior samples. We chose the samples from negative 2 times the

logarithm of the posterior density as a way of summarizing the convergence of all parameters involved in the model.^{E7} We obtained a z score of -0.021 , indicating the chain had satisfactorily converged.

Kernel Density Approach for Estimating Risk of Mortality Before the Heart Operation

Before the Norwood operation, a patient's demographic, and pre-Norwood characteristics are known (and fixed), but the variables related to the heart operation are still unknown. To overcome this hurdle, we computed a weighted average of scores of mortality, averaged over all possible combinations of these variables and coupled with a known set of preoperative characteristics. This was achieved using a kernel-density approach on the space of variables related to the heart operation.^{E8} For the 2 continuous variables, crossclamp time and bypass time, we fitted a bivariate distribution using a Gaussian kernel as in

$$\hat{f}(z|\Sigma) = \frac{1}{n} \sum_{i=1}^n \phi(z; z_i, \Sigma),$$

where n is the number of observations, z is the 2-dimensional vector (crossclamp time, bypass time), and z_i is the value of z for the i^{th} observation in the data. The kernel is a 2-dimensional Gaussian density function with mean vector z_i and dispersion matrix Σ evaluated at the point z .

$$\phi(z; z_i, \Sigma) = \frac{1}{2\pi} |\Sigma|^{-0.5} \exp \left\{ -\frac{(z - z_i)^T \Sigma^{-1} (z - z_i)}{2} \right\}$$

This measures the weight of the information z_i in determining the density at z using the proximity between z and z_i . The weight depends on the parameters of the kernel-dispersion Σ , usually referred to as bandwidth parameters in kernel-based techniques. Larger values along the diagonal of Σ usually result in observations farther away from z being given greater importance in determining $\hat{f}(z|\Sigma)$ whereas smaller bandwidth parameters lead to more localized density estimation. We estimated the entries of Σ using plug-in bandwidth selectors.^{E9} After estimating density, we evaluated $\hat{f}(z|\Sigma)$ at 13 different sample quantiles and determined the weights based on normalized values of the kernel density at those points. For the 6 binary variables related to the heart operation, we chose a 6-dimensional kernel that assigns weight to every combination of these variables based on its proportion of occurrence in the observed sample. Hence, we obtained a set of weights for several different combinations of these eight variables related to the heart operation. The kernel-based approach for calculating the weights of continuous variables has been implemented with the *ks* package in R software.^{E10}

The bandwidth parameters play a key role in deciding the smoothness of the kernel density estimate for the

continuous operative variables. Hence, selection of bandwidths assumes importance. For this work, we used the bandwidth selection technique of Wand and Jones.^{E9}

Here, $\Sigma = \begin{bmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{21} & \sigma_{22} \end{bmatrix}$ is a 2×2 symmetric positive definite matrix ($\sigma_{21} = \sigma_{12}$). The diagonal entries σ_{11} and σ_{22} control the extent of local averaging in constructing the density estimates for crossclamp time and bypass time, respectively. The off-diagonal entry σ_{12} allows for sharing of information between the 2 variables based on the strength of their association. Using a simpler diagonal structure for Σ would be equivalent to independently fitting 2 separate kernel densities to crossclamp time and bypass time, but given a significant value of correlation coefficient ($r = 0.63$) between these 2 variables in our sample, it would not be a reasonable assumption. The plug-in method used here minimizes the mean integrated squared error (MISE, defined as $MISE(\Sigma) = E \int_z (f(z) - \hat{f}(z|\Sigma))^2 dz$) as a func-

tion of Σ , where f is true bivariate joint density of cross clamp time and bypass time. This method starts with an initial bandwidth matrix (referred to as the pilot bandwidth) that is plugged-in to create a closed-form expression for asymptotic MISE, and Σ is obtained by numerically minimizing that expression. Alternatively, bandwidth selection also can be performed with cross-validation-based techniques.

Percent of Variability Explained by the Model

The percentage of variability in the outcomes that is captured by the predictor variables is particularly

intuitive for a Bayesian framework. This measure is based on the continuous latent variable representation of binary data, which is what we used in our model to create the score through $Y^* = (Y_1^*, Y_2^*)$. The measure is given by the ratio of variability in the covariate-dependent mean to the total variability of these latent variables. We obtained an empirical distribution of this measure with MCMC simulations. The mean of this measure was 0.90, or 90%, suggesting that there is a significant amount of variability among Y^* that is explained by the covariates.

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