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

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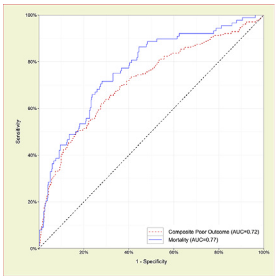
ABSTRACT

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]

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

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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:

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

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:

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

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