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Outcomes and risk factors for listing for heart transplantation after the Norwood procedure: An analysis of the Single Ventricle Reconstruction Trial

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BACKGROUND: Infants with hypoplastic left heart syndrome after palliation have the worst survival among heart transplant recipients. Heart transplantation is often reserved for use in patients with sub-optimal results after palliative surgery. This study characterized outcomes after listing in infants with a single ventricle who had undergone the Norwood procedure and identified predictors of the decision to list for heart transplantation.

METHODS: The public-use database from the multicenter, prospective randomized Single Ventricle Reconstruction trial was used to identify patients who were listed for heart transplantation. Outcomes on the waiting list and after transplantation were determined. Risk factors were compared between those who were listed and those who survived without listing.

RESULTS: Among 555 patients, 33 patients (5.9%) were listed and 18 underwent heart transplantation. Mortality was 39% while waiting for a heart and was 33% after heart transplantation. Overall, 1-year survival after listing (including death after transplantation) was 48%. Factors associated with listing were a lower right ventricular fractional area change at birth, non-hypoplastic left heart syndrome diagnosis, and a more complicated post-Norwood course, defined as a higher need for extracorporeal membrane oxygenation, longer intensive care unit stay, more complications, and a higher number of discharge medications.

CONCLUSIONS: Worse right ventricular function, non-hypoplastic left heart syndrome diagnosis, and complex intensive care unit stay were significant risk factors for listing for heart transplantation after the Norwood procedure. Heart transplantation as a rescue procedure after the Norwood procedure in the first year of life carries a significant risk of mortality.

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Single-ventricle (SV) physiology is the most common form of congenital heart disease (CHD) present in children undergoing heart transplantation (HT).[1] Because the results of palliative surgery have improved, HT is often reserved for patients who are not good candidates for palliative surgery or in whom palliation has failed.[2] Data from the United Network for Organ Sharing registry and the Pediatric Heart Transplant Study indicate that patients with SV are at

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a very high risk for waiting list and HT mortality.[1,2] Infants who undergo HT with hypoplastic left heart syndrome (HLHS) and previous surgery have the worst survival, and in some reports, are twice more likely to die than infants with cardiomyopathy.[2] Reports of listing and outcomes in this population are limited by a lack of data about patient course before listing and sparse data regarding the course of the patients while listed.

The National Institutes of Health/National Heart, Lung, and Blood Institute–funded Pediatric Heart Network completed a prospective, multicenter, randomized trial, the Single Ventricle Reconstruction (SVR) trial, comparing outcomes after the Norwood procedure performed with a modified Blalock-Taussig shunt vs a right ventricle–to–pulmonary artery shunt in infants with SV. The methods and results have been published previously.[3,4] The primary outcome was the incidence of death or HT. The occurrence and age at listing for HT was collected during the trial. 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. This data set offers the unique opportunity to characterize outcomes after listing for HT and evaluate predictors of the need for listing for HT in a large, well-characterized population of neonates with SV physiology who had undergone the Norwood procedure.

Methods

The SVR trial public-use data set was queried to identify patients who were listed for HT and those who were alive without listing. The median age at death in the trial was 1.6 months (interquartile range, 0.6–3.7 months), and 75% of the patients died during the initial neonatal hospital stay.[5] Patients who died and were not listed were not included in the analysis because the low likelihood of finding a suitable organ in the neonatal period precluded transplantation in most of the patients who died.

In the cohort of patients listed for HT, outcomes after listing to the last known follow-up were collected, and potential risk factors for listing for HT were collected from the data set. These included demographic variables of gender, gestational age, birth weight, fetal intervention, prenatal diagnosis, anatomic variables of aortic atresia, ascending aortic dimension, HLHS morphology, total anomalous pulmonary venous return, and variables from the first echocardiogram at birth of tricuspid regurgitation (TR), right ventricular fractional area change, and right ventricular end diastolic volume indexed to body surface area.

Before study initiation, sites received training from the echocardiographic core laboratory in protocol image acquisition, and during the course of the study, the core laboratory provided regular quality assurance feedback. All echocardiograms were analyzed in the echocardiography core laboratory at the University of Wisconsin.[6] TR was graded in the database as 0, 1, 2, and 3 for none, mild, moderate, or severe degrees of TR.[6] The following variables up to the time of Norwood discharge were included in the analysis: the type of shunt (modified Blalock-Taussig vs right ventricle–to–pulmonary artery), age at Norwood, extracorporeal membrane oxygenation (ECMO) use before and after the Norwood, ventilated days, intensive care unit (ICU) days, complications, catheterizations, other surgeries during Norwood hospitalization, length of stay (LOS), and number of medications at discharge from the Norwood hospitalization.

Statistical methods

Survival after listing, including death on the waiting list and death after transplantation, was determined using Kaplan-Meier analysis. Mutually exclusive states of listing for HT and survival without HT were defined for the purposes of identifying potential risk factors for listing for transplantation in the population of patients for whom transplantation was a feasible. Descriptive data are expressed as mean ± standard deviation for normally distributed data and as median and interquartile range (IQR) for non-normally distributed data. Differences in baseline patient characteristics and Norwood-associated variables between listing for HT and survival without listing for HT were compared using chi-square or Fisher's exact tests for categoric variables and Student's *t*-tests or Wilcoxon rank sum tests for continuous variables. Poisson regression model was used to compare differences in ICU days between the 2 groups. Logistic regression was performed to assess effects of baseline characteristics and Norwood-associated variables on the likelihood of listing for HT. Because only 33 patients were listed for HT, variables with a univariate p-value <0.1 and more than 10 patients per group were included for multivariate analysis. Analyses were performed using SAS 9.3 software (SAS Institute Inc, Cary, NC). A p-value <0.05 was considered significant for all analyses.

Results

Patient population

Figure 1 demonstrates the outcomes in the randomized patients. Within the randomized cohort of 555 patients, 33 (5.9%) were listed for HT, and 363 were alive and not listed at the end of follow-up. Death without listing for transplantation occurred in 159 of 555 patients, with a 1-year mortality rate of 29%. The mean follow-up for all randomized patients was 2.1 years (1.7 ± 2.9 years).

Outcomes after listing

The median age at listing was 114 days (IQR, 6–713 days). Listing in 30 of 33 patients was at status 1A , with 2 at status 7 and 1 at status 2. The median time from Norwood to

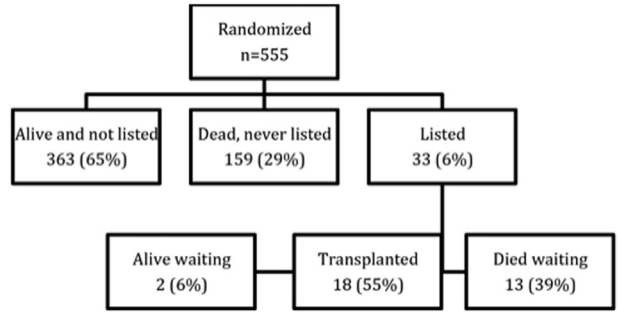

Figure 1 Outcome amongst all randomized patients in the Single Ventricle Reconstruction trial. (One patient amongst the alive patients who were not listed was lost to follow-up.)