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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

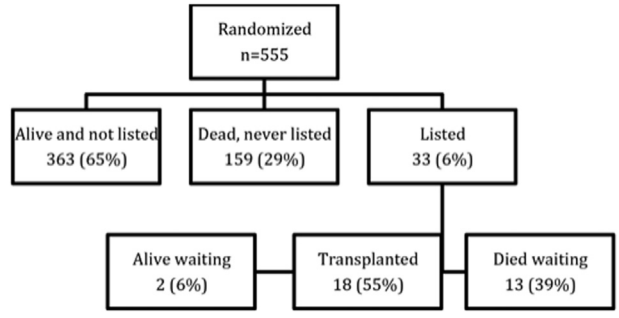

Figure 1 Outcome amongst all randomized patients in the Single Ventricle Reconstruction trial. (One patient amongst the alive patients who were not listed was lost to follow-up.)

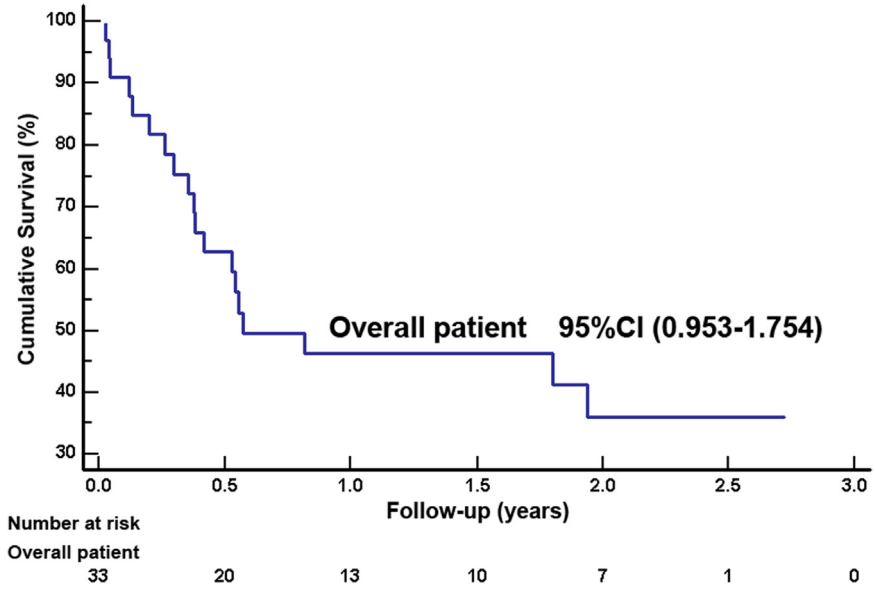

Figure 2 Kaplan-Meier curve of all listed patients and patients who underwent heart transplantation. The 1-year survival for all listed patients was 48%. CI, confidence interval.

listing was 110 days (IQR, 1–707 days). There were 15 patients listed for HT after the stage II procedure. During the follow-up period of the SVR trial, none of the patients in the data set had undergone the Fontan procedure. Of the 33 patients who were listed, 18 (55%) received HT by the end of the study follow-up. The median time from listing to HT was 25 days (IQR, 2–271 days). Death on waiting list occurred in 13 patients (39%), with a median time to death from listing of 129 days (IQR, 10–707 days). Causes of death on the waiting list included cardiac in 10 patients, renal in 1, and unknown in 2.

Survival after listing, including death on the waiting list and death after HT, was determined using Kaplan-Meier analysis (Figure 2). In addition to the 13 patients who died on the waiting list, 6 patients (33%) died after HT with a median time of death of 166.5 days (IQR, 48–658 days). One-year mortality after listing was 52%. Overall, 19 of the 33 patients (58%) listed for HT died.

Risk factors for listing

Results from the univariate comparison of baseline characteristics between the patients who were listed and those who were alive at last follow-up without listing are summarized in Table 1. Pre-natal diagnosis, fetal intervention, gender, gestation age, birth weight, diagnosis of aortic atresia, and ascending aortic dimensions did not predict listing. The right ventricular size before the Norwood procedure was significantly more dilated in the listed cohort than in those alive and not listed, and a significantly higher proportion of listed infants had TR

Table 1 Baseline Comparisons Between Listed and Survival Groups

Baseline variables[a]	Listed ($n = 33$)	Survival without listing ($n = 362$)	p-value[b]
Pre-natal diagnosis	21 (63.6)	282 (77.9)	0.063
Fetal intervention	1/22 (4.5)	9/282 (3.2)	0.534[c]
Male gender	16 (48.5)	229 (63.3)	0.094
Gestational age, weeks	38.3 ± 1.2	38.3 ± 1.4	0.828
Birth weight, kg	3.1 ± 0.5	3.1 ± 0.5	0.694
Aortic atresia	20 (60.6)	228 (63)	0.787
TAPVR	2 (6.1)	1 (0.3)	0.019[c]
HLHS	26 (78.8)	321 (88.7)	0.1[c]
Ascending aorta dimension, mm	2.9 ± 1.7	3.2 ± 1.7	0.334
RVEDVI at birth, ml/m^2	104.5 ± 24.5	85.8 ± 22.9	<0.001
Significant TR > 2	9/23 (39.1)	34/237 (14.3)	0.006[c]
RVFAC at birth, %	29.7 ± 9	35.1 ± 8.8	0.002

HLHS, hypoplastic left heart syndrome; RVEDVI, right ventricular end diastolic volume indexed; RVFAC, right ventricular fractional area change; TAPVR, total anomalous pulmonary venous return; TR, tricuspid regurgitation.

[a]Categoric data are shown as number (%) and continuous data as mean ± standard deviation.

[b]The p-values were obtained by Pearson chi-square test for categoric variables or the Student's t-test for continuous variables, unless otherwise specified.

[c]Fisher's exact test was used for this analysis.

Table 2 Norwood-Associated Comparisons Between Listed and Survival Groups

Variables[a]	Listed ($n = 33$)	Survival without listing ($n = 362$)	p-value[b]
RVPAS	19 (57.6)	196 (54.3)	0.717
Age at Norwood, days	7.1 ± 3.5	6.6 ± 3.8	0.549
ECMO support			
Before Norwood	7 (21.2)	9 (2.5)	<0.001[c]
After Norwood	10 (30.3)	17 (4.7)	<0.001[c]
Ventilated days	34.8 ± 58.3	11.1 ± 24.9	<0.001[d]
Length of stay, days			
ICU	51.2 ± 65.4	22.3 ± 30.2	0.005[d]
Hospital	55.8 ± 64.2	33.3 ± 32.7	0.226[d]
Other surgeries	2.7 ± 2.8	1.5 ± 1.4	<0.001[e]
Complications	4.8 ± 5	2.3 ± 2.8	<0.001[e]
Catheterizations ≥ 1	5 (15.2)	25 (6.9)	0.093[c]
Medications on discharge	5.9 ± 6.1	5.1 ± 2.1	<0.001[e]

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RVPAS, right ventricle–to–pulmonary artery shunt.
[a]Continuous data are shown as mean ± standard deviation and categoric data as median (%).
[b]The p-values were obtained by Pearson chi-square test for categoric variables or Student's t-test. for continuous variables, unless otherwise specified.
[c]Fisher's exact test was used for this analysis.
[d]Wilcoxon rank test was used for this analysis.
[e]Poisson regression model was used for this analysis.

grade >2. Right ventricular fractional area change before the Norwood procedure was significantly lower in the listed cohort than in those alive and not listed. A comparison of variables associated with the Norwood operation between the 2 cohorts is reported in Table 2. The shunt type and the age at Norwood did not affect listing status. The listed patients had a significantly higher need for ECMO before and after the Norwood operation. The listed cohort was ventilated longer compared with the alive and not listed cohort. They had longer ICU stay and more complications. There were also more patients in the listed cohort who required catheterizations and more other surgical procedures performed during the Norwood hospitalization. The listed cohort was discharged home after the Norwood procedure on more medications.

The results of the multivariate analysis are reported in Table 3. A significantly lower odds ratio (OR) for listing was associated with a better right ventricular fractional area change (OR, 0.69; $p = 0.002$) and a diagnosis of HLHS (OR, 0.36; $p = 0.043$). A higher OR for listing was associated with longer ICU stay (OR, 2.42; $p < 0.001$). A more complex course consisting of increased LOS, more surgeries, more complications, and more discharge medication after the Norwood was correlated with the need for listing (Table 4).

Table 3 Multivariate Analysis of Factors Associated With Listing for Heart Transplantation

Variable	Odds ratio	95% CI	p-value
RVFAC (5% increment)	0.689	0.543–0.874	0.002
HLHS	0.362	0.136–0.966	0.042
ICU days (log transformation)	2.416	1.572–3.713	<0.001

CI, confidence interval; HLHS, hypoplastic left heart syndrome; ICU, intensive care unit; RVFAC, right ventricular fractional area change.

Discussion

In this large, multicenter population of infants with HLHS and variants of HLHS, listing for HT was rare (6%), and only 3.2% of the patients underwent transplantation. The decision to place a patient on the waiting list was based on individual center preference and not dictated by the study; thus, these results are a reflection of the clinical practice at 15 large centers in the United States and Canada. The 48% mortality after listing, including death on the waiting list and death after transplantation, indicates the limitations of HT when used as a treatment strategy for infants with a failed palliation. Of the patients listed for HT, 46% were listed after their stage II operation. HT occurred in 55% of the listed patients. Waiting list mortality was high in this cohort of patients (39%), and post-transplantation mortality was also high (33%). Analysis of the U.S. Scientific Registry of Transplant Recipients has previously shown high waiting list mortality in patients supported with ECMO and with a longer duration of mechanical ventilation.[7] Previous reports have also described poor survival and similar rates of mortality on the waiting list and after transplantation in SV patients.[2,8]

This report describes risk factors for the decision to list for HT and outcomes after listing in a large, well-characterized, multicenter population of infants with

Table 4 Correlation Between Norwood Hospitalization Variables

Variable	Length of stay	Other surgeries	Compli-cations	Discharge medications
Correlation coefficient (r)	0.933	0.644	0.756	0.496
p-value	<0.001	<0.001	<0.001	<0.001

HLHS or SV variant. The prospective nature of the SVR study provided an opportunity to assess risk factors present at birth, at the Norwood operation, and during the initial Norwood hospitalization that predicted listing for HT. Practice patterns, patient characteristics, and small numbers preclude a similar analysis at the individual center level.

Demographic data were comparable between the listed and the survival cohort. Worse right ventricular function, non-HLHS diagnosis,[4] and complex ICU stay were significant risk factors for listing for HT after the Norwood procedure. This study identified several differences in the risk factors associated with listing compared with the risk factors associated with death or transplantation in prior SVR publications. The rate of listing for transplantation was similar between the 2 types of shunt, although transplantation-free survival was higher in the right ventricle–to–pulmonary artery shunt group at age 12 months.[4,9–11] Lower gestational age, smaller ascending aortic diameter, presence of a genetic syndrome, and obstructed pulmonary venous return were risk factors for death or transplantation in the SVR trial.[9,11] Gestational age and ascending aortic dimensions were not associated with listing. Genetic syndromes and obstructed pulmonary venous return were not identified as risk factors for listing, presumably because patients with these findings were unlikely to survive to listing for HT. Patients with TR of moderate to severe degree had a high risk of death at Norwood and during the interstage period.[10,12] The small number of patients who were listed precluded analysis of the effect of TR on listing, because 9 of 33 patients had TR >2.

Not surprisingly, several of the risk factors for listing identified in this study were similar to those associated with transplantation in previous analysis from the SVR trial.[11] These included non-HLHS anatomy and lower pre-Norwood right ventricular fractional area change. These data may be useful in clinical decision-making in patients with HLHS. The finding of low right ventricular fractional area change on echocardiograms at birth in neonates with non-HLHS may identify patients in whom performing the Norwood operation carries a higher risk of failure and encourage clinicians to consider alternatives, such as HT or even comfort care, at an early stage. The effect of earlier referral and listing in this high-risk group requires further study in a larger cohort of listed patients.

This analysis also identified variables associated with a more complicated course during the Norwood hospitalization as a risk factor for listing, suggesting that the listed cohort was sicker than the survival cohort. Hospital course after the Norwood procedure was not included in the analysis by Tweddell et al[11] of risk factors for transplantation.

Limitations

This analysis had some limitations. The SVR trial was not primarily designed to assess listing for HT. The decision to list for HT was not part of a protocol and was left to the discretion of the individual centers, The indication for HT was not defined in the data set. Data regarding known risk factors for listing, such as blood type, creatinine, and glomerular filtration rate, are not available in the data set. However, HT was a primary outcome in this trial, and therefore, accurate data are available in this cohort of patients with regards to this outcome and the listing status.

There was a low power to identify the effect of potential risk factors with a low incidence because of the small sample size. There may be a selection bias within our analysis from the patients who were only randomized into the SVR trial. However, the rate of listing among all patients screened for the SVR trial was similar to the rate of listing in the randomized cohort that was analyzed (4.5% vs 5.9%, respectively).

The mean age of follow-up on the public-use database was 2.1 years; therefore, risk factors for listing at the time of the Fontan operation could not be assessed in this analysis.

Conclusions

HT as a rescue procedure after the Norwood procedure carries a significant risk of mortality in SV patients. This analysis highlights the limitations of HT in this population and indicates the need to assess the effect of earlier referrals for listing on outcomes.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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