The reality of limping to pediatric heart transplantation

Kyle W. Riggs, MD,a Farhan Zafar, MD,a Angela Lorts, MD,b Clifford Chin, MD,b Roosevelt Bryant III, MD,a James S. Tweddell, MD,a and David L. S. Morales, MDa

ABSTRACT

Objective: Improvements in surgical technique, critical care, and early repair for congenital heart disease (CHD) have led to improved outcomes with heart transplantation, often used as a salvage procedure after failed palliation, especially in infants. These patients, however, often have several risk factors for poor posttransplant survival. We aimed to identify the reality of survival after heart transplantation in patients “limping to transplant” with common risk factors.

Methods: All heart transplant recipients younger than 18 years were identified from the UNOS data set from 2000 to 2017. Modifiable risk factors (MRFs) of mechanical ventilation, renal dysfunction, and liver dysfunction at transplant and nonmodifiable risk factors of infancy at listing or CHD were examined. One-year posttransplant survival was analyzed with logistic regression.

Results: Of 4101 transplants, 1459 patients (36%) had 1 or more MRFs. There was a decrease in 1-year survival with additional MRFs up to a 9.1-times increased risk of death in an infant with CHD. A noninfant without CHD and no MRFs had a 95% 1-year survival, in contrast to an intubated patient with CHD without other end-organ dysfunction, who had 1-year survival of 76%, which decreased to 58% if they were an infant and also had renal dysfunction.

Conclusions: Patients “limping to transplant” with multiple risk factors demonstrates decreasing early survival relative to those without other end-organ dysfunction. It is imperative that we have transparent discussions about expected outcomes with these families and identify ways to optimize patients’ conditions through other supportive avenues to improve posttransplant outcomes. (J Thorac Cardiovasc Surg 2020;159:2418-25)

CENTRAL MESSAGE

Patients with multiple risk factors present at pediatric heart transplantation have significantly reduced 1-year posttransplant survival, which worsens with increasing number of risk factors.

PERSPECTIVE

Early survival in pediatric heart transplantation has continued improving since its inception, but providers need be aware of realistic expectations for certain groups of pediatric heart transplant candidates to facilitate transparent conversations with families and to stimulate the search for better methods of optimizing patient condition before transplantation.

See Commentaries on pages 2426, 2427, and 2429.
Those for whom palliation fails, however, have no option other than transplantation. This may explain why patients with CHD account for the majority of donor heart usage in infancy and after the age of 10 years. This has led to a growing number of children who receive cardiac transplants who often have a number of the known risk factors for worse posttransplant survival at listing and transplantation. These risk factors include extracorporeal membrane oxygenation (ECMO), mechanical ventilation, younger age, diagnosis of CHD, lower weight (<4 kg), renal dysfunction, and poor functional status. Although some of these factors are not modifiable (eg, age at listing, diagnosis), others are somewhat unappreciated (eg, intubation), as they are commonly seen in our inpatients awaiting transplantation. Also common is the increasing number of patients being bridged to transplantation with ventricular assist devices (VADs), which has been demonstrated to afford recipients with and without CHD the same transplantation outcomes as those not supported with a VAD.

The reality of modern pediatric heart transplantation is that many of our patients are at risk. Rizwan and colleagues demonstrated this through an analysis of survival from the day of transplant listing, in which they found that even patients with commonly seen risk profiles had worse outcomes than expected. For example, an infant with congenital heart disease who was just mechanically ventilated with no other risk factors had a 40% survival at 1 year from listing. Having previously demonstrated the expected outcomes from the day of listing, we sought to identify outcomes for those patients who ultimately underwent transplantation to elucidate possible areas for improvement as well as to provide realistic expectations to caregivers, patients, and families in a clinically relevant format.

METHODS

Patients
After obtaining institutional review board approval from the Cincinnati Children’s Hospital, we retrospectively reviewed data from the United Network for Organ Sharing database for pediatric heart transplant recipients from 2000 to 2017. Preoperative risk factors were selected from well-known risk factors for early mortality previously identified by multivariate analysis in other studies. Risk factors were classified as modifiable risk factors (MRFs) and nonmodifiable risk factors. The MRFs selected at the time of transplant were need for mechanical ventilation; impaired renal function, as defined as estimated glomerular filtration rate less than 60 mL/min/1.73 m² by use of the Schwartz method or dialysis after listing; and impaired liver function, defined as total bilirubin greater than 3.0 mg/dL. The nonmodifiable risk factors included age less than 1 year at listing and a diagnosis of CHD. Age was considered a categorical variable rather than a continuous variable, because approximately 40% of pediatric patients receiving transplants were infants (younger than 1 year), making this a reasonable midway split of the data. Furthermore, age is routinely analyzed this way by the International Society of Heart and Lung Transplantation. Patients with VAD support at transplant were excluded from the analysis, because VAD support has been shown to mitigate the effects of end-organ dysfunction on posttransplant outcomes.

Statistical Analysis
Overall descriptive statistics were compared between patients with MRFs at the time of transplant and without MRFs at the time of transplant. Categorical variables were reported as percentages and frequencies and compared with the χ² test. Continuous variables were presented as median with interquartile range when nonparametric and compared with the Mann-Whitney U test. Univariate analysis of the selected risk factors for 1-year survival was performed, and univariate risk factors with a P value less than .1 were included into multivariate Cox regression model censored at 1 year with backwards elimination. Hazard ratios for 1-year mortality with 95% confidence intervals were reported. A multivariate analysis was repeated, excluding CHD as a risk factor. The defined risk factors were subsequently presented as mutually exclusive patient groups with percentage of 1-year survival reported as an alternative to the multivariate hazard ratios. Secondary presentation of data excluded ECMO as a separate risk factor, because it had a substantially smaller patient number than the other risk factors. Kaplan-Meier survival curves were compared with log-rank tests and 95% confidence intervals to demonstrate 1-year survival as it related to long-term survival.

RESULTS
There were 8989 heart transplant candidates listed when younger than 18 years old. Of those, 6028 patients underwent heart transplants, and only 4927 of these patients had complete data regarding estimated glomerular filtration rate, bilirubin, and ventilator status with 1-year follow-up. Another 826 were excluded from the analysis for VAD support before transplantation. Of the remaining 4101 patients, 2642 (64%) had no MRFs, whereas 1459 (36%) had 1 or more MRFs (Figure 1).

Patient Population
Overall characteristics for the patients are displayed in Table 1, as well as a comparison between patients with and without MRFs at transplant. Of the transplant recipients, 32% (n = 1314) were infants, 46% (n = 1892) were female, and 48% (n = 1947) had CHD. Of the transplant recipients had at least 1 MRF, either renal dysfunction (21%; n = 851), liver dysfunction (8.8%; n = 359), mechanical ventilation (18%; n = 738) or some combination. Notably, 6% of patients (n = 265) were on ECMO support at transplant. Patients with MRFs were younger (<1 year vs 7 years), mostly infants (52% vs 20%), more likely to have CHD (54% vs 44%), and more frequently bridged with ECMO support (16% vs 1%; all significant at P < .001). The patients with MRFs were more likely to be sensitized (27% vs 24%; P = .049) and had longer ischemic times (3.7 hours vs 3.6 hours; P = .003).
Multivariate Analysis of Risk Factors

Univariate analysis confirmed many of the previously identified risk factors. The final multivariate models are shown alongside the univariate hazard ratios in Table 2. Two models were generated, because CHD and age younger than 1 year (infancy) were confounding factors. In model A, which eliminated age younger than 1 year as a risk factor, ECMO at time of transplant was the greatest risk factor (hazard ratio, 2.92; 95% confidence interval, 2.25-3.79), whereas CHD, renal dysfunction, mechanical ventilation, eGFR, total bilirubin, and 1-year follow-up status were also significant risk factors.

TABLE 1. Baseline demographic data at transplant

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall (n = 4101)</th>
<th>No modifiable risk factors (n = 2628)</th>
<th>Any modifiable risk factors (n = 1473)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at listing (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant at listing</td>
<td>4 (1-12)</td>
<td>7 (1-13)</td>
<td>&lt;1 (&lt;1-9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>46.1% (1892)</td>
<td>47.3% (1243)</td>
<td>44.1% (649)</td>
<td>.046</td>
</tr>
<tr>
<td>Black</td>
<td>19.2% (786)</td>
<td>19.2% (504)</td>
<td>19.1% (282)</td>
<td>.246</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>47.5% (1947)</td>
<td>44.1% (1159)</td>
<td>53.5% (788)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Functional status &lt;50%</td>
<td>17.6% (723)</td>
<td>18.2% (479)</td>
<td>16.6% (244)</td>
<td>.121</td>
</tr>
<tr>
<td>UNOS status 1A</td>
<td>77.6% (3181)</td>
<td>72.3% (1900)</td>
<td>87.0% (1281)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>18.0% (738)</td>
<td>0% (0)</td>
<td>50.1% (738)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>On dialysis or eGFR &lt;60 mL/min</td>
<td>20.8% (851)</td>
<td>0% (0)</td>
<td>58.3% (851)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total bilirubin &gt;3.0 mg/dL</td>
<td>8.8% (359)</td>
<td>0% (0)</td>
<td>24.6% (359)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Albumin &lt;2.0 g/dL</td>
<td>2.3% (86)</td>
<td>2.4% (57)</td>
<td>2.2% (29)</td>
<td>.783</td>
</tr>
<tr>
<td>PRA sensitized ≥10%</td>
<td>24.1% (617)</td>
<td>23.4% (398)</td>
<td>25.5% (219)</td>
<td>.312</td>
</tr>
<tr>
<td>ECMO at transplant</td>
<td>6.5% (265)</td>
<td>1.1% (28)</td>
<td>16.2% (237)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ischemic time (h)</td>
<td>3.60 (2.93-4.28)</td>
<td>3.57 (2.93-4.23)</td>
<td>3.67 (2.95-4.38)</td>
<td>.003</td>
</tr>
</tbody>
</table>

Data are given as percentage and number of patients or as median with interquartile range. Functional status ≤50% is defined as requiring considerable assistance and frequent medical care or lying around much of the day with no active play. UNOS, United Network for Organ Sharing; eGFR, estimated glomerular filtration rate; PRA, panel-reactive antibody; ECMO, extracorporeal membrane oxygenation.
at transplant, and hepatic dysfunction were all independently associated with increased risk of 1-year mortality. Model B, which eliminated CHD as a risk factor, identified similar risk factors, with age less than 1 year being an independent risk factor for 1-year mortality (hazard ratio, 1.35; 95% CI 1.10-1.64).

Secondary Analysis: Impact of Increasing Risk Factors

One-year mortalities with increasing numbers of MRFs were compared for all patients (Figure 2). The proportion of patients dying by the end of the first year steadily increased with increasing number of risk factors, from 15% for patients who were only mechanically ventilated to 32% for patients who were mechanically ventilated with renal dysfunction. When considering patients with CHD relative to all patients without risk factors, the proportion of patients dying in the first posttransplant year demonstrated a similar upward trend with increasing number of MRFs (Figure 3). Again, 1-year survival ranged from 69% to 60% for patients with renal insufficiency and any other MRF. A patient with CHD and mechanical ventilation as the only MRF had 76% 1-year posttransplantation survival. For infants with CHD, 3 groups had more than 100 patients, and these groups demonstrated the highest 1-year mortality, with the worst 1-year survival of 58% for those with mechanical ventilation, listing as an infant, CHD, and renal dysfunction (Figure 4). Kaplan-Meier curve analysis revealed the same stepwise progression of worsening survival with varying combinations of risk factors, with the majority of the mortality coming in the first year. This is best demonstrated in the mechanically ventilated patients (Figure 5). An analysis of the most recent era (2011-2017) confirmed a similar impact of increasing risk factors in

TABLE 2. Multivariate analysis for 1-year mortality in pediatric heart transplantation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate HR (95% CI)</th>
<th>P value</th>
<th>Model A multivariate HR (95% CI)</th>
<th>P value</th>
<th>Model B multivariate HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMO at transplant</td>
<td>4.89 (3.91-6.12)</td>
<td>&lt;.001</td>
<td>2.92 (2.25-3.79)</td>
<td>&lt;.001</td>
<td>2.97 (2.30-3.84)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>2.64 (2.16-3.22)</td>
<td>&lt;.001</td>
<td>2.32 (1.90-2.83)</td>
<td>&lt;.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>eGFR at transplant</td>
<td>2.75 (2.28-3.31)</td>
<td>&lt;.001</td>
<td>1.99 (1.64-2.42)</td>
<td>&lt;.001</td>
<td>1.97 (1.62-2.40)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ventilator at transplant</td>
<td>2.93 (2.42-3.54)</td>
<td>&lt;.001</td>
<td>1.53 (1.22-1.92)</td>
<td>&lt;.001</td>
<td>1.52 (1.21-1.91)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total bilirubin &gt;3.0 mg/dL</td>
<td>2.26 (1.77-2.89)</td>
<td>&lt;.001</td>
<td>1.44 (1.12-1.85)</td>
<td>.005</td>
<td>1.48 (1.15-1.91)</td>
<td>.002</td>
</tr>
<tr>
<td>&lt;1 y old</td>
<td>1.94 (1.62-2.33)</td>
<td>&lt;.001</td>
<td>—</td>
<td>—</td>
<td>1.35 (1.10-1.64)</td>
<td>.003</td>
</tr>
</tbody>
</table>

Multivariate model A excluded age less than 1 year from the risk factors, whereas model B excluded congenital heart disease, to demonstrate the effect of each independently because the 2 factors are confounding. HR, Hazard ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate.

FIGURE 2. Proportion of patients surviving the first year posttransplant compared with patients with no modifiable risk factors. There was an increasing proportion of patients dying by 1 posttransplant year with an increasing number of risk factors. Ref., Reference population; Dysfxn, dysfunction.
mechanically ventilated patients (Figure E1). When we analyzed an ideal patient (no CHD, noninfant listing, no MRFs), survival was 95% at 1 year.

**DISCUSSION**

The pediatric patient with severe heart failure awaiting cardiac transplantation in the intensive care unit is a common clinical scenario, especially with improving surgical and medical support. This study reviewed a national transplantation database to demonstrate the significant reduction in 1-year survival as common inpatient pretransplant risk factors accumulate. Alarmingly, 1-year survival of less than 75% was found in numerous patient cohorts. By uniquely analyzing groups of patients with defined risk factors confirmed by multivariate analysis relative to patients without those risk factors, this study has helped to define

**FIGURE 3.** Proportion of patients surviving the first year posttransplant for patients with CHD relative to patients with no modifiable risk factors. There was an increasing proportion of patients dying by 1 year posttransplant with an increasing number of risk factors for those who have congenital heart disease (CHD). Ref., Reference population; Dysfxn, dysfunction.

**FIGURE 4.** Proportion of patients surviving the first year posttransplant for infant patients with congenital heart disease (CHD) relative to patients with no modifiable risk factors. There was an increasing proportion of patients dying by 1 year posttransplant with an increasing number of risk factors for those who had CHD. Only groups with more than 100 patients are shown. Ref., Reference population; Dysfxn, dysfunction.
FIGURE 5. Kaplan-Meier curves for 4 commonly encountered mechanically ventilated patients compared with reference curves of an idealized patient population without congenital heart disease, infancy, or modifiable risk factors. There is clear demonstration of considerably worse survival in patients who were mechanically ventilated alone (A) with those with additional risk factors of congenital heart disease (B), congenital heart disease and renal dysfunction (C), and lastly a mechanically ventilated infant with congenital heart disease and renal dysfunction (D). Mortality is primarily attributed to early mortality but sustained during the long term as well. The 95% confidence intervals are represented by the shaded areas around the curves.
better the expectations for early posttransplant survival. These findings can be discussed knowledgably on a patient-by-patient basis among the care team and with patient families in a clinically relevant manner.

Often, the focus in severe heart failure is to get the child to transplantation, even when significant comorbid risk factors for death after transplantation are present. Obvious risk factors include ECMO and multiorgan failure; however, common intensive care unit risk factors, including mechanical ventilation and renal insufficiency, affect listing and posttransplant survival. In our current study, the MRFs analyzed are commonly seen among children listed for heart transplantation and are especially common (>40%) in those with status 1A, which now comprises 85% of all the transplants performed. In our analysis, it was important to develop 2 multivariate models because of the high frequency of patients having CHD in addition to being younger than 1 year old. This pattern led to confounding of the risk factors; however, both are actually highly significant for patients awaiting transplantation. Although it is not suggested that those with risk factors for poor survival should never receive transplants, we hope to shed light on the reality that a number of the very ill patients who are listed and receive transplants have significantly worse early outcomes that are associated with their status entering transplantation. This reality should be communicated with the families to provide realistic expectations.

We were surprised to find that a patient with CHD awaiting transplant while being mechanically ventilated as the only MRF had a 1-year survival of only 75% after receiving a transplant, because such a patient would not commonly be considered a high-risk candidate. Even more concerning was that if that patient had renal dysfunction, 1-year survival approached 60%, and it was even less than 60% if the patient was also an infant. This cascade exemplifies how risk factors common in our intensive care units can quickly add up to contribute to significantly worse posttransplant survival in patients “limping to transplantation.” Whereas several groups of patients with common MRFs had 1-year survival in the 60% range, we found that an ideal transplant recipient has an astounding 95% 1-year survival after transplant. Importantly, most of the drop in survival occurs within the first year, and even the decrease in first year survival in reality is mostly confined to the first 6 months, with perioperative survival being a critical contributor. Although this finding may be unsurprising to some, it goes to emphasize further the importance of patient selection, timing of transplantation, and maximal preoperative optimization, which are understandably not always opportunities one has when discussing pediatric cardiac transplantation.

In light of these findings, we are obligated to search our armamentarium for better ways to optimize patient condition before cardiac transplantation to achieve improvement in short- and long-term survivals. One potential way to do this is through the use of VADs. We excluded patients with VAD support from our study because their numbers were limited by poor granularity (ie, type, implant and explant dates). Furthermore, these patients have previously been shown to have similar posttransplant survival despite higher pretransplant severity of illness in a linked Pediatric Interagency Registry for Mechanical Circulatory Support–Pediatric Heart Transplant study of 147 patients transplanted with VAD support compared with 630 medically supported patients.

In patients bridged with VAD support in the Pediatric Interagency Registry for Mechanical Circulatory Support–Pediatric Heart Transplant study, ventilator dependence dropped from 44% at listing to 11% at transplant, whereas estimated glomerular filtration rate and total bilirubin both showed signs of improvement, changing from 78 mL/min/1.73 m² to 103 mL/min/1.73 m² and 1.43 mg/dL to 0.94 mg/dL, respectively. Although there is a risk of stroke, bleeding, and infection during VAD support, wait-list mortality decreases by more than 50% with a VAD, and MRFs can be improved. We therefore believe that attempting to maximize overall survival by accepting some upfront risk during the bridge to transplantation for potential improvement in posttransplant survival seems sensible in a time of an ever-growing organ shortage and constantly improving technology.

**Limitations**

Limitations of our study are those typical of a retrospective database review. We found the poor outcomes associated with ECMO to be well known, and the small number of patients with ECMO support limited the power of our findings if we made it a separate risk factor variable. Wait-list survival was not analyzed in this study and may lead to selection bias if the sickest patients do not survive to transplant; however, this important concept was analyzed by us in a previous article, and if the healthier patients survived to transplant, one would expect this to improve posttransplant outcomes. No true control group could be used, so patients were compared with those without the identified risk factors. Although different forms of CHD may be associated with different survivals after transplant, this variable is indiscernible in the United Network for Organ Sharing database. Similarly, such important factors as duration of mechanical ventilation and nutritional status are difficult to assess with the predetermined variables of the United Network for Organ Sharing database but may contribute to survival differences.

**CONCLUSIONS**

Cardiac transplantation is often presented to families as an attractive solution for a child’s heart failure, with the expectation that in the modern era such patients should enjoy life-changing improvement in symptoms, as well as...
decades of survival. Although this is true for many patients, there are several risk factors that we often see in our patients that significantly decrease 1-year survival. Some factors are static, but other potentially modifiable factors could be targeted with intense pretransplant therapy to improve post-transplant survival. We must therefore be realistic with ourselves and with families regarding the chance of survival for children who are “limping to transplant” and vigilantly search for other avenues to optimize their conditions before transplantation.

Conflict of Interest Statement
Dr Morales reports, outside the submitted work grants, personal fees, and nonfinancial support from Syncardia, Inc; grants, personal fees, and nonfinancial support from Berlin Heart, Inc; personal fees and nonfinancial support from Medtronic Inc (HeartWare Division); and personal fees and nonfinancial support from Abbot Medical Inc (Thoratec Division). Dr Lorts reports, outside the submitted work, other support from Syncardia, Inc; other support from Berlin Heart, Inc; grants from Medtronic Inc; and other support from Abbott. All other authors have nothing to disclose with regard to commercial support.

References

Key Words: pediatric, heart transplantation, risk factors, mortality
FIGURE E1. An analysis of the most recent era (2011-2017) confirmed the effect of increasing risk factors in mechanically ventilated patients. Curve 1.0 is reference population of an idealized patient with no modifiable risk factors. KM, Kaplan-Meier; MV, mechanical ventilation; CHD, congenital heart disease; RD, renal dysfunction; INF, infant.