Extracorporeal Membrane Oxygenation (ECMO) as a Bridge to Pediatric Heart Transplantation: Impact on Post-Listing and Post-Transplantation Outcomes

Dipchand et al: ECMO as a Bridge to Pediatric Heart Transplant

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Abstract

Background—Current organ allocation algorithms direct hearts to the sickest recipients to mitigate death while waiting. This may result in lower post-transplant (Tx) survival for high risk candidates mandating close examination to determine the appropriateness of different technologies as a bridge to Tx.

Methods and Results—We analyzed all patients (<18 years old) from the Pediatric Heart Transplant Study database listed for heart Tx (1993 - 2013) to determine the impact of ECMO support at the time of listing and the time of Tx on waitlist mortality and post-Tx outcomes. 8% of patients were listed on ECMO and, within 12 months, 49% had undergone Tx, 35% were deceased and 16% were alive waiting. Survival at 12 months after listing (censored at Tx) was worse in patients on ECMO at listing (50%) compared to VAD at listing (76%) or not on ECMO/VAD at listing (76%, p<0.0001). 203 (5%) patients underwent Tx from ECMO; 135 (67%) had been on ECMO since listing and 67 (33%) had deteriorated to ECMO support while waiting. Survival after Tx was worse in patients Tx from ECMO (3y: 64%) vs on VAD at Tx (3y: 84%) or not on ECMO/VAD at Tx (3y: 85%, p<0.0001). Patients transplanted from ECMO at age <1year had the worst survival.

Conclusions—Pediatric patients requiring ECMO support prior to heart Tx have poor outcomes. Prioritization of donor hearts to children waitlisted on ECMO on warrants careful consideration due to ECMO’s high pre- and post-Tx mortality.

Key Words: ECMO extracorporeal circulation, ventricular assist device, pediatrics, transplantation
Mechanical circulatory support for the failing heart has been extensively used as a bridge to heart transplantation in both adult and pediatric populations.1-5 Extracorporeal membrane oxygenation (ECMO) has long been the primary means of mechanical support for pediatric patients with end stage cardiac failure. However, ECMO is associated with many known complications, including thromboembolic events, bleeding, immobilization, infection, end-organ dysfunction, and risk of neurological impairment, thus making the need for alternative methods of pediatric mechanical circulatory support necessary.6 Bridge to transplant with ECMO support is associated with high waitlist mortality and a poor survival to hospital discharge.5-12

Current organ allocation algorithms have been developed to direct hearts to the sickest recipients to mitigate death while waiting. Such a strategy may result in suboptimal post-transplant survival for certain high risk candidates, including those on ECMO. In the evolving era of mechanical support, outcomes must be closely examined to determine the appropriateness of existing allocation algorithms, criteria for candidacy for heart transplantation, and the impact of different technologies as a bridge to transplant.11

The purpose of this study was to describe and analyze the outcomes for pediatric patients waitlisted and/or transplanted from ECMO support in comparison to those without ECMO support, and to attempt to define risk factors associated with worse outcomes so as to gain an understanding of when it might be futile to perform a transplant on candidates on ECMO.

**Methods**

*Patient population and data collection*

This study uses data from the Pediatric Heart Transplant Study (PHTS) database, an event-driven, multicenter, prospective registry of children <18 years of age listed for primary
transplantation from 35 pediatric heart transplantation centers in North America and the United Kingdom (see Supplement). PHTS data collection and management have been described previously.13 Institutional Review Board approval was obtained at the transplant centers and the data analysis and coordinating center.

All patients who were listed for heart transplantation between January 1, 1993 and December 31, 2013 with a record of ECMO as a bridge to transplant were included. Comparisons were made to all patients in the registry who were not bridged to transplantation from ECMO support. Data collected included demographics, United Network for Organ Sharing (UNOS) status at listing, support at listing (intravenous inotropes, ventilator, prostaglandin, ECMO, ventricular assist device (VAD), timing of ECMO support or VAD placement post-listing, hemodynamics at listing and any during follow up, human leukocyte antigen (HLA) sensitization, surgical palliation while waiting, clinical condition at listing, death while waiting, delisting, indications for removal from wait list, transplant, UNOS status at transplant, support at time of transplant (e.g. ECMO, VAD), cardiopulmonary bypass time, ischemic time, donor characteristics, hospital stay, days in intensive care unit, date of most recent follow-up, incidence of primary graft failure, rejection, infection, malignancies, allograft vasculopathy, death post-transplant, and cause of death.

Statistical Methods

Standard Kaplan-Meier and parametric analyses were used for survival analysis. Competing-outcomes methods were used to analyze outcome after listing.14 Multivariate analysis in the hazard-function domain was used to identify risk factors for death while waiting, death after transplant and overall survival after listing, including death while waiting and death after
transplant using a step-wise selection technique. Candidat variables entered into the multivariable risk factor analysis for death after listing (censored at transplant) included demographics at listing, blood type, listing status, underlying cardiac diagnosis, surgical history, other clinical diagnoses/co-morbidities, and hemodynamics. Variables entered into the multivariable risk factor analysis for death after transplant included demographics at transplant, status at transplant, underlying cardiac diagnosis, surgical history at listing, other clinical diagnoses/co-morbidities, hemodynamics at transplant, donor variables (demographics, blood type, medical history), and donor-recipient mismatch variables (race, gender, age, blood group, body surface area (BSA) ratio).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient Population (Tables 1, 2)

Patient demographics and clinical characteristics at listing and transplant are summarized in Table 1. Of the 5,360 patients listed over this time period, there were 453 (8%) patients listed on ECMO support at a median age of 0.56 years (0.05 – 2.69 y), who were significantly younger, smaller, sicker, and more likely to have renal insufficiency than those not supported on ECMO at listing. Fifty-eight percent had a diagnosis of congenital heart disease. Of the 3,826 transplanted patients, 203 (5%) were on ECMO support at a median age of 0.80 years (0.22-4.37 years), who were similarly younger, smaller, sicker and more likely to have renal insufficiency than those not on ECMO at transplant. Patients on ECMO support at the time of transplant had a significantly shorter waitlist duration (24 vs. 93 days, p<0.0001). One hundred thirteen patients (56%) had a
diagnosis of congenital heart disease. Table 2 gives the frequencies at listing by age at listing of patients on ECMO support (n=453), ventricular assist device, VAD (n=198), and neither ECMO nor VAD (n=4,709). Age at the time of listing on ECMO support was <1 month (n=128; 28%), 1 month to 1 year (n=141; 31%), 1 to 5 years (n=100; 22%), 5 to 10 years (n=45; 10%), and >10 years (n=39; 9%). Of the total number of listed patients, 668 transitioned to VAD support while listed (12%) but were analyzed according to their support at the time of listing and/or at the time of transplant as appropriate (73 of these patients were on ECMO support and transitioned to VAD).

**Overall Survival**

Overall survival post-listing and post-transplant for patients waitlisted on ECMO is depicted in Figure 1A (including deaths and follow up after transplant) with a significantly decreased overall survival for this group (p<0.0001).

**ECMO at Listing, Death while Waiting (Figure 1, 2; Table 3)**

Patients waitlisted on ECMO support had significantly decreased survival post-listing (censored at transplant) compared to patients on VAD support or no mechanical support (p<0.0001). (Figure 1B) Figure 2 shows the competing outcomes after listing for ECMO, VAD and neither ECMO nor VAD. Overall waitlist mortality by 1 and 6 months post-listing for any pediatric patient waitlisted on ECMO was 28% and 35% respectively, in contrast to the remarkably low waitlist mortality for VAD patients of 6% and 12% respectively. By 12 months post-listing, 49% of patients listed on ECMO support were transplanted compared to 79% of VAD patients.
and 72% of all others (Figure 2). Causes of death post-listing for patients on ECMO are summarized in Table 3.

*Impact of Age on Post-Listing Survival (Figure 3)*

Younger age at listing was significantly associated with waitlist mortality, with the smallest of infants (<1 month) having the highest mortality, even without a need for mechanical support. (Figure 3A) This was worsened significantly by the need for ECMO support at the time of listing and was seen in all age groups. (Figure 3B) The youngest infants continued to have the worst outcomes with a waitlist mortality of 67% by 3 months post-listing if on ECMO support at the time of listing. (p<0.0001).

*Impact of other risk factors on post-listing survival (Figure 4)*

The PHTS database did not begin to accurately capture duration of mechanical support until January 1, 2005. Figure 4 illustrates survival after listing by duration of time on ECMO prior to listing which did not seem to have a significant impact on survival post-listing overall (p=0.66). In univariate analysis, renal insufficiency did not have a significant impact on overall survival (p=0.12); though it is notable that a significant proportion of patients on ECMO had renal insufficiency (Table 1).

*Impact of Underlying Cardiac Diagnosis on outcomes post-listing (Figure 5)*

There was a significant difference in survival based on underlying etiology (Figure 5A), with patients with myocarditis having the best overall survival post-listing, followed by cardiomyopathy and subsequently a diagnosis of congenital heart disease (p=0.0008). This being
said, of the 59 myocarditis patients, only 10 were removed from the list for recovery. Only 7 of
the 25 transplanted myocarditis patients on ECMO at listing were not on ECMO at the time of
transplant.

**ECMO at Transplant, Death Post-Transplant (Figure 1C, 5B)**

Patients transplanted while on ECMO support had significantly decreased survival post-
transplant compared to patients on VAD support or no mechanical support (p<0.0001).(Figure
1B) Patients with myocarditis had the worst outcomes when transplanted from ECMO support,
followed by congenital heart disease, with cardiomyopathy patients having the best post-
transplant survival (p=0.0005) (Figure 5B). Infants less than 1 year of age had significantly
worse post-transplant survival when transplanted from ECMO (p<0.0001). (Figure 6)

**ECMO at Listing and/or at Transplant and impact on overall survival (Tables 4-6, Figure 7)**

Table 4 summarizes the scenarios for mechanical support as a bridge to transplantation in the
transplant recipients. Figure 7 illustrates the survival for each of the 4 possible ECMO
combinations. *(There were 46 patients listed on ECMO but were weaned and removed from
listing because they were considered too well. These patients were censored at the time of
removal from listing.)* Notably, if a patient was on ECMO at listing but weaned off prior to
transplantation or converted to VAD, their outcome was just as good as not being on ECMO at
the time of listing or transplantation. ECMO at the time of transplantation (with or without
ECMO support at the time of listing) was significantly associated with worse outcomes
(p<0.0001).
Unadjusted hazard for death while waiting for patients waitlisted on ECMO censored at transplant was 2.46 (p<0.0001). After adjustment, the hazard ratio remained significant at 1.73 (p=0.03). Table 5 summarizes the risk factors for death on the waitlist, censored at transplant, from the multivariable hazard analysis.

On multivariate analysis, overall survival after transplantation for patients on ECMO at the time of transplantation was not affected by age, ischemic time, or duration of time on ECMO. However, lower weight (RR 1.37 for a 10 kg decrease in weight, p=0.04), higher serum creatinine (RR 2.36 for a one unit increase in creatinine, p=0.007) and an underlying diagnosis of congenital heart disease or myocarditis (RR 2.68, p=0.009) were risk factors in the early phase. (Table 6)

Discussion
We present a large multicentre experience with ECMO as a bridge to transplant in the pediatric population. Pediatric patients requiring ECMO support prior to heart Tx have poor outcomes and serious consideration needs to be given to the candidacy of these patients. Prioritization of donor hearts to children waitlisted on ECMO on warrants careful consideration due to ECMO’s high pre- and post-Tx mortality, most specifically infants less than 1 year of age, a diagnosis of congenital heart disease, and patients with renal insufficiency.

Single centre reports of waitlist mortality from ECMO range from 29-61% in small cohorts of patients.4,9,16,17 Almond et al recently reported on a merged cohort from both the Organ Procurement and Transplant Network (OPTN) and the Extracorporeal Life Support Organization (ELSO) who were bridged to transplantation from ECMO support with overall waitlist mortality in this cohort of 28%, similar to the 35% at 6 months found in this analysis.
However, infants fared much worse in the current analysis with a waitlist mortality of over 50% at 3 months. We did not see an association between duration of time on ECMO prior to listing and waitlist mortality; perhaps being related to this being the most recent cohort of patients after 2005 and the lack of data available prior to this time. Diagnosis of congenital heart disease in and of itself, as has been reported elsewhere, was associated with the highest waitlist mortality.5,11,18 Unfortunately, listed patients on ECMO support were more likely to be younger and have a diagnosis of congenital heart disease (Table 1), pointing already to the problem of accumulation of multiple risk factors in these complex patients.

As has been recognized by others, survival post-transplant from ECMO support is also clearly suboptimal compared to other transplant recipients. Survival to hospital discharge post-transplant in single center reports range from 66 – 100%,4,8,9,16,17,19 with 1 year survival ranging from 67 – 83%, and 5 year survival 44 – 54%.7,8,9,13,19

Despite these overall poorer outcomes reported utilizing ECMO, there are subpopulations of patients on ECMO who clearly are higher risk for pre- and post-transplant mortality. Identification of risk factors associated with a very poor outcome on ECMO would be helpful for clinical decision making and for counseling of parents. The key areas of import would be 1) identification of the patient who should not be placed on to ECMO support as a bridge to transplantation because of a prohibitively high post-listing and post-transplantation morbidity, and 2) identification of the patient already on ECMO who acquires a risk factor that would make further support and transplantation futile. These two points are paramount in the era of significant organ donor shortages, especially in the infant population. Previous reports are predominantly single center and small numbers that make risk factor analysis not
feasible. We also need to learn through additional analysis about the impact of converting these high risk patients to VAD support.

Interestingly age, ischemic time, and time on ECMO support prior to listing did not impact post-transplant survival in the ECMO cohort; the latter being somewhat surprising given the reported impact on survival of length of time on ECMO post-heart transplant and post-cardiotomy (albeit in a single center experience). In fact, Almond et al reported an ECMO run of >14 days predicted non-survival in the larger OPTN cohort. Perhaps this discrepancy can be explained by an era effect with the data extending back over a 15 year time period in the report by Almond and colleagues compared to a more contemporary cohort (2005-2013) from PHTS. In addition, the total time on ECMO was not taken into account in this analysis.

Though a diagnosis of myocarditis boded well for post-listing survival, it was associated with the lowest post-transplant survival from ECMO which has also been observed in other series, and hypothesized to be related to immune activation in the setting of active myocarditis or recurrent viral infection in the transplanted heart under immunosuppression. The impact of a diagnosis of congenital heart disease on post-ECMO, post-heart transplant survival varies in single centre experiences from not significantly different to survival rates as low as 25%, perhaps related to center experience and volume amongst other factors. However, in this larger registry-based analysis, those with a diagnosis of congenital heart disease clearly fare poorly. The impact of impaired renal function has also produced conflicting results with some reports of a negative impact and one report showing no significant impact. In the present study, one unit incremental increases in serum creatinine was significantly associated with worse outcome in this larger series and bears strong consideration as a risk factor.
Though not the focus of this analysis, we have noted the important impact that VAD support has had on post-listing and post-transplant survival. This has also been observed in a prior PHTS study as well as in the registry for the International Society for Heart and Lung Transplantation.\textsuperscript{1,21} Both studies, as well as the present one, have demonstrated that outcomes on VAD are now equivalent to outcomes without VAD support. Further analysis is required to determine if these excellent results can be recapitulated for pediatric ECMO patients who are converted to VADs in the pre-transplant period. In most cases a VAD can be implanted without prior ECMO support. However, there are certain circumstances where initial ECMO stabilization is desired. Adult transplant programs have increasingly been using ECMO stabilization for INTERMACS 1 patients.\textsuperscript{22} There may also be certain subsets of patients such as young children with single ventricle, for whom short-term support with ECMO may be more practical than available pulsatile VAD support.

Deceased organ donor availability remains the limiting factor in heart transplantation, more so in pediatrics – especially young infants. Current organ allocation algorithms have been developed to direct hearts to the sickest recipients to mitigate death while waiting. Such a strategy may reduce post-transplant survival as evidenced in this analysis by the 69.3\% one year survival following transplantation from ECMO support in comparison to 89.7\% for those not requiring ECMO support. The concept of net survival benefit from transplantation in adults has been explored by Singh, et al. in an adult cohort in the US. The accompanying clinical perspective on children concluded that sicker children on the waiting list benefit more from heart transplantation unless the post-transplant mortality is predicted to be too high.\textsuperscript{23} Where does one draw the line? For an individual patient on ECMO, mortality is close to 100\% without transplantation and it is up to the treating medical team to decide if bridging to transplant is a
feasible option. However, knowledge of the risk factors and likelihood of a good outcome should be considered in this decision-making. In this evolving era of mechanical support, outcomes must continue to be closely examined to determine the appropriateness of existing allocation algorithms, criteria for candidacy for heart transplantation, and the impact of different technologies as a bridge to transplantation.

Although this reflects a large, multicenter cohort of over 400 patients supported with ECMO as a bridge to heart transplantation, when seeking factors that influence survival, the numbers in subgroups are small making robust statistical statements challenging. Individual institutions contributing data to the PHTS may well have different criteria for listing and bridging patients to heart transplantation. The data forms are not all-inclusive which limited the ability to identify potential risk factors. Despite these limitations the information is valuable in predicting outcomes and counseling families.

Conclusions

Pediatric patients requiring ECMO support prior to heart transplant generally have poor outcomes. Identifiable subgroups fare worse while those weaned off prior to transplantation fare better. Serious consideration needs to be given to the candidacy of these patients, especially in light of the evolving and improving results utilizing VAD support as a bridge to transplant. Prioritization of donor hearts to children waitlisted on ECMO on warrants careful consideration due to ECMO’s high pre- and post-Tx mortality.

Disclosures

None.
References


<table>
<thead>
<tr>
<th>Demographics</th>
<th>ECMO (n=453)</th>
<th>No ECMO (n=4,907)</th>
<th>p-value</th>
<th>ECMO (n=203)</th>
<th>No ECMO (n=3,623)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>241 (53%)</td>
<td>2729 (56%)</td>
<td>0.3182</td>
<td>111 (55%)</td>
<td>1984 (55%)</td>
<td>0.9819</td>
</tr>
<tr>
<td>White</td>
<td>323 (71%)</td>
<td>3469 (71%)</td>
<td>0.7857</td>
<td>143 (70%)</td>
<td>2540 (70%)</td>
<td>0.9190</td>
</tr>
<tr>
<td>Age (yrs) (mean±SD)</td>
<td>2.5 (+4.0)</td>
<td>5.6 (+6.1)</td>
<td>&lt;0.000</td>
<td>3.2 (+4.6)</td>
<td>6.4 (+6.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BSA (m²) (mean±SD)</td>
<td>0.50 (+0.40)</td>
<td>0.77 (+0.56)</td>
<td>&lt;0.000</td>
<td>0.55 (+0.42)</td>
<td>0.83 (+0.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Etiology: Congenital</td>
<td>262 (58%)</td>
<td>2549 (52%)</td>
<td>0.0163</td>
<td>113 (56%)</td>
<td>1741 (48%)</td>
<td>0.0347</td>
</tr>
<tr>
<td>Waitlist time (days)</td>
<td></td>
<td></td>
<td></td>
<td>93 (+202)</td>
<td>24 (+45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Status at Listing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status 1</td>
<td>449 (99.8%)</td>
<td>3797 (78%)</td>
<td>&lt;0.000</td>
<td>197 (98%)</td>
<td>2808 (78%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ventilator</td>
<td>419 (92%)</td>
<td>1105 (23%)</td>
<td>&lt;0.000</td>
<td>159 (78%)</td>
<td>728 (20%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inotropes</td>
<td>375 (83%)</td>
<td>2773 (57%)</td>
<td>&lt;0.000</td>
<td>170 (84%)</td>
<td>2076 (57%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinical condition at listing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>44 (10%)</td>
<td>940 (19%)</td>
<td>&lt;0.000</td>
<td>23 (11%)</td>
<td>677 (19%)</td>
<td>0.0083</td>
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<tr>
<td>Renal Insufficiency</td>
<td>40 (9%)</td>
<td>156 (3%)</td>
<td>&lt;0.000</td>
<td>19 (9%)</td>
<td>111 (3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>139 (31%)</td>
<td>1148 (23%)</td>
<td>0.0005</td>
<td>57 (28%)</td>
<td>887 (24%)</td>
<td>0.2474</td>
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Table 2. Age of Listed Patients by Presence and Type of Pre-transplant Mechanical Support

<table>
<thead>
<tr>
<th>Age at Listing</th>
<th>ECMO n</th>
<th>ECMO %</th>
<th>VAD n</th>
<th>VAD %</th>
<th>Neither ECMO nor VAD n</th>
<th>Neither ECMO nor VAD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mo</td>
<td>913</td>
<td>128</td>
<td>14.0</td>
<td>6</td>
<td>0.7</td>
<td>779</td>
</tr>
<tr>
<td>1 mo – &lt; y</td>
<td>1293</td>
<td>141</td>
<td>10.9</td>
<td>32</td>
<td>2.5</td>
<td>1120</td>
</tr>
<tr>
<td>1 – &lt;5 y</td>
<td>1066</td>
<td>100</td>
<td>9.4</td>
<td>30</td>
<td>2.8</td>
<td>936</td>
</tr>
<tr>
<td>5 – 10 y</td>
<td>615</td>
<td>45</td>
<td>7.3</td>
<td>23</td>
<td>3.7</td>
<td>547</td>
</tr>
<tr>
<td>&gt; 10 y</td>
<td>1473</td>
<td>39</td>
<td>2.7</td>
<td>107</td>
<td>7.3</td>
<td>1327</td>
</tr>
<tr>
<td>Total</td>
<td>5360</td>
<td>453</td>
<td>8.5</td>
<td>198</td>
<td>3.7</td>
<td>4709</td>
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Table 3. Cause of death post-listing and post-transplant for patients on ECMO

<table>
<thead>
<tr>
<th>Primary Cause of Death</th>
<th>Post-Listing (n=157)</th>
<th>Post-Transplant (n=77)</th>
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<tr>
<td>Accidental</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Anoxic Insult</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Fatal Arrhythmia</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Post-operative hemorrhage</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary Hypertension/R.V. Failure</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Rejection Hyperacute</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Rejection, Acute</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Sudden Cardiac Death</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Unknown</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>88</td>
<td>38</td>
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Table 4. Summary of possible combinations of mechanical support at listing and at transplantation in the transplant recipients

<table>
<thead>
<tr>
<th>At Listing</th>
<th>At Transplant</th>
<th>Died Waiting</th>
<th>Alive Waiting</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>ECMO</td>
<td>VAD</td>
<td>Neither</td>
<td>ECMO</td>
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<tr>
<td>ECMO</td>
<td>135</td>
<td>42</td>
<td>42</td>
<td>56</td>
</tr>
<tr>
<td>VAD</td>
<td>1</td>
<td>136</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Neither</td>
<td>67</td>
<td>295</td>
<td>3094</td>
<td>44</td>
</tr>
<tr>
<td>Sub Total</td>
<td>203</td>
<td>473</td>
<td>3150</td>
<td>105</td>
</tr>
<tr>
<td>Total</td>
<td>3826</td>
<td>809</td>
<td>725</td>
<td></td>
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Table 5. Multivariable hazard of death after listing censored at transplant

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Early Phase of Risk</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Listing (younger)</td>
<td>1.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ECMO at Listing</td>
<td>1.73</td>
<td>0.03</td>
</tr>
<tr>
<td>No Myocarditis</td>
<td>1.93</td>
<td>0.01</td>
</tr>
<tr>
<td>Non Dilated Cardiomyopathy</td>
<td>4.23</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

1 In the model on the natural log scale; compares 1 year old to 10 year old.
Table 6. Pretransplant risk factor multivariate analysis for death post-transplant in patients on ECMO at time of transplant (n=203)

<table>
<thead>
<tr>
<th>PreTx risk factors</th>
<th>Early Phase of Risk</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology congenital or myocarditis</td>
<td>2.68</td>
<td>0.009</td>
</tr>
<tr>
<td>Creatinine at transplant (higher)</td>
<td>2.36(^1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Weight at transplant (lower)</td>
<td>1.37(^2)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

1 represents the increased risk of a one unit increase in creatinine
2 represents the increased risk of a 10 kg decrease in weight
Figure Legends

Figure 1. PHTS 1993 – 2013 Survival a) overall (post-listing and post-transplant), b) after listing for patients waitlisted on ECMO support (censored at transplant), c) after transplant for patients transplanted from ECMO support

Figure 2. Outcomes of patients waitlisted a) on ECMO support, b) on VAD support, and c) without ECMO or VAD support.

Figure 3. Impact of age on waitlist mortality in a) patients not requiring mechanical support at the time of listing, and b) patients requiring ECMO support at the time of listing for heart transplantation.

Figure 4. Impact on overall post-listing survival by a) time on ECMO prior to listing 2005-2013, b) history of renal insufficiency 1993-2013.

Figure 5. Impact of diagnosis on survival for a) patients waitlisted on ECMO; b) patients transplanted from ECMO

Figure 6. Survival after transplant for infants less than 1 year

Figure 7. Survival outcomes post-transplant based on ECMO at Listing and/or Transplantation
Overall Survival by MCSD Type at Listing
PHTS Listed Patients 1993-2013

% Survival

At Risk:

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Years Post Listing

Shaded areas indicate 70% confidence limits
p (log-rank) = <.0001
Event: Death after listing, not censored at transplant

ECMO (n = 453, Deaths = 225)
VAD (n = 198, Deaths = 48)
No ECMO or VAD (n = 4709, Deaths = 1355)
Shaded areas indicate 70% confidence limits

p (log-rank) = <.0001
Event: Death after listing, censored at transplant
Post-Transplant Survival by MCSD Type at Transplant
PHTS Transplanted Patients 1993-2013

Shaded areas indicate 70% confidence limits
p (log-rank) = <.0001
Event: Death after Transplant
Competing Outcomes for Patients on VAD at Listing
PHTS 1993 - 2013 (n=198)

- Alive
- Dead
- Transplanted

Proportion of Patients

72.7%
14.8%
11.9%

Months Post Listing
Competing Outcomes for Patients Not on ECMO or VAD at Listing
PHTS 1993 - 2013 (n=4709)

- Alive
- Dead
- Transplanted

Proportion of Patients

Months Post Listing

66.1%
21.6%
11.9%
Post-Listing Survival by Age at Listing
PHTS Patients Not on ECMO at Listing 1993-2013

Survival %

At Risk:
1434
1536
1152
785

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

Years Post Listing

- Age < 1 month (n = 785, Deaths = 186)
- Age 1 month - 1 Year (n = 1152, Deaths = 181)
- Age 1 - 10 Years (n = 1536, Deaths = 178)
- Age 10+ Years (n = 1434, Deaths = 107)

Shaded areas indicate 70% confidence limits
p (log-rank) = <.0001
Event: Death after listing, censored at transplant
Post-Listing Survival by Age at Listing
PHTS Patients on ECMO at Listing 1993-2013

Shaded areas indicate 70% confidence limits
p (log-rank) = <.0001
Event: Death after listing, censored at transplant
Post-Listing Survival by Duration of ECMO prior to Listing
PHTS Patients on ECMO at Listing 2005-2013

Shaded areas indicate 70% confidence limits
p (log-rank) = 0.66
Event: Death after listing, censored at transplant
Post-Listing Survival by History of Renal Insufficiency at Listing
PHTS Patients on ECMO at Listing 1993-2013

Shaded areas indicate 70% confidence limits
p (log-rank) = 0.12
Event: Death after listing, censored at transplant
Post-Listing Survival by Etiology
PHTS Patients on ECMO at Listing 1993-2013

Shaded areas indicate 70% confidence limits
p (log-rank) = 0.0008
Event: Death after listing, censored at transplant
Shaded areas indicate 70% confidence limits

\( p \) (log-rank) = 0.0005

Event: Death after Transplant
Shaded areas indicate 70% confidence limits

p (log-rank) = <.0001
Event: Death after Transplant
Post-Transplant Survival by ECMO Status at Listing and Transplant
PHTS Transplanted Patients 1993-2013

Shaded areas indicate 70% confidence limits
p (log-rank) = <.0001
Event: Death after Transplant
Extracorporeal Membrane Oxygenation (ECMO) as a Bridge to Pediatric Heart Transplantation: Impact on Post-Listing and Post-Transplantation Outcomes
Anne I. Dipchand, William T. Mahle, Margaret Tresler, David C. Naftel, Christopher Almond, James K. Kirklin, Elizabeth Pruitt, Steven A. Webber and the Pediatric Heart Transplant Study Investigators.

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