Risk Stratification and Transplant Benefit in Children Listed for Heart Transplant in the United States

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Background—The sickest children among those listed for heart transplant (HT) are also at higher risk of post-transplant mortality. We hypothesized that transplant benefit, defined as percentage reduction in risk of 1-year mortality on receiving HT, increases with higher risk of wait-list mortality.

Methods and Results—We analyzed all children aged <18 years listed for first HT in the United States between July 2004 and December 2010. We developed a model for 90-day wait-list mortality (or removal because of deterioration) and stratified listed children into deciles based on their risk of wait-list mortality. Listed children were followed up for 1 year to assess cumulative 1-year wait-list mortality among the 10 risk groups. We developed a model for 1-year post-transplant mortality to estimate the risk of post-transplant mortality for children in each risk group. Of 2979 listed children, 15% reached the wait-list end point within 90 days and 18% within 1 year. Of 2034 HT recipients, 6.8% died within 90 days and 10.8% within 1 year. The risk of 90-day wait-list mortality increased progressively from 2.4% to 51.6% from the first to the tenth risk decile. Transplant benefit increased progressively across the wait-list risk groups (P<0.001 for trend). However, transplant benefit for children in the top 5% of risk (7.4%) was lower than that for children in the 91st to 95th percentile of risk (10.3%).

Conclusions—Sicker children on the wait-list benefit more from HT unless the post-transplant mortality is predicted to be very high. Whether consideration of transplant benefit in allocation policy can improve overall survival among listed children requires further analysis. (Circ Heart Fail. 2013;6:800-808.)

Key Words: heart failure ■ pediatrics ■ risk factors ■ survival ■ transplantation

Heart transplantation (HT) can be life-saving in children with end-stage heart failure. In theory, HT listing is offered when HT is expected to result in a meaningful survival advantage compared with conventional medical or surgical therapy. However, an accepted method to quantify survival benefit from HT compared with not pursuing transplant that may also be used to compare listed candidates for this benefit has not been described. Although it may be assumed that the sicker HT candidate is more likely to benefit from transplant, the actual relationship between heart failure severity and transplant benefit is likely to be complex and is currently unknown. In large part, this is because the risk factors for wait-list mortality are very similar to risk factors for early post-transplant mortality and that a patient at high risk for dying on the wait-list is also significantly less likely to survive transplant. Assessing transplant benefit and clarifying the relationship between the risk of wait-list mortality and transplant benefit will be useful as it will provide clinicians with a tool that systematically estimates the relative benefit of HT in their patients and will provide organ allocation experts with a potential framework for incorporating transplant benefit into a modern pediatric heart allocation system.

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We hypothesized that transplant benefit, defined as the percentage reduction in risk 1-year mortality on receiving a HT, will be higher in children with a higher risk of death (or becoming too sick to transplant) within 90 days of listing. The specific objectives of this study were to (1) risk stratify children listed for HT based on their risk of death within 90 days of listing and (2) quantify transplant benefit across risk strata of wait-list mortality.

Study Population

We identified all children aged <18 years in the Organ Procurement and Transplantation Network database who were listed for their first HT in the United States between July 1, 2004, and December 31, 2010. The Organ Procurement and Transplantation Network database includes demographic and clinical information at listing in all wait-listed...
candidates and at transplant in all HT recipients in the United States as submitted by their transplant centers and provided to investigators as deidentified data. Such analyses are waived for review by our institutional review board (Boston Children’s Hospital). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the Organ Procurement and Transplantation Network contractor, United Network of Organ Sharing. Children listed for heart retransplantation or multiorgan transplantation were excluded.

Study Design and Definitions
The primary study hypothesis was that transplant benefit on receiving a HT will be higher in children at a higher risk of death on the wait-list (or becoming too sick to transplant). Transplant benefit was defined as percentage reduction in risk of 1-year mortality on receiving a HT and was assessed as follows. First, we developed a model to predict the risk of wait-list mortality (or becoming too sick to transplant) within 90 days of listing and stratified listed children into 10 risk groups based on risk of wait-list mortality. The groups were followed up for 1 year to assess cumulative 1-year wait-list mortality in each group. Second, we developed models for 90-day and 1-year post-transplant mortality/graft loss and estimated the risk of 90-day and 1-year post-transplant mortality in each risk group using these models. Third, transplant benefit was calculated by subtracting the risk of 1-year post-transplant mortality at listing from the observed 1-year wait-list mortality for each risk group.

The primary end point for wait-list outcomes was a composite of death on the wait-list or becoming too sick to transplant (removal from the list because of clinical deterioration). The primary end point for post-transplant outcomes was death or graft loss (retransplantation). All children analyzed for wait-list and transplant outcomes had 1 year of follow-up available.

Race/ethnicity was recorded as reported by the transplant center and was analyzed as white (non-Hispanic white), black (non-Hispanic black), Hispanic, or other. Renal function was analyzed as estimated glomerular filtration rate (in mL/min per 1.73 m²) using the modified Schwartz formula. Normal renal function in children aged ≥1 year was defined as GFR > 60, moderate dysfunction as 30 to 60, and severe dysfunction as <30 or dialysis support. Because of lower GFR in normal infants <1 year, normal, moderate dysfunction, and severe dysfunction categories in infants were defined as >40, 20 to 40, and <20 or dialysis support, respectively.

None of the children had missing data for the variables age, sex, race/ethnicity, blood type, mechanical support at listing or at transplant, medical insurance (Medicaid), United Network of Organ Sharing listing status, dialysis and the dates of listing, transplant, death, or removal from the wait-list. We imputed GFR values for children with missing values at listing (4%) and at transplant (3%) using a multiple imputation technique (linear regression model) and clinical variables at listing and transplant, respectively; 10 imputations were used for each missing value.

Statistical Analysis
Summary data are presented as median (25th, 75th percentile) or number (%). Wait-list outcomes in study children were first assessed using competing outcomes analysis. Univariate associations of clinical variables at listing with wait-list mortality (or removal because of deterioration) and of variables at transplant with post-transplant mortality or graft loss were assessed using logistic regression. A multivariable logistic regression model for 90-day wait-list mortality (or removal because of deterioration) was developed using a forward selection procedure retaining variables significant at 0.10 level based on a likelihood ratio test; all variables at listing were considered. The model’s ability to discriminate children who reached the wait-list end point from those who did not was quantified using the area under the receiver-operating characteristic (ROC) curve (C-statistic). Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. We then estimated the risk of 90-day wait-list mortality (or removal because of deterioration) in all listed children by applying their specific covariate values to the model. Listed children were stratified into 10 groups based on their risk of wait-list mortality (deciles). All listed children were followed up for 1 year to assess cumulative 1-year mortality on the wait-list (or removal because of deterioration) in each risk group.

A multivariable logistic regression model for predictors of post-transplant 90-day mortality (or graft loss) and a model for 1-year mortality (or graft loss) were developed using variables at the time of transplant in HT recipients and model performance evaluated, as above. The models were used to estimate the risk of 90-day and 1-year post-transplant mortality at listing by applying the variable values at listing to the coefficients of the model. Transplant benefit was calculated by subtracting the average risk of 1-year post-transplant mortality in each risk group from the observed cumulative 1-year mortality on the wait-list in each group. Because of a trend for higher transplant benefit in risk groups with a higher risk of wait-list mortality, we divided children in the 10th risk group into 2 equal size groups to assess whether transplant benefit would decline in children in the top 5% risk of wait-list mortality because of a disproportionate increase in risk of post-transplant mortality.

Data were analyzed using Statistical Analysis System software version 9.3 (SAS Institute, Inc, Cary, NC). All statistical tests were 2 sided and a P value of <0.05 was used to define statistical significance.

Results
Study Population
During the study period, 3207 children aged <18 years were listed in the United States for HT. Of these, 211 children were listed for heart retransplant and 17 children for multiorgan transplant. The remaining 2979 children formed the study cohort. Of these, 1436 (48%) had cardiomyopathy and 1434 (48%) had congenital heart disease. The median age of the study cohort was 2 years, 38% were <1 year, 67% were listed as urgent status 1A, 30% were listed on ventilator support, and 18% were on a mechanical support (including 12% on extracorporeal membrane oxygenation, 2% on biventricular assist device, and 4% on a left ventricular assist device) at listing (see Table 1 for baseline characteristics at listing and Table I in the online-only Data Supplement for baseline characteristic at transplant).

Figure 1 illustrates competing outcomes during the first year after listing in the study cohort. Of 2979 children on the wait-list, 539 (18%) reached the composite wait-list end point within 1 year of listing (12% died on the wait-list and 6% were removed from the list because of clinical deterioration). Of these 539 children, 297 (55%) reached the wait-list end point within 30 days, 452 (84%) within 90 days, and 508 (94%) within 180 days of listing. Of 2044 children who received a HT, post-transplant vital/graft status was available in 2034 children. Of these, 139 (6.8%) reached the post-transplant end point by 90 days and 219 (10.8%) by 1 year post transplant (9.9% deaths and 0.9% retransplant).

Table 2 summarizes baseline characteristics of children at listing with corresponding 1-year wait-list mortality and at transplant with corresponding 1-year post-transplant mortality/graft loss. Both wait-list mortality and post-transplant mortality seemed to be associated with age, cardiac diagnosis, history of previous cardiac surgery, listing status, inotropes, ventilator support, mechanical support, and renal function.

Model for Wait-List Mortality
In a multivariable model (Table 3), risk factors for death on the wait-list (or removal because of deterioration) within 90 days...
Table 1. Baseline Characteristics of Children at Listing for Transplant

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cardiomyopathy (n=1436)</th>
<th>CHD (n=1434)</th>
<th>Other (n=109)</th>
<th>Total (N=2979)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>6 (1, 14)</td>
<td>0 (0, 6)</td>
<td>3 (0, 12)</td>
<td>2 (0, 11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age categories, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;1</td>
<td>350 (24%)</td>
<td>739 (52%)</td>
<td>44 (40%)</td>
<td>1133 (38%)</td>
<td></td>
</tr>
<tr>
<td>1–10</td>
<td>542 (38%)</td>
<td>462 (32%)</td>
<td>33 (30%)</td>
<td>1037 (35%)</td>
<td></td>
</tr>
<tr>
<td>11–17</td>
<td>544 (38%)</td>
<td>233 (16%)</td>
<td>32 (29%)</td>
<td>809 (27%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>692 (48%)</td>
<td>585 (41%)</td>
<td>45 (41%)</td>
<td>1322 (44%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Listing status&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>1A</td>
<td>949 (66%)</td>
<td>988 (69%)</td>
<td>69 (63%)</td>
<td>2006 (67%)</td>
<td></td>
</tr>
<tr>
<td>1B</td>
<td>184 (13%)</td>
<td>157 (11%)</td>
<td>14 (13%)</td>
<td>355 (12%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>303 (21%)</td>
<td>289 (20%)</td>
<td>26 (24%)</td>
<td>618 (21%)</td>
<td></td>
</tr>
<tr>
<td>Blood type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>A</td>
<td>450 (31%)</td>
<td>517 (36%)</td>
<td>40 (37%)</td>
<td>1007 (34%)</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>53 (4%)</td>
<td>50 (3%)</td>
<td>3 (3%)</td>
<td>106 (4%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>199 (14%)</td>
<td>151 (11%)</td>
<td>13 (12%)</td>
<td>363 (12%)</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>734 (51%)</td>
<td>716 (50%)</td>
<td>53 (49%)</td>
<td>1503 (50%)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>697 (49%)</td>
<td>858 (60%)</td>
<td>61 (56%)</td>
<td>1616 (54%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>368 (26%)</td>
<td>240 (17%)</td>
<td>26 (24%)</td>
<td>634 (21%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>249 (17%)</td>
<td>269 (19%)</td>
<td>19 (17%)</td>
<td>537 (18%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>122 (9%)</td>
<td>67 (5%)</td>
<td>3 (3%)</td>
<td>192 (6%)</td>
<td></td>
</tr>
<tr>
<td>Inotropes</td>
<td>678 (47%)</td>
<td>600 (42%)</td>
<td>46 (42%)</td>
<td>1324 (44%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ventilator</td>
<td>360 (25%)</td>
<td>486 (34%)</td>
<td>33 (30%)</td>
<td>879 (30%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECMO</td>
<td>129 (9%)</td>
<td>197 (14%)</td>
<td>17 (16%)</td>
<td>343 (12%)</td>
<td></td>
</tr>
<tr>
<td>BIVAD</td>
<td>55 (4%)</td>
<td>10 (1%)</td>
<td>4 (4%)</td>
<td>69 (2%)</td>
<td></td>
</tr>
<tr>
<td>LVAD</td>
<td>84 (6%)</td>
<td>19 (1%)</td>
<td>3 (3%)</td>
<td>106 (4%)</td>
<td></td>
</tr>
<tr>
<td>None of above</td>
<td>1168 (81%)</td>
<td>1208 (84%)</td>
<td>85 (78%)</td>
<td>2461 (83%)</td>
<td></td>
</tr>
<tr>
<td>Prior cardiac surgery</td>
<td>83 (6%)</td>
<td>1147 (80%)</td>
<td>23 (21%)</td>
<td>1253 (42%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (n=1389, 1373, 103)</td>
<td>0.6 (0.4, 0.8)</td>
<td>0.5 (0.3, 0.7)</td>
<td>0.6 (0.4, 0.7)</td>
<td>0.5 (0.4, 0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR (n=1389, 1372, 103)</td>
<td>83 (63, 105)</td>
<td>72 (46, 100)</td>
<td>78 (48, 107)</td>
<td>79 (54, 103)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis</td>
<td>21 (1%)</td>
<td>41 (3%)</td>
<td>1 (1%)</td>
<td>63 (2%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Normal</td>
<td>808 (56%)</td>
<td>831 (58%)</td>
<td>61 (56%)</td>
<td>1700 (57%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>515 (36%)</td>
<td>436 (30%)</td>
<td>36 (33%)</td>
<td>987 (33%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>66 (5%)</td>
<td>107 (7%)</td>
<td>6 (6%)</td>
<td>179 (6%)</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>47 (3%)</td>
<td>60 (4%)</td>
<td>6 (6%)</td>
<td>113 (4%)</td>
<td></td>
</tr>
<tr>
<td>Mean PAP, mmHg (n=790, 590, 42)</td>
<td>28 (21, 36)</td>
<td>20 (15, 29)</td>
<td>28 (18, 42)</td>
<td>24 (17, 34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥30</td>
<td>353 (25%)</td>
<td>141 (10%)</td>
<td>20 (18%)</td>
<td>514 (17%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;30</td>
<td>437 (30%)</td>
<td>449 (31%)</td>
<td>22 (20%)</td>
<td>908 (30%)</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>646 (45%)</td>
<td>844 (59%)</td>
<td>67 (61%)</td>
<td>1557 (52%)</td>
<td></td>
</tr>
<tr>
<td>PCWP, mm Hg (n=749, 454, 40)</td>
<td>19 (13, 25)</td>
<td>14 (10, 18)</td>
<td>18 (11, 22)</td>
<td>17 (12, 23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥20</td>
<td>373 (26%)</td>
<td>99 (7%)</td>
<td>16 (15%)</td>
<td>488 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;20</td>
<td>376 (26%)</td>
<td>355 (25%)</td>
<td>24 (22%)</td>
<td>755 (25%)</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>687 (48%)</td>
<td>980 (68%)</td>
<td>69 (63%)</td>
<td>1736 (58%)</td>
<td></td>
</tr>
<tr>
<td>Medicaid insurance</td>
<td>621 (43%)</td>
<td>678 (47%)</td>
<td>49 (45%)</td>
<td>1348 (45%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Data are presented as number (percent) or median (25th percentile, 75th percentile). GFR is expressed as mL/min per 1.73 m<sup>2</sup>. BIVAD indicates biventricular assist device; CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; LVAD, left ventricular assist device; PAP, pulmonary artery pressure; and PCWP, pulmonary capillary wedge pressure.
of listing were age, listing diagnosis, ventilator support, type of mechanical support, and renal function (see Table II in the online-only Data Supplement for odds ratios and confidence intervals associated with the variables). The overall model was highly significant (likelihood ratio \( \chi^2 \) statistic=433.5). The model’s ability to discriminate survivors from nonsurvivors on the wait-list (C-statistic=0.783) and to calibrate the risk of wait-list mortality (Hosmer–Lemeshow \( P \) value=0.89; Figure 2A) was very good. On the basis of model (Table 3), the probability of wait-list mortality within 90 days of listing for a given patient may be calculated as 

\[
P = \frac{X}{X+1},
\]

where \( X = \exp \left( \text{intercept} + \text{coefficient for each variable in the model for the patient} \right) \).

Using this model, the predicted risk of dying on the wait-list or becoming too sick to transplant within 90 days was 2.4% for the lowest risk group (first decile). This group included children aged 11 to 17 years with cardiomyopathy who were not on ventilator support, had normal renal function, and were either on no mechanical support or were supported on a left ventricular assist device (see Table III in the online-only Data Supplement for distribution of model risk factors among the 10 risk groups). The risk increased progressively to 30% for children in the ninth risk decile (observed wait-list mortality, 35.9% and predicted post-transplant mortality, 36.7%) but decreased to 7.4% for children in the top 5% of risk (observed wait-list mortality, 59.6% and predicted post-transplant mortality, 52.2%).

**Models for Post-transplant Mortality**

The models for post-transplant 90-day and 1-year mortality/graft loss (Table 3) using variables age, diagnosis, ventilator support, type of mechanical support, and renal function at the time of transplant were also highly significant (see Table II in the online-only Data supplement for odds ratios associated with the variables). The model’s ability to discriminate survivors from nonsurvivors (C-statistic=0.803 for 90-day model and C-statistic=0.740 for 1-year model) and the model fit to the data (Hosmer–Lemeshow \( P \) value=0.88 for 90-day model and \( P \) value=0.45 for 1-year model; Figure 2B and 2C) was very good for the 3-month mortality model and good for the 1-year model. Serum bilirubin, a risk factor for early post-transplant mortality, was not significant (\( P = 0.38 \)) when added to the 1-year model and was not included.

**Transplant Benefit From Heart Transplantation at Listing**

Figure 3A illustrates a progressive increase in risk of 90-day wait-list mortality among the 10 risk groups with the corresponding risk of 90-day post-transplant mortality in each group if patients received HT at the time of listing. The observed cumulative 1-year wait-list mortality also increased progressively in the 10 risk groups, as did the risk of 1-year post-transplant mortality (Figure 3B). The reduction in risk of 1-year mortality on receiving HT close to listing (transplant benefit) in each risk group is illustrated in Figure 3C. Although there seemed to be minimal or no transplant benefit in lowest risk groups (risk of post-transplant mortality similar to or higher than observed wait-list mortality), overall, there was an increase in transplant benefit with increasing risk of wait-list mortality (\( P < 0.001 \) for trend). Among the highest risk groups, transplant benefit increased from 7.4% in the eighth decile to 9.7% for children in the ninth decile (observed wait-list mortality, 35.9% and predicted post-transplant mortality, 26.2%), increased further to 10.3% for children in 91st to 95th percentile (observed wait-list mortality, 47% and predicted post-transplant mortality, 36.7%) but decreased to 7.4% for children in the top 5% of risk (observed wait-list mortality, 59.6% and predicted post-transplant mortality, 52.2%).

**Discussion**

There are 3 major findings of this study. First, there is a large heterogeneity in risks of wait-list and post-transplant mortality among children listed for primary HT in the United States. Although 18% of children die on the wait-list (or are removed from the list because of deterioration) within 1 year of listing and 11% of those who receive a HT die or lose their graft within 1-year post-transplant, risk stratification using clinical variables at listing identifies a 20-fold variability in risk of 90-day wait-list mortality, a 25-fold variability in observed, cumulative 1-year wait-list mortality, and a 10-fold variability in risk of 1-year post-transplant mortality between the lowest and the highest risk deciles. Second, there is a progressive increase in risk of post-transplant mortality as the risk of wait-list mortality increases. Finally, although most children benefit from HT as it improves their 1-year survival, the magnitude of transplant benefit varies widely according to their risk of wait-list mortality. For most children, the magnitude of transplant benefit rises in direct proportion to their risk of
wait-list mortality. However, for children at the highest risk of wait-list mortality (top 5%), transplant benefit falls because of a disproportionate increase in risk of post-transplant mortality. These findings suggest that sicker children on the wait-list benefit more from HT unless the post-transplant mortality is predicted to be very high.

This is the first study to quantify transplant benefit in children listed for HT and combines observed 1-year mortality on the wait-list (in groups stratified by their 90-day risk of wait-list mortality) with risk prediction of 1-year post-transplant mortality. Although the concept of transplant benefit is just emerging in the field of pediatric heart transplantation, assessment of transplant benefit is routinely performed in lung transplant candidates aged >12 years where it is an integral part of the allocation score used to allocate donor lungs.14,15 Our analysis—using data from a contemporary cohort of listed children—demonstrates the feasibility of developing relatively robust models to estimate the risk of death while awaiting HT and in post-transplant period using routinely collected clinical variables at listing. These estimates can then be used to estimate transplant benefit in listed children.

Because HT may provide the only opportunity for survival for the sickest children on the wait-list, the goal of reducing...
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wait-list mortality may be best served by prioritizing allocation solely on urgency of transplant. This is indeed the intent of the current heart allocation, which divides listed candidates into status 1A (most urgent), 1B, and 2. A similar approach is currently used for liver allocation algorithms in the United States. The only organ for which both transplant urgency and post-transplant survival are considered in assigning allocation priority is during the calculation of lung allocation score, which analyzes transplant benefit at the individual level and seeks to avoid transplantation in patients at a very high risk of post-transplant mortality. Because this score gives the risk of wait-list mortality a higher weight than post-transplant survival, it is not surprising that recipients with higher lung allocation scores at transplant have higher post-transplant mortality compared with those with lower allocation scores. Nonetheless, the approach represents an elegant, real-world application of transplant ethics to allocation policy as it applies both justice/fairness (sicker first) and utility/benefit in assigning allocation priority.

As our data show, two thirds of all children listed for HT in the present cohort were listed 1A, despite marked variability in their risk of wait-list mortality. This finding suggests that a revision of the current allocation policy is needed even if the current intent of prioritization based on urgency remains paramount. Whether the revision should be based solely on transplant urgency, such as by adding several additional tiers of transplant urgency, or should also consider transplant benefit is an important dialogue for the transplant community and the allocation experts to have. Our analysis demonstrates that in 95% of children listed for HT, assigning higher transplant urgency based on risk of wait-list mortality will also be associated with greater transplant benefit compared with children in a lower risk stratum.

The current allocation of deceased-donor organs in the United States is based on the Final Rule published by the US Department of Health and Human Services, which recommends avoiding futile transplants as an explicit goal in any allocation policy. Although the term broadly refers to transplants where the risk of post-transplant mortality is predicted to be too high, labeling a future transplant as futile is difficult in clinical practice. Although a predetermined risk of post-transplant mortality may be used for defining it, the challenges in clinical practice have been 2-fold. First, the prediction models to estimate the risk of post-transplant mortality have been reported only recently. Second, the estimated risk of post-transplant mortality when a child is no longer a transplant candidate and when HT may be considered futile is hard to define and is potentially contentious because of associated uncertainty and because it may differ among centers, depending on referral patterns and outcomes. Nevertheless, using a model-based estimation rather than a qualitative, subjective risk assessment of post-transplant mortality in high-risk children may facilitate a more informed discussion on the transplant candidacy of such children. Whether consideration of transplant benefit during heart allocation will help avoid futile transplants and reduce overall (wait-list and post-transplant) mortality among listed children requires further, more complex analyses. Our analysis serves as an example of how such modeling could be done to inform decision making with more precision in the future, with analyses that not only consider patient variables at listing, but also the changes in clinical states of listed patients and in their risks while waiting. Such simulations are considered essential before considering any changes in allocation policy.

Figure 2. Model-predicted vs observed 90-day wait-list mortality (including children removed because of deterioration) in children listed for heart transplant (A). Model-predicted vs observed 90-day post-transplant mortality/graft loss (B) and 1-year post-transplant mortality/graft loss among heart transplant recipients (C). The dotted line is the line of identity in each graph and the points represent groups (deciles) with increasing risk of wait-list mortality.
This study has several limitations. First, this was a retrospective analysis of a national database, which may lack the quality control seen in data collected during a prospective, controlled study. However, because these data are collected prospectively at the time of listing and transplant and are used by United Network of Organ Sharing for real-time organ allocation, for periodic audits of the transplant centers and for generating center-performance reports, certain safeguards to data quality are to be expected. Second, we were able to assess transplant benefit only at the time of listing, an analysis that assumes HT close to listing such that the values of model variables for listed patients remain unchanged. We were unable to analyze the effect of changes in patient states during the wait-list period as the Organ Procurement and 

Figure 3. Percentage risk of 90-day wait-list and 90-day post-transplant mortality at the time of listing in children listed for heart transplant (A). Observed cumulative 1-year wait-list and predicted 1-year post-transplant mortality at the time of listing (B). Transplant benefit (percentage risk reduction in 1-year mortality) on receiving a transplant close to listing in children stratified by increasing risk of wait-list mortality (C).
Transplantation Network database lacks these details. Third, some variables, such as serum bilirubin and sensitization status, are not recorded by United Network of Organ Sharing at the time of HT listing and, therefore, cannot be used in modeling transplant benefit at the present time. Furthermore, details of congenital heart disease diagnosis are not recorded either at the time of listing or at transplant. We were unable to study the potential effect of these variables on wait-list mortality and transplant benefit. Finally, the risk of wait-list mortality using the reported model is applicable only in the context of current heart allocation in the United States. Any change in policy that favors allocation of hearts to sicker children will help to reduce their risk of wait-list mortality. Because the risk of post-transplant mortality will be less sensitive to policy changes, we speculate that such an allocation change will shift the inflection point when transplant benefit drops to an earlier group along the risk spectrum. Therefore, periodic reappraisal of risk models for wait-list and post-transplant mortality will be essential to keep these models current.

In conclusion, there is large variability in risk of wait-list mortality among children listed for HT. Children stratified based on their increasing risk of wait-list mortality are at a progressively higher risk of post-transplant mortality. Sicker children on the wait-list benefit more from HT unless the post-transplant mortality is predicted to be very high. Further analysis, that incorporates changes in relative risks while waiting for HT, is needed to determine whether considering transplant benefit in allocation policy can improve overall survival among listed children.

Sources of Funding

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Disclosures

Dr Gauvreau had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. The data were supplied by the United Network of Organ Sharing as the contractor for the Organ Procurement and Transplantation Network (OPTN). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the OPTN or the US Government. The other authors have no conflict to report.

References

19. Russo MJ, Iriarte A, Hong KN, Davies RR, Rydas S, Takayama H, Ibrahimii A, Geljins AC, Bacciotta MD, D’Oviedo F, Arcasoy S, Sonett JR. High lung allocation score is associated with increased...

CLINICAL PERSPECTIVE

The sickest children among those listed for heart transplant (HT) are also at a higher risk of post-transplant mortality. Although it may be assumed that the sicker child waiting for HT is more likely to benefit from transplant, the actual relationship between heart failure severity and transplant benefit is unknown. We defined transplant benefit as percentage reduction in risk of 1-year mortality on receiving HT and analyzed all 2979 children aged <18 years listed for first HT in the United States between July 2004 and December 2010. We stratified study children into 10 groups (deciles) based on increasing risk of death or becoming too sick to transplant within 90 days of listing. The groups were followed up for 1 year to assess cumulative 1-year wait-list mortality. We estimated the risk of 1-year post-transplant mortality (or graft loss) on receiving HT close to listing in each of the 10 risk groups. Overall, 18% of listed children died or became too sick to transplant within 1 year. Of 2034 children who received HT, 10.8% died within 1 year. The risk of 90-day wait-list mortality increased from 2.4% to 51.6% from the first to the tenth risk group. Transplant benefit increased progressively among the 10 risk groups. However, transplant benefit for children in the top 5% of risk was lower than estimated benefit for children in the 91st to 95th percentile of risk. We conclude that the sicker children on the wait-list benefit more from HT unless the post-transplant mortality is predicted to be very high.

Risk Stratification and Transplant Benefit in Children Listed for Heart Transplant in the United States

Tajinder P. Singh, Christopher S. Almond, Gary Piercey and Kimberlee Gauvreau

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### Table S1. Baseline Characteristics of Children at Transplant

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<th>Other (N=73)</th>
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<td>Not known</td>
<td></td>
<td>55 (5%)</td>
<td>58 (7%)</td>
<td>6 (8%)</td>
<td>119 (6%)</td>
</tr>
<tr>
<td><strong>Medicaid Insurance</strong></td>
<td></td>
<td>478 (43%)</td>
<td>410 (48%)</td>
<td>32 (44%)</td>
<td>920 (45%)</td>
</tr>
</tbody>
</table>

Data are presented as number (percent) or median (25th percentile, 75th percentile). yr (year), ECMO (extracorporeal membrane oxygenation), BIVAD (bi-ventricular assist device), LVAD (left ventricular assist device), GFR (glomerular filtration rate), PAP (pulmonary artery pressure), PCWP (pulmonary capillary wedge pressure), PRA (panel reactive antibodies), hr (hours). GFR is expressed as ml/min/1.73 m².
Table S2. Odds Ratios for Models of 90-day Wait-list Mortality, 90-Day Post-Transplant Mortality and 1-yr Post-Transplant Mortality

<table>
<thead>
<tr>
<th>Age Categories (yr)</th>
<th>Odds Ratios for 90-Day Wait-list Mortality* (95% CI)</th>
<th>Odds Ratios for 90-Day Post-HT Mortality† (95% CI)</th>
<th>Odds Ratios for 1-yr Post-HT Mortality† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>2.9 (2.0, 4.3)</td>
<td>1.4 (0.8, 2.4)</td>
<td>1.1 (0.7, 1.7)</td>
</tr>
<tr>
<td>1-10</td>
<td>1.7 (1.2, 2.5)</td>
<td>0.9 (0.5, 1.6)</td>
<td>0.8 (0.5, 1.2)</td>
</tr>
<tr>
<td>11-17</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>CHD</td>
<td>2.5 (1.9, 3.2)</td>
<td>4.0 (2.6, 6.3)</td>
<td>2.8 (2.0, 3.9)</td>
</tr>
<tr>
<td>Other</td>
<td>1.6 (0.9, 3.0)</td>
<td>1.2 (0.3, 4.3)</td>
<td>1.7 (0.8, 3.9)</td>
</tr>
<tr>
<td>Ventilator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.8 (2.1, 3.6)</td>
<td>3.1 (1.9, 5.0)</td>
<td>3.0 (2.1, 4.5)</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mechanical Support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>1.8 (1.3, 2.5)</td>
<td>2.4 (1.4, 4.2)</td>
<td>1.8 (1.1, 3.0)</td>
</tr>
<tr>
<td>BIVAD</td>
<td>2.3 (1.1, 4.8)</td>
<td>3.4 (1.6, 7.3)</td>
<td>2.1 (1.1, 4.1)</td>
</tr>
<tr>
<td>LVAD</td>
<td>1.7 (0.9, 3.2)</td>
<td>0.6 (0.2, 2.0)</td>
<td>0.6 (0.3, 1.4)</td>
</tr>
<tr>
<td>None of above</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>1.7 (1.3, 2.2)</td>
<td>1.4 (0.9, 2.2)</td>
<td>1.4 (0.9, 1.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>3.1 (2.1, 4.5)</td>
<td>3.9 (2.2, 6.9)</td>
<td>2.7 (1.7, 4.6)</td>
</tr>
<tr>
<td>Intercept</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

* Includes children removed from the list due to clinical deterioration. † Includes children with graft loss. yr (year), HT (heart transplant), CHD (congenital heart disease), ECMO (extracorporeal membrane oxygenation), BIVAD (bi-ventricular assist device), LVAD (left ventricular assist device).
Table S3. Distribution of Model Risk Factors in Risk-Groups and Associated 1-yr Wait-list Mortality

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Wait-List Decile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Age Category</td>
<td></td>
</tr>
<tr>
<td>&lt;1 yr</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1-10 yr</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>11-17 yr</td>
<td>207 (100%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>195 (94%)</td>
</tr>
<tr>
<td>CHD</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (5.8%)</td>
</tr>
<tr>
<td>Ventilator</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>No</td>
<td>207 (100%)</td>
</tr>
<tr>
<td>Mechanical Support</td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>BIVAD</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>LVAD</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>None of above</td>
<td>186 (90%)</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>207 (100%)</td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Observed 1-yr Wait-list Mortality</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Data are presented as frequency (percent).