Creation of a Quantitative Score to Predict the Need for Mechanical Support in Children Awaiting Heart Transplant

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Background. Due to the availability of new devices, the use of ventricular assist devices (VADs) in children has been increasing; however, patient selection and optimal timing of device implantation in this population remains uncertain.

Methods. A retrospective review of the United Network for Organ Sharing dataset identified 5,200 listings without mechanical circulatory support (MCS) for isolated pediatric heart transplant, 1995 to 2012. Patients were randomly divided into a derivation and validation cohort. A multivariable logistic regression model predicting the likelihood of death or need for MCS within 60 days was built using the derivation cohort and tested in the validation cohort. A simplified score (PedsMCS score) was developed and evaluated for accuracy.

Results. The predictive model consisted of variables present at listing (age, albumin level, creatinine clearance, serum bilirubin, mechanical ventilation, and inotropic support). It had good predictive ability (C statistic 0.7304) within the validation cohort. The simplified PedsMCS score was also predictive (C statistic 0.7217) and there was a strong correlation between predicted and expected outcomes ($r = 0.91, p < 0.0001$). Patients with PedsMCS score 16 or greater had a significantly higher risk of death or MCS within 2 months (36.6%) than those with low scores (< 6) (1.5%, $p < 0.0001$). A single point increase in PedsMCS score was associated with a 16.7% increase in the risk of death or MCS with 2 months ($p < 0.0001$).

Conclusions. We have developed and validated a simplified score to predict the need for MCS based on risk factors present at listing. This will provide more accurate prognostication in children awaiting heart transplant, and may improve patient selection.

Study Population and Design
The analysis includes 5,200 patients. Statistical analysis was performed using SAS 9.21 for AIX (SAS Institute, Cary, NC). The date of MCS initiation was defined as the earliest date (listing status change or transplantation) at which MCS use was documented. The primary outcome was a composite of death or the institution of MCS (either VAD or ECMO) within 60 days of listing. Secondary outcomes included likelihood of eventual transplantation and posttransplant mortality (within 30 days or prior to hospital discharge).

For derivation and validation of the model, the dataset was randomly divided into a derivation cohort (90%) and a validation cohort (10%). All model development was performed in the derivation cohort and tested in the validation cohort. Only variables present at listing were included.

Statistical Analysis
Variables were assessed by univariable and multivariable (backward selection, \( p < 0.20 \)) logistic regression for association with the primary outcome. All variables were evaluated in the multivariable model because of the relatively small sample size in pediatric populations (compared with adult transplant datasets) and the likelihood of multiple interactions between factors within pediatric transplant datasets, including age, etiology, weight, blood type, and race. The final model contained factors that improved the explanatory power as assessed by Akaike information criterion, likelihood ratio test, area under the receiver operating curve C statistic, and the Hosmer-Lemeshow (HL) goodness of fit test.

Missing variables were imputed using multiple imputation (Markov chain method, imputations = 10). The probability of each outcome in each patient was calculated as the mean probability across all 10 imputations. The predictive power of the modeled probability was tested using logistic regression within the validation dataset and secondarily within the derivation cohort and the entire population.

Score Generation
From the final predictive model, a 40-point waitlist score (PedsMCS score) was developed to predict the need for MCS. The predictive ability of the score was analyzed by logistic regression. Correlation between predicted and observed incidence of the primary outcome was estimated by Pearson correlation coefficient. Because of small sample sizes at some score levels, scores were also aggregated into the following 4 risk groups: low, 0–5; moderate, 6–10; high, 11–15; and very high, 16 or greater. Cumulative survival on the waitlist was estimated using the Kaplan-Meier method.

Results
Cohort Statistics
A total of 3,459 (66.5%) of the 5,200 patients underwent transplantation. Of these, 99 (2.9%) were placed on ECMO prior to transplantation and 205 (5.9%) had a VAD implanted. Six patients who were not transplanted had a change in listing status indicating initiation of MCS; no additional data on the use of mechanical support in nontransplanted patients were available. The 2-month waitlist mortality was 11.5% (\( n = 600 \)); 234 (4.5%) additional patients died after waiting more than 2 months. The primary outcome of death or VAD implantation within 2 months of listing occurred in 794 (15.3%) patients; an additional 351 (6.8%) patients reached the primary outcome beyond 2 months on the waitlist. Random stratification yielded a derivation cohort of 4,681 patients (90.0%) and a validation cohort of 519 patients (10.0%). Baseline characteristics and the incidence of the primary outcome in the 2 populations were similar (Table 1).

Development of the Model Within the Derivation Cohort
Exploratory univariable analysis demonstrated significant associations between risk factors at listing and the primary outcome (Table 2). In addition to variables meeting the selection criteria, albumin less than 3.5 was included in the model because of its strong effect in univariable analysis as well as the improvement in model predictive ability. Within the derivation dataset, the final model was predictive (C statistic 0.6943), but there was a poor fit within the middle deciles of risk (HL \( p < 0.0001 \)). Within the validation cohort (\( n = 519 \)) the model was both predictive (C statistic 0.7304) and a good fit throughout the distribution of risk (HL \( p = 0.12 \)).

Simplified Score
A simplified score predictive of death or the need for MCS within 2 months of listing (PedsMCS score) was created by summing points assigned to each risk factor based on odds ratios within the model (Table 2). The score approximated a normal distribution (Fig 1) and was predictive within both the derivation (C statistic 0.6834) and validation cohorts (C statistic 0.7217); it also demonstrated good fit (derivation: HL test, \( p = 0.26 \); validation: HL test, \( p = 0.72 \)).

Use of Predictive Model and Score
An increase in PedsMCS score was associated with a higher risk of the primary outcome in both derivation (\( p < 0.0001 \)) and validation cohorts (\( p < 0.0001 \)). Higher aggregated risk groups were associated with an increased risk of the primary outcome (low, 1.5%; moderate, 11.2%; high, 17.8%; versus very high, 36.6%; \( p < 0.0001 \)) in the validation cohort (Fig 2C); similar outcomes were observed in the derivation cohort (Fig 2B) and the overall study population (Fig 2A). There was a corresponding decrease in the likelihood of eventual transplant in the high-risk PedsMCS score risk groups within the validation cohort (low, 75.4%; moderate, 66.0%; high, 59.7%; and very high, 48.4%; \( p = 0.0028 \)). Logistic regression demonstrated that PedsMCS score was highly predictive of actual outcomes (odds ratio 1.17, 95% confidence interval [CI] 1.11 to 1.23) (Fig 3). Predicted occurrence of death or institution of MCS within 2 months for individual patients can be calculated as...
The resultant predicted probability correlates with the actual incidence in the validation cohort at each score (Pearson correlation coefficient, 0.91; Fig 3).

Long-term survival on the waitlist without MCS was correlated with aggregated risk groups (Fig 4). Among patients who underwent transplantation and were not supported by MCS at transplant, posttransplant mortality was increased within higher aggregated risk groups (low, 5.7%; moderate, 5.4%;
While unadjusted posttransplant mortality was higher among patients on MCS (12.7% vs 7.0%, \( p = 0.0004 \)), the PedsMCS score risk group did not correlate with posttransplant mortality in these patients (low, 20.8%; moderate, 9.2%; high, 13.1%; and very high, 16.1%, \( p = 0.3 \)).

**Table 2. Univariable and Multivariable Logistic Regression Modeling of the Likelihood of Death or Mechanical Circulatory Support Within 2 Months of Listing Within the Derivation Cohort**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>p Value</th>
<th>Multivariate Analysis</th>
<th>p Value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>1.04 (0.89–1.21)</td>
<td>0.6</td>
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<tr>
<td>Age</td>
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<tr>
<td>Neonate</td>
<td>1.26 (1.00–1.58)</td>
<td>&lt;0.05</td>
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<tr>
<td>Infant (2 months to 1 year)</td>
<td>Reference</td>
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<tr>
<td>2 to 5 years</td>
<td>1.18 (0.93–1.49)</td>
<td>0.17</td>
<td>1.54 (1.22–1.94)</td>
<td>0.0003</td>
<td>3</td>
</tr>
<tr>
<td>6 to 12 years</td>
<td>1.04 (0.80–1.35)</td>
<td>0.8</td>
<td>1.53 (1.16–2.01)</td>
<td>0.0025</td>
<td>3</td>
</tr>
<tr>
<td>13 to 18 years</td>
<td>1.04 (0.91–1.32)</td>
<td>0.8</td>
<td>1.53 (1.18–1.99)</td>
<td>0.0015</td>
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<tr>
<td>Weight</td>
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<tr>
<td>&lt;10 kg</td>
<td>1.13 (0.94–1.36)</td>
<td>0.18</td>
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<td>10–30 kg</td>
<td>1.07 (0.85–1.33)</td>
<td>0.6</td>
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<td></td>
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<tr>
<td>( \geq 30 ) kg</td>
<td>reference</td>
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<tr>
<td>Race</td>
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<tr>
<td>Asian</td>
<td>1.30 (0.88–1.94)</td>
<td>0.19</td>
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<tr>
<td>African-American</td>
<td>1.14 (0.94–1.38)</td>
<td>0.2</td>
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<tr>
<td>Hispanic</td>
<td>1.21 (0.99–1.48)</td>
<td>0.07</td>
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<tr>
<td>Caucasian (non-Hispanic)</td>
<td>reference</td>
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<tr>
<td>Heart failure etiology</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Dilated cardiomyopathy</td>
<td></td>
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<tr>
<td>Congenital heart disease</td>
<td>1.17 (0.99–1.37)</td>
<td>0.06</td>
<td></td>
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<tr>
<td>Restrictive cardiomyopathy</td>
<td>0.77 (0.46–1.27)</td>
<td>0.3</td>
<td></td>
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<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1.30 (0.77–2.20)</td>
<td>0.3</td>
<td></td>
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<tr>
<td>Retransplant</td>
<td>1.17 (0.82–1.67)</td>
<td>0.4</td>
<td></td>
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<tr>
<td>Ischemic heart disease</td>
<td>1.48 (0.73–2.99)</td>
<td>0.3</td>
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<tr>
<td>Valvular heart disease</td>
<td>1.85 (0.79–4.35)</td>
<td>0.16</td>
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<tr>
<td>Transplant listing status</td>
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<tr>
<td>Status 1A</td>
<td>0.99 (0.84–1.15)</td>
<td>0.9</td>
<td></td>
<td></td>
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<tr>
<td>Status 1B</td>
<td>reference</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mechanical ventilation</td>
<td>2.58 (2.21–3.02)</td>
<td>&lt;0.0001</td>
<td>2.23 (1.84–2.73)</td>
<td>&lt;0.0001</td>
<td>7</td>
</tr>
<tr>
<td>Inotropes at listing</td>
<td>1.56 (1.33–1.84)</td>
<td>&lt;0.0001</td>
<td>1.32 (1.10–1.59)</td>
<td>0.0034</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine clearance &lt;40 cc/min</td>
<td>1.68 (1.29–2.17)</td>
<td>&lt;0.0001</td>
<td>1.49 (1.19–1.86)</td>
<td>0.0006</td>
<td>3</td>
</tr>
<tr>
<td>Albumin &lt;3.5</td>
<td>1.53 (1.22–1.93)</td>
<td>&lt;0.0001</td>
<td>1.13 (0.90–1.41)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Total bilirubin level (serum)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0–0.99</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1.00–1.99</td>
<td>0.44 (0.32–0.59)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>2.00–2.99</td>
<td>0.63 (0.40–1.02)</td>
<td>0.058</td>
<td>1.76 (1.27–2.43)</td>
<td>0.0007</td>
<td>4</td>
</tr>
<tr>
<td>( \geq 3.00 )</td>
<td>0.34 (0.31–0.67)</td>
<td>&lt;0.0001</td>
<td>1.98 (1.50–2.61)</td>
<td>&lt;0.0001</td>
<td>5</td>
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<tr>
<td>ABO blood type</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>A</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1.60 (1.25–2.05)</td>
<td>0.0002</td>
<td>1.60 (1.22–2.10)</td>
<td>0.0007</td>
<td>4</td>
</tr>
<tr>
<td>AB</td>
<td>0.96 (0.62–1.50)</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>1.48 (1.24–1.76)</td>
<td>&lt;0.0001</td>
<td>1.52 (1.27–1.83)</td>
<td>&lt;0.0001</td>
<td>3</td>
</tr>
</tbody>
</table>

Cl = confidence interval; OR = odds ratio.

Comment

We have developed and validated a model predictive of mortality and the need for mechanical circulatory support within 2 months of listing for heart transplantation in children. The model is accurate within the derivation cohort, and had strong predictive accuracy within the validation cohort. The simplified PedsMCS score has
patients with renal insufficiency as well as those requiring mechanical ventilation at listing are more likely to show improvement in these parameters when supported with a VAD than if left unsupported [2]. In this context, especially where both factors result in higher posttransplant mortality, we feel that both renal insufficiency and the need for mechanical ventilation are strong indications for VAD implantation. While certain patients (especially neonates and those with single-ventricle circulations) may not be amenable to mechanical support without ECMO, in most patients VAD implantation is preferable to the continuation of endotracheal intubation and mechanical ventilation or ongoing renal insufficiency.

Although hypoalbuminemia and hyperbilirubinemia have been less frequently associated with poor outcomes among children on the waitlist for cardiac transplantation, in the PedsMCS scoring both were associated with strong prediction of death or need for MCS. Hypoalbuminemia commonly results from the inability to tolerate enteral nutrition and resultant cardiac cachexia, or may indicate volume overload and decompensated heart failure, the presence of protein losing enteropathy, or a combination of these factors [15–17]. Similarly, while hyperbilirubinemia may be associated with right heart failure (and is clearly a risk factor for poor outcomes in adults and after transplantation in children) [18, 19], in children it may also reflect younger age (including liver immaturity in neonates) or concomitant congenital anomalies [20, 21]. In both cases further research is needed to clarify the importance of these factors and whether mechanical support may ameliorate the underlying causes.

Age greater than or equal to 2 years was associated with a higher predicted probability of death or MCS within 2 months of listing. This likely reflects, at least in part, the historically higher incidence of VAD use among older patients amenable to the use of first and second generation adult devices [1–3] because 2-month mortality waitlist is higher among neonates [11, 12, 22]. The risks of VAD implantation and support are lower among the older patient in whom the implant is easier, more advanced devices are available in the appropriate size, and increased flow reduces thromboembolic risk [1–3, 6, 8, 23].

Notably, the etiology of heart failure was not a powerful predictor of outcome and is not included in the score. This may reflect the fact that patients with congenital heart disease or nondilated cardiomyopathies are both more likely to die on the waitlist and less likely to be supported by a VAD [9, 10, 24, 25]. Thus, the 2 components of the composite endpoint cancel each other out. These patients may be more difficult to support on a VAD; requiring novel cannulation strategies, different devices, and technical alterations to the implant procedure [26]. However, these data suggest that etiology alone should not guide the decision to implant a VAD. Rather, in patients with elevated PedsMCS score consideration for initiation of MCS is indicated, taking into account the individualized risk of implantation.

Fig 1. Distribution of prediction scores within (A) derivation cohort and (B) validation cohort. (MCS = mechanical circulatory support.)

similar accuracy to the more complex multivariable modeling, but has the advantage of relative simplicity to enable rapid calculation of risk in the clinical setting.

There was a strong correlation between PedsMCS score and observed outcomes in both cohorts. Within the validation cohort, each additional point on the PedsMCS score increased the odds of death or need for MCS by 16.7%. Patients with scores 16 or greater had a 36.6% incidence of death or MCS, compared with only 1.7% among patients in the low-risk group. The simplified score enables rapid and facile calculation at the bedside to provide patients and their families with realistic estimates of likely outcomes on the waitlist.

It is important to note that the risk of death in the absence of mechanical support is only one aspect of the decision to initiate MCS. The flip side of the risk-benefit calculation has to include the risks of VAD implantation including previous cardiac surgery, patient size, and the etiology of heart failure [6–8]. Further research is required to provide some estimate of the real risks associated with VAD insertion.

Not surprisingly, most of the variables included in the PedsMCS score are related to clinical condition. Consistent with previous studies [9–14], mechanical ventilation and renal insufficiency were strongly predictive of poor outcomes. Recently, our group has demonstrated that
Blood type is an important component of the score, probably due to its affecting the likelihood of receiving a timely allograft offer. Patients with ABO type O have consistently longer wait times than others, while the effect of type B is less consistent [27, 28]. Because of the longer waiting times, centers may have a lower threshold for VAD implantation in specific blood types. In addition, longer waiting times indicate a lower probability of receiving an allograft offer each day; therefore, with a constant hazard of death, type O patients will be less likely to survive until a donor allograft becomes available. Based on the PedsMCS score, it makes sense to have a lower threshold for initiating MCS in blood group O patients than in blood group A patients, who are likely to have significantly shorter wait times.

While we did not perform rigorous statistical evaluation of the score as a predictor of posttransplant outcomes, higher scores are associated with early posttransplant mortality rates. This is not surprising because many of the component variables in the PedsMCS score are also powerful components of posttransplant survival models [3, 9, 10, 12]. However, among patients who were placed on to MCS prior to transplantation the score was no longer predictive of posttransplant survival. This may reflect the neutralization of some of these risk factors by mechanical support (including resolution of respiratory and renal failure) [2]. While the unadjusted mortality rate among transplant patients supported with MCS was higher than unsupported patients, this reflects the extremely poor outcome among MCS patients supported on ECMO as well as the lack of risk adjustment for underlying clinical conditions among patients requiring MCS. Risk-adjusted outcomes indicate that VAD use increases the likelihood of surviving to transplantation without worsening posttransplant survival [1–3].

**Limitations**

The primary limitation of this score is that despite its relative accuracy, the C statistic is still only 0.71. This score is comparable with other risk indexes, including the impact score in adult heart transplant outcomes [18], but slightly lower than the risk-adjusted congenital heart surgery and STS-EACTS Mortality Category (STAT) scores [29] in congenital heart surgery and the waitlist model of Singh and colleagues [30]. This suggests that the limited number of variables available in the UNOS dataset leave substantial variability in outcomes unaccounted for. Variables reporting functional status, ability to tolerate enteral nutrition, and detailed congenital diagnostic information would likely improve the score.

Due to the limitations of sample size, we chose to include all patients across both age and etiology categories, as well as the type of MCS (ECMO or VAD) required within a single model. It is possible that developing separate models for congenital heart disease for different age groups, and for different types of support will result in more accurate risk scores; however, the loss of statistical power limits the strength of such analyses.

Because UNOS does not contain information on the exact date of institution of MCS, we used the date of
transplant as the last possible date that they would have been without MCS. This underestimates the risk of MCS institution; the actual incidence is likely higher and time to MCS institution shorter than shown here. Combining or linking the UNOS dataset with additional datasets such as the Society of Thoracic Surgeons Congenital Heart Surgery Database or the PediMACs registry may mitigate some of these shortcomings by providing additional, potentially important, data such as detailed congenital diagnostic information and the exact date of institution of MCS.

Finally, external validation is important. Although the PedsMCS score has been developed in 1 cohort and internally validated in a separate randomly-selected cohort, replication of the findings through a prospective analysis (especially in a non-UNOS transplant population) would be ideal in confirming its utility.

Summary

We have developed and validated a simplified score (PedsMCS score) to predict the need for MCS based on risk factors present at listing. The score is primarily determined by the patient’s clinical condition at listing, although factors affecting wait times are also important. The PedsMCS score should enable both improved clinical decision-making and more accurate prognostication when discussing potential risks and benefits of MCS implantation.

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References

CONGENITAL HEART


DISCUSSION

DR YVES UDEKEM (Victoria, Australia): There is, first, one thing I am not sure that I have well understood. In your endpoints, you have death and a need for mechanical support within two months. If the patient needs it in two months’ time, that does not mean that you should put it now. I mean, these two months may be useful. These are two months where the patients would not suffer from complication from VAD [ventricular assist device]. Can you explain it to me a little bit more?

DR DAVIES: I think that is true. It still makes it hard to get the exact timing right. We chose two months because I think it is sort of a subjectively reasonable period. It is hard if you cut it down to one month to get much of an endpoint in there all at, partly because of the way the data is collected in the UNOS [United Network for Organ Sharing] database.

There were two ways you could have a positive outcome from transplanting children. One was if you were transplanted within two months on mechanical support or if you had a status change involving mechanical support within two months. And so if we had shortened it to one month or two weeks, I think the end gets extremely small and it is hard to really tell anything.

So I agree, I think two months off mechanical support is probably better than two months not on mechanical support, but we had to pick a time point in which it was important.

DR UDEKEM: It is a beautiful study and it is an important question because it is always very difficult decisions to take. The predictive model is obviously valid only for the US, and in Australia the waiting time for organs is two or three times longer than in the US, and that is why our practice may differ slightly.

But we end up putting patients on VAD in children usually when they are on inotropic support. But one of the most frequent indications is the inability of the child to feed, so a poor nutritional status and inability to keep up.

I know that these kind of data are not as well recorded usually, but did you try to look at nutritional status?

DR DAVIES: Unfortunately, nutritional status is one of the preoperative risk factors that is not captured in the UNOS database. It would certainly be of interest to evaluate the impact of nutrition and enteral feeding on waitlist outcomes. First, because we believe that it is an important component of waitlist and posttransplant outcomes (and a likely explanation for the fact that our model only explains 72% of the variability in outcomes). And, second because it is one of the more controversial indications for VAD use. Centers with a high level of experience with VAD support may use it as an indication for implantation, while centers with less familiarity may be less likely to implant a VAD purely to optimize nutrition. Centers
that do less may be less likely to use nutritional status as an indication.

Regrettably, our analysis is limited by the data collected by UNOS, and nutritional status and enteral feeding tolerance are not currently available in the dataset.

DR LUCIEN A. DURHAM III (Corpus Christi, TX): That is a really good start to something we really all need to be looking at, particularly as we are finding out that a lot of patients that go on ECMO [extracorporeal membrane oxygenation] just need the VADs and we do not have to cause issues with the lungs by adding an oxygenator.

My question is, did you attempt to separate the patients who required ECMO versus those who only required a VAD? Oftentimes those are widely disparate patient groups and I know UNOS does not take into account oxygenation index and the like.

DR DAVIES: In this analysis, we did not evaluate these two outcomes separately. Our group has recently published data demonstrating that when patients need ECMO prior to transplant they are in much worse shape, and both waitlist and posttransplant mortality are higher.

However, in this analysis we chose to combine them in a single outcome. In order to obtain a large sample size, we included a wide time range. In the earlier patients (between 1995 and 2000), there are likely some who went on ECMO, who today would get a VAD. And more broadly, we were trying to identify patients who were not capable of living two months without mechanical support or a new heart. So for those reasons, we chose to aggregate ECMO and VAD patients.

However, the distinction between VAD and ECMO outcomes is an important point. Given the negative impact of ECMO on both waitlist survival and posttransplant outcomes, initiation of ECMO should have much higher threshold than insertion of a VAD.

DR DURHAM: I agree and I think it is a really nice start to answer some complex questions. Because our knee-jerk is go to ECMO when a lot of these kids just need VADs, we have to shift our thinking to differentiate between the patients needing cardiac support and those needing ECMO. Congratulations, nice presentation.

DR JEFFREY P. JACOBS (St. Petersburg, FL): Ryan, I would first congratulate you for this research, which is important. And I would also congratulate you for your leadership in trying to create a way to link the UNOS registry to the STS [Society of Thoracic Surgeons] database, which is a linkage that will have influence not only in the congenital database but ultimately in the adult cardiac database as well.

And the question I have is do you think that when we do operationalize the linkage between the STS database and UNOS, that would then lead to potential revisions in the model that you have described that would increase its power?

DR DAVIES: The linkage of the STS database with UNOS data demonstrating that when patients need ECMO prior to transplant they are in much worse shape, and both waitlist and posttransplant mortality are higher.

However, in this analysis we chose to combine them in a single outcome. In order to obtain a large sample size, we included a wide time range. In the earlier patients (between 1995 and 2000), there are likely some who went on ECMO, who today would get a VAD. And more broadly, we were trying to identify patients who were not capable of living two months without mechanical support or a new heart. So for those reasons, we chose to aggregate ECMO and VAD patients.

However, the distinction between VAD and ECMO outcomes is an important point. Given the negative impact of ECMO on both waitlist survival and posttransplant outcomes, initiation of ECMO should have much higher threshold than insertion of a VAD.

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And the question I have is do you think that when we do operationalize the linkage between the STS database and UNOS, that would then lead to potential revisions in the model that you have described that would increase its power?

DR DAVIES: The linkage of the STS database with UNOS data has the potential to result in a significantly more accurate model for at least two reasons. The most important is that the STS dataset would provide more accurate data regarding the timing of mechanical support initiation. With only the UNOS dataset, the timing is an important limitation because we cannot know exactly when the mechanical support was initiated.

Furthermore, with UNOS data alone, we miss the negative consequences of device implantation; that is, what is the mortality of the implant itself (and is it altered by when the implant occurs while waiting). There are patients listed without support who have a device placed and then die on the waiting list. Those patients are not accurately captured in the UNOS dataset. The addition of STS data has the potential to provide a much more accurate estimate of the mortality associated with device implantation.

Finally, there are multiple risk factors that STS captures that are not present in the UNOS database, particularly factors relevant to children, such as congenital diagnosis and previous procedures. We were not able to accurately assess the impact of those risk factors on outcomes. In our current model, all patients with congenital heart disease were analyzed together and it turns out congenital heart disease was not a risk factor for death or institution of mechanical support. That may be because they have a lower risk of having a VAD implanted (due to anatomic, physiologic, and technical considerations) but a higher risk of dying while waiting, so the two components of the composite endpoint cancel each other out. But linkage to the STS database would provide much better data and a much more accurate model.

DR JACOBS: Well, I agree, and congratulations. This is great work.

DR DAVIES: Thank you.

DR CARL LEWIS BACKER (Chicago, IL): Ryan, it is curious to me that the endpoint that you are looking at is mechanical circulatory support, but your methods state that patients on mechanical circulatory support at listing were excluded.

So how does that enter into the analysis that all the patients that, for whatever reason, were put on ECMO or a VAD before your analysis are already excluded? To me that seems to be a major confounding factor. Can you explain that potential analysis problem?

DR DAVIES: The reason that we excluded patients who were mechanically supported at listing was that we were trying to answer the question, Given a patient without mechanical support, what is the likelihood that they will either need support or die within two months. In terms of waitlist data, UNOS collects clinical information primarily at two time points; listing and removal from the waitlist (usually for transplant but also for death). We wanted to identify the patients who were not on support at the first time point, and what was the likelihood that they would either need support or die within two months.

If we had included the patients who were already on support at listing, it would have been a much less clear set of data, because it would not have been clear whether the clinical condition at listing was influenced by the institution of mechanical support. For example, was the patient mechanically ventilated at listing because they were not extubated immediately following the implantation procedure? or had they had a complication of mechanical support that made them unable to ventilate spontaneously? Similarly, were they no longer in renal failure because of the improvement in cardiac output after VAD implantation, or were they in renal failure due to embolic complications?

The goal here was to evaluate the outcomes among patients who were not (yet) receiving mechanical circulatory support, and evaluate what is the likelihood that they are going to survive for two months without being mechanical support.

It is a different question as to whether patients who are on support are more likely to survive to transplant than those who are not. Other data from our group would suggest that (adjusting for the risk of their underlying clinical condition) patients...
supported by a ventricular assist device are more likely to survive to transplant than those without.

Ultimately, we are going to have to combine these two questions, because what we really want to know is the balance of the risks between VAD implantation and medical management on the waitlist. The most important modeling will be identifying a specific patient’s likelihood of surviving to transplant with and without a device, and use those two numbers to choose the best path to transplantation.

DR BOHDAN MARUSZEWSKI (Warsaw, Poland): I have one question. Did you differentiate between the patients with univentricular physiology and patients with biventricular physiology?

Just listening to you, I just thought that in both databases, we should add the univentricular morphology as a single preoperative risk factor. In any analysis that we did, the univentricular morphology alone both in the neonates and older patients, has been a strong risk factor for early and late death.

DR DAVIES: Unfortunately, we could not evaluate the impact of single ventricle physiology because the UNOS database does not contain the data, which reinforces, to go back to Dr Jacob’s point, the importance of linking the STS and UNOS databases. Because the only UNOS variable with information regarding the etiology of heart failure is only able to identify congenital heart disease, yes or no.

Detailed information regarding congenital heart diagnoses is important both for the current question of when does a patient need a VAD, but it may be even more important to address the question of how likely a patient is to survive following implantation of a VAD or ECMO because single ventricle patients have much more complicated options for mechanical support.

DR BACKER (Chicago, IL): Ryan, one final question. There must be a huge institutional variation in strategies for these patients. Did you get any of that information or is that all blinded?

DR DAVIES: It is blinded, but even with the blinded data, one could look at the influence of center variation. We felt that the current analysis was sufficiently complex that adding further analysis regarding center variation might be more confusing. However, it is an important point, and one that would be interesting to look at.

DR BACKER: Well, I congratulate you. I think this is a huge effort in the right direction to give us some evidence-based criteria of how to care for these patients.

DR DAVIES: Thank you very much.