Model for End-Stage Liver Disease Score Predicts Left Ventricular Assist Device Operative Transfusion Requirements, Morbidity, and Mortality

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Background—The Model for End-Stage Liver Disease (MELD) predicts events in cirrhotic subjects undergoing major surgery and may offer similar prognostication in left ventricular assist device candidates with comparable degrees of multisystem dysfunction.

Methods and Results—Preoperative MELD scores were calculated for subjects enrolled in the University of Michigan Health System (UMHS) mechanical circulatory support database. Univariate and multiple regression analyses were performed to investigate the ability of patient characteristics, laboratory data (including MELD scores), and hemodynamic measurements to predict total perioperative blood product exposure and operative mortality. The ability of preoperative MELD scores to predict operative mortality was evaluated in subjects enrolled in the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS), and results were compared with those from the UMHS cohort. The mean±SD MELD scores for the UMHS (n=211) and INTERMACS (n=324) cohorts were 13.7±6.1 and 15.2±5.8, respectively, with 29 (14%) and 19 (6%) perioperative deaths. In the UMHS cohort, median total perioperative blood product exposure was 74 units (25th and 75th percentiles, 44 and 120 units). Each 5-unit MELD score increase was associated with 15.1±3.8 units (β±SE) of total perioperative blood product exposure. Each 10-unit increase in total perioperative blood product exposure increased the odds of operative death (odds ratio, 1.05; 95% confidence interval, 1.01 to 1.10). Odds ratios, measuring the ability of MELD scores to predict perioperative mortality, were 1.5 (95% confidence interval, 1.1 to 2.0) and 1.5 (95% confidence interval, 1.1 to 2.1) per 5 MELD units for the UMHS and INTERMACS cohorts, respectively. When MELD scores were dichotomized as ≥17 and <17, risk-adjusted Cox proportional-hazard ratios for 6-month mortality were 2.5 (95% confidence interval, 1.2 to 5.3) and 2.5 (95% confidence interval, 1.1 to 5.4) for the UMHS and INTERMACS cohorts, respectively.

Conclusion—The MELD score identified left ventricular assist device candidates at high risk for perioperative bleeding and mortality. (Circulation. 2010;121:214-220.)

Key Words: heart-assist devices ■ heart failure ■ hemorrhage ■ mortality ■ risk factors

Clinical Perspective on p 220

In addition to the obvious need for increased blood product transfusions, bleeding significantly increases left ventricular (LV) assist device (LVAD) operative morbidity. Bleeding subjects up to 60% of LVAD recipients to the associated risks of reoperation.1 Massive blood transfusions can trigger cytokine storms that may provoke respiratory insufficiency and reactive pulmonary vascular hypertension with resultant RV failure.1 Blood transfusions are also associated with increased disseminated intravascular coagulation in the setting of multi-system organ failure, and device-induced coagulopathies.1,2

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risk for nosocomial infections, blood-borne diseases, and allosensitization. However, accurately assessing perioperative bleeding risk in LVAD candidates is difficult, and scant literature on the topic exists.

The Model for End-Stage Liver Disease (MELD) was originally developed to assess prognosis in subjects with cirrhosis undergoing transjugular, intrahepatic portosystemic shunts. The United Network for Organ Sharing (UNOS)—modified MELD score is a weighted sum of serum creatinine, bilirubin, and the international normalized ratio (INR) with a minimum score set at 6 and no set maximum. The clinical utility of the MELD score has been extended to prioritization of liver transplantations and to predicting operative morbidity and mortality in cirrhotics undergoing major surgeries.

Although the MELD was originally derived for a different patient population, the variables making up the score are markers of multisystem dysfunction and coagulopathy. To date, no study has evaluated the ability of the MELD to predict outcomes in LVAD candidates who often have similar degrees of end-organ dysfunction. The aims of this study were to better assess the morbidities and mortality associated with perioperative LVAD transfusion requirements, to assess the utility of preoperative MELD scores in predicting perioperative transfusions, and to assess the ability of the MELD to predict operative morbidity and mortality in LVAD recipients.

Methods

The University of Michigan Health System (UMHS) MCS database, containing 211 initial LVAD implantations (1996 to 2007), was analyzed. Demographic, clinical, preoperative pharmacological, and laboratory data were recorded prospectively: perioperative transfusions were tallied retrospectively from the UMHS blood-bank database. Perioperative transfusions were defined as products administered intraoperatively, ≤24 hours after LVAD implantation, or within 24 hours of reperfusion for sternal closure or LVAD-associated bleeding. Transfusions were at the discretion of the treating physician. General indications for transfusions included signs or symptoms of active bleeding, severe anemia (hemoglobin ≥8.0 mg/dL), thrombocytopenia (platelet count <100,000 K/mm³ intraoperatively or <50,000 K/mm³ ≤48 hours after surgery), or profuse coagulopathy (INR >1.8 or partial thromboplastin time >45 seconds without anticoagulant therapy).

Institution of perioperative extracorporeal RV or LV MCS was clinically driven or was in place at the time of arrival to UMHS. Typically, extracorporeal MCS is implemented in those with advanced multisystem organ failure who require rapid circulatory support or those with RV or LV failure refractory to inotrope or balloon-pump support. Our strategy is to transition subjects to extracorporeal support after subsequent hemodynamic and end-organ stabilization, taking into account limitations placed on extracorporeal support duration because of infectious and thromboembolic risks.

In the operating room, subjects received intravenous vitamin K 1 mg/h at the beginning of surgery, bolus-dose heparin (goal activate clotting times >480 seconds) and aprotinin on initiation of cardiopulmonary bypass, and protamine at bypass termination. Recombinant factor VIIa and aminocaproic acid were administered only for significant intraoperative bleeding.

MELD Score Calculation

Laboratory data were obtained ≤24 hours before LVAD implantation, and UNOS-modified MELD scores were calculated according to the following formula: MELD = 9.57(log creatinine) + 3.78(log bilirubin) + 11.2(log INR) + 6.43. Per the UNOS modification, variable lower limits were set at 1.0, and the creatinine upper limit was set at 4.0 mg/dL. Subjects receiving preoperative renal replacement therapy were assigned a creatinine of 4.0 mg/dL. For example, the MELD score for an individual on preoperative dialysis with a creatinine of 2.2 mg/dL, INR of 1.2 seconds, and bilirubin of 2.2 mg/dL is 25.

Study Aims

The primary aim of the study was to assess the ability of preoperative MELD scores to predict total perioperative blood product exposures (TBPE), defined as the sum of packed red blood cells (PRBCs), platelets, fresh frozen plasma, and cryoprecipitate units administered perioperatively. Secondary aims focused on the ability of the MELD to predict operative death (defined as intraoperative death, death ≤30 days after LVAD implantation, or death before hospital discharge), 6-month survival (censoring for transplantation or LVAD wean), and postoperative morbidities. Morbidities included RV failure requiring RV MCS (extracorporeal membrane oxygenation or RV assist device), renal failure requiring renal replacement therapy, intensive care unit and total index hospital lengths of stay, device infection (≤3 months after implantation), device malfunction (≤1 month after implantation), and cerebrovascular events (transient ischemic attack, stroke, or new seizure ≤1 month after implantation).

MELD Validation With the Interagency Registry for Mechanically Assisted Circulatory Support

The ability of the MELD to predict death (operative and 6 month) was validated with the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry (2006 to 2008), a national database containing prospectively collected information on implantations of Food and Drug Administration–approved MCS intended for long-term use. No subject in the cohort of study had preoperative MCS in place. Complete data for MELD score calculation were available in 324 of 372 subjects. Because traditional operative death criteria, as defined above, are not tallied in INTERMACS, operative death for the purpose of this analysis was defined as death within 1 month of LVAD implantation. Likewise, information on perioperative dialysis requirements was not available, so uncorrected creatinine measures were used for MELD calculation.

Statistical Analysis

Descriptive statistics for the primary dependent and independent variables of the UMHS and INTERMACS cohorts were calculated, along with other preoperative clinical, demographic, laboratory, and hemodynamic variables. Data analysis was performed with SAS (SAS Institute Inc, Cary, NC) version 9.1.

Bleeding Analyses

Logistic regression was used in the UMHS cohort to investigate operative morbidity and mortality odds ratios (ORs) associated with increasing transfusion requirements. Simple linear regression (PROC REG in SAS) was used to evaluate the ability of preoperative MELD scores and other covariates to predict perioperative transfusion requirements in the UMHS cohort, so that the regression coefficient represents the per-unit increase in blood product exposure per applicable unit increase in the covariate. Manual stepwise linear regression with PROC GLM in SAS was then used to assess independent predictors of TBPE. Entry criterion for the covariates (including MELD score) identified on univariable analysis was set at P = 0.15. Covariates clinically relevant to the bleeding analysis (body surface area, age, prior sternotomy, preoperative right atrial pressure and pulmonary vascular resistance, preoperative MCS, and intraoperative heparin dose and cardiopulmonary bypass time) were forced into modeling. During model development, the likelihood ratio test and Akaike Information Criterion (for nonnested data) were used to optimize fit, and the criterion for covariate model exit was set at P < 0.05.

Morbidity and Mortality Analyses

Baseline characteristics, preoperative laboratories, and cardiopulmonary hemodynamic data were compared between operative deaths and survivors in the UMHS cohort using ORs calculated by logistic
Table 1. Transfusion Requirements by Perioperative Outcome and Univariable ORs (95% CI) for Death and Postoperative Morbidity Based on Transfusion Requirements in the UMHS Cohort

<table>
<thead>
<tr>
<th>Transfusion Units, Alive (n=182)</th>
<th>Transfusion Units, Death (n=29)</th>
<th>OR (95% CI), †‡</th>
<th>OR (95% CI), †‡</th>
<th>OR (95% CI), †‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC 13 (7, 20)</td>
<td>22 (13–40)</td>
<td>1.3 (1.1–1.5)‡</td>
<td>1.3 (1.1–1.4)‡</td>
<td>1.3 (1.2–1.5)‡</td>
</tr>
<tr>
<td>FFP 13 (9, 20)</td>
<td>15 (10–24)</td>
<td>1.2 (0.96–1.4)</td>
<td>1.3 (1.1–1.5)‡</td>
<td>1.2 (1.1–1.4)‡</td>
</tr>
<tr>
<td>Platelets 30 (16, 50)</td>
<td>35 (20–80)</td>
<td>1.1 (1.0–1.1)</td>
<td>1.08 (1.04–1.12)</td>
<td>1.08 (1.03–1.11)‡</td>
</tr>
<tr>
<td>Cryo 14 (6, 26)</td>
<td>16 (8–27)</td>
<td>1.0 (0.93–1.1)</td>
<td>1.08 (0.97–1.1)</td>
<td>1.06 (0.98–1.13)</td>
</tr>
<tr>
<td>TBPE 73 (40, 115)</td>
<td>86 (60–172)</td>
<td>1.05 (1.01–1.10)‡</td>
<td>1.08 (1.04–1.13)‡</td>
<td>1.05 (1.01–1.10)‡</td>
</tr>
</tbody>
</table>

FPF indicates fresh frozen plasma; Cryo, cryoprecipitate. ORs were generated by logistic regression. Values are medians (25th and 75th percentiles) when appropriate.

*OR per 5-unit transfusion of individual blood product.
†OR per 10-unit TBPE.
‡P<0.050.

Regression. In both the UMHS and INTERMACS cohorts, logistic regression was used to calculate unadjusted morbidity and mortality ORs associated with increasing MELD scores. Subjects in both cohorts were then categorized into either a high MELD or low MELD group. Dichotomization was determined a priori and was based on the UMHS 75th MELD percentile. Kaplan–Meier survival curves were then generated for the strata, and risk-adjusted Cox mortality hazard ratios (95% confidence intervals [CIs]) were calculated. Proportional-hazards assumptions were confirmed by visual inspection of log-minus-log plots and by assessment of time-dependent interactions with the MELD score strata.

The use of PROC REG in SAS, MELD scores in the UMHS cohort were then regressed on TBPE, yielding residuals that represented the unique component of MELD scores that was unrelated to subject TBPE. These residuals, along with the clinically relevant covariates age, preoperative vasopressor requirement, and sex, were then entered manually into stepwise logistic regression to examine for operative mortality associations (covariate exit criteria = P<0.05).

Unless otherwise specified, data are expressed as mean±SEM or median (25th and 75th percentiles) for normal and nonnormal data, respectively. For all analyses, a value of P<0.05 was considered statistically significant.

This study was approved by the UMHS Institutional Review Board. Written informed consent was obtained before subject participation. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Implanted devices (n=211) at UMHS included the first-generation HeartMate (n=163, 77%; IP1000, Ve, XVE) and HeartMate II (n=29, 14%; Thoratec Corp, Pleasanton, Calif), Micromed-DeBakey (n=2, 1%; MicroMed Cardiovascular Inc, Houston, Tex), and Novacor LVADs (n=4, 2%; World Heart Inc, Oakland, Calif), as well as Thoratec percutaneous VADs and intravascular VADs (n=13, 6%; Thoratec Corp).

Perioperative Transfusion Requirements and Perioperative Morbidity and Mortality

Median perioperative transfusion requirements for the UMHS cohort were 13 (25th and 75th percentiles, 8 and 22) PRBC units, 14 (25th and 75th percentiles, 9 and 20) fresh frozen plasma units, 30 (25th and 75th percentiles, 20 and 50) platelets units, and 14 (25th and 75th percentiles, 6 and 26) cryoprecipitate units, yielding a median of 74 (25th and 75th percentiles, 44 and 120) units of TBPE. In the UMHS cohort, there were 182 survivors and 29 (14%) perioperative deaths. The odds of death increased 30% per 5-unit transfusion of PRBCs (unadjusted OR, 1.3; 95% CI, 1.1 to 1.5) and 5% (unadjusted OR, 1.05; 95% CI, 1.01 to 1.10) per 10 units of TBPE (Table 1). Mortality was not significantly increased with escalating transfusions of other individual blood products.

Morbidities in the UMHS cohort associated with perioperative transfusion requirements are displayed in Table 1. In short, blood product exposures were associated with increased univariable odds of developing postoperative RV failure, renal failure (30%, 30%, and 8% per 5-unit transfusion of PRBCs, fresh frozen plasma, and platelets, respectively, for both morbidities), and neurological events (20% per 5 units of PRBCs) (all P<0.050). Transfusion requirements were not related to the development of postoperative device malfunction (n=3; P>0.050; data not shown).

MELD Score Predicts Perioperative Transfusion Requirements

The mean ± SD MELD score for the UMHS cohort (n=211) was 13.7±6.1 (median, 12; 25th and 75th percentiles, 9 and 16), with a mean creatinine, bilirubin, and INR of 1.8±1.3 mg/dL, 1.8±2.8 mg/dL, and 1.2±0.3 seconds, respectively. Figure 1 shows the scatterplot for TBPE score regressed on MELD score (Pearson correlation coefficient, 0.33; P<0.001). Each 5-unit increase in MELD score was associated with an additional (unadjusted β±SE) 20±4.0 units of TBPE.
Undergoing LVAD

Table 2. Predictors of Bleeding (TBPE) in Subjects Undergoing LVAD

<table>
<thead>
<tr>
<th>Unadjusted TBPE ± SE</th>
<th>P</th>
<th>Adjusted TBPE ± SE</th>
<th>P</th>
</tr>
</thead>
</table>
| Body surface area    | −14.2 ± 22.4 | 0.53             | ... | ...
| Age                  | −0.12 ± 0.39 | 0.76             | ... | ...
| Preop RV MCS         | 48 ± 17      | 0.0047           | ... | ...
| Preop LV MCS         | 43 ± 12      | 0.0004           | ... | ...
| Preop renal replacement | 87 ± 18 | <0.0001          | ... | ...
| Preop ventilatory support | 67 ± 11 | <0.0001          | 46 ± 12 | 0.0001 |
| Preop postcardiotomy shock | 32 ± 19 | 0.085            | ... | ...
| Prior sternotomy      | 12 ± 11      | 0.26             | ... | ...
| Preop RA pressure, per 1 mm Hg | 1.3 ± 0.89 | 0.15            | ... | ...
| Preop PVR, per WU     | −4.2 ± 3.2  | 0.20             | ... | ...
| Preop MELD score, per 5 units | 20 ± 4.0 | <0.0001         | 15 ± 3.8 | 0.0001 |
| Preop hemoglobin, per 1 mg/dL | −6.7 ± 2.6 | 0.012            | −9.7 ± 2.3 | <0.0001 |
| Preop platelets, per 1 K/mm² | −0.28 ± 0.06 | <0.0001       | −0.16 ± 0.06 | 0.0043 |
| Preop PTT, per 1 s    | 0.24 ± 0.26 | 0.34             | ... | ...
| Intraop heparin, per 1000 U | 0.23 ± 0.57 | 0.68            | ... | ...
| Cardiopulmonary bypass time, per 1 min | 0.90 ± 0.13 | <0.0001    | ... | ...

Preop indicates preoperative; RA, right atrial; PVR, pulmonary vascular resistance; PTT, partial thromboplastin time; and Intraop, intraoperative.

TBPE ($R^2=0.11; P<0.001$), $3.3±0.89$ ($R^2=0.07; P<0.001$) units of PRBCs, $2.0±0.55$ ($R^2=0.06; P<0.001$) units of fresh frozen plasma, $11±2.2$ ($R^2=0.10; P<0.001$) units of platelets, and $4.3±1.2$ ($R^2=0.06; P<0.001$) additional units of cryoprecipitate. Other predictors of perioperative bleeding are shown in Table 2.

Although the relationship between MELD score and TBPE by univariable linear regression analysis was not strong ($R^2=0.11$), the MELD score remained a predictor of perioperative bleeding on multivariable analysis (Table 2). Each 5-unit increase in preoperative MELD score increased TBPE (adjusted $\beta±SE$) by 15.1 ± 3.8 units ($P<0.001$). Other predictors of bleeding included the need for preoperative ventilatory support (46 ± 12 units; $P<0.001$), lower preoperative serum hemoglobin ($−9.7±2.3$ per mg/dL; $P<0.001$), and lower platelet counts ($−0.16±0.06$ per K/mm²; $P=0.0043$) (Table 3; model $P<0.001$; adjusted $R^2=0.27$). Although subjects with higher MELD scores were more likely to have had other known risks for operative bleeding, including requirements for preoperative RV (unadjusted OR = 2.0; 95% CI, 1.4 to 2.8 per 5 MELD units) and/or LV (unadjusted OR = 1.6; 95% CI, 1.2 to 2.1 per 5 MELD units) MCS, elevated preoperative right atrial pressures (by 1.5 ± 0.33 mm Hg per 5 MELD units), and longer cardiopulmonary bypass times (by 6 ± 2 minutes for each 5 MELD units; $P=0.002$), these variables were not predictive of operative bleeding on multivariable analysis (Table 2).

Table 3. Predictors of Operative Mortality in LVAD Patients*

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD residual, per 5 units</td>
<td>1.4 (1.03–1.9)</td>
<td>0.034</td>
<td>1.6 (1.1–2.3)</td>
<td>0.013</td>
</tr>
<tr>
<td>Preop vasopressor use</td>
<td>5.2 (2.2–13)</td>
<td>0.0003</td>
<td>4.9 (1.8–13)</td>
<td>0.002</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.4 (1.01–5.6)</td>
<td>0.046</td>
<td>4.4 (1.6–12)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age, per 10 y</td>
<td>1.04 (1.01–1.08)</td>
<td>0.023</td>
<td>2.0 (1.3–3.1)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Preop indicates preoperative.

*Unadjusted ORs for covariates not included in the multivariable analysis are shown in Table 1 of the online-only Data Supplement.

MELD Score Predicts Perioperative Mortality

Baseline characteristics and preoperative laboratory and cardiopulmonary hemodynamic data for the 29 (14%) operative deaths and 182 survivors in the UMHS cohort are shown in Table I of the online-only Data Supplement. In general, operative deaths tended to occur in older and female patients with evidence of multisystem organ dysfunction. Patients who died operatively had significantly longer times on cardiopulmonary bypass (128 ± 7.3 minutes) than survivors (103 ± 2.6 minutes; $P=0.003$) and received fewer units of heparin (25 000 versus 31 000 U; $P=0.03$), but there were no significant differences in the use or dose of other intraoperative procoagulants or anticoagulants (data not shown; all $P>0.05$).

The mean MELD scores for operative deaths and survivors in the UMHS cohort were 14 (25th and 75th percentiles, 11 and 22) and 12 (25th and 75th percentiles, 9 and 15), respectively ($P=0.008$). The unadjusted odds of perioperative death increased 50% (1.5; 95% CI, 1.1 to 2.0) per 5-unit increase in preoperative MELD score. In the INTERMACS cohort, there were 19 (6%) operative deaths and 305 survivors with mean ± SEM MELD scores of 18 ± 1.8 and 15 ± 0.33, respectively ($P=0.036$). Each 5-unit increase in MELD score in the INTERMACS cohort increased the unadjusted odds of perioperative death by 1.5 (95% CI, 1.1 to 2.1).

In the UMHS cohort, after taking into account female sex, age, and need for preoperative vasopressor requirement, MELD score remained a significant predictor of operative death (Table 3). A 5-unit increase in the unique component of MELD (not shared with its ability to predict bleeding) increased the odds of operative mortality by 60% (adjusted OR, 1.6; 95% CI, 1.1 to 2.3 per 5 MELD units; model adjusted $R^2=0.25$; model $P<0.001$).

MELD Score Predicts Perioperative Morbidity in the UMHS Cohort

Preoperative MELD scores were also predictive of perioperative morbidity in the UMHS cohort. Each 5-unit MELD increment increased the unadjusted odds of requiring postoperative renal replacement therapy by 2.1 (95% CI, 1.5 to 2.8) and RV MCS by 2.1 (95% CI, 1.6 to 2.8), with scores ≥17 affording equivalent 5.0-fold greater odds (both $P<0.001$) of...
developing the aforementioned complications. Similarly, each 5-unit increase in MELD score was associated with a 1.7 (95% CI, 1.2 to 2.5) greater odds of developing an LVAD infection (unadjusted OR, 3.9; 95% CI, 1.4 to 12 for MELD score ≥17) and an additional 3±1 days in the intensive care unit and 6±2 days of total hospital stay (both \( P = 0.001 \)).

### Six-Month Survival by MELD Score

Six-month Kaplan–Meier survival curves for the UMHS and INTERMACS cohorts are shown in Figure 2. In the UMHS cohort, survival at 6 months for subjects with MELD scores ≥17 and <17 was 74±6% and 88±3%, respectively (log-rank \( P = 0.009 \); Figure 2A). The risk-adjusted hazard ratio for death in subjects with MELD scores ≥17 was 2.5 (95% CI, 1.2 to 5.3) times that of those with lower scores. In the INTERMACS cohort, 6-month survival for INTERMACS subjects with MELD scores ≥17 was 67±5% compared with 82±3% in subjects with lower scores (log-rank \( P = 0.032 \); Figure 2B). The risk-adjusted hazard ratio for death during the 6-month follow-up period for INTERMACS patients with MELD scores ≥17 was 2.5 (95% CI, 1.1 to 5.4).

### Discussion

Bleeding in the LVAD perioperative period is associated with increased morbidity and mortality. In this cohort, each 10-unit TBPE increased the odds of perioperative death by 5% with equivalent 8% increases in the odds of developing postoperative RV and renal failure. This is the first tool to accurately assess an LVAD candidate’s risk of bleeding in the perioperative period. In the UMHS cohort, the MELD score was a univariable predictor of hospital stay and the development of postoperative device infections, RV failure, and renal failure. In both the UMHS and INTERMACS cohorts, the MELD score was predictive of operative and 6-month mortality.

The MELD was originally developed to assess mortality in subjects with cirrhosis undergoing cardiopulmonary bypass for cardiac interventions (coronary bypass, valve, pericardectomy), the mean±SD preoperative MELD score in operative deaths and survivors was 18.3±6.9 and 10.2±3.7, respectively (\( P = 0.004 \)). In our analysis of subjects without known cirrhosis, mean preoperative MELD scores for perioperative LVAD deaths in the UMHS and INTERMACS cohorts were comparable at 16.7±7.0 and 17.9±7.7, respectively, but survivors had slightly higher MELD scores (13.2±0.4 and 15.0±5.7) than in the aforementioned study, reflecting a greater severity of end-organ dysfunction in these LVAD cohorts. In another study examining 772 surgical patients with cirrhosis (n=79 underwent cardiac surgery), subjects (n=58) with MELD scores >15 had ~5-fold higher odds of 30-day death than those (n=714) with lower scores.12 Using a slightly different threshold, we found that preoperative MELD scores ≥17 offered 3-fold increased odds of perioperative LVAD death in the UMHS cohort, with hazard ratios for death at 6 months of 2.5 in both cohorts.

Cirrhotics with higher preoperative MELD scores have been shown to have greater perioperative PRBC transfusion requirements.15,16 In LVAD candidates, perioperative transfusions have been associated with increased risks for various postoperative morbidities.17 Similar to prior studies,17 our results demonstrated increased odds of developing postoperative RV and renal failure in subjects requiring greater numbers of perioperative transfusions. In the UMHS cohort, there was an independent, linear relationship between preoperative MELD score and transfusions, with each 5-unit increase in MELD score affording an additional 15 units of TBPE. Furthermore, each 5-unit increase in MELD score was associated with an identical 200% increase in the univariable odds of requiring postoperative RV MCS and renal replacement therapy.

The associations between perioperative transfusion requirements, preoperative MELD score, and the development of postoperative RV and renal failure are likely multifactorial. UMHS patients with high MELD scores had greater transfu-
sion requirements and longer times on bypass. Thus, postoperative RV failure in subjects with high MELD scores may result from increased RV preload after perioperative blood product administration and from increased pulmonary vaso-reactivity secondary to cytokine release during transfusions and prolonged bypass.\textsuperscript{2,18} The association between MELD score and renal dysfunction is due in large part to the fact that creatinine is a component of the MELD score calculation. However, an association was also noted in the UMHS cohort between RV failure and renal failure (OR for renal failure in subjects with RV failure, 3.4). Thus, the MELD score may be predictive of postoperative renal failure because it identifies those at risk for cardiorenal syndrome from RV failure in the setting of high transfusion requirements.

In this analysis, we found a 70% increase in the odds of developing a postoperative device infection for each 5-unit increase in MELD score. It can be surmised that the association between MELD score and infection may be related to increased microbial exposures during patient instrumentation and management of a critically ill state. Prolonged hospital stays have also been associated with elevated MELD scores in liver transplantations\textsuperscript{19} and high transfusion requirements in LVAD recipients.\textsuperscript{20} In this analysis, higher MELD scores were associated with prolonged intensive care unit and total hospital stays, again increasing risks for microbial inoculations.

Finally, studies have demonstrated increased allosensitization risk in subjects receiving greater numbers of transfusions during LVAD support.\textsuperscript{4–6} Although measures of allosensitization were not available in this sample, the positive relationship between preoperative MELD score and transfusions is important. Allosensitization before transplantation has been associated with longer time on the transplant wait list and worse posttransplant outcomes,\textsuperscript{21} and studies are needed to determine whether higher MELD scores are predictive of allosensitization, more frequent posttransplant graft dysfunction, and reduced transplantation survival.

\section*{Clinical Utility of the MELD in LVAD Candidates}

Although subjects in this cohort were not known to have hepatic cirrhosis, the MELD score succeeded as an LVAD risk assessment tool likely because it is a marker of multisystem dysfunction (renal, hepatic, cardiac) and coagulopathy. The association between multisystem organ dysfunction and LVAD perioperative morbidity and mortality is not in itself novel, so the utility of the MELD lies in its ability to provide important patient-specific measures of LVAD perioperative risk in the preoperative setting. The score is composed of routinely collected laboratory values and is available for rapid calculation on several Web sites. The usefulness of the MELD score will especially apply to those individuals with multiple, potentially conflicting, univariable predictors for LVAD mortality, allowing one to gauge mortality odds using a single independent predictor. Although dichotomization of MELD scores was undertaken in subsets of this data analysis, the MELD demonstrated independent risk prediction for operative bleeding and death as a continuous variable. As such, the MELD score will function best when used as a continuous variable for risk assessment, making it potentially useful for those subjects with intermediate pretest probabilities. Finally, foresight gained through MELD risk stratification may also provide clinicians with a proactive, rather than reactive, means of managing perioperative complications via targeted improvement in end-organ function through earlier or increased use of preoperative RV and/or LV inotrope or extracorporeal MCS and correction of coagulation abnormalities with aggressive factor or vitamin K repletion. Studies are needed to determine whether strategies directed at reducing preoperative MELD scores improve postoperative outcomes.

\section*{Limitations}

This study has several limitations, many of which are inherent to the nature of cohort studies. Because this was a nonblinded evaluation, patient selection and management biases likely exist that may have influenced study end points and MELD dichotomization thresholds. This is especially important when preoperative, intraoperative, and postoperative interventions can significantly affect bleeding risk. Intraoperative dose requirements for heparin, protamine, vitamin K, and factor VIIa were available in only 52% of UMHS subjects. Although individuals without this data did not differ clinically from those with available data, we acknowledge this as a source of information bias. We hoped to validate all of the UMHS findings using a national LVAD database. However, detailed transfusion requirements and preoperative and postoperative morbidity tallies using the same event definitions were not available in INTERMACS, preventing us from accurately examining events other than 6-month mortality. For these same reasons, we had to use a surrogate end point for operative mortality (death at 1 month) in the INTERMACS analysis. Nonetheless, on a continuous basis, the MELD was predictive of operative death and was categorically associated with increased risk for 6-month LVAD mortality in the INTERMACS cohort.

Because of the relative rarity of the LVAD intervention, study power was also limited. Although the UMHS cohort size was similar to the 231-patient sample used in the derivation of the original MELD formula, the larger CIs and the reduced power may account for nonsignificant trends noted in analyses of the impact of transfusion requirements on mortality. Power also limited the number of variables that could be examined in the mortality multivariable analysis. Finally, subjects in this cohort did not have liver biopsies to rule out concomitant cirrhosis as a confounder of results, which is of concern in subjects with a high prevalence of concomitant RV dysfunction and chronic hepatic congestion. No UMHS subject with a MELD score $\geq$17 had preoperative ultrasound evidence of cirrhosis, and MELD scores were not associated with lower preoperative albumins (data not shown).

\section*{Conclusions}

Bleeding in the perioperative LVAD period is associated with increased morbidity and mortality. The preoperative MELD score is a noninvasive, simple means of assessing an LVAD candidate’s operative bleeding risk and identifies individuals at increased risk for renal failure, RV failure, device infection, and prolonged hospital stays. The MELD score was also
a predictor of operative and 6-month mortality in the UMHS and INTERMACS cohorts. Further studies are needed to determine whether clinical intervention to improve MELD scores could affect perioperative outcomes.

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Disclosures
Drs Aaronson and Pagani have received grant support from Terumo and HeartWare not directly related to this study. Dr Aaronson has a consulting relationship with Thoratec, HeartWare, and Circulite. Dr Matthews is a paid speaker for Terumo and Thoratec. The other authors report no conflicts.

References

CLINICAL PERSPECTIVE
Bleeding after implantation of a left ventricular assist device (LVAD) is associated with increased mortality and an increased risk for several morbidities that can affect a patient’s quality of life on LVAD therapy and candidacy for future cardiac transplantation. Causes for perioperative bleeding in LVAD patients are often multifactorial. Identifying patients at high risk for perioperative LVAD bleeding would assist with LVAD candidate risk stratification and may offer the potential for improving LVAD outcomes by triggering clinicians to institute therapies in the preoperative period directed at reducing bleeding risk. The present study uses the Model for End-Stage Liver Disease in the LVAD preoperative period to assess patient risk for perioperative bleeding, morbidity, and mortality.
Model for End-Stage Liver Disease Score Predicts Left Ventricular Assist Device Operative Transfusion Requirements, Morbidity, and Mortality
Jennifer C. Matthews, Francis D. Pagani, Jonathan W. Haft, Todd M. Koelling, David C. Naftel and Keith D. Aaronson

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Supplemental Data

CIRC/AHA/2008/838656
**Supplementary Table.** Preoperative characteristics, laboratories, and hemodynamics by operative vital status.

<table>
<thead>
<tr>
<th></th>
<th>Operative death (n=29)</th>
<th>Survivors (n=182)</th>
<th>Odds Ratios [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>55±1.7</td>
<td>49±13</td>
<td>1.04 [1.01, 1.08]</td>
</tr>
<tr>
<td>Female, n(%)*</td>
<td>10 (35%)</td>
<td>33 (18%)</td>
<td>2.4 [1.01, 5.6]</td>
</tr>
<tr>
<td>Caucasian race, n(%)</td>
<td>27 (93%)</td>
<td>148 (81%)</td>
<td>3.1 [0.70,14]</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.9±0.05</td>
<td>2.0±0.02</td>
<td>0.24 [0.04,1.4]</td>
</tr>
<tr>
<td>Diabetes mellitus, n(%)</td>
<td>8 (32%)</td>
<td>45 (25%)</td>
<td>1.4 [0.58, 3.5]</td>
</tr>
<tr>
<td>ISCM, n(%)*</td>
<td>20 (69%)</td>
<td>89 (49%)</td>
<td>2.3 [1.0,5.4]</td>
</tr>
<tr>
<td>Prior sternotomy, n(%)</td>
<td>14 (48%)</td>
<td>61 (34%)</td>
<td>1.9 [0.84,4.1]</td>
</tr>
<tr>
<td>Post-cardiotomy shock, n(%)*</td>
<td>6 (21%)</td>
<td>12 (7%)</td>
<td>3.6 [1.3,11]</td>
</tr>
<tr>
<td>Renal replacement therapy, n(%)</td>
<td>5 (17%)</td>
<td>11 (6%)</td>
<td>1.9 [0.84,4.1]</td>
</tr>
<tr>
<td>Ventilator support, n(%)*</td>
<td>12 (41%)</td>
<td>38 (21%)</td>
<td>2.7 [1.2,6.1]</td>
</tr>
<tr>
<td>Vasopressor support, n(%)*</td>
<td>11 (38%)</td>
<td>19 (10%)</td>
<td>5.2 [2.2,13]</td>
</tr>
<tr>
<td>Inotrope support, n(%)*</td>
<td>21 (72%)</td>
<td>161 (89%)</td>
<td>0.34 [0.13,0.87]</td>
</tr>
<tr>
<td>Intraaortic balloon pump, n(%)</td>
<td>9 (31%)</td>
<td>48 (26%)</td>
<td>1.3 [0.53,2.9]</td>
</tr>
<tr>
<td>Preop LV bridge, n(%):</td>
<td>9 (31%)</td>
<td>38 (21%)</td>
<td>1.7 [0.72,4.0]</td>
</tr>
<tr>
<td>ECMO</td>
<td>4 (14%)</td>
<td>15 (8%)</td>
<td></td>
</tr>
<tr>
<td>Abiomed</td>
<td>3 (11%)</td>
<td>12 (7%)</td>
<td></td>
</tr>
<tr>
<td>Tandem Heart</td>
<td>2 (7%)</td>
<td>11 (6%)</td>
<td></td>
</tr>
<tr>
<td>Preop RV-MCS, n(%)*</td>
<td>7 (24%)</td>
<td>14 (8%)</td>
<td>3.8 [1.4, 10]</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>ECMO</td>
<td>4 (14%)</td>
<td>9 (5%)</td>
<td>1.3 [0.23, 6.1]</td>
</tr>
<tr>
<td>Abiomed BVS 5000</td>
<td>3 (10%)</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>Bridge to transplant, n(%)</td>
<td>27 (93%)</td>
<td>172 (95%)</td>
<td></td>
</tr>
</tbody>
</table>

**Laboratories:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mg/dL</td>
<td>133±1.4</td>
<td>134±0.46</td>
<td>0.99 [0.93, 1.1]</td>
</tr>
<tr>
<td>Creatinine, mg/dL*</td>
<td>1.7[1.2-2.2]</td>
<td>1.3[1.0-1.8]</td>
<td>1.3 [1.02, 1.6]</td>
</tr>
<tr>
<td>White count, K/mm³*</td>
<td>11[7.8-13]</td>
<td>8.6[6.8-12]</td>
<td>1.1 [1.01, 1.2]</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.6±0.43</td>
<td>11.7±0.14</td>
<td>0.96 [0.77, 1.2]</td>
</tr>
<tr>
<td>Platelets, K/mm³</td>
<td>146[101,242]</td>
<td>185[125,229]</td>
<td>1.0 [0.99, 1.0]</td>
</tr>
<tr>
<td>INR, sec</td>
<td>1.2 [1.1-1.3]</td>
<td>1.1[1.0-1.3]</td>
<td>1.6 [0.49, 5.0]</td>
</tr>
<tr>
<td>PTT, sec</td>
<td>39[30,56]</td>
<td>39[28,53]</td>
<td>1.0 [0.99, 1.03]</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>34[22,71]</td>
<td>49[28,83]</td>
<td>1.0 [0.99, 1.0]</td>
</tr>
<tr>
<td>Bilirubin, mg/dL*</td>
<td>1.2[0.75,3.3]</td>
<td>1.0[0.70,1.8]</td>
<td>1.13 [1.01, 1.26]</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.3[2.7,3.8]</td>
<td>3.3[2.8,3.8]</td>
<td>0.82 [0.45, 1.5]</td>
</tr>
</tbody>
</table>

**Hemodynamics:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA pressure, mmHg</td>
<td>12[9,16]</td>
<td>12[8,16]</td>
<td>1.0 [0.96, 1.1]</td>
</tr>
<tr>
<td>Mean PA pressure, mmHg</td>
<td>32[21,40]</td>
<td>35[27,39]</td>
<td>0.98 [0.94, 1.0]</td>
</tr>
<tr>
<td>PVR, WU</td>
<td>1.8[1.0,3.6]</td>
<td>2.2[1.4,3.0]</td>
<td>1.1 [0.84,1.3]</td>
</tr>
<tr>
<td>Wedge pressure, mmHg</td>
<td>22±1.7</td>
<td>23±0.55</td>
<td>0.99 [0.94, 1.0]</td>
</tr>
<tr>
<td>RVSWi, mmHg-mL/m²</td>
<td>359[247,635]</td>
<td>470[299,719]</td>
<td>1.0 [0.99, 1.0]</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>2.1±0.13</td>
<td>2.2±0.05</td>
<td>0.72 [0.37, 1.4]</td>
</tr>
</tbody>
</table>
Continuous data expressed as mean±SEM or median [25\textsuperscript{th}, 75\textsuperscript{th} percentile]. *p≤0.050.

ALT=alanine aminotransferase, ECMO= extracorporeal membrane oxygenation, ISCM=
ischemic cardiomyopathy, INR=international normalized ratio, LV= left ventricular, LVAD=
left ventricular assist device, PA= pulmonary artery, Preop= preoperative, PTT= partial
thromboplastin time, PVR= pulmonary vascular resistance, RA=right atrial, RV-MCS= right
ventricular mechanical support, RVSWi= right ventricular stroke work index.