The Effects of MELD Scoring on Liver Transplant Anesthesia

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The Model for End-Stage Liver Disease (MELD) is a scoring system adopted in the United States in February 2002 to prioritize recipients on the liver transplant waiting list. Originally, the MELD score was intended to predict short term outcomes after transjugular intrahepatic portosystemic shunt placement and later, to predict 3 month mortality rate in patients who are cirrhotic. Many studies have confirmed that the MELD score is as an excellent indicator of severity for various liver diseases. In patients undergoing orthotopic liver transplantation (OLT), studies have shown that a higher preoperative MELD score is associated with higher morbidity and mortality. Recently, studies also suggest that higher MELD scores are associated with increased intraoperative risks. Here we review the evidence on MELD scoring and its potential effects on postoperative morbidity and mortality as well as on intraoperative anesthetic management.

The MELD score and the effects of its components on the perioperative outcomes

The MELD score is a composite of three laboratory values: serum creatinine, serum bilirubin, and international normalized ratio (INR). MELD = 9.6 X loge(creatinine) + 3.78 X loge(bilirubin) + 11.2 X loge(INR) + 6.43. When broken down into its individual components, abnormally elevated values of any one of these laboratory tests may suggest greater severity of disease. It is well known, for instance, that renal dysfunction prior to liver transplantation confers greater intraoperative risks and is a predictor for worse postoperative outcomes. Patients with pre-existing renal dysfunction are at risk for presenting to the operating room at the time of surgery with altered fluid balance; depending on when the patient may have last been dialyzed. It is sometimes difficult to assess whether the patient is hypovolemic, euvoletic, or hypervolemic. Furthermore, this patient population is particularly at risk for presenting with and/or developing significant electrolyte abnormalities and acidosis. If severe, these abnormalities may lead to a need for intraoperative renal replacement therapy (RRT). In a study involving 102 liver transplant candidates receiving RRT, Wong, et al demonstrated that overall mortality was increased to 30% compared to 9.7% for all other liver transplant recipients, reflective of worsened 3-month and 1-year survival. As creatinine is a significant component of the MELD score, the patients requiring RRT in this study exhibited higher MELD scores, which was predictive of death after liver transplantation. The study group also found that patients who required RRT prior to transplantation had lower mean arterial pressures (58 vs. 67.3), higher mean APACHE II scores (31.2 vs. 24.1), were more likely to be intubated (59% vs. 8%), and were more likely to be on vasopressors (62% vs. 14%) (Table 1). Of note, the study excluded patients who were receiving outpatient hemodialysis prior to surgery; therefore, one could
assume that the patients included in the study not only had more advanced renal dysfunction, but that they might also suffer from more advanced liver and/or systemic disease, preventing them from tolerating the hemodynamic shifts involved with single pass dialysis. (8)

Table 1. Survival for pretransplant RRT liver recipients versus all other liver recipients

<table>
<thead>
<tr>
<th></th>
<th>Initiated RRT pretransplant (n=32)</th>
<th>All other OLT patients (n=220)</th>
<th>Initiated RRT posttransplant (n=28)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-month mortality</td>
<td>5/32 (15.6%)</td>
<td>9/220 (4.1%)</td>
<td>6/28 (21.4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>1-yr mortality</td>
<td>9/30 (30.0%)</td>
<td>20/206 (9.7%)</td>
<td>7/27 (33.3%)</td>
<td>0.0045</td>
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</table>


Renal dysfunction that continues into the postoperative period also has an impact on morbidity. In a retrospective review of 144 liver transplant recipients, Oberkofler, et al identified the need for post-operative renal replacement therapy as an independent predictor of mortality. Even mild renal failure in the post-transplantation period was associated with longer hospital stays, an increased incidence of infections, and increased overall mortality. In fact, mortality was observed to be up to 60% in patients requiring RRT at 30 days following surgery. Of note, the study did include patients with preserved renal function preoperatively, and whose renal dysfunction only presented after transplantation. However, the authors also note that hepatorenal syndrome prior to transplantation along with RRT post-transplantation is a strong predictor for mortality and increased ICU length of stay. (9)

It has been hypothesized that it is possible to predict the degree of intraoperative blood loss and transfusion requirements based on the severity of preoperative coagulopathy, one of the MELD components. Investigators have found positive correlations between preoperative INR and platelet counts with intraoperative blood transfusions. (10) These assumptions have been challenged by some including the same authors in previous studies who argue that the presence and degree of portal hypertension and the history of prior abdominal surgeries, not preoperative coagulopathy, is more predictive of blood loss. (11)

The MELD score is constantly modified to better predict pre- or post-transplant mortality. In addition to the 3 laboratory values mentioned above, several new components have been proposed in various studies. If added to the MELD formula, they have potential to influence intra- and post-operative outcomes and anesthesia management as well.

**The effects of the MELD score on the postoperative outcomes**

As an overall marker for disease severity, the MELD score has been used to predict postoperative morbidity and mortality following OLT. Several groups have demonstrated that high pretransplant MELD scores were predictive of worsened survival rates. (12, 13) A MELD
score of greater than 24 was associated with worse 1-year survival when compared to patients with MELD scores of less than 24. (4) Another study suggests that an increase of the MELD score by one point increases the possibility of death by 1.2 times. (14) Similarly suggestive of poorer outcomes, others have associated elevated MELD scores with more hospital days in the 3 month post-operative period in the living donor liver transplant population. (15) Even amongst cirrhotic patients undergoing non-liver transplant surgery, MELD scores are correlated with outcomes. In a retrospective analysis, Northrup, et al found the MELD score to be a statistically significant predictor of 30-day mortality, with an approximate 1% increase in mortality for each one point increase in MELD score from 5 to 20, and a 2% increase in mortality for each one point increase in MELD score above 20. (16) Similarly, Kim, et al found a positive association between MELD score and mortality in 160 patients undergoing non-liver transplant surgery. (17) Even studies that have not demonstrated a difference in survival post-liver transplantation in patients with elevated MELD scores, there is data to suggest that these patients may experience greater morbidity. Patients with higher MELD scores in a study involving 178 liver transplants had longer hospital stays. Mean hospital length of stay in patients with mean MELD scores of 34 was 24 days, compared to a mean hospital stay of 15.55 days in patients with a mean MELD score of 16. Parallel with the increased hospital stays were the ICU stays, with higher MELD patients staying on average of 12.6 days in the ICU versus 5.13 ICU days in the lower MELD group. (18) Notably, however, this study did not demonstrate a difference in overall survival. Others have also shown that patients with higher MELD scores undergoing liver transplantation incur higher healthcare costs due to greater resource utilization during their care, implying greater complexity and severity of their disease, in spite of exhibiting no significant differences in overall outcomes. (19)

The MELD score has also been associated with several other perioperative risks that may alter perioperative care and increase the acuity of this patient population. Postoperative pulmonary complications have been identified as a significant source of increased mortality. In a study involving 107 patients undergoing liver transplantation, mortality was 18.5% in patients who developed postoperative pulmonary complications versus 4.8% in those who did not. The MELD score was identified as an independent risk factor for the development of postoperative pulmonary complications. Those with a MELD score greater than 25 were at higher risk of developing these complications. Other risk factors included intraoperative fluid administration of greater than 10L and intraoperative blood transfusion volume of greater than 4L. These complications prolonged hospital stays and/or contributed to overall morbidity and mortality. (20) The MELD score has also been linked to alterations in cerebral perfusion, possibly contributing to the incidence of perioperative neurological complications, another major contributor to morbidity and mortality after liver transplant surgery. Patients with higher MELD scores have been shown to be at greater risk for developing mental status changes post OLT. (21) Others have demonstrated a significant difference in cerebral tissue oxygenation and hemoglobin indices intraoperatively, suggestive of clinically significant alterations in cerebral perfusion. These changes were demonstrated to be more exaggerated in patients with higher MELD scores. Cerebral hyperperfusion episodes in this patient population, some of whom demonstrate a functional loss in CBF autoregulation, may contribute to cerebral hypertensive episodes, predisposing the patient to cerebral vascular accidents and cerebral edema. (22)
Increasingly, as the liver transplant population is evolving, the transplant community is also encountering more candidates with underlying cardiac disease. In addition, patients with cirrhosis may present with cardiomyopathy, further increasing their chances of developing postoperative cardiac complications. In addition to adverse intraoperative cardiovascular events and history of pre-existing cardiac disease, advanced liver disease as quantified by a modified MELD score has been shown to be predictive of postoperative cardiac complications. In a study involving 197 patients, the MELD score, MELD-Na score, and i-MELD score were all associated with the incidence of cardiac events; however the i-MELD score, a score that incorporates the age as well as the serum sodium, was the most strongly correlated. Presumably, this is due to the link between degree of liver failure and extent of cardiovascular anomalies such as cirrhotic cardiomyopathy, peripheral vasodilatation, and hyperdynamic circulation.

Cardiac complications have been reported to be the third leading cause of death post OLT, following infection and rejection. It has been estimated to be the cause of 22% of all late mortalities. Thus, the increased risk for these events in the perioperative period in patients with higher MELD scores creates a need for more vigilant perioperative care, particularly since the overall severity of disease is great in this patient population. (23)

It should be noted that despite many studies suggesting an association between the MELD score and postoperative mortality, the overall mortality in the U.S. has not changed since the adoption of the MELD system in organ allocation in 2002.

**The effects of the MELD score on the intraoperative management**

In the MELD based organ allocation system, the available graft will go a patient with the highest MELD score. In a study comparing low vs. high MELD scores, Xia, et al (5) found that upon presentation for OLT, patients with higher MELD scores have more comorbidities and require a higher level of pretransplantation care. Specifically, patients with high MELD scores have lower starting hemoglobin and fibrinogen concentrations. In addition, patients with the higher MELD scores are more frequently require hemodialysis, mechanical ventilation, and hemodynamic support by pressors. Intraoperatively, patients with higher MELD scores require on average 5 more units of red blood cell (RBC) and 7 more units of FFP during OLT compared to those with lower MELD scores. (5) Other blood products such as platelets and cryoprecipitate have very similar patterns. Although the higher MELD score is generally correlated with higher transfusion requirements, these patterns are particularly noticeable when the MELD score exceeds 30 (Table 2).

In another retrospective review of 26 living donation transplants and 69 cadaveric donation transplants, Frasco, et al (24) found significant associations between the MELD score and preoperative coagulation tests with intraoperative transfusion of blood and component therapy. Specifically, the MELD score was associated with the total number of transfusions required, while aberrancies in individual coagulation and hematologic tests were associated with the need for respective component therapy transfusions. On average, an increase in 3 MELD score points correlated with one additional blood product transfusion. The factors most strongly associated

\[
\text{MELD-Na} = \text{MELD} + 1.59(135 - \text{serum Na}) \quad \text{where minimum serum Na is 120mmol/L and maximum serum Na is 135mmol/L}
\]

\[
\text{i-MELD} = \text{MELD} + (\text{age} \times 0.3) - (\text{serum Na} \times 0.7) + 100
\]
with the number of transfusions in this study were the MELD score, starting fibrinogen concentration, and hemoglobin concentration. Although the fibrinogen value is not integral in the calculation of the MELD score, many have associated high MELD scores with decreased fibrinogen levels, perhaps suggesting that high INR values contributing to elevated MELD scores may be an overall indicator of severity of coagulopathy. As a case in point, others have associated high MELD scores with decreased starting hematocrit and fibrinogen levels. Subsequently, the same study correlates high MELD scores with increased intraoperative transfusion requirements and an increased intraoperative vasopressor administration.

Table 2. Requirements of Total Transfusion in 5 Groups (in units, M±SD)

<table>
<thead>
<tr>
<th>MELD Scores</th>
<th>6-20</th>
<th>21-25</th>
<th>26-30</th>
<th>31-35</th>
<th>36-40</th>
<th>rs</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>25</td>
<td>24</td>
<td>24</td>
<td>23</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td>10.6±8.4</td>
<td>9.7±6.4</td>
<td>11.5±9.5</td>
<td>14.1±7.5</td>
<td>17.3±10.9</td>
<td>0.29</td>
<td>0.001</td>
</tr>
<tr>
<td>FFP</td>
<td>14.5±8.7</td>
<td>14.8±8.3</td>
<td>16.2±12.1</td>
<td>19.3±11.9</td>
<td>24.4±16.0</td>
<td>0.26</td>
<td>0.004</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.7±0.7</td>
<td>1.0±1.0</td>
<td>0.9±0.9</td>
<td>1.3±0.8</td>
<td>1.4±1.0</td>
<td>0.26</td>
<td>0.004</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>0.6±0.7</td>
<td>0.5±0.7</td>
<td>0.5±0.9</td>
<td>1.0±0.8</td>
<td>1.1±1.0</td>
<td>0.26</td>
<td>0.004</td>
</tr>
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</table>


Mangus, et al (25) conducted a retrospective review of 526 liver transplants and also found that MELD score and initial fibrinogen, along with low preoperative hemoglobin and overall anesthesia care time, were strongly predictive of RBC usage. Those with increased transfusion requirements experienced longer postoperative hospital stays and lower 90-day and 1-year graft and patient survival. Of note, this study only included transplants that used the piggyback hepatectomy technique. In another retrospective study involving 90 patients, increased MELD scores were associated with increased intraoperative blood loss. Although other studies have failed to show a statistically significant link between MELD score and blood transfusion requirements, there still remains a trend toward greater transfusion requirements with increasing MELD scores.(26) Greater transfusion requirements in this patient population have been associated with an increase in mortality and increased post-operative ICU stays. Oberkofler, et al (9) identified RBC transfusions of greater than 7 units intraoperatively to be an independent risk factor for post-operative mortality. Likewise, the study group also identified FFP transfusion of greater than 10 units as an independent risk factor for post-operative morbidity. Similarly, Wiederkehr et al associated the need for blood transfusions and higher MELD scores with worse survival rates.(27)

Intraoperatively, patients with higher MELD scores have also been shown to have more ascites, a potential new addition to the MELD calculation. Independently, the presence of pre-transplantation ascites has been associated with increased transfusion requirements.(28) Patients with high MELD scores may present with other anesthetic risks as well.(5) Intraoperatively,
requirements of vasopressor, both in boluses and in continuous infusion, are significantly greater in patients with higher MELD score than in those with lower MELD score.(5) Analysis after exclusion of those patients who require vasopressors before transplantation shows the similar results (Table 3). Although the analyses fail to show that the MELD score is an independent for intraoperative hyperkalemia, MELD-related transfusion is a significant contributor to intraoperative hyperkalemia.(29)

Table 3. Requirements for Intraoperative Vasopressors

<table>
<thead>
<tr>
<th></th>
<th>Low MELD Group</th>
<th>High MELD Group</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Exclusion</td>
<td>73</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Infusion</td>
<td>14 (19.2)</td>
<td>27 (52.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bolus</td>
<td>12 (16.4)</td>
<td>21 (41.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Infusion or Bolus</td>
<td>20 (27.4)</td>
<td>32 (62.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After Exclusion</td>
<td>73</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Infusion</td>
<td>14 (19.2)</td>
<td>22 (50.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bolus</td>
<td>12 (16.4)</td>
<td>18 (40.9)</td>
<td>0.011</td>
</tr>
<tr>
<td>Infusion or Bolus</td>
<td>20 (27.4)</td>
<td>27 (61.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Conclusion

It is prudent to note that although there have been many studies correlating MELD scores with various perioperative findings such as blood product transfusions, vasopressor requirements, hospital stays, and overall morbidity and mortality, utilization of the MELD score to predict perioperative risks has its shortcomings. First, the MELD score is designed to predict pretransplant mortality, not intra- or post-operative outcomes. Therefore, it is not surprising to see inconsistent and sometimes conflicting results from various studies. Second, the MELD scores utilized across these studies are not uniform. The definition of what constitutes a “high” MELD score is disparate and ranges from values as low as 18 to those as high as 30 and above. A 12 point difference (or more) in MELD score may very well have significant implications on severity of illness and, as a result, on overall outcomes. Nevertheless, as a widely available index for severity of liver disease, the MELD score may be used by anesthesiologists to predict those who present with more complex comorbidities and require additional resources, monitoring, and higher level of care during the perioperative period.
References

Multiple choice questions
1) The MELD score was initially developed to predict outcomes in
   a. Patients with hepatorenal syndrome
   b. Patients who have received transjugular intrahepatic portosystemic shunts (TIPS)
   c. Patients with cirrhosis
   d. B and C
   e. A and C
2) Liver transplant candidates with co-existing renal dysfunction often arrive to the OR
   a. Euvolemic
   b. Hypervolemic
   c. Hypovolemic
   d. None of the above
   e. All of the above

3) Studies suggest that liver transplant patients in renal failure have
   a. A 5% increase in overall mortality compared to those with normal renal function
   b. A 10% increase in overall mortality compared to those with normal renal function
   c. A 20% increase in overall mortality compared to those with normal renal function
   d. A 30% increase in overall mortality compared to those with normal renal function
   e. A 40% increase in overall mortality compared to those with normal renal function

4) Studies suggest that liver transplant candidates on RRT prior to transplantation exhibit
   a. Lower mean arterial pressures
   b. Greater need for pre-operative transfusions
   c. Higher incidence of vasopressor infusions
   d. B and C
   e. A and C

5) Studies have indicated that patients with MELD scores greater than 30 may require on
   average
   a. 3 more units of PRBC and 5 more units of FFP
   b. 7 more units of PRBC and 5 more units of FFP
   c. 5 more units of PRBC and 3 more units of FFP
   d. 3 more units of PRBC and 7 more units of FFP
   e. 5 more units of PRBC and 7 more units of FFP

6) Studies suggest that the following are predictive of intraoperative transfusion
   requirements
   a. MELD score and fibrinogen
   b. MELD score and INR
   c. MELD score and bilirubin
   d. MELD score and creatinine
   e. MELD score and PTT

7) Studies have shown that a MELD above what value is correlated with worsened 1-year
   survival?
   a. 18
   b. 20
   c. 24
   d. 30
   e. 35

8) Studies have suggested that patients with elevated MELD scores are
a. Approximately 5% more likely than those with low MELD scores to develop postoperative pulmonary complications
b. Approximately 10% more likely than those with low MELD scores to develop postoperative pulmonary complications
c. Approximately 15% more likely than those with low MELD scores to develop postoperative pulmonary complications
d. Approximately 20% more likely than those with low MELD scores to develop postoperative pulmonary complications
e. Approximately 25% more likely than those with low MELD scores to develop postoperative pulmonary complications

9) Studies have suggested that patients with higher MELD scores may be at increased risk for developing post-operative mental status changes due to
   a. Increased propensity for cerebral AVM’s
   b. Disruption in cerebral autoregulation
   c. Increased CMRO$_2$
   d. B and C
   e. A and B

10) Which of the following, alone with elevated MELD scores, have been shown to be predictive of postoperative cardiac complications?
   a. Adverse intraoperative cardiac events
   b. Abnormal preoperative angiogram
   c. Abnormal preoperative stress test
   d. A and B
   e. A and C

ANSWERS

   1) D
   2) E
   3) C
   4) E
   5) E
   6) A
   7) C
   8) C
   9) B
   10) A