How can we best use MELD and Child-Pugh scores to assess the liver at baseline and during treatment of CHC and NASH?

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Mayo Clinic, College of Medicine
Rochester MN USA
MELD and Child-Pugh scores at baseline and during treatment of CHC and NASH?

- Survival Models: the basics
- CTP/MELD/MELD Na Scores
- MELD + Lille Model Combination
- Monitoring during CHC and NASH treatment
- Future Directions
MELD and Child-Pugh scores at baseline and during treatment of CHC and NASH?

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Prognostic Models

• Prognostic models assess risk

• “The revolutionary idea that defines the boundary between modern times and the past is the mastery of risk: the notion that the future is more than the whim of the gods and that men and women are not passive before nature”.

*Against The Gods: The Remarkable Story of Risk: Peter L Bernstein*

• Models not restricted to medicine
Penalty Kick: Assessing Risk

Risk of kicking left vs right?

Risk of diving left vs right?
Penalty Kick: Assessing Risk
Bar-Eli M, Azar OH. Soccer and Society 2009:10:183

• 85% of kicks placed within goal are successful
• 100% of kicks placed in upper 1/3 successful; but most misses
• Goalkeepers dive left or right 94% of times
• Goalkeepers dive correct only 40% (save 25% shots – 10% penalties). Staying in center can save 33% shots.
• More goals: center 87% vs 83% to sides

CONCLUSION: Goalkeepers should raise their hands and not move
How Do You Determine Accuracy of Model

• Discrimination:
  Rank patients at risk for mortality
  ‘c’ statistic: ROC-AUC measure
  Who will die first?
  *Useful for populations*

Calibration:
  When will individual patient die?
  *Useful for individual patient/DILI*
Discrimination: Which teams will win

MARCH MADNESS
2016 BRACKET

NATIONAL CHAMPIONSHIP
Houston, TX
April 4 TBS

National Championship Winner

Houston, TX
April 2 TBS

WILLIAM & MARY
North Carolina

First Four
Dayton, OH
3/15-16 TV

First Round
3/17-19 TV

Second Round
3/23-25 TV

Sweet Sixteen
3/29-31 TV

Elite Eight
4/1-2 TV

NATIONAL CHAMPIONSHIP
Arizona

First Round
3/17-19 TV

Second Round
3/23-25 TV

Sweet Sixteen
3/29-31 TV

Elite Eight
4/1-2 TV

Fifteen

Elite Eight
4/1-2 TV

West
Auburn, AL

First Round
3/17-19 TV

Second Round
3/23-25 TV

Sweet Sixteen
3/29-31 TV

Elite Eight
4/1-2 TV

Midwest
Chicago, IL

First Round
3/17-19 TV

Second Round
3/23-25 TV

Sweet Sixteen
3/29-31 TV

Elite Eight
4/1-2 TV

Northeast
Philadelphia, PA

First Round
3/17-19 TV

Second Round
3/23-25 TV

Sweet Sixteen
3/29-31 TV

Elite Eight
4/1-2 TV

South
New Orleans, LA

First Round
3/17-19 TV

Second Round
3/23-25 TV

Sweet Sixteen
3/29-31 TV

Elite Eight
4/1-2 TV

Regional Bids

Northeast

Philadelphia, PA

West

Auburn, AL

South

New Orleans, LA

Midwest

Chicago, IL

National Championship Winner

PrintableTeamSchedules.com
Calibration: What are the scores going to be

Hard to Predict
Static Versus Dynamic Models

- **Static:** Predict at specific time point (usually baseline)
  - MELD/CTP
  - Maddrey DF

- **Dynamic:** Predict over time course (Response to therapy)
  - Lille Score (Alcoholic Hepatitis)
  - DILI: ? Static and dynamic score desirable
  - ? Delta MELD
MELD and Child-Pugh scores at baseline and during treatment of CHC and NASH?

• Survival Models: the basics
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# Child Turcotte Pugh Score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>PT (sec prolonged)</td>
<td>&lt;4</td>
</tr>
<tr>
<td>or INR</td>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>

CTP score is obtained by adding the score for each parameter.

**CTP class:**

- **A** = 5-6 points
- **B** = 7-9 points
- **C** = 10-15 points
CTP Score: Probability using a Simple Calculator

- Accuracy in discriminating mortality risk in decompensated cirrhosis:
  - 75-80%
• What is the MELD?
Model for End-Stage Liver Disease (MELD)

- Mathematical survival model created from data on patients undergoing TIPS (for variceal bleeding/ascites)
- MELD score estimates risk of mortality, usually 3 months
- Uses 3 easily obtained laboratory values:
  - Serum total bilirubin
  - Serum creatinine
  - INR for prothrombin time
MELD Equation

\[
\text{MELD} = (0.957 \times \log(\text{creatinine}) + 0.378 \times \log(\text{bilirubin}) + 1.12 \times \log(\text{INR}) + 0.643) \times 10
\]

## Sample MELD Scores

<table>
<thead>
<tr>
<th>INR</th>
<th>Bilirubin</th>
<th>Creatinine</th>
<th>MELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Score</td>
<td>3 Month Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>80%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Discrimination of Various MELD Modifications: C Statistics UNOS 2007-2008

- MELD: 0.868
- MELD-Na: 0.877
- Refit MELD: 0.872
- Refit MELD-Na1: 0.880
- Refit MELD-Na2: 0.879
Calibration of Various MELD Modifications:
Observed vs. predicted probability of death at day 90

<table>
<thead>
<tr>
<th>MELD score</th>
<th>Observed</th>
<th>Predicted with MELD</th>
<th>Predicted with MELDNa</th>
<th>Predicted with RefitMELD</th>
<th>Predicted with RefitMELD-Na1</th>
<th>Predicted with RefitMELD-Na2</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-14</td>
<td>1.7</td>
<td>2.1</td>
<td>1.8</td>
<td>1.7</td>
<td>1.9</td>
<td>1.8</td>
</tr>
<tr>
<td>15-19</td>
<td>5.5</td>
<td>5.4</td>
<td>5.7</td>
<td>6.1</td>
<td>6.5</td>
<td>6.1</td>
</tr>
<tr>
<td>20-24</td>
<td>13.9</td>
<td>12.4</td>
<td>13.9</td>
<td>14.0</td>
<td>15.6</td>
<td>14.7</td>
</tr>
<tr>
<td>25-29</td>
<td>27.9</td>
<td>27.4</td>
<td>29.0</td>
<td>30.5</td>
<td>31.9</td>
<td>29.7</td>
</tr>
<tr>
<td>30-34</td>
<td>48.8</td>
<td>52.6</td>
<td>52.4</td>
<td>51.2</td>
<td>49.0</td>
<td>47.2</td>
</tr>
<tr>
<td>35-40</td>
<td>89.4</td>
<td>89.4</td>
<td>88.2</td>
<td>81.9</td>
<td>81.9</td>
<td>81.9</td>
</tr>
</tbody>
</table>
MELD Score: Probability Using a fancy Calculator

- Accuracy in discriminating mortality risk in decompensated cirrhosis: 80-85%.
- CTP range: 5-15; MELD 6-40 (0 – infinity)
- CTP has discrimination but limited calibration ability
- MELD score: Both fine calibration and discrimination possible
- PROPOSAL: Use MELD score for DILI studies
MELD and Child-Pugh scores at baseline and during treatment of CHC and NASH?

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Combining Data From Liver Disease Scoring Systems Better Predicts Outcomes of Patients With Alcoholic Hepatitis

MELD + Lille performed better than Maddrey + Lille or ABIC + Lille
Combining the Static MELD and the Dynamic Lille gives the optimal prognostic scoring system

MELD score: 21
Lille Score 0.45

2-month mortality: 15.3%
6-month mortality: 24%

www.lillemodel.com

Louvet Gastro 2015
Kamath and Shah Gastro 2015
Delta MELD (change in MELD) and Mortality
Predicting Survival among Patients Listed for Liver Transplantation: An Assessment of Serial MELD Measurements

Kiran Bambha\textsuperscript{a}, W. Ray Kim\textsuperscript{a,b,*}, Walter K. Kremers\textsuperscript{b}, Terry M. Therneau\textsuperscript{b}, Patrick S. Kamath\textsuperscript{a}, Russell Wiesner\textsuperscript{a}, Charles B. Rosen\textsuperscript{c}, Jeff Thostenson\textsuperscript{b}, Joanne T. Benson\textsuperscript{b} and E. Rolland Dickson\textsuperscript{a}

American Journal of Transplantation 2004; 4: 1798–1804
Delta MELD Study Design

Figure 1: Illustration of time-lagged Cox regression model design. The time lag represents a period of 0–14 d immediately preceding the end of a patient’s period of observation (event). The most recent MELD score preceding the time lag was designated the Current MELD.
Delta MELD more reflective than predictive
MELD and Child-Pugh scores at baseline and during treatment of CHC and NASH?

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Scoring Systems for DILI

- No validated gold standard for EARLY determination of mortality risk in DILI by AST/ALT alone
- Increase in absolute 3 month mortality risk by 5% over control seems reasonable indication to stop new drug.
- If no baseline mortality risk, even 5% mortality risk is high
- Baseline mortality risk variable for different underlying diseases – hepatitis/cholestatic/alcoholic hepatitis/compensated cirrhosis/decompensated cirrhosis
HCV Cirrhosis Patients at Baseline: Sofosbuvir/Veltpatasvir

Median MELD score: 10  
Median CTP score: 8
MELD for Prognosis in DILI

DILI superimposed on cirrhosis/chronic liver disease as prototype for Acute on Chronic Liver Failure
Second Infections

Fungemia

GI bleed

Surgery

Viral, drug, other

Sepsis

DILI precipitated Systemic Inflammatory Response Syndrome in Cirrhosis

Alcoholic hepatitis

Infection
Multiple Organ Dysfunction Syndrome

- Occurs with diverse precipitating events
- **Predictable pathway** irrespective of the inciting event

**Cardiovascular (hemodynamic alterations)**

**Pulmonary (ALI, ARDS)**

- Hepatic dysfunction
- GI dysfunction
- Renal failure
- “Brain failure”

**Immune paralysis**

**Myocardial dysfunction**
## Acute on Chronic Liver Failure Predicted Mortality (90 Days)

<table>
<thead>
<tr>
<th>MELD Predicted</th>
<th>0-20%</th>
<th>20-40%</th>
<th>40-60%</th>
<th>60-80%</th>
<th>80-100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>165</td>
<td>55</td>
<td>25</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Deaths</td>
<td>9</td>
<td>11</td>
<td>14</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Death Rate</td>
<td>5%</td>
<td>21%</td>
<td>56%</td>
<td>60%</td>
<td>86%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Child-Pugh Class</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>31</td>
<td>132</td>
<td>76</td>
</tr>
<tr>
<td>Deaths (90 days)</td>
<td>0</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>Death Rate</td>
<td>0%</td>
<td>11%</td>
<td>47%</td>
</tr>
</tbody>
</table>

**CTP Score has only limited calibration ability**
Assessment of Severity of DILI-ACLF

- Severity of liver disease: MELD
- Assessment of organ dysfunction: SOFA score
  
  APACHE score
- Assessment of liver disease severity and organ dysfunction score: CLIF-SOFA score

- PROBLEM: Organ failure scores reflect the dying process rather than predict death. Most accurate near death, that is, when process is irreversible
MELD Score in Prognosis of DILI
Outcome and determinants of mortality in 269 patients with combination anti-tuberculosis drug-induced liver injury

Harshad Devarbhavi,* Rajvir Singh,† Mallikarjun Patil,* Keyur Sheth,* Channagiri Krishnamurthy Adarsh* and Girisha Balaraju*

Outcome and determinants of mortality in 269 patients with combination anti-tuberculosis drug-induced liver injury

Figure 2 Receiver operating characteristic (ROC) curves for anti-tuberculosis (TB) drug-induced liver disease (DILI) model (blue) and model for end-stage liver disease (MELD) (green): Anti-TB DILI model (0.97), MELD (0.88). ---, MELD; ——, predicted probability.
Model for end-stage liver disease score as a predictor of short-term outcome in patients with drug-induced liver injury

Rubi Jeong, Yoon-Seon Lee, Changhwan Sohn, Jin Jeon, Shin Ahn & Kyoung Soo Lim

Model for end-stage liver disease score as a predictor of short-term outcome in patients with drug-induced liver injury

Table IV. Logistic regression for liver transplantation or mortality within 30 days.

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.005</td>
<td>0.977 - 1.034</td>
</tr>
<tr>
<td>Female</td>
<td>1.291</td>
<td>0.579 - 2.879</td>
</tr>
<tr>
<td>Multiple drugs</td>
<td>2.304</td>
<td>1.030 - 5.150</td>
</tr>
<tr>
<td>Concurrent alcohol consumption</td>
<td>3.687</td>
<td>1.032 - 13.179</td>
</tr>
<tr>
<td>HBV</td>
<td>1.503</td>
<td>0.520 - 4.344</td>
</tr>
<tr>
<td>Injury type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>3.143</td>
<td>0.402 - 24.548</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>6.176</td>
<td>0.657 - 58.031</td>
</tr>
<tr>
<td>Hbv's case</td>
<td>2.444</td>
<td>0.946 - 6.317</td>
</tr>
<tr>
<td>WBC</td>
<td>1.167</td>
<td>1.068 - 1.270</td>
</tr>
<tr>
<td>Hb</td>
<td>0.601</td>
<td>0.490 - 0.738</td>
</tr>
<tr>
<td>Platelet</td>
<td>0.993</td>
<td>0.987 - 0.998</td>
</tr>
<tr>
<td>ALT</td>
<td>1.000</td>
<td>0.999 - 1.000</td>
</tr>
<tr>
<td>AST</td>
<td>1.000</td>
<td>0.999 - 1.000</td>
</tr>
<tr>
<td>ALP</td>
<td>0.998</td>
<td>0.994 - 1.002</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1.094</td>
<td>1.056 - 1.132</td>
</tr>
</tbody>
</table>

*Creatinine, total bilirubin and PT excluded for multivariate analysis.
†Backward elimination after choosing variables with $p < 0.1$ on univariable analysis.
Abbreviations: ALT = Alanine aminotransferase; OR = Odds ratio; CI = Confidence interval; HBV = Hepatitis B virus; MELD = Model for end-stage liver disease.
Model for end-stage liver disease score as a predictor of short-term outcome in patients with drug-induced liver injury

<table>
<thead>
<tr>
<th>Variables</th>
<th>AUC 1</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD</td>
<td>0.93</td>
<td>0.89</td>
<td>0.97</td>
<td>20.5</td>
<td>0.89</td>
<td>0.84</td>
</tr>
<tr>
<td>MELD + Hb</td>
<td>0.94</td>
<td>0.90</td>
<td>0.97</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUC, area under the curve; CI, confidence interval; MELD, model for end-stage liver disease; Hb, hemoglobin.
Drug-Induced Acute Liver Failure: Results of a U.S. Multicenter, Prospective Study

Adrian Reuben¹, David G. Koch¹, William M. Lee², and the Acute Liver Failure Study Group

Drug-Induced Acute Liver Failure: Results of a U.S. Multicenter, Prospective Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transplant-Free Survival</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 36) (%)</td>
<td>No (n = 97) (%)</td>
</tr>
<tr>
<td>BMI</td>
<td>29.0 (25.1-34.4)</td>
<td>28.5 (24.3-32.5)</td>
</tr>
<tr>
<td>MAP</td>
<td>91.0 (76.0-96.5)</td>
<td>86.0 (77.0-95.0)</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>12.6 (5.2-24.1)</td>
<td>22.2 (16.3-29.8)</td>
</tr>
<tr>
<td>INR</td>
<td>2.0 (1.7-3.5)</td>
<td>2.9 (2.1-4.4)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1 (0.8-3.1)</td>
<td>1.2 (0.8-2.8)</td>
</tr>
<tr>
<td>AST</td>
<td>588.5 (389.0-1418.5)</td>
<td>551.0 (267.0-1106.0)</td>
</tr>
<tr>
<td>ALT</td>
<td>784.5 (258.0-2013.5)</td>
<td>544.0 (253.0-1277.0)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>166.0 (130.0-239.0)</td>
<td>165.0 (118.0-220.0)</td>
</tr>
<tr>
<td>MELD score</td>
<td>29.0 (23.0-36.0)</td>
<td>34.0 (28.0-41.0)</td>
</tr>
</tbody>
</table>
MELD Score as a Predictor of Liver Failure and Death in Patients with Acetaminophen-Induced Liver Injury

Lars E. Schmidt and Fin Stolze Larsen

Hepatology 2007;45:789-796
MELD Score as a Predictor of Liver Failure and Death in Patients with Acetaminophen-Induced Liver Injury
MELD Score and DILI

- High discrimination (> 0.85) as a predictor of mortality in DILI related ALF (acetaminophen, anti-tubercular treatment, other drugs) in studies from Asia, Europe, USA
- Suggest MELD use at baseline for DILI studies
- Suggest MELD scores in monitoring of patients with underlying liver disease or decompensated cirrhosis
DILI that does evolve to ALF carries a poor prognosis, with 40% requiring liver transplantation and 42% dying of the episode. Advanced coma grade and high MELD scores are associated with bad outcomes.

*Am J Gastroenterol* advance online publication, 17 June 2014; doi:10.1038/ajg.2014.131
MELD and Child-Pugh scores at baseline and during treatment of CHC and NASH?

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Approach to Diagnose DILI: AST/ALT

- Diagnosis of DILI often requires adjudication
- In alcoholic hepatitis: AST or ALT > 500 U/L on treatment likely **NOT** related to underlying disease and suggests DILI
- In CHC and NASH: AST/ALT > 5-8 X increase from baseline without increase in bilirubin and asymptomatic: likely DILI
- Increase in AST/ALT with symptoms (fever, RUQ pain, nausea) and increase in bilirubin > 3 mg/dL likely to be DILI: STOP
- **NEED PROSPECTIVE DATA FROM TREATMENT TRIALS**
DILI in patients with Decompensated Cirrhosis: Bilirubin/MELD

- **Decompensated Cirrhosis**: Ascites, HE, variceal bleed, jaundice
- Increase in MELD score > 10 points from baseline of 6 is indicator of *absolute* increase in mortality risk of about 5%
- Creatinine 1  Bilirubin 1  INR 1:  MELD 6
- Creatinine 1  Bilirubin 3  INR 1:  MELD 11
- Creatinine 1  Bilirubin 12 INR 1:  MELD 16
- Creatinine 1.3 Bilirubin 3  INR 1.3:  MELD 16
- Bilirubin elevations alone are associated with smaller increase in mortality
MELD versus CTP For DILI: SUMMARY

- Use whatever you are comfortable with to determine liver disease severity at baseline
- CTP better for broad classification – however, subjective elements which regulatory bodies cannot assess
- Coarse discrimination and lack of calibration make CTP poor tool to make management decisions in individual patient.
- MELD better for fine calibration. Objective
- Objective system with accurate calibration required for early diagnosis of DILI
Messi kicked left
Goalkeeper dived left and saved!
CONCLUSION: No model is perfect and neither is Messi
Take Home Messages: MELD/CTP/DILI

• Prognostic models for DILI: work in progress
• MELD score recommended for current and near future studies
• Need for models to predict DILI risk and mortality
• Additional parameters (organ failure scores) may add to accuracy but with diminishing incremental gain
• Balance between accuracy of prediction and practical problems in implementation