Estimation of Prognosis and Need for Transplant Evaluation in End-Stage Liver Disease

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Outline

• Review of natural history of cirrhosis
• Association between decompensation and mortality
• MELD and other predictors of liver-related mortality
• Limitations of the MELD-based economy
• Limitations of the current organ allocation system
Case

- 58 year old Hispanic with h/o blood transfusion in Mexico in his 20s was diagnosed with HCV after PMD detected elevated aminotransferases
- Cirrhosis diagnosed after abdominal US showed nodular liver contour, mild splenomegaly, no ascites
- He feels well and works in construction
- No h/o encephalopathy, GI bleeding or ascites
- INR 0.9, Cre 0.8, Tbili 1.1, albumin 4.0, Na 138, platelets 160K
- “Do I need a transplant? How long do I need to wait?”

Natural history of cirrhosis

Fattovich et al. Gastro 1997;112:163-172
Case

- 58 year old Hispanic man with h/o blood transfusion in Mexico in his 20s was diagnosed with HCV after PMD detected elevated aminotransferases
- Episodic hepatic encephalopathy treated with lactulose and rifaximin
- Esophageal variceal bleed 2 years ago banded x4
- Moderate ascites despite furosemide and aldactone
- INR 1.6, tbili 2.5, Cre 1.6, albumin 3.1, Na 128, platelets 45K, blood group O, MELD 20
- “Do I need a transplant? How long do I need to wait?”

Natural history of cirrhosis

Compensated cirrhosis 10% 5 year mortality
Decompensated cirrhosis 50% 5 year mortality

- Ascites
- Encephalopathy
- Variceal bleeding
- SBP
- Hepatorenal syndrome
- HCC

Fattovich et al. Gastro 1997;112:163-172
Hepatic encephalopathy and mortality

- Overt HE occurs in 30-45% of pts with cirrhosis
- Risk of death or transplant after 1st episode of acute HE
  - 58% after 1 year
  - 77% after 3 years

Bajaj et al. Aliment Pharmacol Ther 2011;33:739-747
Sharma et al. Gastro 2009;137:885-91
Bustamante et al. J Hepatol 1999;30:890-95

Impact of moderate ascites on waitlist mortality

Hepatorenal syndrome and mortality

- Median survival: 6 months (HRS 2)
- Median survival: 17 days (HRS 1)

Organ allocation

Disease severity
Maximal utility
## Child-Turcotte-Pugh classification

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>1-2</td>
<td>3-4</td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Slight</td>
<td>Moderate</td>
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<tr>
<td>Bilirubin (mg/dL)</td>
<td>1-2</td>
<td>2-3</td>
<td>&gt;3</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
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<tr>
<td>PT (seconds prolonged)</td>
<td>1-4</td>
<td>4-6</td>
<td>&gt;6</td>
<td></td>
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<tr>
<td>Or INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>CTP Class</th>
<th>Mortality risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>10% at 5 years</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>20% at 5 years</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>34% at 1 year 65% at 2 years</td>
</tr>
</tbody>
</table>

Shetty et al. Hepatology 1997

## Organ allocation systems pre-MELD era

**Pre-MELD (before Feb 2002)**

- Status 1
- Status 2A
- Status 2B
- Status 3

**Child-Pugh Class**
- Encephalopathy
- Ascites
- Bilirubin
- Albumin
- PT/INR

**Location**
- ICU
- Floor bed
- Home
Model for end-stage liver disease (MELD) score

- Dept of HHS issues “the final rule mandate” in 1998
  - Deceased donor liver allocation should be based on objective, reproducible medical criteria rather than waiting time or “accidents of geography”

\[
\text{MELD Score} = 9.57 \times \ln(\text{creatinine mg/dL}) \\
+ 3.78 \times \ln(\text{bilirubin mg/dL}) \\
+ 11.2 \times \ln(\text{INR}) \\
+ 6.43
\]

Range: 6-40 points


3 Month waitlist mortality by MELD

- MELD originally developed to predict 90 day mortality after transjugular intrahepatic portosystemic shunt (TIPS) placement
- Predictor of 90 day mortality on the liver transplant waitlist

Kamath et al. Hepatology 2001;33:464-470
Freeman et al. Liver Transpl 2001;7:173-178
MELD compared to CTP score

ROC curves MELD vs CTP

MELD
CTP
MELD Area = 0.83
CTP Area = 0.76
p < 0.001

Survival benefit of LT by MELD score

Mortality risk of LT by MELD score

Limitations of MELD

- Does not always accurately reflect an individual patient’s severity of illness
  - i.e. Episodic or persistent encephalopathy requiring intubation and ICU support but low MELD score
  - Criteria for Regional Review Board petition to award MELD exception points is not standardized
- Geographical variation in access to organs

MELD exceptions

- HCC within Milan criteria
- Hepatopulmonary syndrome (PaO2 <60 mm Hg)
- Portopulmonary hypertension
- Primary hyperoxaluria
- Familial amyloid polyneuropathy
- Cystic fibrosis (listed for liver only)
- Small-for-size syndrome (re-LT)
- Hepatic artery thrombosis (re-LT)

Freeman et al. Liver Transpl 2006;12:S128-S136
Milan Criteria for HCC

1 HCC
>2 cm and <5 cm

2-3 HCCs
None >3 cm in diameter

Mazzaferro et al. NEJM 1996

The MELD-based economy

Region 5: Patients transplanted with MELD exceptions (Jan 2010-Dec 2010)

37%
N=263

63%
N=446

MELD exceptions
No exceptions

UC San Diego
School of Medicine
MELD at transplant in 2010 (Region 5)

Median MELD at Transplant

- MELD Exceptions: N=263, Median MELD 28
- No MELD Exceptions: N=446, Median MELD 37

www.UNOS.org

How to build a better mousetrap
Complications of Cirrhosis

**Portal hypertension**
- Ascites
- Hydrothorax
- SBP
- Variceal bleeding
- Encephalopathy (shunting)
- HPS
- POPH

**Hepatocellular dysfunction**
- Coagulopathy
- Encephalopathy
- Hepatocellular carcinoma

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Risk of decompensation increased with HVPG ≥10

- 213 patients with compensated cirrhosis
- At baseline all pts had HVPG >5 but no varices
- Followed every 3 months
- Median follow-up 51 months

Ripoll et al. Gastro 2007
Liver stiffness predicts hepatic decompensation

- 100 patients with chronic liver disease underwent HVPG measurement and transient elastography (Fibroscan) on same day
- Followed for 2 years or until they developed decompensation (41 pts developed at least 1 liver-related complication)
- Fibrosis stage:
  - F0  8
  - F1  5
  - F2  11
  - F3  10
  - F4  65

Robic et al. J Hepatology 2012
vWF levels as predictor of portal HTN, decompensation, and death

- 286 patients with cirrhosis
- Higher vWF levels associated with:
  - Varices (OR 3.27)
  - Ascites (OR 3.93)
  - Death (OR 4.41)
- Compensated cirrhosis
  - vWF level <315%: 25% mortality after 53 months
  - vWF level >315%: 25% mortality after 15 months
- Decompensated cirrhosis
  - vWF level <315%: 25% mortality after 37 months
  - vWF level >315%: 25% mortality after 7 months

Limitations:
- Pathophysiologic explanations for correlation unclear
- Unknown effects of infections, malignancy, renal failure, IFN therapy have on vWF levels

Ferlitsch et al. Hepatology 2012
Serum sodium predicts risk of death in cirrhosis

- 6769 registrants on the UNOS waiting list in 2005
- 1781 underwent transplant
- 422 died within 90 days of listing
- HR for death 1.21 per MELD point
- HR for death 1.05 per 1-unit decrease between 125-140 mmol/L

Incorporation of serum sodium into MELD

Kim et al. NEJM 2008
MELD-Na applied to 477 registrant deaths in 2006

<table>
<thead>
<tr>
<th>MELD Score</th>
<th>MELDNa Score</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>10–19</td>
<td>67</td>
<td>121</td>
</tr>
<tr>
<td>20–29</td>
<td>122</td>
<td>165</td>
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<td>30–39</td>
<td>116</td>
<td>116</td>
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<tr>
<td>40</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>TOT</td>
<td>558</td>
<td>477</td>
</tr>
</tbody>
</table>

- Applied predictive model to 2006 registrant data
- 110 patients would have had higher MELD-Na scores that may have increased their chances of liver transplant

**Case**

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- Episodic hepatic encephalopathy treated with lactulose and rifaximin
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Change in MELD score over time

UNOS Regions

UNOS REGIONAL MAP
Summary

- Natural history of compensated and decompensated cirrhosis is very different
- MELD is currently the best predictor of mortality
- Alternative/modified predictors exist (MELD-Na, HVPG, liver stiffness, vWF levels)
- Use of MELD exceptions (HCC, HPS, etc) narrows the window for transplant for non-MELD exception patients and may lead to “MELD inflation”
- Geographic disparities in access to transplant continue to exist
Thank you!