TIMING, INDICATIONS AND RESULTS OF LIVER TRANSPLANTATION IN 2008

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EUROPEAN LIVER TRANSPLANT REGISTRY
23 Countries - 131 active Institutions
70,862 Transplantations – 63,584 Patients
05/1968 - 06/2006
Evolution of 70,862 Liver Transplantations in Europe
Evolution of Number of LT in France

Rapport ABM-EFG 2005
Evolution of Recipient Age
05/1968 - 06/2006

- 0 to 2: 2723
- 2 to 15: 3701
- 15 to 45: 18291
- 45 to 60: 28733
- >= 60: 9946
Primary Diseases leading to Liver Transplantation in Europe
01/1988 - 06/2006

- Metabolic diseases: 3594 (6%)
- Cholestatic diseases: 6256 (11%)
- Acute hepatic failure: 5291 (9%)
- Cancers: 7659 (13%)
- Cirrhosis: 34811 (58%)
- * Others: 1852 (3%)

* Others: Budd Chiari: 587
Benign liver tumors or Polycystic diseases: 666
Parasitic diseases: 57
Other liver diseases: 542
Liver Transplantation in Europe
Indications in 34811 Cirrhosis
01/1988 - 06/2006

- Primary Biliary: 3828 (11%)
- Virus related: 14359 (41%)
- Alcoholic: 11504 (33%)
- Autoimmune: 1515 (4%)
- Secondary Biliary: 386 (1%)
- Others: 458 (1%)
- Unknown causes: 2761 (8%)
Evolution of Indications for Cirrhosis in Europe
05/1968 - 06/2006

- Alcoholic cirrhosis: 11598
- Primary biliary cirrhosis: 4145
- Virus related cirrhosis: 14493
Evolution of Primary Diseases leading to Liver Transplantation in Europe

05/1968 - 06/2006

Cirrhosis: 35650
Cancers: 8164
Acute hepatic failure: 5438
Others: 12473

0% 20% 40% 60% 80% 100%


June
Evolution of Primary Indication of LT in Europe
ELTR Data

[Bar chart showing the evolution of primary indications for liver transplants in Europe from 1991 to 2007. The chart indicates the percentage of each indication over the years, with categories such as VHC, VHB, CHC, ALCOHOL, PBC, SC, FUHE, and OTHERS.]
INDICATIONS OF LIVER TRANSPLANTATION

• Liver transplantation should be considered in patients with chronic liver disease threatening life within the next -3 years.

• However the exact timing for Lt should take into account:
  – The expected waiting time for LT
  – The possibility to control progression of liver disease
  – The aetiology of liver disease
  – The less good results in case of very severe liver disease
  – The risk of drop out from the waiting list due to appearance of contraindications to LT
GENERAL CONTRAINDICATIONS TO LIVER TRANSPLANTATION

- Age > 70 years*
- Uncontrolled HIV disease with AIDS
- Severe cardiac disease
- Portopulmonary hypertension with mean AP > 45mmHg
- Current active uncontrolled extrahepatic cancer

* Depending centres, relative CI can be considered if good general status
SPECIFIC CONTRAINDICATIONS TO LIVER TRANSPLANTATION

- HBV Cirrhosis
  » Uncontrolled HBV replication due to multidrug resistant HBV
- HCV fibrosing cholestatic hepatitis post-LT
- Diffuse HCC outside UCSF criteria
- HCC with tumoral portal thrombosis
GRAFT ALLOCATION IN FRANCE

• Until March 2007
  – Graft allocation
    » Local priority then regional then national
    » To the team who choose the recipient
    » Exception: Super emergency for FHF or emergency retransplantation: national nominative priority
  – Major waiting time differences between teams, regions
  – Graft allocation to the team:
    » Drawback: deleterious for the more severe patients
    » Advantage: more flexible: possibility of donor-recipient matching for CMV, size…
MELD SCORE

9.57 \times \log_e (\text{creatinine mg/dl}) + 3.78 \times \log_e (\text{Bilirubin mg/dl})

11.20 \times \log_e (\text{INR}) + 6.43 \text{ (constant for liver disease etiology)}]

* R. Wiesner et al; Gastroenterology 2003; 124: 91-96
Graft Allocation

» Allocation of organs to patients by an agency or organ sharing (UNOS USA, Eurotransplant)
  • More rigid
  • More equitable
  • Severity is the main factor
  • Problem of patients with HCC:
    – Which degree of priority?
  • Patients with no cirrhosis (metabolic diseases, PSC…)

* R. Wiesner et al; Gastroenterology 2003; 124: 91-96
# Graft Allocation

## 3 Months Mortality according to Meld Score

<table>
<thead>
<tr>
<th></th>
<th>&lt; 9</th>
<th>10 -19</th>
<th>20 - 29</th>
<th>30 - 39</th>
<th>&gt; 40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>1.9 %</td>
<td>6 %</td>
<td>19.6 %</td>
<td>52.6 %</td>
<td>71.3 %</td>
</tr>
<tr>
<td><strong>Mortality+ too sick</strong></td>
<td>2.9 %</td>
<td>7.7 %</td>
<td>23.5 %</td>
<td>60.2 %</td>
<td>79.3 %</td>
</tr>
</tbody>
</table>

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* R. Wiesner et al; Gastroenterology 2003; 124: 91-96
Mortality Risk on the Waiting List by Meld score

Figure 2. Box plots of mortality risk on the waiting list, by MELD score.
SPECIAL CASE MELD UPGRADE

# of Requests (n=807)

![Bar chart showing the number of requests in different UNOS Regions for various conditions.](chart_image)

- **FAP**
- **MET**
- **HCC other**
- **HCC I**
- **HCC II**
- **HPS**
- **Oxaluria**
- **Other**

UNOS Regions:

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11.
Diagnostic Categories
Exceptional requests, non HCC/non established Dxs
N=827

- Ascite
- Encephalopathy
- Biliary
- Cholangitis
- Bleeding
- Regional Agreement
- Hydrothorax
- Worsening
- Cholangiocarcinoma
- Malnutrition
- Renal failure
- Other
Allocation of grafts to patients by ABM

- Priority
  - Superemergency list (FHF, Artery thrombosis)
  - Pediatric
  - Combined liver-kidney graft
- National Score
### Table 2
Diagnoses for which mortality endpoints may not be appropriate for assessing liver transplant need

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
<th>Recommended MELD score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Stage 1 or 2 disease (Milan criteria)</td>
<td>Stage 1 = no increase; stage 2 = 24 points</td>
</tr>
<tr>
<td>Hepatopulmonary(^a) syndrome</td>
<td>Portal hypertension; Room Air PaO(_2) &lt; 60 torr; Evidence of pulmonary shunt</td>
<td>15% mortality risk = 24 points(^b)</td>
</tr>
<tr>
<td>Familial amyloidosis(^a)</td>
<td>No criteria</td>
<td>Likely to receive a transplant within 3 months(^b)</td>
</tr>
<tr>
<td>Primary oxaluria(^a)</td>
<td>No criteria</td>
<td>Likely to receive a transplant within 3 months(^b)</td>
</tr>
<tr>
<td>Metabolic disease(^a)</td>
<td>No criteria</td>
<td>Likely to receive a transplant within 3 months(^b)</td>
</tr>
</tbody>
</table>

In order for candidates with one of the diagnoses listed below to receive increased priority, centers must request the increase MELD score to be reviewed and accepted or denied by Regional Review Boards. For familial amyloidosis, primary oxaluria, and metabolic diseases, centers are directed to request MELD scores that are likely to result in a liver offer in the center’s OPTN Region within 3 months. For a full explanation of the Regional Peer Review Process see: [http://www.optn.org/PoliciesandBylaws/policies/docs/policy_8.doc](http://www.optn.org/PoliciesandBylaws/policies/docs/policy_8.doc).
ALLOCATION OF GRAFTS France 2008

\[
\text{SCORE}_{FV10} =
\begin{align*}
1000 \cdot f_1(\text{MELD}) \\
+ 200 \cdot \text{Si(\text{CHCTNM}_1)} \cdot f_2(\text{DA}; \text{seuil}=12 \text{ mois}) \\
+ 200 \cdot \text{Si(\text{CHCTNM}_\geq2)} \cdot f_2(\text{DA}; \text{seuil}=6 \text{ mois}) \\
+ 300 \cdot \text{Si(\text{HMFS})}. f_2(\text{DA}; \text{seuil}=12 \text{ mois}) \\
+ 80 \cdot \text{Si(\text{ReTxE})}. f_2(\text{DA}; \text{seuil}=6 \text{ mois}) \\
+ 10 \cdot \text{Si(\text{Cirrhose})}. f_2DA; \text{seuil}=180 \text{ mois}) \\
+ 300 \cdot f_3(\text{Dist}_{R;D}; \text{Sdist}(\text{Equipe}_R)) \\
+ 10000 \cdot f_4(\text{CentrePrel}_D; \text{Equipe}_R) \\
+ 1000 \cdot \text{Si(\text{EXPT})}. f_2(\text{DA}; \text{seuil}= [0, 3, 6, 12 \text{ mois}])
\end{align*}
\]
Survival With and Without Transplantation In Relation with Meld Absence of Benefit of LT in Low Meld?

Fig. 2. Comparison of average number of days alive for MELD score ranges. For patients with MELD scores <15 on average, they have a higher number of survival days without a transplant. For all other MELD score ranges ≥15, patients accrue more survival days with a transplant. From Wolfe, R.A., presented at the Evolving Concepts in Liver Allocation In the MELD/PELD Era National Conference, Washington, D.C., 9 December 2003.
Figure 2. Distribution of serum sodium in patients with and without ascites. Ascites was commonly (63%) present in our patients, whereas low serum sodium (<130 mEq/L) was relatively uncommon (8%). Most patients (90%) with low serum sodium had ascites.
Figure 2. Computation of the MELDNa Score on the Basis of the MELD Score and the Serum Sodium Concentration. The graph shows the allocation points a patient would receive for a given Model for End-Stage Liver Disease (MELD) score and serum sodium concentration. Boxes of the same color share the same allocation points.
Figure 3. Observed and Predicted Probability of Death at 90 Days.

Panel A shows the observed probability of death for the 2005 data and the predicted probability according to the Model for End-Stage Liver Disease–sodium (MELDNa) score in 10 groups (deciles) of patients. Panel B shows the observed probability of death for the 2006 data and the predicted probability according to the MELDNa and MELD scores in 10 groups (deciles) of patients.
# MELD NA

<table>
<thead>
<tr>
<th>MELD Score</th>
<th>MELDNa Score</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>10–19</td>
<td>54</td>
<td>121</td>
</tr>
<tr>
<td>20–29</td>
<td>122</td>
<td>165</td>
</tr>
<tr>
<td>30–39</td>
<td>116</td>
<td>116</td>
</tr>
<tr>
<td>40</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>477</strong></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Distribution of MELD and MELDNa Scores among the 477 Patients Who Died while on the Waiting List, 2006.

Kim NEJM 2008
Figure 1. Probability of development of renal failure in the 106 patients with cirrhosis and sepsis (solid line) and in the 100 patients with cirrhosis without infection (dashed line) included in the study.
Survival in Cirrhotic Patients with Renal Failure According to the Presence of SIRS

Fig. 2. Cumulative survival at 2 months of patients with cirrhosis and acute functional renal failure, divided according to the presence or absence of SIRS at inclusion.
Survival in Cirrhotic Patients with Renal Failure According to the Presence of SIRS

Table 5. Predictive Factors of In-Hospital Mortality in Multivariable Analysis in the 83 Patients with Functional Renal Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Coefficient</th>
<th>Standard Error</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD score</td>
<td>0.12</td>
<td>0.04</td>
<td>1.12 (1.04-1.21)</td>
<td>0.002</td>
</tr>
<tr>
<td>Presence of SIRS</td>
<td>1.48</td>
<td>0.58</td>
<td>4.38 (1.41-13.56)</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>0.02</td>
<td>0.05</td>
<td>1.02 (0.93-1.13)</td>
<td>0.63</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>0.35</td>
<td>0.13</td>
<td>1.46 (1.15-1.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of SIRS</td>
<td>1.31</td>
<td>0.50</td>
<td>3.72 (1.41-9.84)</td>
<td>0.008</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.003</td>
<td>0.002</td>
<td>1.01 (0.99-1.02)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Thabut Hepatology 2007
ACCESS TO TRANSPLANT FOR HCC IN THE PRE AND POST MELD ERA IN THE USA

Figure 1. The percentage of adult, first-time, cadaveric liver transplant recipients with HCC, presented by year of liver transplantation.

Ioannou Gastroenterology 2008
Table 4. Malignancy as a Cause of Posttransplantation Death Presented Among Recipients With and Without Hepatocellular Carcinoma for Periods 1997–2002 and 2002–2007

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No hepatocellular</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td></td>
<td>carcinoma</td>
<td>carcinoma: no</td>
</tr>
<tr>
<td></td>
<td>n = 15,175</td>
<td>exception n = 731</td>
</tr>
<tr>
<td>Number who died, n (%)</td>
<td>2314 (15.3)</td>
<td>141 (19.3)</td>
</tr>
<tr>
<td>Number who died as a result of malignancy, n (%)</td>
<td>161 (1.1)</td>
<td>50 (6.8)</td>
</tr>
</tbody>
</table>
Figure 2. Kaplan–Meier curves of survival after liver transplantation in 2002–2007, presented according to presence of HCC* and MELD level. *Limited to patients with tumors ≥2 cm who obtained an “HCC-MELD-exception” from the MELD-based allocation system.
Figure 1. Cox survival estimate according to MELD strata. There is a statistical difference between survival estimates for patient survival ($P = .0006$).

S Saab, Liver Transplantation 2003; 9: 473-476
Post-Transplant Survival According to Meld Score

Habib Liver Transplant 2006
Post-Transplant Survival According to Meld Score

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Follow-up Time from Transplant (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>103</td>
<td>0.0</td>
</tr>
<tr>
<td>73</td>
<td>2.0</td>
</tr>
<tr>
<td>57</td>
<td>4.0</td>
</tr>
<tr>
<td>42</td>
<td>6.0</td>
</tr>
<tr>
<td>22</td>
<td>8.0</td>
</tr>
<tr>
<td>12</td>
<td>10.0</td>
</tr>
<tr>
<td>1114</td>
<td>0.0</td>
</tr>
<tr>
<td>828</td>
<td>2.0</td>
</tr>
<tr>
<td>671</td>
<td>4.0</td>
</tr>
<tr>
<td>510</td>
<td>6.0</td>
</tr>
<tr>
<td>356</td>
<td>8.0</td>
</tr>
<tr>
<td>199</td>
<td>10.0</td>
</tr>
<tr>
<td>22</td>
<td>0.0</td>
</tr>
<tr>
<td>14</td>
<td>2.0</td>
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<tr>
<td>14</td>
<td>4.0</td>
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<tr>
<td>12</td>
<td>6.0</td>
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<tr>
<td>11</td>
<td>8.0</td>
</tr>
<tr>
<td>6</td>
<td>10.0</td>
</tr>
<tr>
<td>233</td>
<td>0.0</td>
</tr>
<tr>
<td>154</td>
<td>2.0</td>
</tr>
<tr>
<td>134</td>
<td>4.0</td>
</tr>
<tr>
<td>116</td>
<td>6.0</td>
</tr>
<tr>
<td>88</td>
<td>8.0</td>
</tr>
<tr>
<td>47</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Habib Liver Transplant 2006
### Post-Transplant Survival According to Meld Score

#### No. at risk

<table>
<thead>
<tr>
<th>Gender, MELD Score</th>
<th>No. at Risk</th>
<th>Follow-up Time (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, Low/Medium MELD (6-25)</td>
<td>691</td>
<td>194</td>
</tr>
<tr>
<td>Female, Low/Medium MELD (6-25)</td>
<td>526</td>
<td>184</td>
</tr>
<tr>
<td>Male, High MELD (26+)</td>
<td>170</td>
<td>62</td>
</tr>
<tr>
<td>Female, High MELD (26+)</td>
<td>85</td>
<td>37</td>
</tr>
</tbody>
</table>

*Habib Liver Transplant 2006*
Figure 2. Cox survival estimate according to MELD score above and below at 24. There is a statistical difference between survival estimates for patient survival ($P = < .0001$).
Survival of Liver Transplant Patients According to Meld Score

Figure 11. Six-month patient survival rates for adult recipients stratified by MELD score at the time of transplant ($P < .001$ by log-rank test) between 2/27/02 and 12/31/02.
Patient Survival after Liver Transplantation in Europe

ELTR- 01/1988 - 12/2004

Virus B: 3162
Virus BD: 883
Virus C: 8061
Alcoholic: 10093
PBC: 3578
HDV
HBV
HCV
Patient survival according to the year of LT
HBV and HCV Cirrhosis

ELTR update of December 2004

Patient survival according to the year of LT
HBV and HCV Cirrhosis

ELTR update of December 2004

% Survival

Years

HBV

HCV

% Survival

Years
Evolution de la Survie après Transplantation Hépatique en Europe

Adam Liver Transplantation 2004; 9: 1231-1243
Survie Des Patients
Après Transplantation Hépatique à Paul Brousse
1974 - 2002

Survie Cum. (%) Années
0 2 4 6 8 10

82% 70% 64%
Survie des Patients après Transplantation Hépatique à Paul Brousse 1974 - 2002

Survie des Patients après Transplantation Hépatique à Paul Brousse 1974 - 2002

Survivence des Patients après Transplantation Hépatique à Paul Brousse 1974 - 2002

Survivence des Patients après Transplantation Hépatique à Paul Brousse 1974 - 2002

Log Rank : p=0,0008