Prognostic factors affecting life expectancy in liver transplant patients

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Objectives

I. Understand the evolution of Child’s to MELD score for prognosticating cirrhotics and its role in organ allocation

II. Recognize the various donor options for liver transplantation (OLT) and their impact on outcome

III. List the post OLT complications and discuss how each affects allograft and recipient long term survival

Disclosure: I have no conflicts of interest
Cirrhosis

“A late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and formation of regenerative nodules”

Cirrhosis- Etiology

- Viral Hepatitis (HBV, HCV)
- Autoimmune liver diseases (AIH, PBC, PSC)
- Genetic liver diseases (hemochromatosis, Wilson’s, α1- AT deficiency)
- Fatty liver disease (Alcohol, NASH)
- Other rare causes (e.g. cardiac, Budd Chiari)
- Cryptogenic (10-15%)
Natural History of Chronic Liver Disease

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Development of complications:
- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice

Complications of Cirrhosis Result from Portal Hypertension or Liver Insufficiency

Cirrhosis

Portal hypertension → Variceal hemorrhage

Liver insufficiency → Ascites

Spontaneous bacterial peritonitis

Hepatorenal syndrome

Encephalopathy

Jaundice
Development of Complications in Compensated Cirrhosis

Probability of developing event

Months

Ascites
Jaundice
Encephalopathy
GI hemorrhage

Gines et al., Hepatology 1987; 7:122

Decompensation Shortens Survival

Probability of survival

Months

Median survival ~ 3 years
All patients with cirrhosis
Decompensated cirrhosis
Median survival ~ 1.5 years

Gines et al., Hepatology 1987; 7:122
### Median Survival in Cirrhosis

- **Compensated**: 9 years
- ** Decompensated**: 1.6 years  
  (jaundice, encephalopathy, ascites, variceal bleeding)
- **Hepatopulmonary syndrome**: 10 months
- **Spontaneous bacterial peritonitis**: 9 months
- **Hepatorenal syndrome (HRS)**
  - type 2: 6 months
  - type 1: 2 weeks

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**Baveno IV International Consensus Workshop Staging System for Cirrhosis: 1-Year Outcome Probabilities**

Indications for OLT

Peyton A. and Martin P. Clinical Liver Disease 2013; 2 (4): 146
Limitations with the Child’s score

1) Limited number of categories (2A, 2B, 3…based on location)
2) Limited discriminating ability
3) Uses subjective parameters
4) Subject to laboratory variability (prothrombin time, albumin)
5) Never validated (to predict death)
6) Creatinine not included

“Final Rule” Mandate: issued by US DHHS in 1998 to UNOS

• That “allocation of scarce organs should be based on common medical criteria, not accidents of geography”
• That “organs should be allocated based on patients’ medical need”
• “Less emphasis on keeping organs in the local area where they are procured”
Classification of Cirrhosis Severity
Model for End Stage Liver Disease score

- MELD - determines the severity of liver disease based on:
  - serum bilirubin,
  - serum creatinine
  - international normalized ration (INR)
    - developed in 2002 by UNOS
- Calculation:
  - \[ 0.957 \times (\text{Serum creatinine mg/dL}) + 0.378 \log_e (\text{Total bilirubin mg/dL}) + 1.12 \log_e (\text{INR}) + 0.64 \times 10 \]
- Range: 6 – 40
  - equates to estimated 3-month survival rates from 90% to 7% respectively

MELD calculator

To determine your MELD score, please complete the form below. Please note that the accuracy of your score is based on the amount of information you provide.

MELD Calculator (for ages 12 and older)
Date of Birth (mm/dd/yyyy)

Bilirubin (mg/dl) [INR]
Serum Creatinine (mg/dl)

Had dialysis twice, or 24 hours of CVVHD, within a week prior to the serum creatinine test?
- Yes
- No

For patients who had dialysis twice, or 24 hours of CVVHD, within the last week, the creatinine value will be automatically set to 4 mg/dl.
MELD score

- De-emphasized waiting time
- Focused on disease severity and waiting list mortality risk
- Uses objective parameters

MELD has created an evidence-based gold standard to assess risk equivalency in cirrhosis

Estimated 3-month survival based on MELD score

<table>
<thead>
<tr>
<th>MELD</th>
<th>3-month survival</th>
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<tbody>
<tr>
<td>&lt; 15</td>
<td>92.3%</td>
</tr>
<tr>
<td>15-20</td>
<td>90.7%</td>
</tr>
<tr>
<td>20-29</td>
<td>66%</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>33.8%</td>
</tr>
</tbody>
</table>

Wedd JP and Biggins SW  Clinical Liver Disease 2013; 2(4): 148
Transplant benefit by MELD

MELD < 14
transplant mortality risk↑

MELD ≥ 18
transplant survival benefit↑


MELD exceptions and recent allocation policy changes

- “Milan Stage 2” HCC
  - Patients are granted 22 MELD “exception” points
  - Given a higher priority for transplant
  - Many HCC patients not as sick at time of OLT (may be Child’s A cirrhotic)…often portends a better transplant outcome

- “Share 35 rule”
  - 6/18/13: major change to liver allocation in the US, offering livers first to all candidates in an OPTN region with MELD ≥ 35 before local candidates with MELD < 35

  **IMPACT on OUTCOMES (SRTR 2014)**
  - No change in CIT
  - ↑ transplants MELD ≥ 35, ↓ in transplants MELD 30-34
  - Broader sharing of imports and exports
  - 10% ↓ in adjusted waitlist mortality
  - No change in post-transplant mortality
  - 9% ↓ in overall wait-list mortality
Discrepancy between wait-listed patients and liver transplants

Characteristics of an optimal deceased donor

- Generally young, previously healthy individual
- Developed a fatal brain injury due to head trauma, intracerebral hemorrhage or hypoxia
- Relative paucity of such donors have led transplant centers to consider organs from “extended criteria” donors (previously termed “marginal”)
Factors associated with post-OLT outcome

- **DONOR FACTORS**
  - Advanced donor age (> 60)
  - Donor-recipient sex mismatch
  - Moderate-marked hepatic steatosis (> 40% macrovesicular steatosis)
  - Donor hyponatremia (Na > 155)

- **TECHNICAL FACTORS**
  - Prolonged cold ischemia time (> 12hrs)
  - Donor hemodynamic instability (hypotension/inotropic support)
  - Donor-recipient ABO mismatch

**INNOVATIVE STRATEGIES TO INCREASE AVAILABLE LIVERS**

- Adult living donor LT
- Donation after cardiac death (DCD)
- Use of HCV (+) donors for HCV (+) recipients
- Use of HBSAg (+) donors for HBV (+) and B core (+) recipients
- CDC “high risk” donors
DRI developed to quantify the quality of deceased-donor livers

Inability to compute DRI using back-of-the-envelope calculations: limited its utility for clinical decision-making

Propose an alternative: Donor Quality Score

Study population > 34,000 LT recipients

Most scores fall between 0 and 10

DQS is simpler to calculate, no sacrifice on accuracy and did not lead to a decreased discriminatory power

AASLD Meeting 2013

D-MELD: product of donor age and pre-op MELD

D-MELD cutoff of 1600 to define a subgroup of donor-recipient matches with significantly poorer outcomes

Simple, highly predictive tool for estimating outcomes after OLT
Post-OLT Outcomes: National Benchmarks

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>1 year</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft Survival</td>
<td>96%</td>
<td>88%</td>
<td>77%</td>
</tr>
<tr>
<td>Patient Survival</td>
<td>97%</td>
<td>90.5%</td>
<td>80.6%</td>
</tr>
</tbody>
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Early and long term post OLT complications

- **Allograft Dysfunction**
  - Primary non-function, delayed graft function
  - Biliary complications (leaks/strictures)
  - Vascular complications (venous, arterial, caval)
  - Rejection (acute cellular/chronic)

- **Recurrence of 1° liver disease**
  - Viral (HCV, HBV)
  - Autoimmune (PBC, PSC, AIH)
  - NASH
  - HCC
  - ETOH use

- **Infections**
  - Bacterial
  - De novo viral (EBV, CMV, HSV)
  - Fungal

- **Drug induced hepatotoxicity**
  - Immunosuppressant medications
  - Other drugs

- **Systemic diseases**
  - CV disease, HTN, hyperlipidemia
  - DM, renal dysfunction, obesity
  - Metabolic bone disease

- **Neoplasia**
  - De novo/recurrent
  - Skin (BCC/SCC), lung and oropharyngeal, colorectal
  - EBV-associated PTLD
Post-OLT Hepatitis B

- Hepatitis B cirrhosis OLT recipients enjoy among best outcomes of all groups
- Far easier to prevent and manage HBV recurrence than HCV
- Hepatitis B immune globulin (HBIG) became standard of care in early 1990s
- Late 1990s nucleos(t)ide analogs (NA’s), e.g. lamivudine, introduced
- Currently five FDA-approved NA’s in clinical practice, effective pre-OLT and can be used safely post-OLT
- Many programs use HBIG/NA’s in combination as prophylactic strategy
- Future: HBIG-free regimens using NA’s with a high genetic barrier to resistance, further investigations needed to standardize such protocols

Post-OLT Hepatitis C

- Allograft re-infection due to HCV recurrence is almost universal post OLT
- Accelerated rate of fibrosis progression: 20-54% cirrhotic in 5 years
- Many donor and immunosuppression factors affecting natural history/severity of recurrence
- Treatment: pre-emptive vs waiting for established histologic recurrence
- Historically Peg-IFN/RBV therapy has been ineffective and poorly tolerated (only 25-35% SVR)
- 1st gen. DAA’s (telaprevir/boceprevir): more effective but major d-d interactions with CNI’s
- New DAA’s: minimal s/e’s and toxicities, few d-d interactions: offers hope for more potent and shorter duration post OLT regimens
Prevalence of post OLT complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Acute and chronic rejection</td>
<td>10-15%</td>
</tr>
<tr>
<td>Biliary strictures/leaks</td>
<td>15-20%</td>
</tr>
<tr>
<td>Vascular complications</td>
<td>5%</td>
</tr>
<tr>
<td>Renal dysfunction (pre-dialysis CKD @ 5 years post OLT)</td>
<td>18-27%</td>
</tr>
<tr>
<td>Cardiovascular event rates</td>
<td>9.5% @ 5 yrs, 25% @ 10 yrs</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>70%</td>
</tr>
<tr>
<td>Overt diabetes mellitus</td>
<td>33%</td>
</tr>
<tr>
<td>Obesity</td>
<td>20% lean OLT patients @ 2 years</td>
</tr>
<tr>
<td>Skin cancer (SCC/BCC)</td>
<td>20-70%</td>
</tr>
<tr>
<td>Oropharyngeal Ca</td>
<td>3-14%</td>
</tr>
<tr>
<td>EBV-associated PTLD</td>
<td>2% (in adults)</td>
</tr>
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Reproductive health and QOL

- Menstruation and probability fertility return by 10 months in 90% of premenopausal ♀’s after OLT, in some as early as 1-2 months
- Still regarded as HIGH RISK as pregnancy in the OLT recipient has risks to both mother and fetus
- Higher incidence of prematurity (29-50%) and low birth weight (17-57%)
- NTPR guidelines recommend that ♀ OLT recipients postpone conception until:
  - at least 1 year after OLT
  - allograft function is stable
  - medical comorbidities such as DM and HTN well controlled
  - immunosuppression is at a low maintenance level
  - Mycophenolate mofetil is category D drug (C/I due to first trimester teratogenicity)
- OLT provides an opportunity for improved QOL
- Many patients can return to daily activities and gainful employment
- Meta-analysis of health-related QOL studies after OLT: significant improvement in - physical health, sexual function, daily activities, general QOL and social function, smaller improvements in psychological health

1 Coffin, CS. et.al. Liver Transpl 2010;16:56-63
Thank you for your attention

www.makethemostofyourlife.com