Survival Benefit: Optimal Balance of Sickness and Utility

David Goldberg, MD, MSCE
Associate Professor of Medicine
University of Miami Miller School of Medicine
Disclosures

• Funded by NIDDK R01: DK120561; Using Ethics, Epidemiology and High-Quality Data to Optimize the Allocation of Livers for Transplantation

• Previously funded by NIDDK K08: DK098272; A Population-Based Cohort to Study Outcomes in End-Stage Liver Disease Patients

• Other research support (unrelated to topic): Gilead, Merck, AbbVie
Learning Objectives

• Examine metrics beyond short-term post-transplant survival as a means to define post-transplant success.
• Discuss recent publications exploring alternative measures of post-transplant survival
Personal story

- January 2017 received call from college roommate
- Frustrated was waiting >6 months for a transplant
- MELD score 33 (exceptions) in NYC
  - Frequent admissions for cholangitis
  - Terrible QOL
- Asked how someone could be waitlisted with higher priority
- Said likely people with MELD scores of 34, 35, ... in NYC
- His response, “I am a 37 year-old father of a 1-year old. Doesn’t that matter?”
- My answer: “No, it’s all in the MELD score.”
- His question, “What if the donor is the same age as me, and there’s a 75 year-old with a score of 34, shouldn’t I have higher priority.”
- My answer: “You’re preaching to the choir.”
How should we define success after transplantation?

• Is preventing death on the waitlist enough?
Why do we have to debate this topic?

• 2019 OPTN/UNOS data:
  – 8,765 liver transplants
  – 1,168 waitlisted patients died
  – 1,186 waitlisted patients removed for being “too sick to transplant”

• 5 out of 6 patients who could benefit from a transplant (HCC or decompensated cirrhosis) never waitlisted\(^1,2\)

• Transplant allocation (prioritization) must consider the principles of equality, priority to the worst off, and utility

Background: Principles of organ allocation

• Equality: fair access to transplant for all patients
  – Considering factors such as gender, race/ethnicity, disease etiology
  – Waiting time has been used as an equality metric
    • First come-first served undermined by disparities in access to healthcare (e.g., kidney)

• Urgency-based priority: favoring the ‘worst’ off (‘sickest-first’)
  – Context of transplant → seeks to minimize waitlist mortality

• Utility: maximizing the benefit of transplant
  – Overall survival
  – Net survival benefit
    • Difference of expected pre- and post-transplant survival in years or quality-adjusted life-years

Background: Who are the stakeholders

- Waitlisted patients
  - Don’t want patient to die
  - Want to live a long time
- Patient families
  - Want to see their loved one live
- Donors/donor families
  - Want a live to be saved
  - Want to see good outcome
- Broader population
  - Maximize utilization of a scarce resource
Empiric data on what the public wants

- “Public attitudes towards contemporary issues in liver allocation”¹
- 2 independent surveys
  - 100 online respondents using conjoint analysis
  - 500 online respondents for nonconjoint survey
- Conjoint analysis → respondents valued both posttransplant survival and risk of waitlist mortality
- Comparison of relative weights
  - 18.5% felt that organ should always go to the patient with the higher posttransplant survival
  - 38% felt the organ should always go to the person with the higher waiting list mortality
  - 62% felt posttransplant survival should be considered in allocation decisions

Failure of current sickest-first policy

- Exception system
- Application of MELD score
  - Developed and validated to predict short-term liver-related mortality in “intrinsic renal disease.”\(^1,2\)
  - MELD points for kidney dysfunction only intended for the sickest patients with acute kidney injury (AKI)
  - MELD formula does not distinguish between AKI and CKD
    - AKI in patients with cirrhosis dramatically increases the risk of short-term mortality
    - Elevated creatinine from CKD does not pose same risk of high short-term mortality
  - Creatinine vs eGFR in women

Current failure to consider utility

- MELD score not developed to predict post-LT survival
- Higher MELD scores yield higher waitlist priority but generate lower post-LT survival
- Higher MELD is associated with more post-LT healthcare utilization (hospital days) and costs\(^1,2\)
- AKI vs CKD in the MELD score: CKD increases post-LT mortality by a factor of 2-5\(^3\)

Current failure to consider utility

- Health
  - Substantial resources for post-transplant care
  - Every 1-point increase in MELD = 2.5 fewer days alive outside of the hospital post-transplant

- Increasing MELD score yields increased healthcare costs

What are the implications of focusing on “sickest first” for the individual patient

- **HCC priority**
  - Current allocation system does de...
- ‘**Curable**’
  - Ablation: 5-6 year overall survival: 50-60%
  - Resection: 5-7 year overall survival: 60-70%
  - Transplant: 5-8 year overall survival: 75-80%
- **Gains in overall survival for early stage HCC (MELD<15)**
  - VA population with HCC and MELD<15
  - Time measured from time of diagnosis

What are the implications of focusing on “sickest first” for the broader population

- Thought experiment of deprioritizing HCC patients
- New rule that caps HCC transplants at 50% current level
- Considers key factors
  - Many HCC patients have other options (not as good on an individual level)
  - Patients with decompensated cirrhosis have no other non-transplant options to cure them
- Crude findings over a 5-year time horizon
  - Nearly 15,000 more life-years gained
  - More than 4,500 waitlist deaths averted

### Table 1: Potential impact of changing HCC prioritization*

<table>
<thead>
<tr>
<th>Prioritization system (high HCC priority)</th>
<th>Patient cohort</th>
<th>Number</th>
<th>Estimated 5-year post-LT survival</th>
<th>Aggregate post-LT life-years over 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC with LT</td>
<td>1,857</td>
<td>74.4%</td>
<td></td>
<td>6,908</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>5,138</td>
<td>76.7%</td>
<td></td>
<td>19,704</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>26,612 life-years</strong>† <strong>Waitlist deaths</strong>: 2,438</td>
</tr>
<tr>
<td>Alternative system (HCC patients not advantaged)</td>
<td></td>
<td></td>
<td></td>
<td><strong>29,504 life-years</strong>† <strong>Waitlist deaths</strong>: 1,510</td>
</tr>
<tr>
<td>HCC with LT</td>
<td>929</td>
<td>74.4%</td>
<td></td>
<td>3,454</td>
</tr>
<tr>
<td>HCC with RFA or resection</td>
<td>928</td>
<td>60%</td>
<td></td>
<td>2,786</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>6,066</td>
<td>76.7%</td>
<td></td>
<td>23,265</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>29,504 life-years</strong>† <strong>Waitlist deaths</strong>: 1,510</td>
</tr>
</tbody>
</table>

Abbreviations: HCC=hepatocellular carcinoma; LT=liver transplant; RFA=radio frequency ablation
* Number of transplants based on 2017 data; 5-year survival for LT recipients in MELD era, excluding patients with HCV
† Waitlist deaths=Waitlist removals for death or becoming “too sick to transplant” in 2017
Why survival benefit is best-approach

• Balances urgency ("worst off") with utility
• Utility alone ignores the benefit
  – Compensated cirrhosis: 80% 10-year survival
  – Cirrhosis with ascites: 50% 2-year survival
• Hypothetical example
  – Patient 1: 40 year-old with compensated HCV cirrhosis with SVR
    • Mean predicted survival over 10-year period without transplant: 8 years
    • Mean predicted survival over 10-year period with transplant: 8 years
  – Patient 2: 60 year-old with decompensated PBC cirrhosis with ascites
    • Mean predicted survival over 10-year period without transplant: 2 years
    • Mean predicted survival over 10-year period with transplant: 7 years
Acknowledgments

• R01 Collaborators
  – Penn
    • Peter Reese, MD, MSCE
    • Ezekiel Emanuel, MD, PhD
    • Kimberly Forde, MD, PhD
    • David Kaplan, MD, MS
    • Craig Newcomb, MS
  – University of Miami
    • Alejandro Mantero, PhD
    • Cindy Delgado, BA, MS
    • Nadine Nuchovich, BS, MPH
    • Barbara Dominguez, BS