Using High Risk Donors in Lower Risk Candidates: Practice versus Policy

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Disclosure

No relevant financial disclosures
Learning Objectives

1. Summarize the current evidence behind the utility of transplantation of higher risk donors in lower risk candidates
2. Identify logistical and ethical barriers to using higher risk donors for lower risk candidates
3. Describe a theoretical policy framework to optimize utilization of high risk donors
Organ Shortage

- 11,844 added to the waitlist in 2018
- 12,820 actively listed and awaiting OLT
- Ongoing regional disparities in OLT metrics

Kwong et al. AJT. 2019
Waitlist Outcomes

- Approximately 30% of listed patients are removed from the waitlist due to death or other reasons.

Kwong et al. AJT. 2019
Increase Donor Supply

Consent

Utilization

Living donation
Risk

Risk is ever present in organ transplantation, but are typically outweighed by benefits

- Patient survival and improvement in quality of life
- Secondary gains for the medical system
- Waitlist and post-transplant outcomes
Donor Risk:  
• Infection transmission  
• Malignancies  
• Graft failure  
• Delayed graft function  
• Ischemic cholangiopathy  

Donor Risk (for our purposes):  
• Graft failure  
• Delayed graft function  
• Ischemic cholangiopathy
High risk donor - DRI

- Derived from 20,023 transplants in the pre-MELD era
- 7 donor factors included in the DRI

Table 3: Donor factors significantly associated with liver allograft failure (1998–2002)*

<table>
<thead>
<tr>
<th>Donor parameter</th>
<th>RR</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>1.00</td>
<td>1.00–1.00</td>
<td>0.960</td>
</tr>
<tr>
<td>40–49</td>
<td>1.17</td>
<td>1.08–1.26</td>
<td>0.0002</td>
</tr>
<tr>
<td>50–59</td>
<td>1.32</td>
<td>1.21–1.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>60–69</td>
<td>1.53</td>
<td>1.39–1.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;70</td>
<td>1.65</td>
<td>1.46–1.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>African-American race (vs White)</td>
<td>1.19</td>
<td>1.10–1.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Donor height (per 10 cm decrease)</td>
<td>1.07</td>
<td>1.04–1.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COD = CVA</td>
<td>1.16</td>
<td>1.08–1.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COD = Other†</td>
<td>1.20</td>
<td>1.03–1.40</td>
<td>0.018</td>
</tr>
<tr>
<td>DCD</td>
<td>1.51</td>
<td>1.19–1.91</td>
<td>0.0006</td>
</tr>
<tr>
<td>Partial/Split</td>
<td>1.52</td>
<td>1.27–1.83</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Model also adjusted for donor sex, serum sodium >170 mEq/L, and HbcAb status; recipient age, sex, race, ethnicity, BMI, hepatitis B status, hepatitis C status, CMV status, previous liver transplant, previous abdominal surgery, angina, diabetes, cerebrovascular disease, transfusion at time of listing, SGOT, total bilirubin, albumin, creatinine, dialysis status at time of transplantation, medical condition, Status 1, life support, grade III or IV encephalopathy, inotropic support, portal vein thrombosis, incidental tumor identified during transplantation, ABO compatibility, cold ischemia time, and regional or national sharing.

†Cause of death was not trauma, stroke, or anoxia.

Feng et al. AJT. 2006
## DRI Outcomes

### Table 6: Adjusted 3-month, 1-year and 3-year graft survival according to donor risk index as determined by donor, graft and transplant factors (1998–2002)

<table>
<thead>
<tr>
<th>Donor risk index</th>
<th>N (%)</th>
<th>Graft survival (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 Months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Years</td>
</tr>
<tr>
<td>0.0 &lt; DRI ≤ 1.0</td>
<td>3701 (18.5)</td>
<td>91.9 (91.0–92.7)</td>
</tr>
<tr>
<td>1.0 &lt; DRI ≤ 1.1</td>
<td>2714 (13.6)</td>
<td>90.3 (89.2–91.4)</td>
</tr>
<tr>
<td>1.1 &lt; DRI ≤ 1.2</td>
<td>2272 (11.4)</td>
<td>89.9 (88.7–91.1)</td>
</tr>
<tr>
<td>1.2 &lt; DRI ≤ 1.3</td>
<td>1873 (9.4)</td>
<td>88.5 (87.1–89.9)</td>
</tr>
<tr>
<td>1.3 &lt; DRI ≤ 1.4</td>
<td>1687 (8.4)</td>
<td>88.8 (87.4–90.3)</td>
</tr>
<tr>
<td>1.4 &lt; DRI ≤ 1.5</td>
<td>1625 (8.1)</td>
<td>86.4 (84.8–88.0)</td>
</tr>
<tr>
<td>1.5 &lt; DRI ≤ 1.6</td>
<td>1446 (7.2)</td>
<td>86.3 (84.5–88.0)</td>
</tr>
<tr>
<td>1.6 &lt; DRI ≤ 1.8</td>
<td>2118 (10.6)</td>
<td>84.4 (82.9–85.9)</td>
</tr>
<tr>
<td>1.8 &lt; DRI ≤ 2.0</td>
<td>1343 (6.7)</td>
<td>83.4 (81.4–85.3)</td>
</tr>
<tr>
<td>2.0 &lt; DRI</td>
<td>1244 (6.2)</td>
<td>80.3 (78.1–82.6)</td>
</tr>
</tbody>
</table>
DRI in Practice

• Variation in DRI outcomes by region and center volume
  – Increased competition leads to higher acceptance of DRI organs (range 1.3-1.7)
  – Higher volume centers (>78 transplants yearly) achieve better outcomes with high DRI organs than low volume centers
  – Higher DRI associated with worse outcomes (HR 1.1 for every 0.1 rise in DRI)

Volk et al. AJT. 2011

What is the ideal recipient for a high DRI donor?
Figure 2. Mean DRI of organs transplanted in each of the 3 eras, according to patient MELD scores.

Figure 3. Survival curves for patients with MELD scores less than 20, transplanted during the pre-MELD era (—) vs the post-MELD era (— —).
Highest DRI

Schaubel et al. AJT. 2008
Lowest DRI

Schaubel et al. AJT. 2008
## DRI in 2020

### DRI Limitations

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Changing epidemiology of liver disease</strong></td>
<td>↓HCV ↑Metabolic/Alcohol related liver disease</td>
</tr>
<tr>
<td><strong>Changing epidemiology of donor population</strong></td>
<td>↑Obesity</td>
</tr>
<tr>
<td><strong>Changing allocation schema</strong></td>
<td>↑Cold ischemia time</td>
</tr>
<tr>
<td><strong>Advances in procurement</strong></td>
<td>↑Utilization of marginal livers</td>
</tr>
</tbody>
</table>
Contemporary Models

- Single center study of 960 marginal grafts
- Included national share, CIT, and steatosis

TABLE 1. Characteristics of Marginal Liver Grafts Used in Our Entire Patient Cohort Showing the Largest 2 Groups Used are Discarded Organs and Elderly Grafts

<table>
<thead>
<tr>
<th>Marginal Liver Type</th>
<th>n (% of Total ML Grafts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discarded livers</td>
<td>649 (67.6)</td>
</tr>
<tr>
<td>Donor age &gt;70</td>
<td>219 (22.8)</td>
</tr>
<tr>
<td>HCV positive donor</td>
<td>150 (15.6)</td>
</tr>
<tr>
<td>Split liver</td>
<td>101 (10.5)</td>
</tr>
<tr>
<td>CIT &gt;12 h</td>
<td>72 (7.5)</td>
</tr>
<tr>
<td>DCD livers</td>
<td>44 (4.6)</td>
</tr>
<tr>
<td>Macrosteatosis &gt;30%</td>
<td>37 (3.8)</td>
</tr>
<tr>
<td>&gt;One ML factor</td>
<td>276 (28.8)</td>
</tr>
</tbody>
</table>

FIGURE 1. Unadjusted patient survival for 2050 patient transplanted at NYP by graft type showing no significant difference between marginal liver grafts (ML grafts) and standard liver grafts (SL grafts), $p = 0.08$.

FIGURE 5. Competing risk regression analysis showing decreased cumulative incidence of waitlist deaths at our center versus national centers.
Recipient Risk

Stratifying Recipient Risk

- MELD-NA score
- Surgical complexity
- Age
- Comorbid conditions

Objective
Subjective
Nagai et al. Gastroenterology. 2018

Removals due to death or medical deterioration
<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator support</td>
<td>1.68</td>
<td>1.57–1.79</td>
<td>&lt;0.0001</td>
<td>1.59</td>
<td>1.48–1.72</td>
<td>&lt;0.0001</td>
<td>5</td>
</tr>
<tr>
<td>Recipient age &gt;60</td>
<td>1.30</td>
<td>1.23–1.36</td>
<td>&lt;0.0001</td>
<td>1.29</td>
<td>1.23–1.36</td>
<td>&lt;0.0001</td>
<td>3</td>
</tr>
<tr>
<td>Recipient age &gt;50</td>
<td>1.17</td>
<td>1.11–1.22</td>
<td>&lt;0.0001</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Preoperative dialysis</td>
<td>1.43</td>
<td>1.33–1.54</td>
<td>&lt;0.0001</td>
<td>1.26</td>
<td>1.16–1.37</td>
<td>&lt;0.0001</td>
<td>3</td>
</tr>
<tr>
<td>Preoperative diabetes</td>
<td>1.24</td>
<td>1.17–1.31</td>
<td>&lt;0.0001</td>
<td>1.20</td>
<td>1.14–1.27</td>
<td>&lt;0.0001</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine preoperative ≥1.5</td>
<td>1.27</td>
<td>1.21–1.34</td>
<td>&lt;0.0001</td>
<td>1.15</td>
<td>1.09–1.22</td>
<td>0.0167</td>
<td>2</td>
</tr>
<tr>
<td>Pre-operative hypertension</td>
<td>1.09</td>
<td>1.03–1.16</td>
<td>0.0034</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Body mass index ≥30</td>
<td>1.02</td>
<td>0.98–1.70</td>
<td>&lt;0.0001</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Body mass index ≥35</td>
<td>1.07</td>
<td>1.10–1.14</td>
<td>0.0510</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Albumin preoperative ≥2.5</td>
<td>0.95</td>
<td>0.90–1.00</td>
<td>0.0534</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Intensive care unit stay</td>
<td>1.48</td>
<td>1.40–1.57</td>
<td>&lt;0.0001</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MELD score &gt;26</td>
<td>1.15</td>
<td>1.10–1.21</td>
<td>&lt;0.0001</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MELD score &gt;31</td>
<td>1.20</td>
<td>1.13–1.27</td>
<td>&lt;0.0001</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>1.26</td>
<td>1.12–1.42</td>
<td>0.0582</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

HR, hazard ratio; MELD, model for end-stage liver disease.
1 Proportional Hazards Modeling: HR, 95% CIs and p values. HR and CI calculations were calculated for presence of the stated attribute.
A significant difference in patient survival probability was observed across different points categories, as indicated by the log-rank test, with a p-value less than 0.01. The graph shows the survival probability over months after transplantation for patients with points categories 0-4, 5-8, and >8. The number of patients at risk for each category at various months after transplantation is as follows:

For points 0-4:
- 0 months: 23,305
- 12 months: 18,908
- 24 months: 16,399
- 36 months: 14,337
- 48 months: 12,472
- 60 months: 10,698

For points 5-8:
- 0 months: 7,717
- 12 months: 5,674
- 24 months: 4,691
- 36 months: 3,922
- 48 months: 3,330
- 60 months: 2,772

For points >8:
- 0 months: 807
- 12 months: 500
- 24 months: 368
- 36 months: 290
- 48 months: 239
- 60 months: 192
Fig. 3. Graft survival within five years among non-HCV recipients stratified by points based on donor characteristics. Suboptimal donor: DRI > 1.7. *Similar findings if consider donor age > 40 yrs., CIT > 10 and DCD. CIT, cold ischemia time; DCD, donor after cardiac death; DRI, donor risk index. Log rank test, \( p < 0.01 \).
Transplantation by donor-recipient risk

• High risk donors are associated with worse outcomes even in low risk recipients
  – With limited resources what risk can we accept?
• Metric for risk acceptance
  – Graft survival, patient survival, survival benefit, quality of life

Could a policy framework around donor risk help?
Benefits of an objective framework

- Allows for improved utilization of higher risk organs
- Increase transplant access at a lower MELD
- Allows for continual evaluation and calibration of policy
Downsides

- Low risk recipients may suffer harm
- Poorly defined donor and recipient risk
- Additional burden on centers when evaluating/accepting a potential donor
Logistical Challenges

- Wider allocation circles (or other policy changes) may increase risk of high risk donors
- May require adding patient decision making into the organ acceptance process
- To do well, have to really know waitlist patients
Ethical Challenges

- Will eligible recipients be passed over?
- Will patients who derive a marginal benefit from OLT be transplanted?
- Can patients be adequately informed of the risk with higher risk donors?
Outcomes in a Policy Framework

• Survival outcomes are traditionally used
  – Survival benefit integrated in several analyses

• Quality of life or correlates (ascites, encephalopathy)

• Other: Costs, healthcare utilization
Policy Framework

• Definition of donor risk metrics
• Definition of a low risk recipient
  – Possible alternate allocation for low risk recipients
• Acceptable outcome parameters

Less stringent outcomes based assessment in using these higher risk donors?
Calibration

• Policy adjustments based on results
  – Organ utilization
  – Recipient outcomes
  – Waitlist outcomes

• Adjustment of risk parameters for donors and recipients
Summary

• Increased utilization of high risk donors would result in increased number of donors but at increased recipient risk

• A policy framework would formalize recipient donor risk management and allow for innovation in OLT

• Better risk stratification strategies are needed to quantify risk and benefit
Thank you