Utility of Marginal Donors in Liver Transplantation

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Contents

- Review of Liver Transplantation (LT) Data
- Marginal Donors in LT
- Steatosis
- Small-for-Size (SFS) Graft
Deceased & Living Donors
1993 – 2002, UNOS

Number of Donors

Year


Deceased Donor
Living Donor

0 1,000 2,000 3,000 4,000 5,000 6,000 7,000

Number of Donor
Waiting List at 1993-2002

UNOS

Number of Registrations

Year


Kidney Liver

SMC
## Deaths on the Waiting List
### 2000, 2001, 2002

<table>
<thead>
<tr>
<th>Organ Type</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>3001</td>
<td>3119</td>
<td>3171</td>
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<tr>
<td>Pancreas</td>
<td>15</td>
<td>40</td>
<td>27</td>
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<tr>
<td>Kidney-Pancreas*</td>
<td>193</td>
<td>221</td>
<td>201</td>
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<tr>
<td>Liver</td>
<td>1784</td>
<td>2012</td>
<td>1756</td>
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<tr>
<td>Intestine*</td>
<td>23</td>
<td>45</td>
<td>52</td>
</tr>
<tr>
<td>Heart</td>
<td>617</td>
<td>637</td>
<td>552</td>
</tr>
<tr>
<td>Lung</td>
<td>492</td>
<td>491</td>
<td>468</td>
</tr>
<tr>
<td>Heart-Lung</td>
<td>43</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>Total *</td>
<td>6054</td>
<td>6455</td>
<td>6077</td>
</tr>
</tbody>
</table>

* Total Unique Patient Deaths
Waiting list in LT, KONOS
Deceased donors in LT

KONOS

- Deceased
- DDLT
- Discard

2000: 34.4% 34.4% 13.8%
2001: 34.4% 34.4% 13.8%
2002: 34.4% 34.4% 13.8%
2003: 13.8%
Deceased and living donors in LT

KONOS

![Graph showing the number of deceased and living donors in LT over the years 2000 to 2003. The graph indicates a steady increase in the number of living donors from 2000 to 2003, while the number of deceased donors remains relatively stable.](image-url)
Liver Transplantation in SMC

Organ Transplantation Center (OTC)

![Graph showing liver transplant data from 1996 to 2003.]
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Ideal Graft in LT

- Deceased donor
- Young adult age
- Enough graft size
- No steatosis
What is the definition of marginal liver donors?

Donor with Potential Risk Factor

- initial poor function (IPF) or primary nonfunction (PNF)
- Increasing age
- Prolonged ischemia
- Hypotension
- Inotrop ic support
- Steatosis
- Partial grafts
- Gender mismatch
- Non-heart beating donors (NHBD)
The limits of donor age

- Donor age of more than 70 years
  - Associated with lower patient and graft survival

Morphologic changes
- Smaller and darker-colored
- Fibrous thickening of capsule

Endothelial cell injury during CIT
- Decreased ATP synthesis after reperfusion
Donor Age

UNOS
Donor age in LT

SMC OTC

~ 29 30~ 39 40~ 49 50~
Prolonged Cold Ischemia Time (CIT)

- Independent risk factor for liver preservation injury
- More than 14 hours: associated with a two-fold increase in preservation damage

- Prolonged postoperative course
- Biliary stricture
- Decreased graft survival
**Prolonged CIT**

- Sinusoidal cell damage & Hypercoaguability
- Metabolic activity 10-fold ↓
- Anaerobic metabolism and lactic acidosis ↑

- Decrease of ATP & hypoxanthine
- Increase of reactive oxygen species

**Ischemia-reperfusion (IR) injury**
Reperfusion – insult on transplant liver

- Endothelial / Kupffer cell swelling
- Vasoconstriction
- Leukocyte entrapment
- Platelet aggregation within sinusoids

interactions between different complex mechanisms

Failure of Microcirculation
Endothelial & Kupffer Cell Swelling

Failure of active transmembrane transport

Intracellular edema
Vasoconstriction

Ischemia Reperfusion

Imbalance between nitric oxide (NO) and endothelin (ET)
1st Step of IR injury

- Liberation of endothelin-1 (ET-1)
  - Activation of Ito cells
  - Constriction of hepatic sinusoids

- Activation of Kupffer cells
  - Release of oxygen derived free radicals (ODFR)

Reduced blood flow
1st Step of IR injury

Hepatic Ischemia Reperfusion Injury

- TISSUE INJURY
  - Platelet Aggregation
  - SEC Apoptosis
- IL-1, IL-8, TNF, PAF, GXC chemokines
- Neutrophils
- Adhesion molecules
- ROI
- Endothelial Cells
- Hepatocytes

Hypoxia → Reduced Blood Flow

Kupffer cell → ET-1
2nd Step of IR injury

- Up-regulation of adhesion molecules
  - Activation of adhesion molecules (i.e., selectins, integrins & Ig)
  - Liberation of chemokines from Kupffer cells
  - Rolling and sticking Neutrophils to endothelial cells

- Platelet aggregation
- Sinusoidal endothelial cell (SEC) apoptosis

Tissue injury
2nd Step of IR injury
Prevention of Preservation Injury

- Allows extended ischemia and rewarming times
- Preventing organ damage during CIT
  - Prolonged storage

- University of Wisconsin (UW) solution
- Histidine-tryptophan-ketoglutarate (HTK) or Bretschneider solution
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What is the role of Steatosis?

- Macrosteatosis: macrovesicular fatty change
- Microsteatosis: small vacuole deposits
- Increase in cell volume: obstruction of hepatic sinusoidal space

1% of steatosis* functional graft mass by 1%

* Marcos et al, Transpl 2000
Impact of Steatosis on Graft Outcome

Steatosis

- Mild (<30%)
  - good result
- Severe (>60%)
  - Primary nonfunction
  - Early poor graft function
  - Graft Failure
Degree of Steatosis Acceptable for LDLT

- Microsteatosis: less injury and graft survival rates similar to normal livers
- Macrosteatosis (<30%): can be used
- Moderate macrosteatosis (<50%): could be used, if GV-to-SLV is more than 40%
Accurate Detection of Steatosis

- Preoperative liver biopsy: standard method
  - Imaging studies: fatty infiltration findings
  - BMI (predictor of steatosis) > 25
Photographs of Moderate Steatosis

- Macrovesicular steatosis: 5%
- Microvesicular steatosis: 20%
Photographs of Severe Steatosis

- Macroscale steatosis: 20%
- Microscale steatosis: 50%
**Approach to Donors with Steatosis**

- **Recommendation**
  - Low calorie diet (25-30 Cal x ideal body weight (kg) per day)
  - Aerobic exercise
  - Abstinence from alcohol

**Overcome of Donor Shortage**
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**Optimal graft size in LT**

- Standard liver volume (SLV) or Estimated standard liver weight (ESLW)
  - Liver volume optimal for the recipient’s metabolic demands

- formula *
  - \( SLV(\text{ml}) = 706.2 \times BSA (\text{m}^2) + 2.4 \)

* Urata et al, Hepatology 1995
Preoperative evaluation of liver volume

- Liver CT (7.5mm slices)
  - RLV (ml):
    - Sum of Areas x thickness (7.5)

- Graft-to-recipient’s weight ratio (GRWR)
- Graft volume to recipient’s SLV (GV/SLV)
**Volumetry Example**

- **Standard liver volume (SLV) of recipient**
  \[ = 706.2 \times \text{(BSA)} + 2.4 = 1204 \text{ cm}^3 \]

<table>
<thead>
<tr>
<th></th>
<th>Donor*</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume</td>
<td>%</td>
</tr>
<tr>
<td>Whole liver</td>
<td>1167 cm³</td>
<td></td>
</tr>
<tr>
<td>Right lobe (excluding MHV)</td>
<td>705 cm³</td>
<td>60.4%</td>
</tr>
<tr>
<td>Left lobe (excluding MHV)</td>
<td>431 cm³</td>
<td>36.9%</td>
</tr>
</tbody>
</table>

*CT volumetry
What is the most important thing in LDLT

Donor safety

Large-for-size

- Primary nonfunction
- Early poor graft function
- Risk of rejection↑

Small-for-size

- Hepatic artery thrombosis
- Portal vein thrombosis

Graft Failure
Minimum Graft Size (?)

- Lo et al*, 40% or less of GV/SLV
- Kiuchi et al**, less than 1% of GRWR
- Kawasaki et al#, 30-40% of SLV or 0.8~1.0% of GRWR

Lower graft survival

* Lo et al, Transplantation 1996
** Kiuchi et al, Transplantion 1999
Graft Survival
According to GRWR : 1.0, OTC in SMC

* From June 1997 to June 2002, 79 patients received adult LDLT
Graft Survival
According to GRWR : 0.9, OTC in SMC

* From June 1997 to June 2002, 79 patients received adult LDLT
Graft Survival
According to GRWR : 0.8, OTC in SMC

* From June 1997 to June 2002, 79 patients received adult LDLT
Marginal- or Small-for-size grafts

- Graft weight: less than 30% of SLV or 0.8% of GRWR

- Kiuchi: 28% GW of recipient SLV, successful transplantation - primary biliary cirrhosis

- Lo: 25% GW of recipient SLV, successful transplantation – fulminant hepatic failure biliary cirrhosis
Small-For-Size (SFS) syndrome

- Graft weight: less than 30% of SLV or 0.8% of GRWR
- Graft weight, greater than 40% of SLV or 1.0% of GRWR; associated with severe portal hypertension or relative impedance to hepatic venous drainage

- Poor bile production
- Delayed synthetic function; coagulopathy
- Prolonged cholestasis
- Intractable ascites
Mechanism of SFS syndrome

- Graft inflow: portal venous flow (PVF)
- PVF increase
  - high cardiac output
  - low peripheral vascular resistance
  - reduced hepatic arterial flow
Mechanism of SFS syndrome

Main factors

- Persistent portal hypertension
- Portal venous hyperperfusion
- SFSS
- Reduced hepatic arterial flow

Preoperative conditions (UNOS status, ascites, bilirunin↑)
- Small functional graft mass
- Postoperative variables (sepsis, bile leak, renal failure)
Histologic changes of graft in SFSS

- Hepatocyte ballooning
- Centrolobular necrosis: Reversible change
- Parenchymal cholestasis

- Graft regeneration: not affected
Prevention of SFS syndrome

- Hepatic venous drainage (S5,S8)- Rt lobe graft
- Extended right-lobe graft including MHV
- Dual left lobe graft
- Auxiliary Partial Orthotopic transplantation
- Splenic artery ligation
- Portosystemic shunt
Hepatic venous drainage
- Rt lobe graft

- Hepatic venous drainage: S5, S8, RIHV
Extended right-lobes graft including MHV

- Increased risk of donor safety
- Extremely limited
Dual left lobe graft

Left lobe grafts from two donors

Lee et al, Surgery 2001
Auxiliary Partial Orthotopic Liver Transplantation (APOLT)

- Concept: native liver support graft function
- Fulminant hepatic failure, metabolic disorders
- Inomata et al, 20 recipients
  - Aid for a SFS graft

Inomata et al, Transplantation 1999
APOLT in SMC

- 29/ F(168 cm, 56kg), fulminant hepatitis; Lt hemihepatectomy
- Donor: 21/M, her brother, extend left lateral segment; 259 gm GRWR: 0.46%
Management of Portal Hyperperfusion

- SFS (GRWR<0.8%), associated with excessive PVF (>250 ml/min/100 gm GW)
  - Poor graft survival

- Splenic artery ligation (Troisi et al)
  - to resolve ascites
  - to increase HAF
  - to prevent thrombocytopenia

Troisi et al, Ann Surg 2003
Management of Portal Hypertension

- Portosystemic shunt; RPV – IVC (end-to-side)
  - Nishizaki et al; taken down after reperfusion
  - Takada et al; sustained opening ➔ portal hypoperfusion / hyperammonemia
Experimental studies for the manipulation of marginal donors

- Failure of active transmembrane transport
- Conversion of adenosine to inosine by adenosine deaminase
- Decreased NO production as a result of decreased cofactors (O₂ + NADPH) essential for its formation.
- Exogenous adenosine or augmentation of endogenous adenosine
- Increasing NO Availability, by using either an NO precursor (such as L-arginine) or an NO donor (such as FK409)
- NO REFLOW
  - Endothelial and Kupffer cell swelling
  - Vasoconstriction and stellate cell contraction

- Bosentan (an ET receptor antagonist)
- Increased ET production as a result of ischemia
Upregulation of Heme Oxygenase System

- Heme Oxygenase-1 (HO-1): hsp32, potent cytoprotective effects
Conclusions

- We should try and develop various clinical or experimental modalities that can be manage marginal donors.