Liver Transplantation for Alcoholic Liver Disease: Adequate Timing and Clinical Outcome

Gi-Won Song

Department of Surgery, Division of Hepatobiliary Surgery and Liver Transplantation, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Korea
DDLT for ALD in Western countries

- Generally not accepted until late 1980’s
  → Fairness and efficacy of deceased organ allocation

- Thereafter, accepted as good indication
  - Strong evidence for genetic and environmental influence on ALD
    → Amelioration of ethical culpability
  - Low relapse rate after patient selection
    → Enhancement of LT efficacy

- Survival of DDLT for ALD is comparable to other indications.
ALD is 2nd Common Indication for Liver Transplantation

European Liver Transplant Registry (2008)

1 Viral + alcoholic 1759 (4%)
2 Autoimmune 1786 (5%)
3 Secondary biliary 495 (1%)
4 Unknown causes 3274 (8%)
5 Primary biliary 4277 (10%)
6 Others 531 (1%)
7 Virus related 15936 (38%)
8 Alcoholic 13638 (33%)
ALD is 2nd Common Indication for Liver Transplantation

UNOS (2009)

1 Cryptogenic 8140 (8%)
2 Cong cholestasis 5261 (5%)
3 Metabolic dis 3967 (4%)
4 Others 17384 (18%)
5 Alcoholic 11641 (12%)
6 Alcoholic + HCV 4946 (5%)
7 Viral 24762 (25%)
8 PSC 5918 (6%)
9 PBC 4932 (5%)
10 Autoimmune 3314 (3%)
11 Sec biliary 586 (1%)
12 Malignancy 8360 (8%)
Lower possibility of DDLT for ALD in Korea

- Relatively small number of deceased organ donors

- Higher proportion of DDLT allocation to urgency: 60% → UNOS status 1 or 2A

- Poor socio-economic condition of ALD patients
LDLT accounted for 76.5% of all LT in Korea.
### 4,000 Liver Transplantations in Asan Medical Center

(1992 Aug~2013 Nov)

<table>
<thead>
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<tbody>
<tr>
<td>DDLT</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>10</td>
<td>16</td>
<td>30</td>
<td>15</td>
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<td>50</td>
<td>86</td>
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<td>612</td>
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<tr>
<td>LDLT</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td>25</td>
<td>33</td>
<td>82</td>
<td>105</td>
<td>123</td>
<td>137</td>
<td>152</td>
<td>210</td>
<td>214</td>
<td>234</td>
<td>286</td>
<td>262</td>
<td>292</td>
<td>317</td>
<td>317</td>
<td>320</td>
<td>263</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>4</td>
<td>8</td>
<td>9</td>
<td>19</td>
<td>49</td>
<td>112</td>
<td>120</td>
<td>134</td>
<td>141</td>
<td>172</td>
<td>230</td>
<td>235</td>
<td>257</td>
<td>320</td>
<td>326</td>
<td>345</td>
<td>367</td>
<td>403</td>
<td>379</td>
<td>332</td>
<td>4000</td>
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</table>

**LDLT occupies 84.7% of all LTs**
Original Disease of Adult LDLT at AMC

(Febrary 1997~August 2013)
2784 Adult LDLTs

- **HBV (N=1886, 75.4%)**
- **FHF (N=167, 6.7%)**
  - Toxic 105
  - HBV 36
  - HAV 20
  - Unknown cause 3
  - EBV 1
  - CMV 1
  - Autoimmune 1
- **ALC (N=155, 6.2%)**
- **HCV (N=113, 4.5%)**
- **BC (N=62, 2.5%)**
  - SBC 32
  - PBC 25
  - PSC 5
- **Cryptogenic LC (N=56, 2.1%)**
- **Combined Viral (N=18, 0.7%)**
  - HBV-HCV 16
  - HBV-HAV 2
- **Autoimmune hepatitis (N=18, 0.7%)**
- **Etc. (N=25, 1.0%)**
  - Budd-Chiari 7
  - PCLD 6
  - Wilson 2
  - Re-TPL 2
  - PFIC 1
  - K-Trm 1
  - Hepatic TBc. 1
  - Portal biliopathy 1
  - Citrullemia type III 1
  - CCC 1
  - CRC liver metastasis 1
  - Glycogen storage ds. 1

- **TMC: HBV-LC (75.4%)**
- **HCC (+) in 1227 pts. (44.1%)**
Change of Trend in Original Disease for Adult LDLT at AMC

1st 1000 Cases
- HBV(81%)
- Alcohol(2.9%)
- HCV(3.3%)
- ALF(4.7%)

1001-2000 Cases
- HBV(73%)
- Alcohol(6.1%)
- HCV(5.2%)
- ALF(8%)

2001-2784 Cases
- HBV(67%)
- Alcohol(11.6%)
- HCV(6%)
- ALF(3.9%)

Current Status of Alcohol Consumption at Korea

From 한국인 간질환 백서 2013 대한간학회
Pattern of Alcohol Consumption at Korea

From 한국인 간질환 백서 2013 대한간학회
Alcohol-related Liver Disease at Korea

세부 상병별 알코올 간질환의 진료환자 수 – 남자
(전체 127,467 명)

세부 상병별 알코올 간질환의 진료환자 수 – 여자
(전체 19,856 명)

From 한국인 간질환 백서 2013 대한간학회
Natural Course of Alcohol-related Liver Disease

Heavy ALC Intake

>90%

Hepatic Steatosis

~30%

Hepatic Cirrhosis

8~20%

HCC(+)

3~10%

Alcoholic Hepatitis

10~20%
LT for Alcohol-related Liver Disease

- **Alcoholic Hepatitis**
  - Mortality s Tx ~50%
  - 6-month mortality 30% (unresponsive to steroid Tx)

- **Decompensated Alc LC**
  - Annual mortality > 10%

- **Alc LC + HCC**
  - Unresectable/Within Criteria

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Liver Transplantation
In-Hospital Mortality Rate in Adult LDLT at AMC

$\frac{154}{2547} = 6.0\%$
Overall Cumulative Patient Survival of LT at Asan Medical Center

<table>
<thead>
<tr>
<th>Survival Period (month)</th>
<th>PED LT</th>
<th>Adult DDLT</th>
<th>Adult LDLT</th>
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<tbody>
<tr>
<td>1/3/5/10-YSR</td>
<td>90.7/88.6/86.5/85.5%</td>
<td>75.4/70.7/67.1/62.0%</td>
<td>90.4/84.2/82.8/78.7%</td>
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P=0.02

Overall Cumulative Patient Survival of LT at Asan Medical Center
# Living Donor Complication Rate

## No Donor Mortality

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Right Liver n</th>
<th>Complication Rate</th>
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<tbody>
<tr>
<td>1997–2001</td>
<td>215</td>
<td>10.7%*</td>
</tr>
<tr>
<td>2001–2005</td>
<td>454</td>
<td>2.0%</td>
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<tr>
<td>2005–2013</td>
<td>2116</td>
<td>1.5%</td>
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</table>

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Left Liver n</th>
<th>Complication Rate</th>
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</thead>
<tbody>
<tr>
<td>1997–2001</td>
<td>113</td>
<td>2.6%</td>
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<tr>
<td>2001–2005</td>
<td>374</td>
<td>1.1%</td>
</tr>
<tr>
<td>2005–2013</td>
<td>513</td>
<td>1.2%</td>
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</table>
Special Issues in LT for ALD

Consideration for Medical Issues in ALD

Pre-Transplant Abstinence
Post-Transplant Recidivism

Long-term Survival Outcome of LT for ALD
Special Issues in LT for ALD

Consideration for Medical Issues in ALD

Evaluation and Preparation for LT in ALD Pt

Multidisciplinary Approach

- General Medical
- Psychosocial
- Neurological
# Special Issues in LT for ALD

## Consideration for Medical Issues in ALD

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<tr>
<th>General</th>
<th>Musculoskeletal</th>
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<td>Myopathy</td>
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<td>Vitamin D deficiency</td>
<td>Osteopenia</td>
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<tr>
<td>Anemia</td>
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<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Psychiatric</th>
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<tbody>
<tr>
<td>Alcoholic dementia</td>
<td>Mood disorders</td>
</tr>
<tr>
<td>Wernicke EP</td>
<td>Personality disorders</td>
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<tr>
<td>Peripheral NP</td>
<td>Anxiety disorders</td>
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<td></td>
<td>Psychosis</td>
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<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Gastrointestinal</th>
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<tbody>
<tr>
<td>Alcoholic CMP</td>
<td>Chronic pancreatitis</td>
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<tr>
<td>Cirrhotic CMP</td>
<td>Malignancy</td>
</tr>
<tr>
<td>CAD</td>
<td>Viral hepatitis</td>
</tr>
</tbody>
</table>
Special Issues in LT for ALD

Pre-TPL Abstinence & Post-TPL Recidivism

Recidivism

- Short-term incidence of recidivism: 5~15%
- Cumulative incidence: 30~50%
- Non-compliance (IS drug/Clinic visit/Follow-up exam)
  Graft injury (ETOH toxicity/Rejection)

- Can be considered as a reason for transplant units and public opinion to deny transplantation
Liver transplantation in patients with alcoholic cirrhosis: selection criteria and rates of survival and relapse

George L A Bird, John G O’Grady, Felicity A H Harvey, Roy Y Calne, Roger Williams

**Design**—Nine year retrospective study.

**Setting**—Cambridge and King’s College Hospital liver transplant programme.

**Subjects**—24 Patients (three women, 21 men) with alcoholic cirrhosis.

Our results suggest that liver transplantation should not be considered as a treatment for alcohol dependence in itself, and the criteria for selecting patients under normal circumstances should include a period of abstinence of at least six months in addition to an assessment of alcohol dependence. With the availability of organs likely to become an increasingly limiting factor as the number of liver transplant operations performed increases, such a policy would also be more likely to be acceptable to the general public and to the families granting permission for organ donation.

Incidence of Recidivism: 16.6%

6-Month Rule
Orthotopic Liver Transplantation for Alcoholic Liver Disease


From July 1982 to April 1988
73 ALD Pts. at Pittsburgh’s Univ.

Incidence of Recidivism: 11.5%

Most liver transplantation centers have set an arbitrary period of abstinence, usually as a requirement before an alcoholic patient can be a candidate for transplantation. Although abstinence is clearly of value in arresting alcoholic liver disease that is not end-stage, the benefit of alcohol abstinence before transplantation is undocumented. Contrary to the logical expectation that abstinence before transplantation would improve outcome, this study does not demonstrate a statistically significant difference between the survival of transplant recipients who abstained from alcohol for at least 6 mo before the transplantation and those who did not (Table 2). It is interesting to note, however, that alcohol consumption in the immediate pretransplantation period did predict postoperative recidivism.
6-Month Abstinence Rule is Minimal Prerequisite for the Prevention of Post-TPL Recidivism?

**Pro: 6-Month Rule**


**Con: 6-Month Rule**


Liver Transplantation for ALD in DDLT Setting

In DDLT, organs are considered to be a public resource that should be shared fairly and effectively.

In US, 85% of transplant programs require a minimum of 6-month abstinence before TPL.


Monitoring:
collateral history
random blood alc. level
Documented sobriety

Relapse (+)
In 97% of centers, remove pt. from list for 3~6 months
In 15%, remove permanently
Data on the accuracy of 6–mo pre–transplant abstinence in predicting recidivism are scanty and controversial.

In 22 studies reporting predictors of recidivism, only 2 of the 11 studies evaluating 6–month abstinence reported it to be an accurate predictor of recidivism.

Social and family support/
Preexisting psychiatric comorbidities/
Poly–substance use/Unsuccessful rehabilitation
Younger age at LT/Family hx. of alcoholism
In LDLT, healthy relatives donate their organs to the patients. The conditions for alcohol relapse may be different after LDLT versus DDLT.

Preoperative alcohol consumption was not a risk factor.

In conclusion, rather than selecting patients on the basis of preoperative alcohol use, we should provide sociomedical support to improve adherence after LT for ALC in Japan.
Experience of LT for ALD at AMC

Among 210 LTs for ALD patients from Jan 2005 to Dec 2012, 190 cases were analyzed. (excluding IHM)

Recipient

- Mean Age: 51.7 ± 8.2 yrs. (31~69)
- Gender Ratio (M/F): 169 (88.9%)/21

Donor Type

- Deceased, 31 (16.3%)
- Living, 159 (83.7%)

Pre-LT Condition

- Mean MELD Score 21.0 ± 9.8

HCC (+) N=32 (16.8%)
Experience of LT for ALD at AMC

Recidivism

- Mean Follow-up Period: 47.6 ± 8.2 months (4.3~114.2)

Questionnaire Survey: Direct survey at OPD/Tele research
From patient/Collateral

Harmful Drinking
1. Relapse within 6 months after LT
2. ≥ 4 times/week
3. ≥ 72gm/d (male) or 48gm/d (female)

- Mean Interval: 22.1 ± 16.4 months (1.0~65.0)

No
70%

Yes
30%

- Slip
- Harmful Drinking
N=26 (46%)
N=31 (54%)
Experience of LT for ALD at AMC

Risk Factor Analysis for Recidivism

- **Gender**
  - Male: 29.6%
  - Female: 26.9%
  - P-value: 0.801

- **MELD**
  - <20: 33.7%
  - ≥20: 26.1%
  - P-value: 0.271

- **Age**
  - <50: 29.9%
  - ≥50: 30.1%
  - P-value: 0.555
Son & Daughter: 43.2%
Parent: 0.6%
Sibling: 14.7%
Spouse: 7.6%
Nephew & Niece: 12.9%
Cousin: 3.4%
Uncle & Aunt: 0.6%
Grandson: 0.4%
Son- & Daughter-in-law: 3.2%
Beyond 4th consanguinity: 3.3%
Unrelated: 10.1%
Experience of LT for ALD at AMC

Risk Factor Analysis for Recidivism

Incidence of Recidivism (%)

<table>
<thead>
<tr>
<th>Donor Type</th>
<th>Living</th>
<th>Deceased</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30.8</td>
<td>25.8</td>
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P = 0.672

Incidence of Recidivism (%)

<table>
<thead>
<tr>
<th>Relation</th>
<th>Son/Daughter</th>
<th>Spouse</th>
<th>Sibling</th>
<th>Other Living</th>
<th>Deceased</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>32.2</td>
<td>40.0</td>
<td>25.0</td>
<td>25.0</td>
<td>25.8</td>
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P = 0.864
Experience of LT for ALD at AMC

Risk Factor Analysis for Recidivism

<table>
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<th>Incidence of Recidivism (%)</th>
<th>Pre-LT Abstinence</th>
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<tbody>
<tr>
<td>&lt;1 month</td>
<td>37.5</td>
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<tr>
<td>≥1 month</td>
<td>29.3</td>
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P = 0.570

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<th>Incidence of Recidivism (%)</th>
<th>Pre-LT Abstinence</th>
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<tbody>
<tr>
<td>&lt;6 month</td>
<td>33.7</td>
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<tr>
<td>≥6 month</td>
<td>26.7</td>
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P = 0.412
Experience of LT for ALD at AMC

Risk Factor Analysis for Recidivism

Incidence of Harmful Drinking

Pre-LT Abstinence

Incidence of Recidivism (%)

P=0.342

34.5

23.8

<1 year

≥1 year

Incidence of Recidivism (%)

P=0.031

19.1

6.3

<1 year

≥1 year

Pre-LT Abstinence
Survival Outcome of LT for ALD

- Worldwide report about survival rate of LT for ALD: 81~92%/78–86%/73~86% (1–/3–/5–year patient survival rate)
- No difference compared to LT for non-alc cirrhosis
- Improvement of QOL, mood status and cognitive function

- Special concern:
  1. Co-infection of HCV/HIV
  2. Substance abuse
  3. Recidivism (especially harmful drinking)
Long-term survival after DDLT for ALD

ALD (n=300)

88% 75%
80% 72%

Department of Surgery, Charité Campus Virchow-Klinikum, University Medicine Berlin, Berlin, Germany

LIVER TRANSPLANTATION 13:197-205, 2007
Survival according to relapse of alcohol abuse
Survival Outcome of LT for ALD

Risk Factors for Alcohol Relapse After Liver Transplantation for Alcoholic Cirrhosis in Japan

LIVER TRANSPLANTATION 20:298–310, 2014

![Survival Curve]

- Abstinence (n = 103)
- Recidivism (n = 22)

Log-rank test, \( P = 0.01 \)

![Survival Table]

<table>
<thead>
<tr>
<th></th>
<th>0 years</th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
<th>7 years</th>
<th>10 years</th>
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<tbody>
<tr>
<td>Recidivism</td>
<td>22</td>
<td>22</td>
<td>19</td>
<td>14</td>
<td>7</td>
<td>2</td>
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<tr>
<td>Abstinence</td>
<td>103</td>
<td>103</td>
<td>70</td>
<td>42</td>
<td>25</td>
<td>5</td>
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<table>
<thead>
<tr>
<th>Histological Findings</th>
<th>Recidivism (n = 20)</th>
<th>Abstinence (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal or normal changes</td>
<td>2 (10.0)</td>
<td>10 (18.9)</td>
</tr>
<tr>
<td>Fatty changes</td>
<td>9 (45.0)</td>
<td>7 (13.2)</td>
</tr>
<tr>
<td>Alcoholic damage</td>
<td>3 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Cholestatic changes</td>
<td>0</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1 (5.0)</td>
<td>6 (11.3)</td>
</tr>
<tr>
<td>Rejection</td>
<td>5 (25.0)</td>
<td>21 (39.6)</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Other changes</td>
<td>0</td>
<td>2 (3.8)</td>
</tr>
</tbody>
</table>
Survival Outcome of LT for ALD

- Abstinent non-ALC Pts. Vs Pts. with harmful drinking: similar initially but become worse after 5–10 years (45%–68% vs 75%–86%)
- The proportion of Pts. dying from liver-related cause: 6%–88%
- Graft loss from recurrent disease related to ALC use is rare: less than 5% at 5 years for alcohol compared with 25% for HCV

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Total No.</th>
<th>Median FU year</th>
<th>Percent recidivism</th>
<th>Percent graft loss alcohol related</th>
<th>LRD as percent of all deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjeevaram et al[55]</td>
<td>68</td>
<td>3.5</td>
<td>8</td>
<td>38</td>
<td>38</td>
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<tr>
<td>Cuadrado et al[52]</td>
<td>99</td>
<td>8.25</td>
<td>26</td>
<td>0</td>
<td>NR</td>
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<td>Pageaux et al[54]</td>
<td>121</td>
<td>4.5</td>
<td>21</td>
<td>1</td>
<td>12</td>
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<tr>
<td>Lucey et al[55]</td>
<td>50</td>
<td>5.25</td>
<td>33</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Pfitzmann et al[59]</td>
<td>300</td>
<td>7.5</td>
<td>7</td>
<td>50</td>
<td>88</td>
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<tr>
<td>Schmeding et al[81]</td>
<td>271</td>
<td>10</td>
<td>27</td>
<td>0</td>
<td>NR</td>
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<td>Dumortier et al[72]</td>
<td>305</td>
<td>5.25</td>
<td>12</td>
<td>2</td>
<td>8</td>
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Liver transplantation for alcoholic liver disease

World J Gastroenterol 2010 September 21; 16(35): 4377-4393

<table>
<thead>
<tr>
<th>Study</th>
<th>Rejection (%)</th>
<th>Infection (%)</th>
<th>Malignancy (%)</th>
<th>Retransplantation (%)</th>
<th>Cardiac events (%)</th>
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<tbody>
<tr>
<td></td>
<td>ALD</td>
<td>Non-ALD</td>
<td>ALD</td>
<td>Non-ALD</td>
<td>ALD</td>
</tr>
<tr>
<td>Burra et al[76]</td>
<td>7.6</td>
<td>10.1</td>
<td>15.5</td>
<td>17.6</td>
<td>13.7/5.4^1</td>
</tr>
<tr>
<td>Pfizmann et al[5]</td>
<td></td>
<td></td>
<td>4.7-6.3^2</td>
<td>9.4-18.8/3.8^2</td>
<td></td>
</tr>
<tr>
<td>Wiesner et al[63]</td>
<td></td>
<td></td>
<td>Bacteremia, overall fungemia, and CMV infection, comparable to non-ALD</td>
<td>De-novo tumors significantly increased in ALD vs non-ALD</td>
<td>3</td>
</tr>
<tr>
<td>Bhagat et al[84]</td>
<td>23/2^3</td>
<td>41/4^3</td>
<td>43^2</td>
<td>53</td>
<td>29^2</td>
</tr>
</tbody>
</table>

- The incidence of rejection, infection, re-LT and cardiac event is also similar to other recipients.
- ALD patients are more prone to develop de-novo malignancy: long term effect of alcohol, tobacco combined with IS
Survival Outcome of LT for ALD at AMC

- Comparison of Clinical Outcome *between* 210 LTs for ALD and 2279 LTs for Other Disease Indication

From Jan 2005 to Dec 2012
Survival Outcome of LT for ALD at AMC

HCC(+): 1035 (45.4%)  
No HCC: 1244

HCC(+): 32 (15.2%)  
No HCC: 178

DDLT: 317 (13.9%)  
LDLT: 1962

DDLT: 41 (19.5%)  
LDLT: 169
Survival Outcome of LT for ALD at AMC

Patient Survival Rate

Graft Survival Rate

P = 0.287

1/3/5-YSR

Others: 89.5/85.2/84.6%

ALD: 88.1/84.0/80.4%

P = 0.287

1/3/5-YSR

Others: 88.4/84.2/83.6%

ALD: 87.6/83.7/79.1%
Survival Outcome of LT for ALD at AMC

HCC(−)

P=0.432

1/3/5-YSR

Others  96.0/93.5/93.2%
ALD     98.1/92.8/89.0%

HCC(+)  

P=0.460

1/3/5-YSR

Others  94.8/88.2/87.4%
ALD     90.6/90.6/90.6%
Survival According to Relapse of Alcohol Abuse

Cumulative Survival Rate

Survival Period (month)

Survival Period (month)

\[ P = 0.882 \]

Recidivism(-) 95.5/91.4/90.2%
Recidivism(+) 98.2/94.6/87.7%

\[ P = 0.032 \]

Slip 100/96.6/96.6%
Harmful 96.2/92.3/76.6%
Survival Outcome of LT for ALD at AMC

Noncompliance-related ACR or CR in 6 patients (4 in relapsed Pts)
Alc-related graft loss or near-loss in 5 patients (4 in relapsed patients)
2 De novo malignancies (AGC/Pancreas CA)
Comparison of Post-transplant Hospital Stay

ALD < MELD 25  
24.5 days

HBV < MELD 25  
21.6 days

Due to delayed recovery of mentality including various psychiatric and neurological complications.
Summary and Conclusion

- ALD is one of important indication for LT in Korea (may be 3rd and about 10% of all cause)

- ALD is an acceptable indication for LT as survival outcome is comparable and ALC-related graft loss rate is no greater even in Pts with recidivism.

- The recidivism after LT is not affected by pre–LT ALC consumption pattern. But, affected by more complicated psychosocial factors. To decrease relapse, systematic multidisciplinary professional support is necessary.

- Although the use of LT for ALC is increasing, alcohol relapse after LT is not yet widely recognized in Korean society. Therefore, we need further study to establish the guideline of LT for ALD.
Thank You For Your Attention!