Role of 6-month abstinence rule in living donor liver transplantation for patients with alcoholic liver disease

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Aim: Although alcoholic liver disease (ALD) is an accepted indication for liver transplantation (LT), there are several controversial issues. The aim of this study is to examine the applicability of the 6-month abstinence rule prior to LT and to evaluate the results in living donor LT for patients with ALD.

Methods: A retrospective study of 102 patients with ALD referred for LT was performed. Clinical data, including alcohol consumption history, were analyzed. A period of abstinence from drinking alcohol of at least 6 months was strictly required.

Results: Among 102 patients, 21 abstained from drinking for at least 6 months. Of these, 13 patients (12%) underwent LT, five patients (5%) recovered without LT and three patients (3%) were listed for deceased donor LT. LT was not indicated for the remaining 81 patients (80%). Eight patients died within 6 months of referral to our program. The Child–Pugh score was higher in these eight patients than in the 21 who achieved 6-month abstinence, although the alcohol consumption history variables did not significantly differ between the two groups. The 5-year overall survival rates after LT in 13 patients with ALD (91%) were similar to those in 387 non-ALD patients (83%). The rate of alcohol consumption relapse after LT was 8% (n = 1/13).

Conclusion: Living donor LT for patients with ALD who complied with the 6-month abstinence rule provides sufficient survival benefit with good compliance, compensating for the potential risks to the donors.

Key words: abstinence period, alcohol recidivism, alcoholic liver disease, liver transplantation

INTRODUCTION

ALCOHOLIC LIVER DISEASE (ALD) is an increasingly important cause of end-stage liver disease, and a recognized indication for liver transplantation (LT), accounting for approximately 2% of all primary transplants in Japan,1 40% in Europe2 and 20% in the USA.3 The proportion of ALD patients undergoing LT remains small in Japan compared to the latter two regions, but the number of ALD patients who underwent living donor LT (LDLT) in Japan is increasing annually based on a report by the Japanese Liver Transplantation Society.1 A fair therapeutic strategy is necessary before considering patients with ALD for LDLT, because deceased donor organs remain scarce in East Asian regions, including Japan.

The outcome of the long-term prognosis of patients transplanted for ALD is at least as good as that of patients transplanted for most other diagnoses.4–6 Although post-LT drinking impairs the long-term survival of ALD patients after LT,7 late graft loss due to recurrence of the original disease, such as viral hepatitis and cholestatic disease, is uncommon. A fixed period of abstinence from drinking alcohol prior to transplantation allows some patients to recover their liver function to the extent that LT is no longer needed and should be adopted as inclusion criteria for LT.8 There have been no studies in the published work focusing on the treatment of ALD, including LT and patient outcome, in regions in which deceased donor organs are scarce.

In the present study, we performed a retrospective analysis of ALD patients to examine the applicability of
the 6-month abstinence rule prior to LT and to evaluate the results of LDLT for patients with ALD.

**METHODS**

**Patients**

Between January 1996 and September 2011, 102 patients with chronic ALD or alcoholic liver cirrhosis were referred to the University of Tokyo Hospital for LT; patients presenting with severe alcoholic hepatitis were not included. The diagnosis of ALD was based on a history of habitual and excessive alcohol consumption in the absence of other causes of liver cirrhosis. The clinical records of these patients were retrospectively reviewed. A history of alcohol intake was also obtained from the clinical records, including duration of heavy drinking, types and amount of alcohol consumed, and previous treatment history. A high-risk alcoholism relapse score was calculated according to Yates et al.9

**Indication criteria of LT for ALD**

The selection criteria for LT at our institution are described elsewhere.10 In addition to our general criteria, patients with ALD are required to fulfill additional criteria as follows: period of abstinence from drinking alcohol of at least 6 months prior to LT; participation in Alcoholics Anonymous or an equivalent rehabilitation program; consultation with a psychiatrist; and signed agreement indicating intention of lifetime abstinence. ALD patients meeting our criteria were considered candidates for LDLT or deceased donor LT (DDLT), irrespective of a high-risk alcoholism relapse score. The indications for LDLT and the type of liver graft were determined according to the ratio of the remnant liver volume to total liver volume in living donors, and that of the graft volume to the standard liver volume11 in recipients.12

**Surgical treatment and management**

Our LT procedure has been described elsewhere.13 For the follow-up evaluation, blood test and ultrasonography findings were examined at every outpatient clinic (usually every 1–2 weeks) beginning immediately after the patients were discharged. Alcohol relapse after LT was defined as re-drinking on the basis of self-report questionnaires and interviews with patients and/or family members.

**Statistical analysis**

Continuous data are expressed as the median values (with range). Quantitative and categorized variables were compared using the Wilcoxon rank sum test and Fisher’s exact test, respectively. Long-term survival was measured from the time at which patients underwent LT. Overall survival curves were constructed using the Kaplan–Meier method, and compared using the log-rank test. A P-value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed with JMP software ver. 9.0.2 (SAS Institute, Cary, NC, USA).

**RESULTS**

The flow of study participants is shown in Figure 1. Among 102 patients, 13 (12%) underwent LDLT, patients (5%) were recognized as recovering from liver failure and three patients (3%) were listed for DDLT after an abstinence period lasting at least 6 months. LT was not indicated for 81 patients (80%) and eight of these (8% of total) died within 6 months of referral to our program. The reasons for rejection are shown in Table 1. Fifty-five patients (68%) were rejected for reasons related to recipient issues, including not abstaining from drinking alcohol in 15 patients (21%).

Demographic data of 21 patients who achieved 6 months of abstinence (“abstinence group”) are shown in Table 2 and compared with the eight patients who died within 6 months (“mortality group”). The Child–Pugh score was significantly higher in the Mortality group than in the abstinence group (median [range], 12

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[Diagram Figure 1 Flow of study participants. ALD, alcoholic liver disease; DDLT, deceased donor living transplantation; LDLT, living donor liver transplantation.]
The Model for End-Stage Liver Disease (MELD) score was not significantly different between the two groups. The alcohol consumption history variables, such as High-Risk Alcoholism Relapse scale, duration of heavy drinking, average daily drinking, lifetime alcohol consumption and previous alcohol treatment, were also not significantly different between the two groups. The reasons for death and rejection in the mortality group are shown in Table 3. Causes of death were liver failure due to chronic ALD or alcoholic liver cirrhosis \((n = 6)\), bleeding of esophageal varices \((n = 1)\) and hepatocellular carcinoma \((n = 1)\).

Table 4 shows the characteristics of 13 patients with decompensated liver cirrhosis due to ALD who underwent LDLT. The median Child–Pugh score was 11 (range, 7–12) and MELD score was 19 (10–23). Alcoholic liver cirrhosis in three patients (cases 2, 9 and 11) was caused by a relatively small amount of lifetime alcohol consumption \((0.59 \text{ ton}, 0.34 \text{ ton} \text{ and} 0.58 \text{ ton})\). Patients with ALD comprised 3% \((13/400)\) of adult LDLT recipients. This proportion was similar to that of LT in Japan, 3.5% of adult recipients \((134/3796)\), reported by the Japanese Liver Transplantation Society. Long-term survival after LT for the ALD group \((n = 13); \text{median follow-up period [range], 38 months [2.1–111]}\) and non-ALD group \((n = 387); 88 months [0.2–197]\) is shown in Figure 2. The 1-, 3- and 5-year overall survival rates were 100%, 91% and 91% in the ALD group, respectively, and 90%, 86% and 83% in the non-

### Table 1 Reasons not indicated for transplantation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 81)</th>
</tr>
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<tbody>
<tr>
<td>Recipient-related reasons</td>
<td></td>
</tr>
<tr>
<td>Declined to undergo transplantaion</td>
<td>55 (68%)</td>
</tr>
<tr>
<td>Lack of abstinence</td>
<td>17 (21%)</td>
</tr>
<tr>
<td>Medical not indicated</td>
<td>23 (29%)</td>
</tr>
<tr>
<td>Others</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Donor-related reasons</td>
<td>26 (32%)</td>
</tr>
<tr>
<td>No donor volunteer</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Medical ineligibility</td>
<td>15 (19%)</td>
</tr>
</tbody>
</table>
ALD group, respectively. Overall survival did not differ significantly between groups ($P = 0.460$). One patient in the ALD group died from recurrence of hepatocellular carcinoma. The rate of alcohol relapse after LT was 8% ($n = 1/13$, patient no. 1 in Table 4) in our series; however, this patient achieved re-sobriety after participating in an abstinence program.

**DISCUSSION**

The findings of the present study demonstrated that LT for ALD within our indication criteria achieved good long-term survival and abstinence rates after LT. An abstinence period of at least 6 months before LT as an indication criterion for LDLT was acceptable to avoid re-drinking after LT and to confirm the possibility of recovery from liver failure.

The Japanese Liver Transplantation Society reported overall survival rates for ALD patients of 81.3% at 1 year, 78.5% at 3 years and 75.7% at 5 years. Similar survival rates for ALD patients were reported in Europe (84% at 1 year, 78% at 3 years and 73% at 5 years) and the USA (92% at 1 year, 86% at 3 years and 5 years). LT for ALD patients within our indication criteria is supported by our findings, as the survival rates for those in our series (100% at 1 year, 91% at 3 years and 91% at 5 years) were higher compared to the three reports mentioned above. Despite the lack of a commonly accepted definition, the rate of alcohol relapse is reported to be relatively high, ranging 11.9–45.6%, compared to the present findings (8%).

Mathurin et al. reported that early LT without an abstinence period can improve survival in patients with a first episode of severe alcoholic hepatitis. Despite different objectives (treating chronic ALD in our series vs acute ALD in Mathurin et al.’s series) and different approaches (LDLT prevailing in East Asia regions vs...
of donors. 21% of ALD patients in our study could not abstain from drinking alcohol before and/or after LT (Table 1). Graft failure and loss induced by re-drinking might be missed if LT without an abstinence period were indicated based on optimism for sobriety after LT. Moreover, abstinence before LT allows for an observation period to confirm recovery from liver failure, avoiding unnecessary LT and the potential risks to the donors, because 5% of ALD patients showed non-impaired liver function after 6-month abstinence (Fig. 1). It may be difficult to predict if ALD patients will achieve abstinence and be eligible for the next treatment step or die prior to transplantation, however, because no variables were found that distinguished the abstinence group from the mortality group without Child–Pugh score (Table 2). Indeed, even a relatively small amount of alcohol consumption can cause ALD requiring LT (Table 4). As for predictors of post-LT relapse, length of abstinence of more than 6 months is supported as necessary for selecting a patient for LT; however, Mackie et al. and Veldt et al. suggested that LT could be considered after as little as 3 months of abstinence. Based on the above points, a fixed period of abstinence, such as 6 months, should be required as an indication criterion for LT, although our data are insufficient for determining how many months of abstinence are necessary.

One of the drawbacks of this study is that, due to the limited number of cases (ALD group, n = 13, 13%), our data are not adequate to conclude whether and how long of an abstinence period is required. In addition, a short median follow-up period (38 months) in our series may overestimate the survival rates, because Cuadrado et al. reported that the mean interval from transplantation to alcohol relapse, which caused a significant decline in survival rates, was 47.5 months with a range of 5.0–86.9 months. Another limitation related to our indication criteria is that a fixed period of abstinence may lead to an increase in waitlist mortality. To achieve a consensus on the pre-LT abstinence period for ALD, a well-organized randomized controlled trial is needed to determine rules supported by evidence.

In conclusion, an abstinence period of at least 6 months allows for the appropriate prediction of alcohol relapse after LT and selection of recovery from liver failure. LDLT for ALD within our criteria allows for acceptable compliance and sufficient survival benefit after LT, providing results that are complementary with the benefits of recipients and potential risks of donors.

REFERENCES


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