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Risk factors for alcohol recidivism after liver transplantation

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Background: Alcoholic liver disease (ALD) has been increasing recently and the second most common indication for liver transplantation (LT) in Korea. Even after LT, alcohol recidivism can be a problem interfering with the patients' long-term survival and graft function. This study was conducted to analyze the clinical course and pre- and post-transplantation risk factors for alcohol recidivism in transplant recipients with ALD.
Methods: Of 592 liver transplant recipients, sixty-two patients underwent LT for ALD between Jan 2005 and Dec 2014. We retrospectively collected and analyzed the data from our electrical medical records.
Results: Out of the 62 ALD recipients, 57 patients were male. Their mean age was 52.4±8.3 years. The mean abstinence period of them before transplantation was 17.7±30.0 months. Sixteen recipients (25.8%) showed alcohol recidivism at 15.9±13.7 months after LT. Patients who showed alcohol recidivism had a significantly longer duration of drink before transplantation than non-recidivism patients (35.4±6.3 vs 30.9±9.4 years, respectively, p=0.038). In terms of alcohol consumption, the recidivism group showed more alcohol drinking than the non-recidivism group (123.0±67.2 vs 81.6±61.0 units, respectively, p=0.026). The abstinence period before LT was not significantly different. In the multivariate analysis, the amount of alcohol consumption before transplantation was considered to play a risk factor for alcohol recidivism after transplantation (p=0.05).
Conclusion: Information about duration and consumption of alcohol drink before LT helps to predict alcohol recidivism after LT in patients with ALD, allowing early awareness and specific postoperative care.

Keywords: Alcohol; Liver transplantation; Recidivism; Survival

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INTRODUCTION

Alcohol liver disease (ALD) becomes one of the most common causes of cirrhosis and liver transplantation worldwide. ALD, alone or in combination with other liver-related diseases such as hepatitis B or C viruses and NASH, is one of the most common indications for LT in North America (24.1%) and Europe (23%) [1,2]. In Korea, its incidence has been increasing recently, the most common indication for deceased donor LT and the second most

common indication for living donor LT [3]. According to a recent report, excessive alcohol consumption even after liver transplantation is 5.8- to 17.4-fold more frequent in patients with ALD than in those with other indications for LT [4].

As the number of LT for ALD patients has been increasing, the number of patients with alcohol recidivism after LT can be increasing. In patients with ALD, alcohol recidivism is still occurring despite a lot of efforts to prevent recidivism after LT. Several approaches have been conducted to reduce alcohol recidivism in alcoholic patients after LT, such as management of alcoholic patients by addiction psychiatrists and presence of an alcohol addiction unit within a transplant center, but there is no standardized approach, and the available data are few and often controversial [5,6]. Although most transplant centers enforce a 6-month rule of abstinence, the alcohol recidivism rate after LT has been reported 20–50% [7,8].

Resumption of alcohol drinking can lead to non-compliance with the transplant follow-up program, which can make worse outcomes for the patients [9]. In Europe, 5- and 10-year survival rates in ALD patients after liver transplantation are 73% and 59%, respectively. However, a significant drop in the survival rate in patients with recidivism was not observed [2,10].

This study was conducted to analyze the clinical course, outcomes, and pre- and post-transplant risk factors for alcohol recidivism in transplant recipients with ALD.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 62 ALD patients among 592 liver recipients who underwent liver transplantation in Severance hospital between Jan 2005 and Dec 2014. Six patients who could not be followed up due to in-hospital mortality were excluded.

The diagnosis of ALD was based on a documented history of alcohol drinking experience that could lead to end-stage liver disease and exclusion of non-alcoholic causes that can lead to end-stage liver disease. Patients were considered for liver transplantation based on standard listing criteria.

During the follow-up visits after LT, patients were routinely questioned about alcohol consumption and were reminded about the necessity to remain abstinent, as well as given advice on the negative effects of alcohol use. And these patients followed up with psychiatric consultation.

Alcohol recidivism was defined as any alcohol consumption that was noticed by the patients and/or their family members during the following periods. We evaluated the incidence of alcohol recidivism, graft function, patient survival rates, and risk factors affecting the recurrence of alcohol. Also, we evaluate the effectiveness of the 6-month abstinence rule on the prevention of alcohol recidivism. To evaluate alcohol drinking amount, we defined 1 unit of alcohol consumption as 10 g/week of alcohol regardless of the alcohol types that the patients drank.

Comparison analysis of liver function was performed between the alcohol recidivism group and non-recidivism group to evaluate the effects of alcohol on the transplanted liver.

Statistical analysis was performed using SPSS 25 (SPSS Inc., Chicago, IL, USA). Data were expressed as the mean± standard deviation for continuous variables and number (proportion) for categorical variables. Continuous variables were tested using independent Student's t-tests and Fisher's exact test for categorical variables. Graft survival rates were calculated using Kaplan-Meier method and the log-rank test was used to evaluate statistical significance. A p-value less than 0.05 was considered statistically significant.

RESULTS

Of the 592 patients included in the study, 67 underwent LT for ALD and 525 for other indications. Among 67 ALD patients, one patient underwent retransplantation for primary non-function of the first graft and 6 patients were excluded due to in-hospital mortality after LT.

A total of 15 patients had type 2 diabetes mellitus and 19 patients had hypertension. Three patients had HBV infection and one patient had HCV infection combined with ALD. The mean abstinence period of those ALD patients before LT was 17.7±30.0 months. The number of patients with Child-Turcotte-Pugh (CTP) classification A, B, and C were 7, 26, and 29, respectively. Their mean MELD score was 19.3±9.1. The donors were mainly primary family members including sons (n=19), daughters (n=4), brothers (n=3), sisters (n=3), a cousin, and a wife. Out of the patients, there was no retransplantation case.

Sixteen patients had alcohol recidivism and their onset time was 15.9±13.7 months after LT. A comparison of clinical characteristics between the alcohol recidivism group and the non-recidivism group is shown in Table 1. Their demographics and pretransplant conditions were not different. Table 2 shows the alcohol-related factors of

the two groups. The alcohol recidivism group had a significantly longer drinking period before transplantation than the non-recidivism group (35.4±6.3 vs 30.9±9.4 years, respectively, p=0.038). In terms of alcohol consumption, the recidivism group showed more alcohol drinking amount than the non-recidivism group (123.0±67.2 vs 81.6±61.0 units, respectively, p=0.026; 1 unit=10 g/week alcohol). Also, the alcohol recidivism group showed a tendency of shorter abstinence periods than the non-recidivism group (8.9±15.5 vs 20.6±33.3 months, respectively, p=0.066). Of the patients with co-infection of hepatitis B or C (n=3), one patient returned to alcohol abuse after LT.

The period of pre-transplantation abstinence was less than 3 months in 27 patients, 3 to 6 months in 6 patients, 6 to 12 months in 10 patients, and above 12 months in 17 patients. Patients who had abstinence periods for more than 6 months are 22 (47.8%) in the non-recidivism group and 5 (31.2%) in the recidivism group. Eight patients died during follow-up. Of the 16 alcohol recidivism cases, four (25%) cases showed recidivism within the first 6 months after LT, 6 to 12 months in 4 (25%) cases, 12 to 18 months in 1 (6.3%) case, and seven (43.8%) recidivism occurred in cases with more than 18 months after LT.

The alcoholic recidivism group showed deterioration of serum AST (127.6±197.2 IU/L), ALT (103.4±150.0 IU/L),

Table 1. Clinical profiles between the Alcoholic recidivism group and non-recidivism group

	Non-Recidivism (n=46)	Recidivism (n=16)	p-value
Age, mean±SD	51.9±8.8	54.4±6.7	0.306
Sex (male%)	42 (91.3%)	15 (93.8%)	0.757
DM, *n* (%)	12 (26.1%)	3 (18.8%)	0.555
HTN, *n* (%)	12 (26.1%)	7 (43.8%)	0.187
HBV, *n* (%)*	2 (4.3%)	1 (6.2%)	0.760
HCV, *n* (%)*	0 (0.0%)	1 (6.2%)	0.087
HCC, *n* (%)	9 (19.6%)	2 (12.5%)	0.524
CTP, *n* (%)			0.650
Class A	6 (13.0%)	1 (6.2%)	
Class B	18 (39.1%)	8 (50.0%)	
Class C	22 (47.8)	7 (43.8%)	
MELD score, mean±SD	19.5±9.1	18.4±8.8	0.676
Type of graft			0.562
LDLT	22 (47.8%)	9 (56.2%)	
DDLT	24 (56.2%)	7 (43.8%)	

DM, diabetes mellitus; HTN, hypertension; HBV, viral hepatitis B; HCV, viral hepatitis C; CTP, Child-Turcotte-Pugh score; MELD, model for end-stage liver disease; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation.
*Viral hepatitis combined cases: all livers were confirmed alcohol dominant hepatitis in the histology.

Table 2. Comparison of preoperative alcohol consumption of recidivism and non-recidivism groups

	Non-Recidivism (n=46)	Recidivism (n=16)	p-value
Duration of drink (year)	30.9±9.4	35.4±6.3	0.038
Consumption of alcohol (unit/week)	81.6±61.0	123.0±67.2	0.026
Duration of abstinence (month)	20.6±33.3	8.9±15.5	0.066
Abstinence <3 months	19 (41.3%)	9 (56.2%)	0.301
Abstinence <6 months	24 (52.2%)	11 (68.8%)	0.249

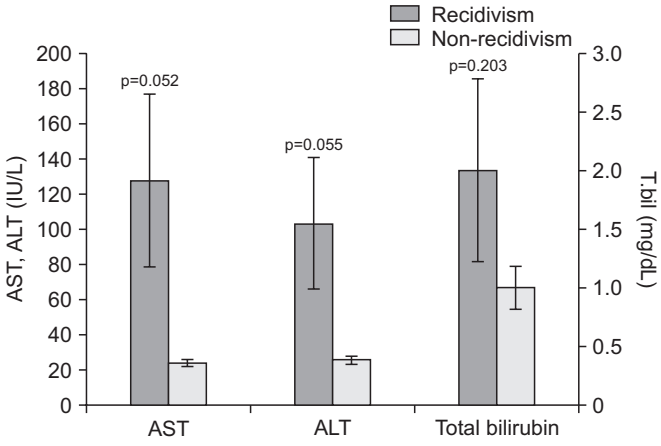

Fig. 1. Mean serum AST, ALT and Total bilirubin levels measured at the time of alcohol relapse in alcohol recidivism group; compared to those of non-recidivism group at 6 months after liver transplantation.

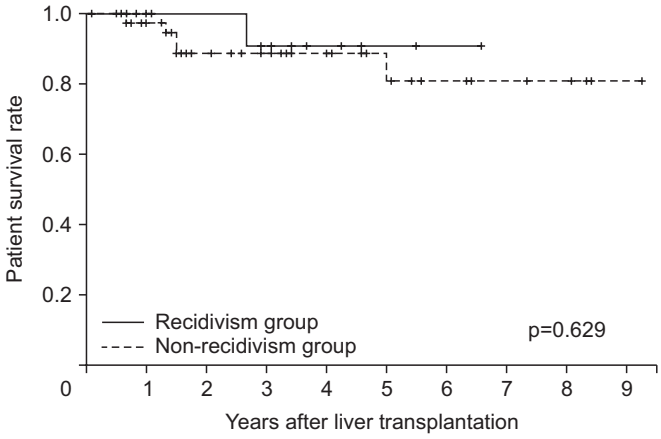

Fig. 2. Cumulative patient survival curves of alcoholic recidivism and non-recidivism groups.

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and total bilirubin levels (2.0±3.1 mg/dL) in the acute stage comparing with the non-recidivism group (Fig. 1). But these functional deteriorations became resolved after the recovery period without alcohol intake. However, in the survival analysis, there was no significant difference between the two groups (Fig. 2).

Out of the analyzed variables, consumption of alcohol was the only independently associated with the risk of alcohol recidivism in both univariate and multivariate analysis (OR=1.00, CI=1.00–1.01, p=0.05; (Table 3). Two recipients with alcohol recidivism died because of sepsis and graft dysfunction.

DISCUSSION

ALD is a liver disease that is associated with chronic alcohol abuse. Even though there are still controversial issues, the most effective treatment for liver cirrhosis originated from ALD is liver transplantation. In the diagnosis of ALD, it is necessary to have enough consumption of alcohol and duration of drink to cause liver disease. There are no definite amount of alcohol consumption and no unified criteria for drinking duration that could induce ALD. Generally, it is known that 60–80 g of alcohol a day for many years may occur ALD [11]. However, this criterion is not absolute and can vary depending on various environmental and host factors.

The spectrum of ALD is wide which begins from fatty liver and proceeds alcoholic hepatitis, and alcoholic cirrhosis according to clinical and pathological findings. The primary treatment for ALD patients should start with abstinence from alcohol. As the alcoholic fatty liver stage can be mostly reversible, when patients stop drinking, it can return to normal within 4–6 weeks [12]. The survival rates of patients with alcoholic hepatitis also increase significantly when they stopped drinking. However, when alcoholic hepatitis occurs repeatedly, irreversible liver damage occurs. Alcoholic hepatitis is known to have very few clinical manifestations, ranging from mild hepatic dysfunction to severe hepatic dysfunction.

The minimum selection criteria of LT for ALD patients should require a CTP score of 7 or greater, a history of portal hypertension, or a history of spontaneous bacterial peritonitis [13]. However, the CTP score has been associated with a large number of subjective interventions and poor prognosis in the evaluation of hepatic encephalopathy and ascites. To correct this, some liver transplantation programs recommend that patients with end stage liver disease with a MELD score of 12 or more should be selected as transplant recipients [14,15]. However, even though the liver failure patients with ALD need LT, there are still many arguments including ethical issues if LT for ALD would be right or not. There would be two issues about LT for ALD. The first one is brought up by the fact that ALD patients ruin their liver by themselves. The second one would be the alcohol recidivism after LT. Alcohol recidivism can lead to damage of preciously transplanted liver and extrahepatic damage caused by alcohol itself, and lower compliance with medication and outpatient visits, resulting in graft failure.

Table 3. Multivariate analysis for prediction of alcohol recidivism

Study characteristics	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.03 (0.96–1.11)	0.30		
Sex (for male)	0.70 (0.07–0.67)	0.75		
DM	0.65 (0.15–2.69)	0.55		
HTN	2.20 (0.67–7.22)	0.19		
HBV	1.46 (0.12–17.3)	0.76		
MELD	0.98 (0.92–1.05)	0.67		
Type of LT (for LDLT)	0.71 (0.22–2.24)	0.56		
Duration of drink (year)	1.06 (0.99–1.14)	0.08	1.06 (0.98–1.14)	0.11
Consumption of alcohol (unit/week)	1.01 (1.00–1.01)	0.03	1.00 (1.00–1.01)	0.05
Duration of abstinence (month)	0.98 (0.95–1.01)	0.20		
Abstinence <3 months	2.16 (0.67–6.96)	0.19		
Abstinence <6 months	2.01 (0.60–6.73)	0.25		

DM, diabetes mellitus; HTN, hypertension; HBV, viral hepatitis B; MELD, model for end-stage liver disease; LDLT, living donor liver transplantation.

In order to minimize alcohol recidivism, most transplant centers have studies the risk factors of recidivism including abstinence period, alcohol consumption amount, and etc (Table 4). In the literatures, the alcohol recidivism rates were reported from 11.9% to 48% [14,16-24]. Factor associated with recidivism varied according to each study such as pretransplant psychological treatment, family awareness, personality disorder, drinking duration, alcohol consumption amount, or abstinence period. Many American centers recommend to keep mandatory six-month abstinence rule before deciding LT. However, in the current study shows alcohol consumption at pre-transplant period appeared to be a more powerful risk factor to predict recidivism than the failure of 6-month abstinence period. Therefore, taking the detailed alcohol history should be done before LT to prepare their life modification after LT.

Although our center does not apply post-operative rehabilitation programs, several studies have shown significant results in reducing recidivism by applying these programs. Björnsson et al. [5]. evaluated the impact of the management of alcoholic patients by addiction psychiatrists, social workers, and tutors in the period before LT and reported a 22% prevalence of alcohol recidivism in the treated group vs 48% in the untreated group. The presence of an alcohol addiction unit within a liver transplant center is not usual, but the study of Addolorato et al. [6]. suggests that it could represent a useful approach to reducing alcohol recidivism after LT. Future studies will be needed to reduce recidivism by applying these rehabilitation programs as well as listening to drinking history before transplantation.

Table 4. Alcohol recidivism rates and risk factors after liver transplantation reported from other studies

Authors	Patients (n)	Recidivism rate	Factors associated with recidivism
Egawa et al. [16]	140	22.9%	History of treatment for psychological diseases
Lucey et al. [17]	59	34%	None
Burra and Lucey [14]	51	33%	Patient and/or family awareness of alcoholism
Gish et al. [18]	61	20%	Personality disorder, lack of compliance
Bellamy et al. [19]	123	13%	Duration×quantity of alcohol
Tang et al. [20]	56	48%	None
Hartl et al. [21]	120	16%	Abstinence <3 months, lack of compliance
De Gottardi et al. [22]	387	11.9%	Abstinence <6months, psychiatric comorbidities, HRAR >3
Osario et al. [23]	43	19%	Abstinence <6 months
Pageaux et al. [24]	53	32%	Abstinence <6 months, age

CONCLUSIONS

Information about drinking duration and consumption of alcohol at pretransplant period helps to predict alcohol recidivism after LT in patients with ALD, allowing early awareness and specific postoperative care.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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AUTHORS' CONTRIBUTIONS

Conceptualization: DJJ. Data curation: All. Formal analysis: DJJ, DHH, GHC, MSK. Funding acquisition: DJJ. Investigation: None. Methodology: DJJ. Project administration: None. Resources: DJJ, JGL. Software: None. Supervision: DJJ. Validation: None. Visualization: DJJ, HJK. Writing - original draft: HJY. Writing - review & editing: DJJ, JSC, SIK.

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