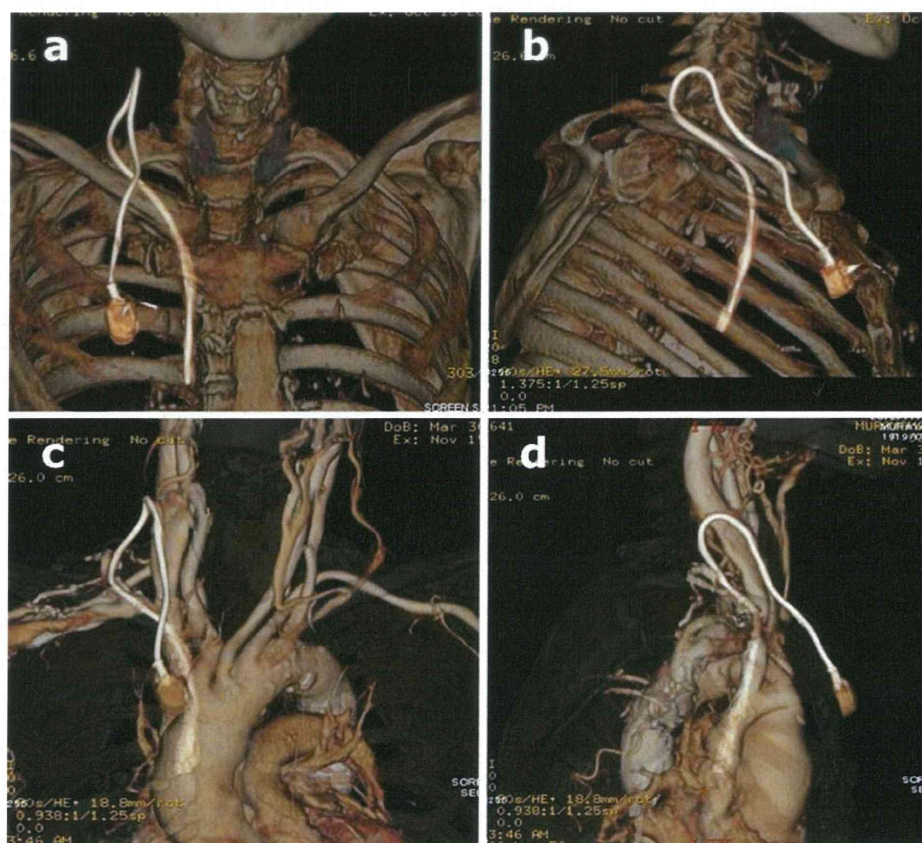**FIG. 4** Follow-up MDCT: anteroposterior (**a**) and lateral (**b**) volume-rendered images. Follow-up MDCT venography: anteroposterior (**c**) and lateral (**d**) volume-rendered images. The MDCT showed the appropriate TIVAP position and the catheter position. *MDCT* multidetector computed tomography, *TIVAP* totally implantable venous-access port

In regard to patient safety, it is worth nothing that in the relatively recent past, the use of peripherally inserted central catheters has obviated some of the risks involved with more central access sites. Therefore, central venous access via the EJV for the placement of TIVAP seems to be an option to consider for vascular access in patients, given our findings of a high success rate and a low complication rate.[18]

The present study has some limitations. Our study was preliminary in its prospective nature and the lack of a control group. The number of reported cases is relatively small, which implies the need for a study involving a large patient population that would permit a more precise assessment. Further studies are needed to determine how these advances in central access compare with the safety profile of the EJV technique with CT-V for the placement of a TIVAP.

CONFLICT OF INTEREST   None of authors have identified any conflicts of interest.

REFERENCES

1. Gorman RC, Buzby GP. Difficult access problems. *Surg Oncol Clin North Am.* 1995;4:453–472.

2. Bermard RW, Stahl WM. Subclavian vein catheterizations: a prospective study. I: non-infectious complications. *Ann Surg.* 1971;173:184–190.

3. Mansfield PF, Hohn DC, Forange BD, Gregurich MA, Ota DM. Complications and failures of subclavian-vein catheterization. *N Engl J Med.* 1994;29:1735–1738.

4. Trerotola SO. You are asked to place a dialysis access catheter in a patient. What is your preferred access site, and why? *J Vasc Interv Radiol.* 1997;8:75–76.

5. Macdonald S, Watt AJB, McNally D, Edwards RD, Moss JG. Comparison of technical success and outcome of tunneled catheters inserted via the jugular and subclavian approach. *J Vasc Interv Radiol.* 2000;11:225–231.

6. Schillinger F, Schillinger D, Montagnac R, Milcent T. Post catheterization vein stenosis in haemodialysis: comparative angiographic study of 50 subclavian and 50 internal jugular access. *Nephrol Dial Transplant.* 1991;6:722–7124.

7. Moss AH, McLaughlin MM, Lempert KD, Holley JL. Use of a silicone catheter with a Dacron cuff for dialysis short-term vascular access. *Am J Kidney Dis.* 1988;12:492–489.

8. Trerotola SO, Kuhn-Fulton J, Johnson MS, Shah H, Ambrosius WT, Kneebone PH. Tunneled infusion catheters: increased incidence of symptomatic venous thrombosis after subclavian versus internal jugular venous access. *Radiology.* 2000;217:89–93.

9. Susan NW: Unconventional venous access. *Tech Vas Interv Radiol.* 2001;5:114–120.

10. Cho SK, Shin SW, Do YS, Park KB, Choo SW, Choo IW. Use of the right external jugular vein as the preferred access site when the right internal jugular vein is not usable. *J Vasc Interv Radiol.* 2006;17:823–829.

11. Povoski SP. External jugular vein cutdown approach for chronic indwelling central venous access in cancer patients: a potentially useful alternative. *World J Surg Oncol.* 2004;2:7–11.

12. Di Carlo I, Barbagallo F, Toro A, Sofia M, Lombard R, Cordio S. External jugular vein cutdown approach, as a useful alternative, support the choice of cephalic vein for totally implantable access device placement. *Ann Surg Oncol.* 2005;12:570–573.

13. Malatinsky J, Kadlic T, Majek M, Samel M. Misplacement and loop formation of central venous catheters. *Acta Anaesth Scand.* 1976;20:237–247.

14. Blitt CD, Wright WA, Petty WC, Webster TA. Central venous catheterization via the external jugular vein. *JAMA.* 1974;229:817–818.

15. Deshpande KS, Hatem C, Ulrich HL, et al. The incidence of infectious complications of central venous catherters at the subclavian, internal jugular, and femoral sites in an intensive care unit population. *Critical Care Med.* 2005;33:13–22.

16. Lenhard DC, Pietsch H, Sieber MA, Ernst R, Lengsfeld P, Ellinghaus P, Jost G. The osmolality of nonionic, iodinated contrast agents as an important factor for renal safety. *Invest Radiol.* 2012;47:503–510.

17. Davidson C, Stacul F, McCullough PA, Tumlin J, Adam A, Lameire N, et al. Contrast medium use. *Am J Cardiol.* 2006;98:42K–58K.

18. Heye S, Maleux G, Claes K, Kuypers D, Oyen R. Stenosis detection in native hemodialysis fistulas with MDCT angiography. *Am J Roentgenol.* 2009;192;1079–1084.

19. Gordon AC, Saliken JC, Johns D, Owen R, Gray RR. US-guided puncture of the internal jugular vein: complications and anatomic considerations. *J Vasc Interv Radiol.* 1998;9:333–338.

20. Shih YC, Chien HL, Hao MC, Huan MH, Jyh CY. A safe and effective method to implantable access port in patients with synchronous bilateral mastectomies: modified femoral vein approach. *J Surg Oncol.* 2008;98:197–199.

ORIGINAL ARTICLE

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

Hiroto Egawa,[1] Katsuji Nishimura,[2] Satoshi Teramukai,[3] Masakazu Yamamoto,[1] Koji Umeshita,[4] Hiroyuki Furukawa,[5] and Shinji Uemoto[6]

[1]Departments of Surgery and [2]Psychiatry, Tokyo Women's Medical University, Tokyo, Japan; [3]Innovative Clinical Research Center, Kanazawa University, Kanazawa, Japan; [4]Department of Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan; [5]Department of Surgery, Asahikawa Medical University, Asahikawa, Japan; and [6]Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Alcoholic liver cirrhosis (ALC) is an established indication for liver transplantation (LT). Most LT procedures in Japan are living donor liver transplantation (LDLT) because of an extreme shortage of deceased donors. Social circumstances enabling LDLT could be favorable for preventing relapse. The aims of this retrospective study were to analyze the outcomes of LDLT for ALC and to evaluate risk factors for relapse in this cohort. One hundred ninety-five subjects underwent LT [LDLT (n = 187), deceased donor LT (n = 5), or domino LT (n = 3)] for ALC in Japan from November 1997 to December 2011. Risk factors for alcohol relapse and the impact of relapse on outcomes were analyzed for 140 patients after the exclusion of 26 patients who died in the hospital and 29 patients without information about alcohol relapse. The incidence of alcohol consumption after LT was 22.9%. The risk factors for patient survival were a donor age ≥ 50 years (P < 0.01) and a Model for End-Stage Liver Disease score ≥ 19 (P = 0.03). The 10-year patient survival rates were 21.9% and 73.8% for patients who had relapsed and patients who had not relapsed 18 months after LT, respectively (P = 0.01). The relapse rates were 50.0%, 34.5%, 13.3%, 19.7%, and 14.3% for patients who had received livers from parents, siblings, spouses, sons/daughters, and deceased or domino donors, respectively. A history of treatment for psychological diseases other than alcoholism before LT was a significant indicator for the risk of recidivism (P = 0.02), and noncompliance with clinic visits after LT and smoking after transplantation were promising indicators for the risk of recidivism (P = 0.06, and P = 0.05, respectively). 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. *Liver Transpl 000:000-000, 2013.* © 2013 AASLD.

Alcoholic liver cirrhosis (ALC) is the second most common indication for deceased donor liver transplantation (DDLT) for chronic liver disease in the Western world. In Japan, following cholestatic liver diseases and viral cirrhosis, ALC is the third most common indication.[1] Most liver transplantation (LT) in Japan involves living donors because of an extreme shortage of deceased donors.

Medical professionals have made considerable efforts to prevent graft loss secondary to the recurrence of the original disease; for example, they provide antiviral therapies to patients with hepatitis B or hepatitis C, and they modify patient selection and organ distribution for patients with hepatocellular carcinoma. A patient with ALC may return to a pattern of alcohol consumption, which potentially can damage

the transplanted liver and affect compliance with the immunosuppressive regimen and follow-up appointments; this may put the graft at risk.[2] Hence, selection criteria for predicting alcohol relapse from preoperative data and postoperative education and support to keep patients away from recidivism have been strengthened.[2-12]

In 1990, Bird et al.[3] reported the usefulness of an abstinence period of at least 6 months. Since then, the 6-month rule has been the most widely used criterion.[4-8] However, the length of abstinence before transplantation has not predicted alcohol relapse in some studies.[2,9,10] DiMartini et al.[11] found that each additional month of pretransplant sobriety lowered the risk of posttransplant drinking by 33%; however, they could not identify a specific length of pretransplant sobriety that predicted abstinence. Tandon et al.[12] obtained similar results in 2009.

De Gottardi et al.[13] applied a high-risk alcohol relapse (HRAR) scale,[14] which was originally designed to predict recidivism in nontransplant patients after alcohol rehabilitation, to the prediction of alcohol relapse after transplantation, and they found that an HRAR score > 3 was associated with harmful relapse. However, the independent predictive ability of the HRAR score for posttransplant recidivism remains controversial.[15] Familial and social support has also been reported to be important for preventing alcohol relapse.[10,16]

In DDLT, organs are considered to be a public resource that should be shared fairly and effectively. Hence, alcohol relapse could be considered a reason for transplant units and public opinion to deny transplantation. In living donor liver transplantation (LDLT), healthy relatives donate their organs to the patients. The conditions for alcohol relapse may be different after LDLT versus DDLT. For example, the relapse rate might be lower when patients are being watched by relatives, including donors; in such cases, LDLT might be favorable. The only report on LDLT for ALC came from a single-center study that showed a low recidivism rate for 13 patients selected according to very strict criteria.[7] No studies of recidivism after LDLT have been performed with a large cohort.

The aims of this study were (1) to analyze the outcomes of LDLT for ALC, (2) to find risk factors for patient survival, and (3) to evaluate risk factors for alcohol relapse in this cohort.

PATIENTS AND METHODS

LT for ALC was performed for 197 patients at 38 institutions according to the registry of the Japanese Liver Transplantation Society. These 38 institutions were sent questionnaires that asked about institutional policies for patient selection, patient characteristics, the preoperative alcohol consumption status of patients, treatments, postoperative living conditions, and clinical courses after transplantation for patients who underwent LT for ALC. Patient characteristics included the following: disease, age, sex, and blood types of the

recipient and donor; relationship between the recipient and the donor; Model for End-Stage Liver Disease (MELD) score[17]; Child-Turcotte-Pugh (CTP) score[18]; hepatitis C, hepatitis B, and hepatocellular carcinoma status; smoking status; living or not living with the family or donor; occupational status; and marital status. The alcohol consumption status before transplantation included the duration of drinking, the amount of ethanol per day, the number of inpatient treatments for alcoholism, a history of psychiatric problems other than alcoholism, and the length of abstinence before transplantation. Treatment data included the graft/recipient weight ratio (GRWR), the standard liver volume ratio (SLVR), and follow-up by psychiatrists. Postoperative living conditions included the smoking status, living with family, living with the donor, and occupational status. The clinical course included alcohol relapse as well as rejection, surgical and infectious complications, renal dysfunction, malignancies, noncompliance with clinic visits (3 absences without notice), and follow-up by psychiatrists. Liver biopsy was performed on demand. Histological findings of liver biopsy specimens were collected from medical records. Data on mortality and causes of death were also collected. This retrospective, multicenter study was approved by the human ethics review board of Tokyo Women's Medical University (2417 on February 29, 2012) as the place of data collection and analysis in accordance with the Declaration of Helsinki (as revised in Seoul, Korea in October 2008).

Selection Criteria for LT for ALC

The indication for LT for ALC was based on a patient's history of alcohol consumption and clinical and laboratory findings determined before LT at each institution. At all institutions, psychiatrists interviewed the patients and their families and confirmed the absence of substance abuse, including alcohol abuse and dependence, and the presence of an agreement indicating the intention of lifetime abstinence after LT. Since 1997, the Assessment Committee of Indication for Transplantation has assessed patients and determined their priority on the waiting list for DDLT in Japan. Currently, this committee accepts only patients with ALC for DDLT who score 2 or lower on the HRAR scale.[14]

Pretransplant Alcohol Use and Other Psychosocial Variables

A history of alcohol intake was also obtained, and this included the duration of drinking, types and amounts of alcohol consumed, and previous treatment history. The HRAR score was calculated. This score consists of 3 variables: the duration of heavy drinking, the number of drinks per day, and the number of earlier inpatient treatments for alcoholism.[14] Other demographic and psychosocial information collected during the pretransplant evaluation included the current or prior use of other substances, the diagnosis of substance use disorders and depressive or anxiety disorders, and

treatment for psychiatric disorders. Pretransplant abstinence was defined as the time between the last consumption of alcohol and the date of the transplant.

Posttransplant Alcohol Use Outcomes

The diagnosis of alcohol relapse was based on patient self-reports, reports by the patient's relatives and friends, comments by the primary care physician, and relevant laboratory or histological findings, and relapse was divided into 2 stages: recidivism and harmful relapse. Recidivism was defined as any alcohol intake after transplantation, and the onset time was reported. Harmful relapse was defined as declared alcohol consumption associated with the presence of alcohol-related damage, either physical (including histological features of alcohol liver injury on liver biopsy specimens and abnormal values on biochemical examinations for which etiologies other than ethanol were ruled out) or mental.[13] The diagnosis of harmful relapse was made at the last follow-up during this study, and the onset time was not available.

Three alcohol relapse patterns were defined [adapted from a study by DiMartini et al.[11]]: (1) relapse within 6 months of transplantation, (2) frequent use (4 drinking days per week), and (3) binge use (72 g of ethanol or more for men and 48 g of ethanol for women per day).

Statistical Analysis

Survival curves were constructed with the Kaplan-Meier method. In univariate and multivariate analyses, the log-rank test and Cox proportional hazards regression analysis were used to evaluate the association between patient characteristics and overall survival. Receiver operating characteristic curves were plotted, and areas under the curve were calculated to assess the optimal cutoff values for the MELD score, GRWR, and SLVR in the analysis of prognostic factors for patient survival.

The log-rank test and Cox proportional hazards regression analysis were also used to evaluate the association between patient characteristics and the incidence of recidivism in univariate and multivariate analyses. The incidence of harmful relapse was compared by means of the chi-square test, and multivariate logistic regression analysis was used to evaluate the association between patient characteristics and harmful relapse.

JMP 10.0 (SAS Institute, Inc., Cary, NC) was used for the statistical analysis.

RESULTS

Patients

Clinical and laboratory data were available for 195 patients who underwent LT at 36 of 38 institutions between November 1997 and December 2011. Among the 195 patients, 26 patients died before discharge after transplantation. Among the 169 patients who were discharged, information about alcohol relapse was available for 140 patients, and information about harmful relapse was available for 139 patients. The length of the follow-up period ranged from 3 to 4962 days with a median of 1319 days.

An analysis of prognostic factors for survival was performed for 195 patients. An analysis of risk factors for recidivism and the impact of recidivism on patient survival was performed for 140 patients, and an analysis of risk factors for harmful relapse and the impact of harmful relapse on patient survival was performed for 139 patients (Fig. 1).

Demographic data for the 195 patients are shown in Table 1. The MELD score ranged from 6 to 48 with a median value of 20. For most patients, the CTP score was C. The recipients' ages ranged from 25 to 69 years with a median age of 35 years. The donors' ages ranged from 17 to 65 years with a median age of 52 years. The blood type combination was identical for 127 patients, compatible for 49 patients, incompatible for 17 patients, and unknown for 2 patients. Six patients had a hepatitis C infection, 4 patients were positive for hepatitis B DNA, and 47 had hepatocellular carcinoma. GRWR ranged from 0.44% to 2.4% with a median value of 0.88%. SLVR ranged from 23.6% to 126% with a median value of 46.0%. Sixty-nine patients were male, and 195 patients were female. One hundred eighty-seven patients underwent LDLT, 5 patients underwent DDLT, and 3 patients had domino LT.

Institutional Policy of Patient Selection for LT for ALC in the Setting of LDLT

A period of abstinence of at least 6 months before LT was absolutely mandated at 21 institutions, was not required at all at 4 institutions, and was preferred but ignored in life-threatening cases at 11 institutions. The HRAR score was used for patient selection for LDLT at 13 institutions and was not used at 23 institutions.

Analysis of Prognostic Factors for Patient Survival

In univariate analyses, prognostic factors that were significantly and favorably associated with patient survival were a low MELD score (<19 versus ≥19) and a low donor age (<50 years versus ≥50 years). Both the MELD score and the donor age were also significant factors in the multivariate analysis (Tables 1 and 2).

Morbidity and Mortality

Postoperative comorbidities are shown in Table 3. The major complications were biliary complications (n = 41), cytomegalovirus infections (n = 38), bacterial infections (n = 37), acute cellular rejection (n = 34), and intra-abdominal hemorrhaging (n = 26). The causes of deaths before discharge for 26 patients are shown in Table 4. The most common causes were
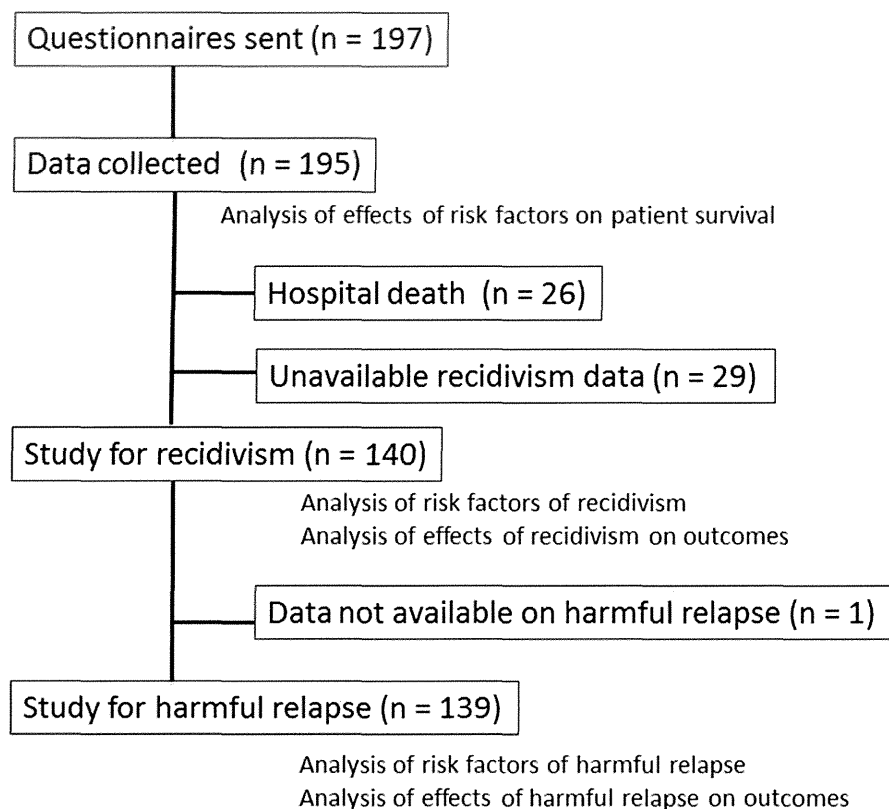
Figure 1. Patient enrollment and inclusion in our analysis. Questionnaires were sent to 38 centers for 197 patients. Clinical data were collected for 195 patients from 36 centers, and risk factors for patient survival were analyzed for these patients. Risk factors for recidivism and the impact of recidivism on patient survival were analyzed for 140 patients after 55 patients were excluded (26 who died in the hospital and 29 without data about recidivism). Data on harmful relapse were obtained and analyzed for 139 patients.

infectious complications (n = 10), small-for-size syndrome (n = 3), acute cellular rejection (n = 3), and hepatic artery thrombosis (n = 2).

The causes of death after discharge for 23 patients and their survival periods are shown in Table 5. Six patients died because of infectious complications; 7 died because of malignancies, including recurrent hepatocellular carcinoma; 2 died because of cerebral or myocardial vascular complications; and 1 died because of chronic rejection. Two patients died because of ALC on postoperative days 2526 and 4641.

There were 5 de novo tumors, including 2 gastric cancers and 3 squamous cell cancers. All 5 patients with these malignancies were abstinent and did not smoke after transplantation. Interestingly, however, all 5 patients had smoked before transplantation and quit after LT. The incidence of de novo malignancies increased as the quantity of daily drinking before transplantation increased on the HRAR scale [2.4% (1/41) with 108 g of ethanol or less each day, 6.1% (2/33) with >108 g-<204 g of ethanol each day, and 9.1% (2/22) with 204 g of ethanol or more each day],

although there was no significant relationship (P = 0.50).

Risk Factors for Alcohol Relapse

The significant risk factors for recidivism were a positive history of treatment for psychological diseases other than alcoholism before transplantation, an absence of a marital history, noncompliance with clinic visits after transplantation, and smoking after transplantation according to univariate analyses adjusted by the time of onset (Table 6). The significant risk factors for harmful relapse were living alone before LT, no marital history before LT, and noncompliance with clinic visits after LT (Table 6). The HRAR score had no relationship with the incidence of recidivism or harmful relapse. Six months of abstinence before LT had no significant impact. Abstinence for 24 months or longer decreased the incidence of harmful relapse (to 3.3%), but this difference was not significant. The occupational status had no impact on the incidence.

Risk factors for recidivism and harmful relapse that were significant (P < 0.05) in the univariate

TABLE 1. Influence of Pretransplant Risk Factors on Patient Survival in 195 Patients With ALC: A Log-Rank Analysis

Characteristic	Patients (n)	Patient Survival (%)				Log-Rank P Value
		1 Year	3 Years	5 Years	10 Years	
Entire cohort	195	82.5	78.4	74.5	50.4	
MELD score						0.04*
≥19	103	76.5	72.0	72.0	40.1	
<19	84	89.2	86.7	82.6	49.5	
Unknown	8	—	—	—	—	
CTP score						0.17
A	5	80.0	80.0	53.3	—	
B	43	83.7	83.7	79.0	67.7	
C	141	82.2	77.4	76.2	40.5	
Unknown	6	—	—	—	—	
Recipient age						0.96
≥50 years	117	82.0	77.1	75.7	66.0	
<50 years	78	81.9	80.3	78.3	39.5	
Donor age						0.01*
≥50 years	44	81.5	72.8	67.9	—	
<50 years	151	83.0	80.0	78.0	64.0	
Blood type combination						0.17
Identical	127	83.4	79.6	76.6	46.3	
Compatible	49	83.6	79.3	76.5	41.2	
Incompatible	17	68.2	64.2	64.2	—	
Unknown	2	—	—	—	—	
Hepatitis C						0.65
Yes	6	83.3	83.3	—	—	
No	186	81.6	77.9	75.2	52.3	
Unknown	3	—	—	—	—	
Hepatitis B DNA–positive						0.65
Yes	4	100.0	100.0	100.0	—	
No	190	81.4	77.8	75.1	51.4	
Unknown	1	—	—	—	—	
Hepatocellular carcinoma						0.97
Yes	47	87.1	77.7	74.1	60.5	
No	148	81.0	78.6	76.2	49.2	
GRWR						0.16
≥0.7%	156	84.5	80.4	77.6	5.4	
<0.7%	34	70.6	67.4	67.4	—	
Unknown	5	—	—	—	—	
SLVR						0.08
≥30%	179	82.6	78.8	75.9	50.2	
<30%	7	57.1	57.1	57.1	—	
Unknown	9	—	—	—	—	

*$P < 0.05$.

TABLE 2. Multivariate Analysis of Pretransplant Risk Factors for Patient Survival in 195 Patients With ALC: A Proportional Hazards Analysis

Risk Factor	Risk Ratio	95% CI	P Value
Donor age ≥ 50 years	2.33	1.28-4.13	<0.01*
MELD score ≥ 19	1.91	1.07-3.55	0.03

*$P < 0.05$.

analysis were chosen for the multivariate analysis. A history of treatment for psychological diseases other than alcoholism before transplantation was a signifi-

cant indicator of the risk of recidivism, and noncompliance with clinic visits after transplantation and smoking after transplantation were promising indicators of the risk of recidivism ($P = 0.06$ and $P = 0.05$, respectively; Table 7). Noncompliance with clinic visits was a significant indicator of the risk of harmful relapse.

The rates of recidivism were similar for patients living with donors (22.9% before LT and 27.9% after LT) and patients not living with donors (26.4% before LT and 25.9% after LT). Recidivism was high when the donors were parents (50.0%) or siblings (34.5%), but it was much lower when the donors were children (19.7%), spouses (13.3%), or nonrelatives (14.3%), although the difference was not

significant (Table 6). Similarly, the incidence of harmful relapse was much higher, but not significantly so, when the donors were parents or siblings

TABLE 3. Comorbidities After Transplantation in 195 Patients	
Comorbidities	Patients (n)
Biliary complications	41
Cytomegalovirus diseases	38
Bacterial infection	37
Acute cellular rejection	34
Intra-abdominal hemorrhage	26
Malignancies*	13
Vascular complications	12
Fungal infection	12
Permanent dialysis	8
Steroid-resistant acute cellular rejection	5
Chronic rejection	2

*Recurrence of hepatocellular carcinoma (n = 8), gastric cancer (n = 2), lung squamous cell cancer (n = 1), tongue squamous cell cancer (n = 1), and frontal sinus squamous cell cancer (n = 1).

TABLE 4. Causes of Hospital Deaths	
Cause of Death	Patients (n)
Infection	10
Small-for-size syndrome	3
Acute cellular rejection	3
Chronic rejection	1
Hepatic artery thrombosis	2
Portal vein flow insufficiency	1
Cerebral hemorrhage	1
ABO-I AMR	1
Graft-versus-host disease	1
Multiorgan failure	1
Biliary stenosis	1
Graft injury	1

versus when the donors had other relationships with the recipients (Table 6).

Impact of Alcohol Consumption After LT on Patient Survival

The survival rates were compared for recidivist patients and abstinent patients 18 months after LT. Five patients for whom the time of relapse was not obtained and 10 patients who had died within 18 months of LT were excluded from this analysis. The survival rates were 100.0%, 94.7%, 89.5%, 65.7%, and 21.9% at 1, 3, 5, 7, and 10 years, respectively, for recidivist patients and 100.0%, 98.6%, 96.4%, 92.7%, and 73.8% at 1, 3, 5, 7, and 10 years, respectively, for abstinent patients. There was a significant difference in survival ($P = 0.01$; Fig. 2).

Impact of Alcohol Consumption Status on Harmful Relapse

The impact of an early onset of drinking, frequent drinking, and the consumption of large amounts of alcohol after LT on the incidence of harmful relapse was analyzed in 32 recidivist patients. The incidence of harmful relapse was higher for patients who consumed alcohol 4 days or more per week (88.9%) versus patients who drank less frequently (35.7%, $P = 0.008$; Table 8), and it was higher for patients who binged (100%) versus patients who drank less (25%, $P = 0.002$; Table 8). One patient showed all 3 patterns of harmful drinking, and 5 patients showed 2 of the 3 patterns.

Histological Changes in the Liver After LT

Liver biopsy was performed for 20 recidivist patients and 53 abstinent patients. Results from biopsy samples obtained before hospital discharge were included. The incidence of fatty changes was greater in the recidivism group (45.0%) versus the abstinent group (13.2%; Table 9). In contrast, the incidence of rejection was greater in the abstinent group (30.6%) versus

TABLE 5. Causes of Death After Discharge		
Cause of Death	Patients (n)	Survival Period (Days)
Infection	6	3802, 2256, 662, 517, 328, 295
Hepatocellular carcinoma recurrence	5	2588, 2057, 422, 357, 300
Gastric cancer	1	2309
Lung cancer	1	195
Cholangitis	2	3302, 1414
Alcoholic cirrhosis	2	2526, 4641
Arachnoid hemorrhage	1	246
Myocardial infarction	1	2983
DIC/lung edema	1	1990
Chronic rejection	1	528
Accident	1	3361
Intra-abdominal hemorrhage	1	373

Risk Factor	Patients (n)	Recidivism: Log-Rank Test [n/N (%)]*	P Value	Patients (n)	Harmful Relapse: Chi-Square Test [n/N (%)]†	P Value
Before transplantation						
HRAR score			0.48			0.24
0	8	1/8 (12.5)		8	1/8 (12.5)	
1	25	8/25 (32.0)		25	6/25 (24.0)	
2	40	8/40 (20.0)		40	4/40 (10.0)	
3	16	4/16 (25.0)		15	3/15 (20.0)	
4	9	1/9 (11.1)		9	0/9 (0.0)	
Unknown	42	—		42	—	
Duration of heavy drinking			0.41			0.50
≥25 years	41	9/41 (22.0)		41	4/41 (9.8)	
<11->25 years	32	7/32 (21.9)		31	6/31 (19.4)	
≤11 years	31	9/31 (29.0)		31	7/31 (22.6)	
Unknown	36	—		36	—	
Daily alcohol consumption‡			0.96			0.47
≤9 g	43	11/43 (25.6)		43	9/43 (20.9)	
<9->17 g	36	8/36 (22.2)		36	4/36 (11.1)	
≥17 g	23	5/23 (21.7)		22	3/22 (13.6)	
Unknown	38	—		38	—	
Pretransplant abstinence			0.39			0.68
≥6 months	100	19/100 (19.0)		99	13/99 (13.1)	
<6 months	31	9/31 (29.0)		31	5/31 (16.1)	
Unknown	9	—		9	—	
Pretransplant abstinence			0.77			0.19
≥24 months	31	5/31 (16.1)		30	1/30 (3.3)	
12-24 months	20	3/20 (15.0)		20	3/20 (15.0)	
6-12 months	49	11/49 (22.4)		49	9/49 (18.4)	
<6 months	31	9/31 (29.0)		31	5/31 (16.1)	
Unknown	9	—		9	—	
History of treatment for psychiatric diseases other than alcoholism			<0.01‡			0.17
Yes	9	5/9 (55.6)		9	3/9 (33.3)	
No	125	27/125 (21.6)		125	18/125 (14.4)	
Unknown	6	—		5	—	
Recipient sex			0.16			0.73
Male	88	23/88 (26.1)		88	14/88 (15.9)	
Female	52	9/52 (17.3)		51	7/51 (13.7)	
Smoking			0.12			0.43
Smoking	46	15/46 (32.6)		46	10/46 (21.7)	
No history	24	5/24 (20.8)		24	3/24 (12.5)	
Quit	59	8/59 (13.6)		58	6/58 (10.3)	
Unknown	11	—		11	—	
Living			0.08			0.03‡
With family	122	27/122 (22.1)		121	16/121 (13.2)	
Alone	9	4/9 (44.4)		9	4/9 (44.4)	
Unknown	9	—		9	—	
Marital status			0.04‡			0.04‡
Stable partner	106	24/106 (22.6)		105	15/105 (14.3)	
Widowed/divorced	10	1/10 (10.0)		10	1/10 (10.0)	
No marital history	13	6/13 (46.2)		13	5/13 (38.5)	
Unknown	11	—		11	—	
Living with donor			0.99			0.28
Yes	70	16/70 (22.9)		69	8/69 (11.6)	
No	53	14/53 (26.4)		53	11/53 (20.8)	
Unknown	17	—		17	—	
Occupational status			0.41			0.85
No	42	9/42 (21.4)		41	7/41 (17.1)	
Part time	13	2/13 (15.4)		13	1/13 (7.7)	
Full time	64	16/64 (25.0)		64	10/64 (15.6)	
Unknown	21	—		21	—	

TABLE 6. Univariate Analysis of Risk Factors for Recidivism and Harmful Relapse After Transplantation

TABLE 6. *Continued*

Risk Factor	Patients (n)	Recidivism: Log-Rank Test [n/N (%)]*	P Value	Patients (n)	Harmful Relapse: Chi-Square Test [n/N (%)]†	P Value
After transplantation						
Noncompliance with clinic visits			<0.01‡			0.03§
Yes	8	4/8 (50.0)		7	4/7 (57.1)	
No	131	8/131 (6.1)		131	17/131 (13.0)	
Unknown	1	—		1	—	
Followed by psychiatrists			0.78			0.78
Yes	29	7/29 (24.1)		29	5/29 (17.2)	
No	108	25/108 (23.1)		107	16/107 (15.0)	
Unknown	3	—		3	—	
Smoking			<0.01‡			0.09
Yes	24	11/24 (45.8)		24	7/24 (29.2)	
No	73	12/73 (16.4)		72	7/72 (9.7)	
Unknown	43	—		43	—	
Living			0.25			0.07
With family	107	25/107 (23.4)		107	17/107 (15.9)	
Alone	8	4/8 (50.0)		8	3/8 (37.5)	
Unknown	25	—		24	—	
Living with donor			0.46			0.07
Yes	43	12/43 (27.9)		43	7/43 (16.3)	
No	58	15/58 (25.9)		57	12/57 (21.1)	
Unknown	39	—		39	—	
Occupational status			0.18			0.34
No	51	14/51 (27.5)		50	8/50 (16.0)	
Part time	14	4/14 (28.6)		14	4/14 (28.6)	
Full time	38	9/38 (23.7)		38	6/38 (15.8)	
Unknown	37	—		37	—	
Donors			0.07			0.07
Parent	6	3/6 (50.0)		6	3/6 (50.0)	
Sibling	29	10/29 (34.5)		29	8/29 (27.6)	
Son/daughter	61	12/61 (19.7)		61	4/61 (6.6)	
Nonrelative	7	1/7 (14.3)		7	1/7 (14.3)	
Spouse	30	4/30 (13.3)		29	3/29 (10.3)	
Nephew	3	1/3 (33.3)		3	1/3 (33.3)	
Cousin	1	0/1 (0.0)		1	0/1 (0.0)	
Brother-in-law	2	1/2 (50.0)		2	1/2 (50.0)	
Nephew-in-law	1	0/1 (0.0)		1	0/1 (0.0)	

*32/140 (22.9%).
†21/139 (15.1%).
One drink = 12 g of ethanol.
‡$P < 0.05$ (chi-square test)

the recidivism group (25.0%; Table 9). Alcoholic damage was found in 3 patients with recidivism.

Information on the presence or absence of acute cellular rejection after discharge was obtained from 130 patients. The incidence of rejection was 6.9% (2/29) for recidivist patients and 5.0% (5/101) for patients who were abstinent.

Patients for Whom Information on Alcohol Relapse Was Not Available

Twenty-nine patients for whom information on alcohol relapse was not available were excluded from the statistical analysis of alcohol relapse. To understand the impact of this exclusion on the results, we analyzed the overall survival and frequency of risks for recidivism for the 29 patients. There was no significant difference in overall survival between abstinent patients, relapsing patients, and patients of an unknown status (data not shown; $P = 0.09$, log-rank test). For abstinent patients, relapsing patients, and patients of an unknown status, the frequency of noncompliance with clinic visits was 3.7%, 12.5%, and 15.4%, respectively ($P = 0.03$); the frequency of smoking after LT was 17.5%, 47.8%, and 100.0%, respectively ($P < 0.001$); the frequency of no marital history was 7.1%, 19.3%,

TABLE 7. Multivariate Analysis of Risk Factors for Recidivism and Harmful Relapse			
		Proportional Hazards Analysis	
Risk Factors for Recidivism	Risk Ratio	95% CI	P Value
History of treatment for psychiatric diseases other than alcoholism: yes versus no	5.15	1.26-17.78	0.02*
Marital status			
Stable partner	1.00	—	
Widowed/divorced	0.45	0.02-2.46	0.41
No marital history	1.24	0.34-4.99	0.75
Noncompliance with clinic visits: yes versus no	4.36	0.92-15.43	0.06
Posttransplant smoking: yes versus no	2.67	0.97-7.00	0.05
		Logistic Regression Analysis	
Risk Factors for Harmful Relapse	Odds Ratio	95% CI	P Value
History of treatment for psychiatric diseases other than alcoholism: yes versus no	5.15	1.26-17.78	0.02*
Marital status			
Stable partner	1.00	—	
Widowed/divorced	0.45	0.02-2.46	0.41
No marital history	1.24	0.34-4.99	0.75
Noncompliance with clinic visits: yes versus no	4.36	0.92-15.43	0.06
Posttransplant smoking: yes versus no	2.67	0.97-7.00	0.05
Pretransplant living: alone versus family	3.21	0.43-23.46	0.25
Pretransplant marital status			
Stable partner	1.00	—	
Widowed/divorced	0.31	0.01-2.32	0.28
No marital history	2.41	0.38-11.76	0.32
Noncompliance with clinic visits: yes versus no	16.32	2.56-149.34	0.004*

*$P < 0.05$.

and 4.2%, respectively ($P = 0.14$); and the frequency of a history of treatment for psychiatric diseases other than alcoholism was 3.9%, 15.6%, and 6.9%, respectively ($P < 0.001$). Although these 29 patients were less compliant with clinic visits than abstinent patients, 21 of the 29 patients visited the clinic regularly, 4 patients fell into noncompliance, 1 patient died, 1 patient changed hospitals, and the data for 2 patients were unknown. However, for 28 of the 29 patients (including 1 deceased patient), data for smoking as well as relapse data were not available.

Interactions Between Recipients Who Returned to Harmful Drinking and Related Donors

We hypothesized that interactions between a recipient who returns to harmful drinking and the family member who donated the liver might affect outcomes. Although we were not able to examine this directly, we compared the survival rates between recipients living with their donors and recipients who lived separately from their donors. The survival rates were 95.2%, 86.4%, 86.4%, 71.2%, and 63.3% at 1, 3, 5, 7, and 10 years, respectively, for recipients living with donors and 100.0%, 98.2%, 92.0%, 83.5%, and 41.8% at 1, 3, 5, 7, and 10 years, respectively, for

recipients living without donors ($P = 0.66$). Although this result does not address the existence or absence of a change in the relationship after the onset of harmful drinking, if such changes do occur, they do not affect survival.

DISCUSSION

Patients undergoing LT for ALC must pledge to remain sober in order to protect the transplanted liver. However, not all recipients are able to maintain sobriety. Alcohol relapse can have a number of negative impacts, including (1) liver dysfunction secondary to alcohol toxicity, (2) noncompliance with medications or clinic visits, (3) rejection secondary to noncompliance, (4) graft failure secondary to rejection or alcohol toxicity, and (5) malignancies and cardiovascular diseases possibly related to smoking (which is highly associated with alcohol relapse). The perception that recipients will relapse may also decrease the willingness of others to donate organs.

Harmful Drinking and Impact

Reports have differed in both the definitions used for harmful drinking and its effects after LT. Schmeding
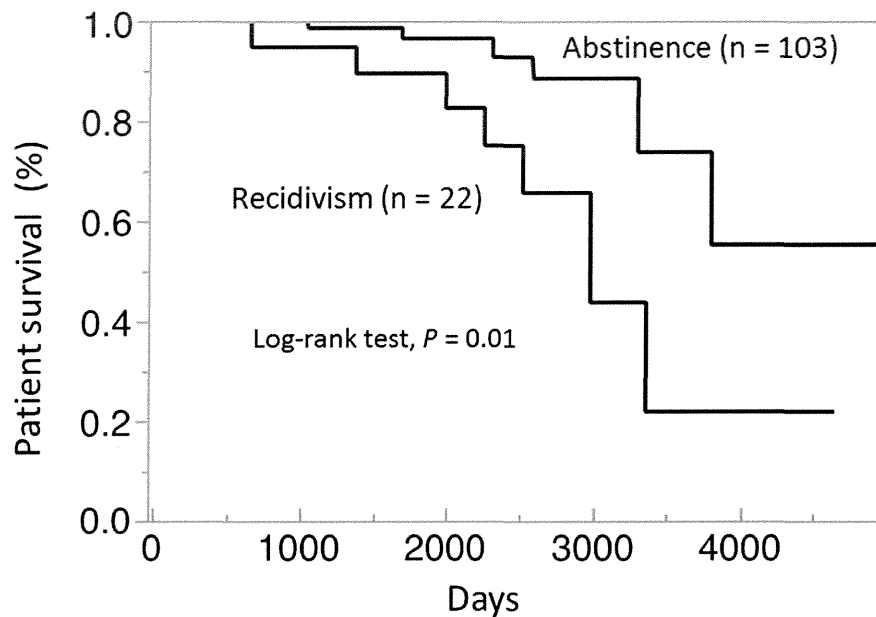
Numbers at risk	0 years	1 year	3 years	5 years	7 years	10 years
Recidivism	22	22	19	14	7	2
Abstinence	103	103	70	42	25	5

Figure 2. Impact of alcohol relapse on patient survival: comparison of recidivism and abstinence 18 months after transplantation. There was a significant difference in survival between the groups (log-rank test, P = 0.01).

TABLE 8. Impact of the Alcohol Consumption Status on Harmful Relapse in 32 Patients With Recidivism

	Patients (n)	Harmful Relapse [n/N (%)]	P Value
Recidivism within 6 months			0.91
Yes	12	8/12 (66.7)	
No	16	11/16 (68.8)	
Unknown	4	—	
Frequent use*			0.008[†]
Yes	9	8/9 (88.9)	
No	14	5/14 (35.7)	
Unknown	9	—	
Binge use[‡]			0.002[†]
Yes	6	6/6 (100.0)	
No	8	2/8 (25.0)	
Unknown	18	—	

*Four drinking days per week.
[†]$P < 0.05$ (chi-square test).
[‡]Seventy-two grams of ethanol or more for men and 48 g of ethanol or more for women.

et al.[15] found significantly lower 10-year patient survival for patients with alcohol consumption of 80 g/day or more for men or 20 g/day or more for women, and Cuadrado et al.[16] found significantly lower 10-year patient survival for patients with alcohol consumption of 30 g/day or more. In contrast, Tandon et al.[12] defined problem drinking as either any drinking to the point of intoxication or drinking above the

TABLE 9. Histological Changes in Liver Biopsy Samples Throughout the Study

Histological Findings	Recidivism (n = 20)	Abstinence (n = 53)
Minimal or normal changes	2 (10.0)	10 (18.9)
Fatty changes	9 (45.0)	7 (13.2)
Alcoholic damage	3 (15)	0
Cholestatic changes	0	4 (7.5)
Hepatitis	1 (5.0)	6 (11.3)
Rejection	5 (25.0)	21 (39.6)
Fibrosis	0	2 (3.8)
Hepatocellular carcinoma	0	1 (1.9)
Other changes	0	2 (3.8)

NOTE: The data are presented as numbers and percentages. $P = 0.01$ (chi-square test).

toxic threshold (>20 g/day for women and >40 g/day for men) on at least 2 separate occasions, and they found no effect of problem drinking on posttransplant mortality in a North American cohort. Frequent use and binge use contributed to harmful relapse, but early relapse did not. Harmful relapse was significantly related to noncompliance with clinic visits, although our study did not reveal whether noncompliance caused harmful relapse or vice versa because we did not have access to the timing of these elements.

Noncompliance and Rejection

Webb et al.[17] noted that the resumption of problem drinking can lead to noncompliance with the transplant follow-up program, which can, in turn, lead to rejection. In our study, the incidence of noncompliance with clinic visits was significantly greater for patients who had resumed drinking, but the rates of acute cellular rejection confirmed by liver biopsy were similar for the groups. The only patient who died because of chronic rejection was abstinent.

Malignancies and Cardiovascular Diseases

Alcohol use can contribute to the mortality of transplant recipients because of a variety of proximal causes. Burra et al.[18] reported that de novo tumors, cardiovascular events, and social causes (including noncompliance with immunosuppressive therapy, suicide, and trauma) were causes of death or graft failure for a higher percentage of those with alcohol disease in comparison with patients with other etiologies in a large cohort from the European Liver Transplant Registry.[18] Cuadrado et al.[16] reported significantly lower patient survival for patients with alcohol relapse and suggested that alcohol consumption and tobacco use may have contributed to cancer and cardiovascular events, which were frequent causes of death; however, they did not compare the incidences of these diseases between patients who relapsed into alcohol use or smoked and patients who did not. In our study, overexposure to the toxicity of alcohol and nicotine before transplantation might have been a risk factor for postoperative extrahepatic malignancies under immunosuppression therapy. Careful follow-up focusing on malignancies is recommended after LT for ALC whether or not the patient relapses.

Relapse Rates in DDLT and LDLT

In DDLT, organs are considered to be a public resource that should be shared fairly and effectively. Hence, alcohol relapse may result in public opposition to transplantation for ALC. In a study that defined relapse as any alcohol use, the rate of posttransplant alcohol consumption appeared to be quite high: approximately 50% of patients (range = 7%-95%) at a follow-up visit 21 to 83 months after transplantation.[19] We had hypothesized that recidivism might be lower among patients in Japan who had received transplants from family members, but our findings were more complicated. The incidence of recidivism for patients who had received donations from unrelated persons, including brain-dead donors and domino donors, was 14.3%, and the incidence for those who had received donations from spouses was 13.3%, whereas the incidence of recidivism for patients who had received donations from relatives other than spouses was higher (23.3%). The rates of recidivism and harmful relapse were quite high (27.6%-50.0%) when the donors were parents or siblings. Thus, contradicting our hypothesis, the relapse rate is not ubiquitously low for LDLT patients; instead, it is high, especially when a parent is the donor. As for interactions between related donors and relapsing patients, there were no episodes such as divorce or disownment due to recidivism after LT in this cohort as far as personal communications show. The related donors who accepted their own risks before LT might have forgiven the recipients who had relapsed after LT because of their voluntary donation on behalf of love.

We feel that DDLT is suitable for LT for ALC from the point of view of the relapse rate, but efforts are required to decrease the rate even further to ensure that public opinion about organ donation for ALC is favorable.

Limitations

The findings of this retrospective, multicenter study are limited by several factors inherent to this type of study, including variability in documentation, differences in selection criteria and data collection, and missing data. To minimize variability, we sent a standardized collection form containing 150 questions to the transplant centers. The answers either were to be chosen from several options or involved providing a name or a specific value. However, the quality of the pretransplant interviews, from which the baseline data were derived, and the quality of the posttransplant follow-up data across the 36 centers may have varied. The HRAR, CTP, and MELD scores were calculated by H.E. and S.T. The results could have been affected by missing data if the patients who were lost to follow-up were lost because of their drinking, but we cannot know if this is the case. Finally, the element of time should be taken into account in the statistical analyses because the subjects had different lengths of follow-up. Although we had data for the onset of recidivism, we did not have data for the onset of harmful relapse and noncompliance. To solve these limitations, a well-designed prospective study will be necessary.

How Can We Decrease Relapse?

The significantly lower survival rate for relapsing patients shown in this study indicates that preventing relapse is the central strategy for LT for ALC. In order to develop good protocols to decrease relapse, it is important to identify the major (and treatable) risks. Tandon et al.[12] reported that the duration of pretransplant abstinence was a strong predictor of posttransplant problem drinking in a North American cohort of patients undergoing transplantation for alcohol-related liver disease, but they failed to show the optimal period of abstinence. De Gottardi et al.[13] reported the utility of the HRAR score for predicting relapse after transplantation. Gish et al.[20] reported that noncompliance and personality disorders independently predicted recidivism. Kelly et al.[10] identified the following 6 potential predictors of harmful relapse: mental illness, the lack of a stable partner, grams of alcohol consumed per day at the time of assessment, reliance on family or friends for posttransplant support, tobacco consumption at the time of assessment, and lack of insight into alcohol as the cause of the liver disease.[10] Our current study showed that a history of treatment for psychological diseases other than alcoholism before transplantation was a significant indicator of the risk of recidivism, and noncompliance with clinic visits after transplantation and smoking after transplantation were promising (but not statistically significant) indicators. Noncompliance with clinic visits was a significant indicator of the risk of harmful relapse. Notably, we did not find that the HRAR score predicted recidivism or harmful relapse. Because of severe organ shortages, the Japanese Assessment Committee of Indication for Transplantation has used an HRAR score ≤ 2 as a selection criterion for DDLT for ALC in accordance with De Gottardi et al. However, on the basis of our findings, the Japanese Assessment Committee of Indication for Transplantation recently removed the HRAR score restriction.

Although the use of LDLT for ALC is increasing, alcohol relapse after transplantation is not yet widely recognized in Japanese society, and this is the first report on the risk factors for and frequency of relapse in patients undergoing LDLT for ALC in Japan. What Japanese society requests from clinical specialists is not punishment but rescue. To decrease the relapse rate, we have 2 options: we can restrict the patients who receive transplants on the basis of pretransplant indicators, or we can use professional personnel, such as psychiatrists, addiction specialists, and well-trained recipient coordinators, to provide systematic support to high-risk patients. We believe that improving compliance through systematic professional support is necessary for patients undergoing LT for ALC in Japan.

and Yokohama City University (Dr. Takeda and Dr. Endo).

REFERENCES

1. Japanese Liver Transplantation Society. Liver transplantation in Japan—registry by the Japanese Liver Transplantation Society [in Japanese]. Ishoku 2010;46:524-536.

2. Mackie J, Groves K, Hoyle A, Garcia C, Garcia R, Gunson B, Neuberger J. Orthotopic liver transplantation for alcoholic liver disease: a retrospective analysis of survival, recidivism, and risk factors predisposing to recidivism. Liver Transpl 2001;7:418-427.

3. Bird GL, O'Grady JG, Harvey FA, Calne RY, Williams R. Liver transplantation in patients with alcohol cirrhosis: selection criteria and rates of survival and relapse. BMJ 1990;301:15-17.

4. Pfitzmann R, Schwenzer J, Rayes N, Seehofer D, Neuhaus R, Nüssler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl 2007;13:197-205.

5. Dew MA, DiMartini AF, Steel J, De Vito Dabbs A, Myaskovsky L, Unruh M, Greenhouse J. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. Liver Transpl 2008;14:159-172.

6. Bravata DM, Keeffe EB, Owens DK. Quality of life, employment, and alcohol consumption after liver transplantation. Curr Opin Organ Transplant 2001;6:130-141.

7. Kawaguchi Y, Sugawara Y, Yamashiki N, Kaneko J, Tamura S, Aoki T, et al. Role of 6-month abstinence rule in living donor liver transplantation for patients with alcoholic liver disease. Hepatol Res 2013;43:1169-1174.

8. Shawcross DL, O'Grady JG. The 6-month abstinence rule in liver transplantation. Lancet 2010;376:216-217.

9. Jauhar S, Talwalkar JA, Schneekloth T, Jowsey S, Wiesner RH, Menon KV. Analysis of factors that predict alcohol relapse following liver transplantation. Liver Transpl 2004;10:408-411.

10. Kelly M, Chick J, Gribble R, Gleeson M, Holton M, Winstanley J, et al. Predictors of relapse to harmful alcohol after orthotopic liver transplantation. Alcohol Alcohol 2006;41:278-283.

11. DiMartini A, Day N, Dew MA, Javed L, Fitzgerald MG, Jain A, et al. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. Liver Transpl 2006;12:813-820.

12. Tandon P, Goodman KJ, Ma MM, Wong WW, Mason AL, Meeberg G, et al. A shorter duration of pretransplant abstinence predicts problem drinking after liver transplantation. Am J Gastroenterol 2009;104:1700-1706.

13. De Gottardi A, Spahr L, Gelez P, Morard I, Mentha G, Guillaud O, et al. A simple score for predicting alcohol relapse after liver transplantation: results from 387 patients over 15 years. Arch Intern Med 2007;167:1183-1188.

14. Yates WR, Booth BM, Reed DA, Brown K, Masterson BJ. Descriptive and predictive validity of a high-risk alcoholism relapse model. J Stud Alcohol 1993;54:645-651.

15. Schmeding M, Heidenhain C, Neuhaus R, Neuhaus P, Neumann UP. Liver transplantation for alcohol-related cirrhosis: a single centre long-term clinical and histological follow-up. Dig Dis Sci 2011;56:236-243.

16. Cuadrado A, Fábrega E, Casafont F, Pons-Romero F. Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcohol liver disease. Liver Transpl 2005;11:420-426.

17. Webb K, Shepherd L, Day E, Masterton G, Neuberger J. Transplantation for alcoholic liver disease: report of a consensus meeting. Liver Transpl 2006;12:301-305.

18. Burra P, Senzolo M, Adam R, Delvart V, Karam V, Germani G, Neuberger J; for ELITA and ELTR Liver Transplant Centers. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant 2010;10:138-148.

19. Lim JK, Keeffe EB. Liver transplantation for alcoholic liver disease: current concepts and length of sobriety. Liver Transpl 2004;10(suppl 2):S31-S38.

20. Gish RG, Lee A, Brooks L, Leung J, Lau JY, Moore DH II. Long-term follow-up of patients diagnosed with alcohol dependence or alcohol abuse who were evaluated for liver transplantation. Liver Transpl 2001;7:581-587.

Pregnancy outcomes after living donor liver transplantation: Results from a Japanese survey

Shoji Kubo,[1,*] Shinji Uemoto,[2] Hiroyuki Furukawa,[3] Koji Umeshita,[4] Daisuke Tachibana,[5] and the Japan Liver Transplantation Society

[1]Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan

[2]Department of Hepato-Biliary-Pancreatic Surgery and Transplantation, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[3]Division of Gastroenterologic and General Surgery, Department of Surgery, Asahikawa Medical University, Asahikawa, Japan

[4]Division of Health Sciences, Graduate School of Medicine, Osaka University, Osaka, Japan

[5]Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine, Osaka, Japan

Running title: Pregnancy after liver transplantation

*Corresponding author: Shoji Kubo, MD, Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan

E-mail: m7696493@msic.med.osaka-cu.ac.jp

2

Abstract

A national survey of pregnancy outcomes after living donor liver transplantation was performed in Japan. Thirty-eight pregnancies in 30 recipients resulted in 31 live births (25 recipients), 3 artificial abortions in the first trimester (3 recipients), 1 spontaneous abortion (1 recipient), and 3 fetal deaths (3 recipients). During 35 pregnancies in 27 recipients (other than the 3 artificial abortions), pregnancy-induced hypertension developed in 6 pregnancies (5 recipients), fetal growth restriction in 7 (6 recipients), acute rejection in 2 (2 recipients), and ileus in 1 (1 recipient). Preterm delivery (<37 weeks) occurred in 10 pregnancies (10 recipients), and cesarean delivery was performed in 12 pregnancies (12 recipients). After delivery, acute rejection developed in 3 recipients. Twelve neonates were born with low birth weights (<2500 g), and 4 of these 12 had extremely low birth weights (<1500 g). Two neonates had congenital malformations. The pregnancy outcomes after living donor liver transplantation were similar to those reported for cadaver liver transplantation. The incidence of pregnancy-induced hypertension in recipients aged ≥33 years at pregnancy diagnosis was significantly higher than that in recipients aged <33 years at pregnancy diagnosis. The incidences of fetal growth restriction, pregnancy-induced hypertension, and extremely low birth weight were significantly higher in the early group (pregnancy

3

-293-

within 3 years after transplantation) than in the late group (≥3 years following transplantation). It is necessary to pay careful attention to complications during pregnancy in recipients who become pregnant within 3 years after liver transplantation, particularly if the age at pregnancy diagnosis is ≥33 years.

(251 words)

4

The number of patients undergoing liver transplantation (LT) has increased;

therefore, the number of women of reproductive age receiving LT has also increased.

In the United States, recipients who become pregnant after organ transplantation are

registered, and their statistics are regularly reported (1–5). Many studies concerning

pregnancy after LT have been reported by the United Kingdom Transplant Pregnancy

Registry and transplantation centers (6–22). Recent case-control studies and

meta-analyses have shown that LT recipients and their infants have an increased risk

of obstetric complications, although most pregnancy outcomes are favorable (23,24).

Although the pregnancy outcomes in some recipients after living donor liver

transplantation (LDLT) have been reported in one study (4), most participants in

previous studies were cadaver LT recipients. Here, the results of a national survey of

pregnancy outcomes after LDLT in Japan are presented and discussed.

Subjects and Methods

In Japan, data on LT, including LDLT and cadaver LT, and the institutes (hospitals

or medical centers) that perform LT are registered with the Japanese Liver

Transplantation Society. By the end of 2011, 139 cadaver LTs and 6503 LDLTs were

registered with the society (25). The Japanese Liver Transplantation Society

5