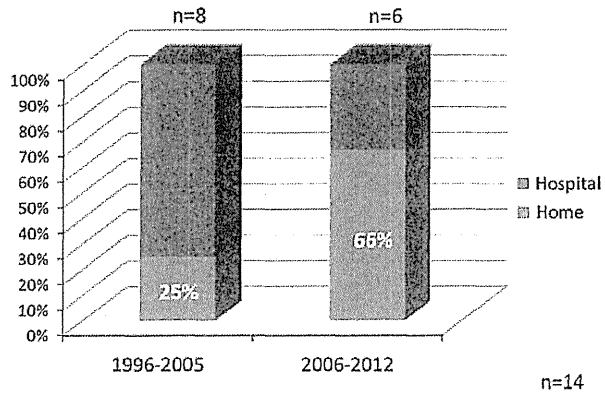

Fig. 2 Pre-transplant patient status

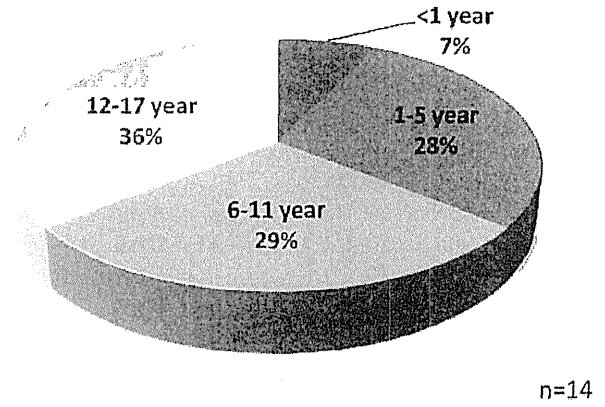

Fig. 3 Recipient age at transplant

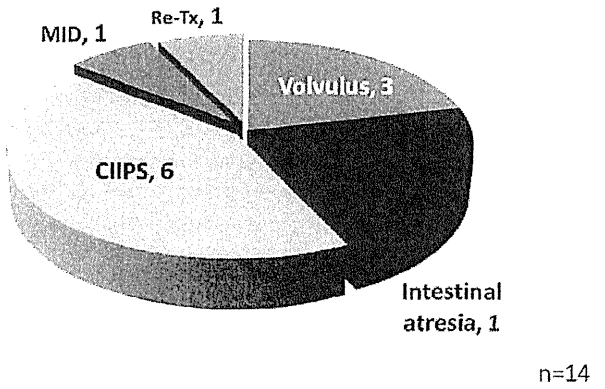

Fig. 4 Cause of intestinal failure *NEC* necrotizing enterocolitis, *CIIPS* chronic idiopathic intestinal pseudo-obstruction syndrome, *MID* microvillus inclusion disease, *Re-Tx* Re-transplant

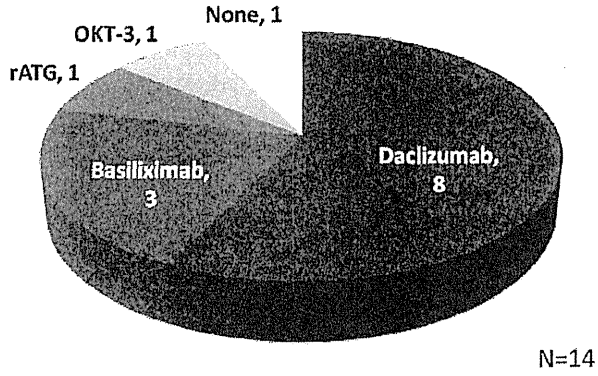

Fig. 5 Induction immunosuppression therapy *rATG* rabbit anti-thymus globulin, *OKT-3* anti-CD3 monoclonal antibody

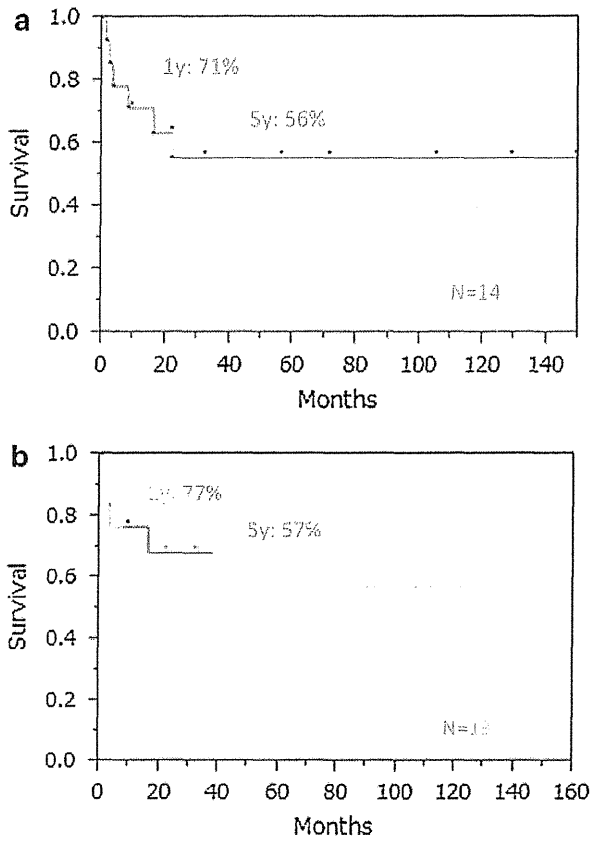

Fig. 6 Overall graft (**a**) and patient (**b**) survival

The causes of death included sepsis ($n = 3$), post-transplant lymphoma ($n = 1$) and intra cranial hemorrhage ($n = 1$).

The 1-year overall graft survival rate was 80 % for cadaveric grafts versus 50 % for living donor grafts ($p = 0.76$), as shown in Fig. 7a. The 1-year overall patient survival rate was 80 % for cadaveric grafts versus 67 % for living donor grafts ($p = 0.88$), as shown in Fig. 7b.

Graft survival improved over the last 5 years. The one- and five-year graft survival rates were 83 and 83 % for 2006–2011 versus 63 and 38 % for 1996–2005 ($p = 0.14$), as shown in Fig. 8a. The 1- and 5-year patient survival rates were 83 and 83 % for 2006–2011 versus 71 and 43 % for 1996–2005 ($p = 0.27$), as shown in Fig. 8b.

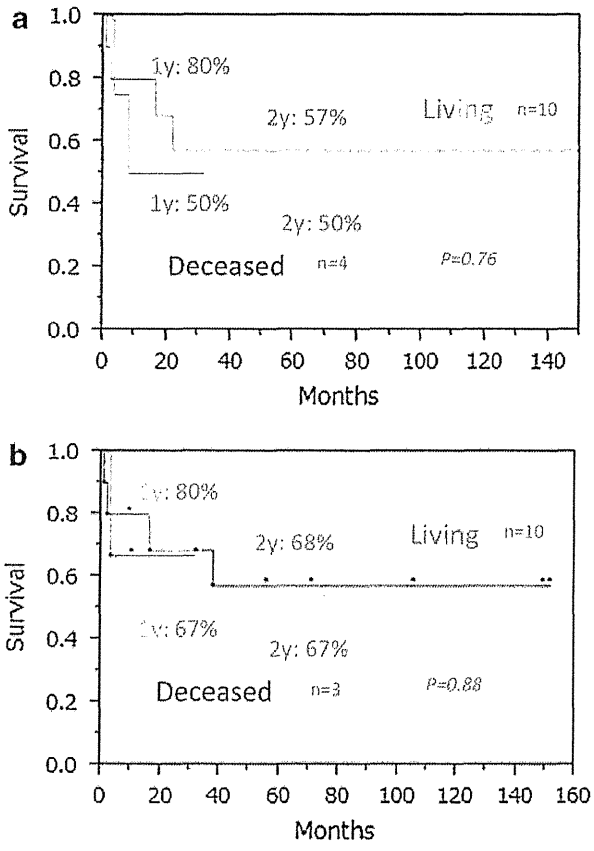

Fig. 7 Graft (**a**) and patient (**b**) survival according to graft type

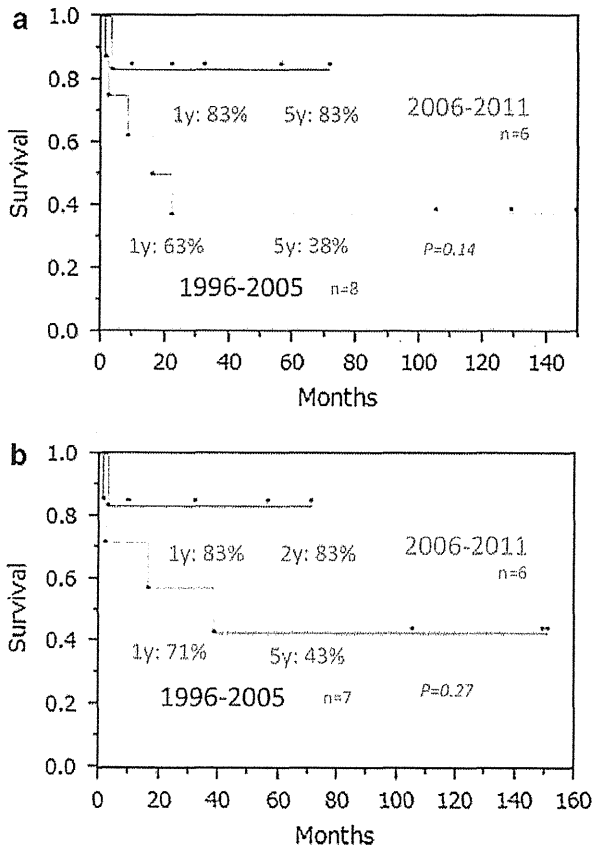

Fig. 8 Graft (**a**) and patient (**b**) survival by era

Graft function in terms of PN dependence was excellent. All patients became PN-free after intestinal transplantation, although two-thirds of patients require continuous or intermittent intravenous fluid support. Of the eight patients who were alive at the time of data collection, all patients were off parenteral nutrition, with three patients requiring intravenous fluids daily, two patients requiring intravenous fluids occasionally (Fig. 9). Most recipients stopped parenteral supplementation, eat, and have resumed normal activities. Of the seven surviving patients 1 year after transplant, six lead a full life.

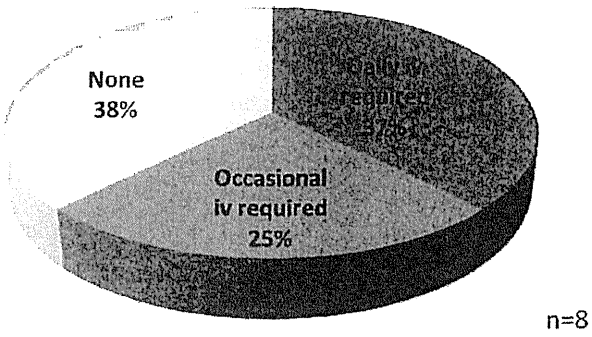

Fig. 9 Intravenous (IV) fluid requirement after intestinal transplantation

Discussion

Children with intestinal failure are at risk for numerous complications, especially PN-related complications. For example, loss of venous access and IFALD are still major problems for patients with intestinal failure because they are potentially life-threatening [4].

Catheter-related bloodstream infections were common in patients with intestinal failure [5]. Survival of children with chronic intestinal failure has increased as result of home PN. Adequate central venous accesses crucial for the successful management of home PN, but venous access can be complicated by episodes of catheter-associated infection, repeated procedures to replace catheters, and catheter-related thrombosis. Management and prevention of catheter-related thrombosis are of vital importance. [6].

IFALD can be a progressive and fatal entity in children with short gut syndrome. Parenteral fish oil-based fat emulsions are safe and may be effective in the treatment of PN-associated liver disease [7]. A lipid reduction protocol may prevent cholestasis [8]. Despite all efforts to prevent

complications, some children develop end-stage intestinal failure.

As outcomes of intestinal transplantation have improved, it has become the definitive treatment for patients with intestinal failure who cannot tolerate PN. Over the past decade, intestinal transplantation has become accepted as standard therapy for patients with life-threatening complications of PN in many countries [9, 10].

Currently, evaluation for transplant is recommended for pediatric patients with intestinal failure who are doing poorly on PN due to loss of more than 50 % of the major intravenous access sites (two out of four sites include both internal jugular veins and subclavian veins); recurrent severe catheter-related sepsis; progressive liver dysfunction; or impaired renal function due to massive gastrointestinal fluid loss.

Timely referral to an intestinal transplant program is important for children with intestinal failure because intestinal transplantation is easier and safer with adequate central venous access and normal liver function [11]. For patients who undergo intestinal transplantation, patient survival is similar to remaining on PN. The inclination is therefore to move towards earlier transplantation and avoiding the need for concomitant liver transplantation [12].

The 2011 report of the intestinal transplant registry confirmed that intestinal transplantation has become a definitive therapeutic option for patients with intestinal failure. By 2011, 2,611 intestinal transplants had been performed throughout the world with 79 participating centers worldwide. Three types of intestinal transplantation are performed: (1) isolated intestinal transplantation (1,184 cases); (2) liver and intestine transplantation (845 cases); and (3) multivisceral transplantation (619 cases). In pediatric patients, two-thirds acquired short gut syndrome as a result of congenital disease, including gastroschisis, intestinal atresia, and necrotizing enterocolitis [10].

On the other hand, only 14 intestinal transplants have been performed in patients under 18 years of age in Japan. The number is relatively small, although it is estimated that 40 pediatric patients require intestinal transplants nationwide [13]. In the Japanese experience, the 1- and 5-year overall patient survival rates are 77 and 57 %. The one-year survival rate was 83 % for the last 5 years. These are considered acceptable results for the treatment of intestinal failure. Our results in Japan are comparable with results worldwide, even though there are only one or two cases per year performed in Japan compared to over 100 intestinal transplants yearly performed in the world. In our opinion, children with intestinal failure should be treated with intestinal transplantation in Japan as well as in other countries when feasible.

There were two major reasons for the low number of intestinal transplants in Japan. One reason is the lack of available organs. For a long time, relatively few donations from deceased donors were obtainable in Japan. As with other solid organs, most intestinal transplants in Japan are performed with living-related donors. Although the situation has changed due to the new Act on Organ Transplantation, which went into effect in 2010, the number of deceased donations has not increased dramatically, especially among pediatric donors.

The financial barrier is the other, more profound reason preventing the greater use of intestinal transplantation in Japan. Since the procedure is not covered by health insurance, either the patient or the transplant center must pay the considerable costs out of pocket.

Some patients develop liver failure with short gut syndrome. These patients need simultaneous liver-intestinal transplants. A combined liver-intestine transplant has less risk of acute rejection than an isolated intestinal transplant because the liver may have protective effects on the intestine [10]. Combined liver and intestine transplants are the most frequent procedure in infants and children, accounting for half of the cases. Current organ allocation guidelines have not allowed for simultaneous combined liver–intestine organ retrieval until the law was revised in 2010; thus, simultaneous liver–intestine transplantation with a deceased donor graft had been impossible. Isolated intestinal transplantation, the preferred procedure, was offered to patients with limited IV access or recurrent line infections. Combined liver–intestine transplants are performed for treatment of irreversible liver disease caused by PN. Isolated intestinal transplantation from deceased donors following living-related liver transplantation, referred to as sequential combined liver-intestine transplantation, has been attempted.

Previously, the law on organ transplantation banned donors below 15 years of age. This is the main reason why there were relatively few pediatric transplant recipients. Intestinal transplant for infants was previously not possible because of donor-recipient size mismatch. Only a small number of pediatric transplants have been performed. Pediatric patients still await the opportunity to benefit from intestinal transplantation. Moreover, younger patients sometimes develop liver failure [3]. Multivisceral transplants are recommended for the treatment of severe gastrointestinal motility disorders [14]. However organ allocation guidelines do not allow for multivisceral organ retrieval. Further reform of allocation guidelines is needed.

This analysis found that improved induction immunosuppression is strongly associated with higher survival rates. The use of antibody induction therapy appears to be particularly important for the success of intestinal transplantation, possibly due to the large lymphoid mass of this type of graft [15]. Induction with rabbit anti-thymus globulin (rATG) minimized the amount of tacrolimus needed for

maintenance immunosuppression, facilitated the long-term control of rejection, and decreased the incidence of opportunistic infections, resulting in a high rate of patient and graft survival [16]. The combination of rATG and rituximab was an effective induction therapy according to our preliminary data. The number and severity of rejection episodes increased when the liver was not included as part of the graft. An immunosuppression regimen including rATG, rituximab, and steroids may have a protective effect against post-transplant lympho proliferative disease (PTLD) and chronic rejection [17]. Sirolimus is a safe rescue therapy in children with intestinal transplants when tacrolimus is not well tolerated. Renal function and hematologic disorders seem to improve, although other simultaneous strategies could be involved [18]. However, those medications are not commercially available with insurance coverage in Japan. Children after intestinal transplant should be managed with limited immunosuppression.

Preemptive assessments are recommended, even for patients doing well on PN, and for infants and adults with an ultra-short gut or for infants with total intestinal aganglionosis or microvillus inclusion disease, since patients with these findings have very poor survival rates on PN [15].

Early referral and listing are important for successful outcomes. Presently, because of the risks involved as well as financial reasons, transplants are rarely offered to pediatric patients in Japan. However, this treatment will undoubtedly become more common over time as the results of intestinal transplantation continue to improve.

Conclusion

Intestinal transplantation has become the definitive treatment for patients with chronic intestinal failure. Since intestinal transplantation in Japan has yielded satisfactory results, indications for the procedure should be expanded. The national health insurance should cover intestinal transplants to reduce the incidence of PN-related complications. Systems facilitating combined simultaneous liver–intestine and multi-organ transplants should be developed. We continue to work on reforming national health insurance coverage and realizing multi-organ transplantation in Japan.

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LIVER TRANSPLANTATION 20:298–310, 2014

ORIGINAL ARTICLE

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

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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 20:298-310, 2014.*** © 2013 AASLD.

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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

Abbreviations: ABO-I AMR, ABO blood type incompatibility–related antibody-mediated rejection; ALC, alcoholic liver cirrhosis; CI, confidence interval; CTP, Child-Turcotte-Pugh; DIC, disseminated intravascular coagulation; DDLT, deceased donor liver transplantation; GRWR, graft/recipient weight ratio; HRAR, high-risk alcohol relapse; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; SLVR, standard liver volume ratio.

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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

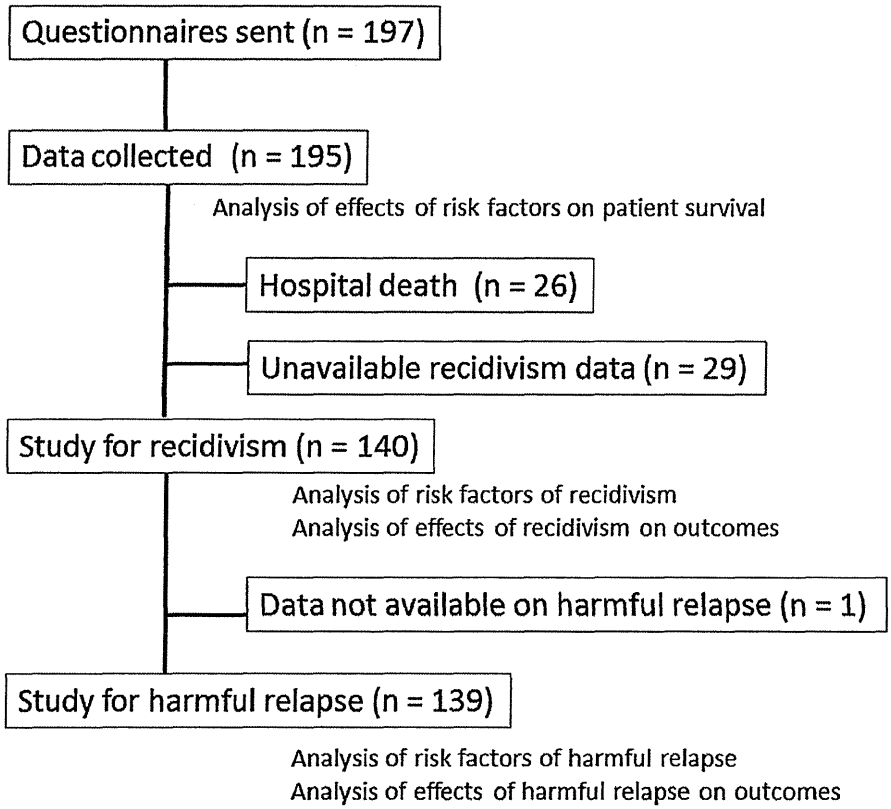


Figure 1. Patient enrollment and inclusion in our analysis. Questionnaires were sent to 38 centers for 197 patients. Clinical data were collected for 195 patients from 36 centers, and risk factors for patient survival were analyzed for these patients. Risk factors for recidivism and the impact of recidivism 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 (%) 1 Year	3 Years	5 Years	10 Years	Log-Rank *P* Value
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 significant 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 versus when the donors had other relationships with the recipients (Table 6).

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

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

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

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. *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

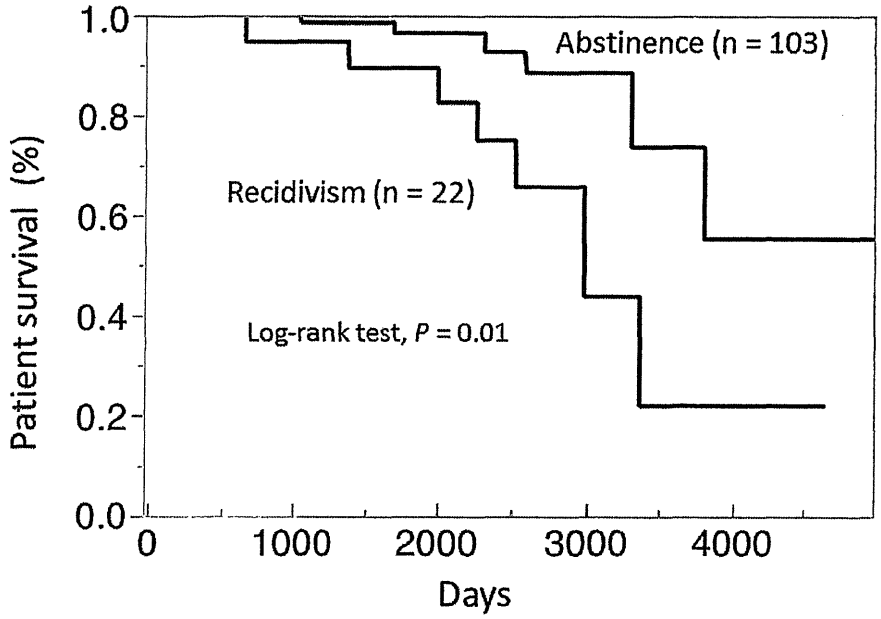
We hypothesized that interactions between a recipient who returns to harmful drinking and the family member who donated the liver might affect outcomes. Although we were not able to examine this directly, we compared the survival rates between recipients living with their donors and recipients who lived 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.

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ORIGINAL ARTICLE

Impact of pediatric intestinal transplantation on intestinal failure in Japan: findings based on the Japanese intestinal transplant registry

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Abstract
Introduction We assessed the impact of intestinal transplantation on Japanese pediatric patients with intestinal failure with data from the Japanese intestinal transplant registry.
Methods Standardized forms were sent to all known intestinal transplantation programs, requesting information on transplants performed between 1996 and June 30, 2012. Patients younger than 18 years were analyzed. Patient and graft survival estimates were obtained using the Kaplan–Meier method.
Results Of the 14 intestinal transplants, 4 were deceased and 10 were living donor transplants. The primary indications were: short gut syndrome ($n = 7$), intestinal functional disorder ($n = 6$), and re-transplantation ($n = 1$). The overall 1- and 5-year patient survival rates were 77 and 57 %, respectively. In transplants performed after 2006 ($n = 6$), the one-year patient survival rate was 83 %, and the 5-year survival rate was 83 %. Graft one- and 5-year survival rates were 83 and 83 %, respectively. The living-related transplant survival rate was 80 % at 1 year and 68 % at 2 years, compared to 67 and 67 % for cadaveric transplant recipients. There were no statistically significant differences in patient ($p = 0.88$) and graft ($p = 0.76$) survival rates between living donor and cadaveric transplant recipients. All current survivors discontinued PN.
Conclusion Intestinal transplantation has become an effective therapy for patients with intestinal failure who cannot tolerate PN.

Keywords Intestinal transplant · Pediatric transplant · Japanese registry

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Introduction

Intestinal failure is caused by a critical reduction of functional gut mass to below the minimal amount necessary for adequate digestion and absorption to satisfy nutrient and fluid requirements for maintenance in adults and growth in children [1]. The most common type of intestinal failure is short bowel syndrome with an estimated incidence of 3–5 cases per 100 000 births per year

[2]. Advances in neonatal intensive care, anesthesia, nutritional support, and surgical techniques have improved the survival of children, so the prevalence of common causes of short bowel syndrome, including gastroschisis, necrotizing enterocolitis, and intestinal atresia has likely increased in recent years [3]. Some survivors, however, develop irreversible intestinal failure. The prognosis for intestinal failure related to short gut syndrome and intestinal motility disorders has improved dramatically owing to the development of parenteral nutrition (PN). Some children achieve long-term survival with PN at home with a relatively good quality of life, but others develop serious side effects that can eventually lead to death. However, PN-related complications, such as loss of venous access and intestinal failure-associated liver disease (IFALD), are still major problems for patients with intestinal failure [4]. Intestinal transplantation can significantly improve their prognosis and quality of life. Early efforts to transplant the small bowel have failed due to refractory graft rejection and sepsis. Outcomes improved during the early 1990s, but survival rates were still inferior to those for other organ transplants. Over the past 5 years, individual centers have reported improved outcomes with better long-term intestinal engraftment.

The first intestinal transplant in Japan was performed in 1996. The total number of intestinal transplants in Japan has increased to 24 as of June 2011. We assessed the impact of intestinal transplantation on Japanese pediatric patients with intestinal failure based on data from the Japanese intestinal transplant registry.

Methods

Standardized forms were sent to all known intestinal transplantation programs, requesting information on intestinal transplants performed between 1996 and June 30, 2012. The data included age, sex, date of birth, date of transplant, type of donor (deceased or living), pre-transplant status (home or hospital), underlying disease, procedure, ABO blood type, immunosuppression regimen (induction and maintenance therapy), and post-transplant status (PN requirement, intravenous (IV) fluid requirement, and daily life restrictions). Patients under 18 years of age were analyzed. The data were entered into a Microsoft Excel spreadsheet and analyzed with JMP version 10.0 (SAS Institute Inc, USA). Patient and graft survival estimates were obtained using the Kaplan–Meier method. For survival analysis, failure was defined as occurring on the date of graft removal or death. A p value <0.05 was considered statistically significant. This study was approved by the institutional review board.

Results

Four programs provided data on 14 grafts in 13 patients who were received transplants between 1 April 1996, and 30 June 2012 in Japan. The participation rate was 100 %. All intestinal transplants performed in Japan are captured in the registry database. All patients were followed, unless the patient has passed way. Ten grafts were obtained from living donors, and four cases involved deceased donors. The annual number of intestinal transplants, according to organ donation type, is shown in Fig. 1. Prior to 2005, 25 % of patients who underwent transplantation were called in from home, as compared with 66 % in the last 5 years (Fig. 2).

There were nine male and five female recipients. The age distribution of the recipients is shown in Fig. 3. Two-thirds of the patients were over 6 years old. The youngest recipient was 8 months. The causes of intestinal failure requiring intestinal transplantation are shown in Fig. 4. Approximately half of the patients had conditions that result in short gut syndrome.

Most patients ($n = 13$) received isolated intestinal transplants. There was only one case of simultaneous liver-intestinal transplantation from two living-related donors. Twelve patients received grafts from donors with an identical ABO blood type. Two patients received grafts from ABO compatible donors. There were no transplants involving ABO incompatibility. All patients were on tacrolimus maintenance therapy. The types of induction therapy used are shown in Fig. 5. Antibody-based induction therapy and tacrolimus-based maintenance immunosuppression were used even if the medication was not commercially available in Japan.

Graft and patient overall survival as of June 2011 are shown in Kaplan–Meier plots (Fig. 6a, b, respectively). The one-year and 5-year patient survival rates were 77 and 57 %, respectively, comparable with rates from the international intestinal transplant registry. Five recipients died.

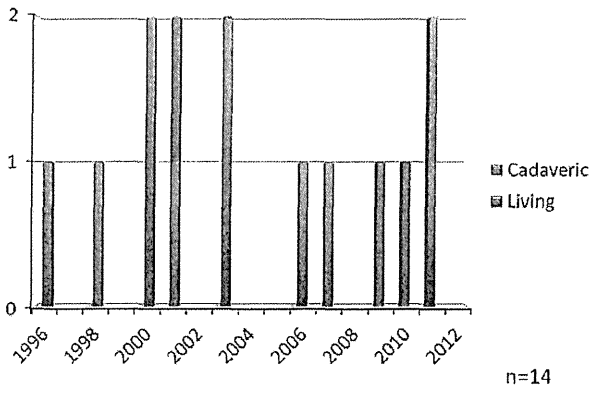

Fig. 1 Number of intestinal transplants by year

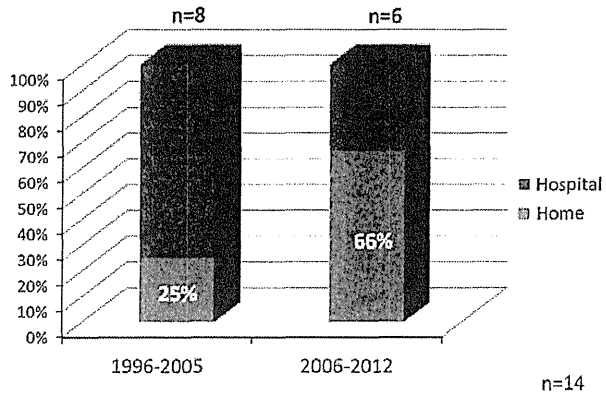

Fig. 2 Pre-transplant patient status

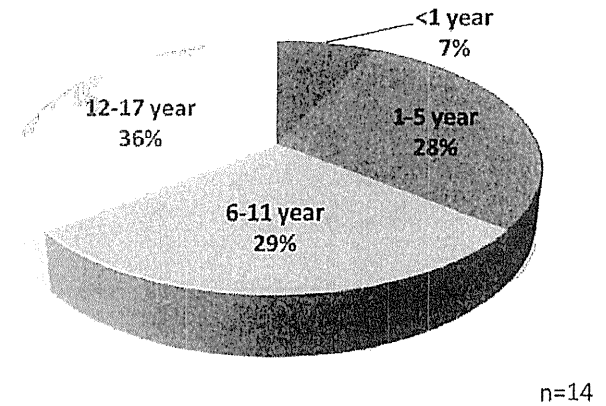

Fig. 3 Recipient age at transplant

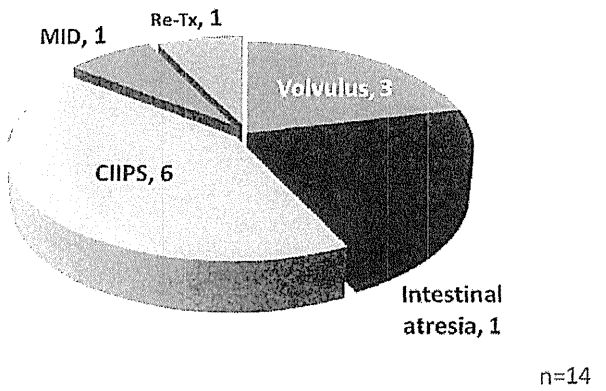

Fig. 4 Cause of intestinal failure *NEC* necrotizing enterocolitis, *CIIPS* chronic idiopathic intestinal pseudo-obstruction syndrome, *MID* microvillus inclusion disease, *Re-Tx* Re-transplant

The causes of death included sepsis ($n = 3$), post-transplant lymphoma ($n = 1$) and intra cranial hemorrhage ($n = 1$).

The 1-year overall graft survival rate was 80 % for cadaveric grafts versus 50 % for living donor grafts ($p = 0.76$), as shown in Fig. 7a. The 1-year overall patient survival rate was 80 % for cadaveric grafts versus 67 % for living donor grafts ($p = 0.88$), as shown in Fig. 7b.

Graft survival improved over the last 5 years. The one- and five-year graft survival rates were 83 and 83 % for 2006–2011 versus 63 and 38 % for 1996–2005 ($p = 0.14$), as shown in Fig. 8a. The 1- and 5-year patient survival rates were 83 and 83 % for 2006–2011 versus 71 and 43 % for 1996–2005 ($p = 0.27$), as shown in Fig. 8b.

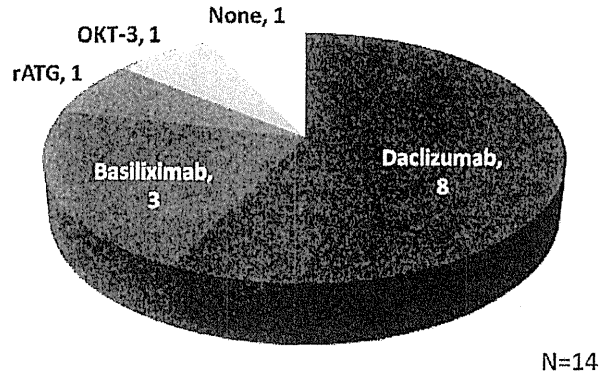

Fig. 5 Induction immunosuppression therapy *rATG* rabbit anti-thymus globulin, *OKT-3* anti-CD3 monoclonal antibody

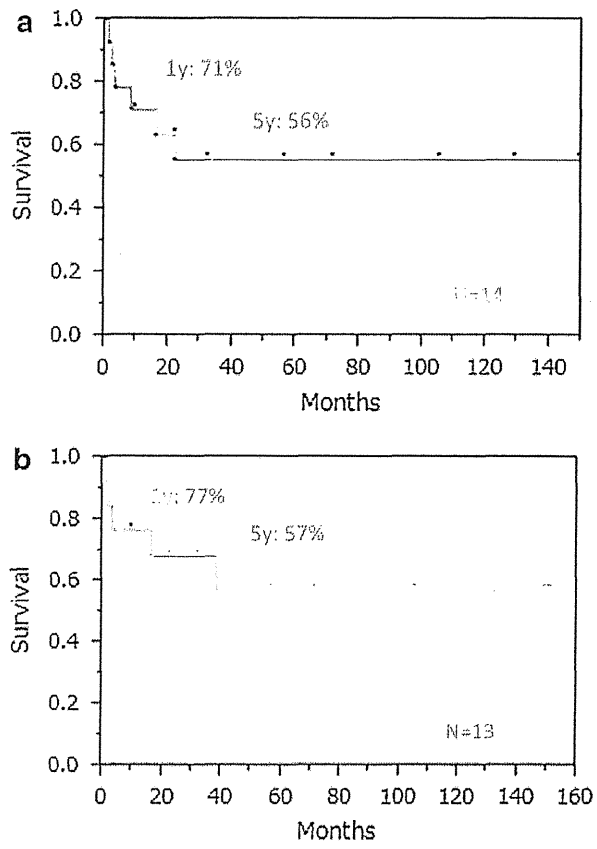

Fig. 6 Overall graft (**a**) and patient (**b**) survival