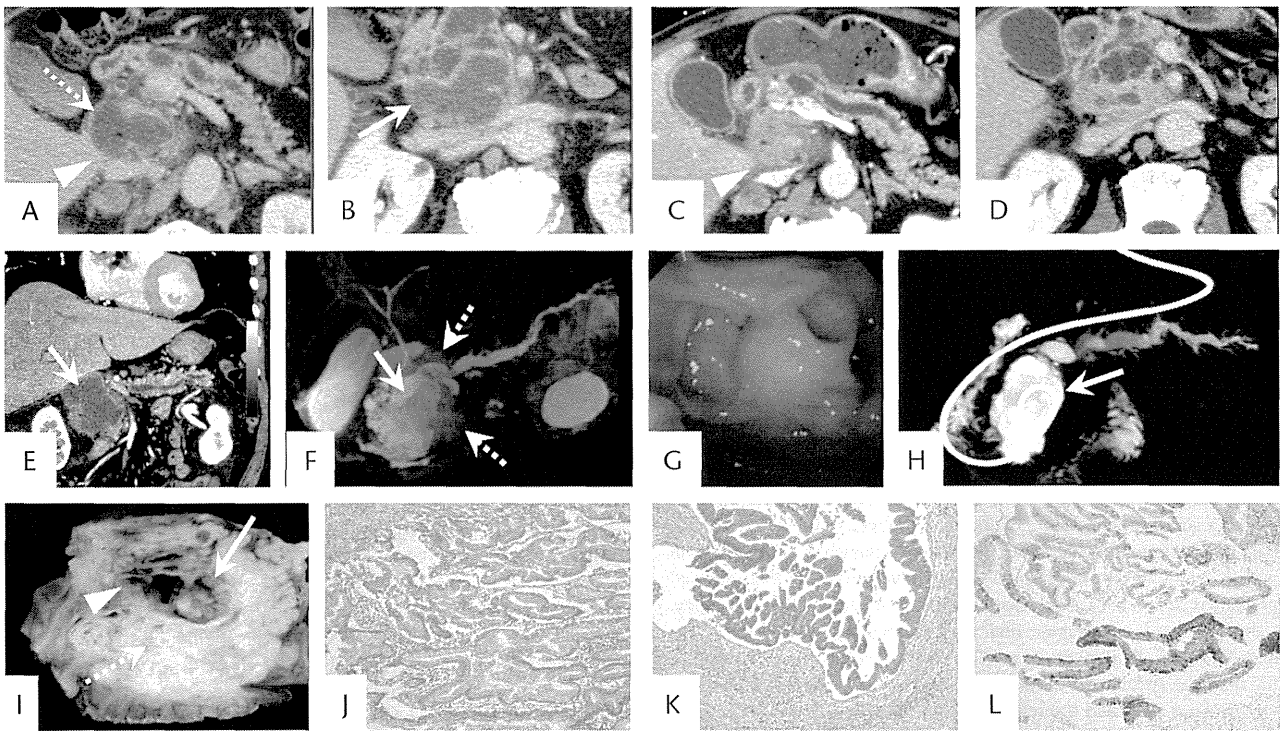

FIGURE 1. Imaging findings and resected specimen of patient 1. Computed tomography images of patient 1 before (A and B) and after (C and D) transpapillary cyst drainage are shown in the top panel; cystic lesions of the pancreas head composed of ventral (arrow) and dorsal part (dashed arrow). Both lesions shrunk markedly after drainage. The interface between dorsal lesion and IVC was poorly demarcated, even after drainage (arrow head). Postdrainage images are demonstrated in the middle panel; multiplanar reconstruction coronal CT (E), magnetic resonance cholangiopancreatography (F), and endoscopic retrograde cholangiopancreatography (G and H) findings are shown. Arrow indicates ventral cyst, and dashed arrow shows dorsal one. The orifice of duodenal papilla (G) was dilated by a copious amount of mucin. The catheter was easily placed transpapillary into the ventral cyst (arrow) connecting to main pancreatic duct (H). Macroscopic (I) and pathological (J, K, and L) findings in the bottom panel. A cystic lesion connected to the main pancreatic duct (arrowhead) at the ventral side of the specimen was observed. The major part of the tumor (J: solid arrow in I) was composed of moderately dysplastic papillary epithelium. The tall columnar tumor cells were characterized by abundant apical mucin with basally located nuclei. Moderate amounts of eosinophilic cytoplasm were revealed by hematoxylin-eosin (H&E) staining. The dorsal part of the pancreas head (dashed arrow) was replaced by yellowish-white sclerotic tissue. This hard area was composed mostly of granulation tissue and partly of high-grade dysplastic columnar epithelium with pseudostratified nuclei and basophilic cytoplasm (K: H&E staining). Neoplastic cells at the inflamed site were diffusely positive for MUC2 staining (L).

were improved by endoscopic drainage, and pylorus-preserving pancreaticoduodenectomy was performed (Figs. 1C, D). During the surgical intervention, adhesive solid tissue between the pancreatic head and inferior vena cava (IVC) was partly preserved, assuming that the mass may have been inflammatory in nature. However, pathological tests revealed that the tumor was composed mostly of gastric-type IPMN with moderate dysplasia, and part of the solid component was intestinal-type IPMN (carcinoma in situ) with massive inflammatory infiltrates (Figs. 1I-L). The patient was free from recurrence 17 months after surgery.

PATIENT 2

A 74-year-old man was admitted to our hospital complaining of abdominal pain and fever. He had a history of alcohol consumption (180 mL of distilled spirits per day) for 33 years, as well as a medical history of AP that had been treated conservatively when he was in his 60s. Laboratory tests at admission revealed severe inflammation (25,960 white blood cells/μL and 22.3 μg/mL CRP) and liver dysfunction (117 IU/L aspartate aminotransferase and 99 IU/L alanine aminotransferase). Hyperamylasemia was not observed. Tumor markers, including carcinoembryonic antigen and CA-19-9, were within reference range. Computed tomography scans showed a multilocular cystic tumor with a diameter of 50 mm located at the pancreatic head, and dilatation of the main pancreatic duct was observed (Figs. 2A, B). Several antibiotics were administered intravenously and nasobiliary transpapillary pancreatic duct drainage tube, 7F in diameter, was inserted to the main pancreatic duct, but his general status was not improved. Therefore, the drainage tube was replaced to drain cyst (branched duct) on the sixth day of hospitalization. This was easily performed, as in patient 1. The patient defervesced immediately after cyst drainage. The amount of drainage fluid was 3 to 20 mL a day. Because slightly high CRP value was prolonged even after defervescence, the tube had been placed for 17 days. *Corynebacterium striatum* was detected in the drained fluid. Atypical regenerative cell clusters in the inflamed background were identified by cytological examination. Macrophages engulfing mucin with positive immunoreactivity for MUC2 and MUC5AC were observed. Symptoms and the inflammatory findings revealed by imaging were significantly improved by endoscopic drainage (Figs. 2C, D). The tumor, with heterogeneous enhancement by intravenous contrast material, persisted after drainage in the pancreatic head; therefore, pylorus-preserving pancreaticoduodenectomy was carried out.

During surgical resection, severe sclerosis/fibrosis of soft tissue in the peripancreatic area was observed, which made it

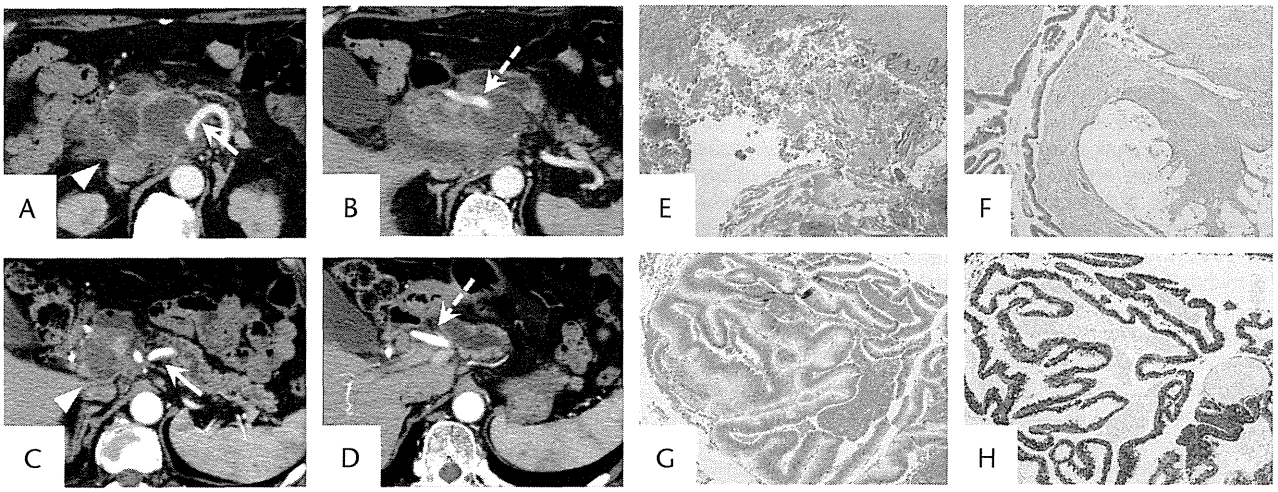

FIGURE 2. Imaging findings and resected specimen of patient 2. Computed tomography scan of patient 2 before (A and B) and after (C and D) transpapillary cyst drainage. A multilocular cystic lesion involving the SPA (solid arrow) and the common hepatic artery (dashed arrow) was observed at the pancreas head. The arteries are clearly separated from the tumor in the postdrainage images. The poorly demarcated boundary between the tumor and IVC was also visualized better following drainage (arrowhead). The cystic lesion was partly lined by papillary proliferating epithelium, and clots of neoplastic cells and necrotic debris were observed in the cavity (E: H&E staining). Severe inflammatory infiltrates were observed in the thickening wall. Invasive tubular adenocarcinoma was observed within the cyst wall (F: H&E staining). The neoplastic epithelium in the branch duct formed tall papillae with columnar cells with pseudostratified nuclei and basophilic cytoplasm (G: H&E staining). The neoplastic cells displayed diffuse MUC2 immunoreactivity (H).

difficult to detach the PV from the tumor; therefore, the PV was excised and reconstructed by external iliac vein graft. The common hepatic artery and the splenic artery (SPA) were preserved, although they were somewhat involved in the indurated tissue periphery of the tumor. Pathologically, the tumor was an adenocarcinoma arising from intestinal-type IPMN with an invasive component on the cyst wall (Figs. 2E-H). The indurated tissue on the surgical margin was an inflammatory change, and it did not appear to contain tumor cells. The patient received adjuvant chemotherapy with gemcitabine and was free from recurrence 18 months after the surgical intervention.

DISCUSSION

Although a growing number of patients are being diagnosed with IPMN of the pancreas, little is known about IPMN with cyst infection. To our knowledge, no previously published reports of the natural history of IPMN have specifically mentioned this rare complication, and there are a few reports concerning this condition as proceedings in Japanese. At Asahikawa Medical University Hospital, we observed only 2 cases of IPMN with cyst infection out of 70 patients who underwent resection to treat IPMN between 1994 and 2012. Acute pancreatitis is one of the major complications of IPMN.[10,11] Pancreatitis associated with IPMN is generally not severe, and it can sometimes recur without any treatment for IPMN. In contrast, in our patients, cyst infection of IPMNs displayed symptoms associated with sepsis and uncharacterized findings on imaging modalities, which prompted us to recognize it as a clinical category independent of the AP more commonly associated with IPMN.

The symptoms associated with cyst infection began with abdominal pain and fever in our patients. Although severe inflammatory reactions can be identified by blood chemistry examinations, pancreatic hyperenzymemia was not evident; both patients had normal serum amylase levels, and the serum elastase 1 level was only slightly greater than the reference range in 1 patient.

Computed tomography imaging was informative; although it was significantly modified by severe inflammation, scans still revealed the typical morphology of IPMN. Evidence of IPMN was more clearly demonstrated after endoscopic drainage. The tumor mass appeared to involve large vessels and their tributaries around the pancreas; however, it should be noted that this does not always indicate an unresectable and highly invasive tumor. Therefore, images collected before drainage need to be carefully interpreted. Typical findings associated with AP, such as edematous changes of the pancreatic parenchyma and peripancreatic fluid collection, were absent,[12] indicating that the cystic lesions observed in our patients were not due to a complication of acute necrotizing pancreatitis.

Histopathological analyses revealed neoplastic cells with typical IPMN phenotypes, accompanied by necrotic tissue with abundant inflammatory infiltrates in the mass (Fig. 2E). The cyst wall was lined at least partly with viable tumor cells, which distinguished these lesions from pseudocysts of the pancreas. Granulation was evident in the walls of the cysts, where aggressive inflammatory cell infiltration was observed. These histological findings were in accordance with the fluid and solid components revealed by CT scan. It should be noted that very little of edema, hemorrhage, and fat necrosis commonly seen in AP were observed.

The effectiveness of endoscopic drainage to treat infected pancreatic pseudocyst was reported previously.[13] This relatively noninvasive procedure was also effective in our patients, and we recommend it as an initial treatment for cyst infection of IPMNs. In addition to removing the infected fluid, endoscopic drainage also allowed for definitive cytological and pathological diagnosis and provided samples for bacterial culture so that we could determine the appropriate antibiotics for treatment. Because of the enteric bacteria present in the drainage specimens from both patients, we considered that the infection route was most likely retrograde, which is common in AP.[14] The laboratory and imaging findings improved remarkably after drainage, and these changes were important not only for differentiating

IPMN with cyst infection from invasive carcinoma, but also for determining whether the patients could be treated with surgical intervention. The predrainage imaging findings of IPMN with cyst infection appeared serious enough that we were unsure whether surgical intervention was appropriate; however, as we found after drainage, most of the "tumor tissue" was actually composed of severely inflamed tissue. Because of the difficulty in predicting tumor margins based on radiographic findings, whole mass resection may be unavoidable. In the present report, the IVC, which was covered by sclerosing connective tissue surrounding the tumor, was also preserved in the first patient (Fig. 1A). The common hepatic artery and SPA, which were thought to be involved by the tumor before drainage, could be preserved in the second patient (Figs. 2A, B). Pathological assessment indicated that the sclerosing tissue was inflammatory granuloma and that the surgical margins were histologically free of invasion by carcinoma cells.

Recent advances in endoscopic procedure have provided options with regard to drainage routes, but the transpapillary route, rather than the transluminal route through the stomach/duodenum, should be considered first, because it is less invasive.[13] Cannulation into the abscess via Vater papilla was feasible in our patients, because the pancreatic duct and the orifices of the papillae were widely dilated because of copious mucin produced by the IPMNs (Figs. 1F, G). Indeed, in both cases, endoscopic drainage was technically easy. However, in patients in whom it would be difficult to reach the infected cyst(s) via the transpapillary route, endoscopic ultrasound-guided drainage via the transluminal route should be considered as an alternative. In general, once infection of neoplastic cysts occurs, it is difficult for antibiotics administration alone to eliminate severe inflammation; therefore, immediate endoscopic abscess drainage should be considered.

Surgical resection of IPMN lesions with cyst infection is highly recommended after sufficient abscess drainage at the earliest possible opportunity for the following reasons. First, cyst infection can relapse easily; the closed space formed by occlusion between the dilated branch and the main pancreatic duct due to the tumor itself or to the presence of viscous mucin is conducive to pathogenesis; therefore, infections may occur repeatedly after endoscopic drainage alone. In patients with AP associated with IPMN, the intestinal subtype has been considered particularly high risk because of copious viscous mucin production.[11] In our report, the tumor was positive for MUC2 staining in the first patient. Although in the second patient the tumor was mostly MUC2 negative, the lesion at the infected area was of the MUC2-positive intestinal type. A retrospective histological review of tumors previously resected in our hospital indicated that 14 patients were intestinal-type out of 17 patients who had symptoms associated with AP (82.4%). Therefore, MUC2-positive IPMN may tend to cause mucin-associated symptoms. Tissue fibrosis and granulation in the cyst wall may be caused by repeated infection; therefore, these lesions should be treated not only by endoscopic drainage, but also by resection to prevent recurrence of infection. Second, IPMN with cyst infection may also indicate a high-grade tumor, as demonstrated by the association between the existence of symptoms and the malignancy of IPMNs.[8] The rate of AP in IPMN patients has been proposed to correlate with malignant potential.[11] It should be noted that both of our patients had tumors that were histologically malignant; moreover, the second patient developed invasive carcinoma.

In conclusion, cyst infection in IPMN should be considered as a potential complication. Transpapillary abscess drainage is effective as an initial treatment, and surgical resection soon after drainage is highly recommended, because of the risk of recurrent infection and the high probability of malignancy.

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LIVER TRANSPLANTATION 20:576–583, 2014

ORIGINAL ARTICLE

Pregnancy Outcomes After Living Donor Liver Transplantation: Results From a Japanese Survey

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A national survey of pregnancy outcomes after living donor liver transplantation (LDLT) 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). After the exclusion of the 3 artificial abortions, there were 35 pregnancies in 27 recipients: pregnancy-induced hypertension developed during 6 pregnancies (5 recipients), fetal growth restriction developed during 7 pregnancies (6 recipients), acute rejection developed during 2 pregnancies (2 recipients), and ileus developed during 1 pregnancy (1 recipient). Preterm delivery (<37 weeks) occurred for 10 pregnancies (10 recipients), and cesarean delivery was performed for 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 neonates had extremely low birth weights (<1500 g). Two neonates had congenital malformations. The pregnancy outcomes after LDLT were similar to those reported for cadaveric liver transplantation (LT). The incidence of pregnancy-induced hypertension in recipients who were 33 years old or older at the diagnosis of pregnancy was significantly higher than the incidence in recipients who were less than 33 years old at the diagnosis of pregnancy. The incidences of fetal growth restriction, pregnancy-induced hypertension, and extremely low birth weight were significantly higher in the early group (<3 years after transplantation) versus the late group (≥3 years after transplantation). In conclusion, it is necessary to pay careful attention to complications during pregnancy in recipients who become pregnant within 3 years of LT, particularly if the age at the diagnosis of pregnancy is ≥33 years. ***Liver Transpl 20:576-583, 2014.*** **© 2014 AASLD.**

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The number of patients undergoing liver transplantation (LT) has increased; therefore, the number of women of reproductive age undergoing 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 UK 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 for some recipients after living donor liver

Abbreviations: γ-GTP, gamma-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the receiver operating characteristic curve; CI, confidence interval; LDLT, living donor liver transplantation; LT, liver transplantation; MMF, mycophenolate mofetil; ROC, receiver operating characteristic.

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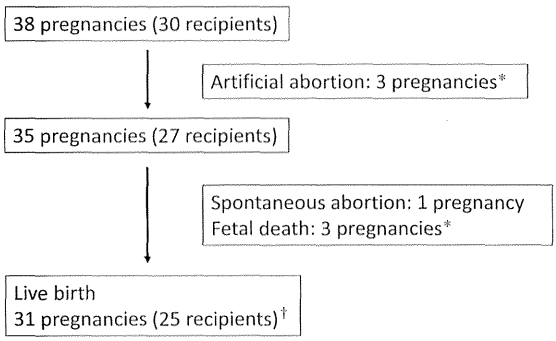

Figure 1. Subjects of this study. *In one recipient, artificial abortion was performed at the first pregnancy, and the second pregnancy was resulted in fetal death. †Six recipients had live births twice.

transplantation (LDLT) have been reported in 1 study,[4] most participants in previous studies have been cadaveric LT recipients. Here, the results of a national survey of pregnancy outcomes after LDLT in Japan are presented and discussed.

PATIENTS AND METHODS

In Japan, data on LT, including LDLT and cadaveric 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 cadaveric LT procedures and 6503 LDLT procedures were registered with the society.[25] The Japanese Liver Transplantation Society performed a national survey of pregnancy outcomes after LDLT in Japan. The society sent questionnaires to the institutes and retrospectively assessed data on pregnancy outcomes after LT until May 2012. The questionnaires included information about LDLT, clinical courses of pregnancies and deliveries, and neonates.

Pregnancy-induced hypertension was defined as a systolic blood pressure $\geq$ 140 mm Hg or a diastolic blood pressure $\geq$ 90 mm Hg after 20 weeks of gestation in a woman with previously normal blood pressure.[26] Fetal growth restriction was defined as an estimated fetal weight < -1.5 standard deviations of the normal reference range. The fetal weight was estimated with formulas from ultrasound measurements based on neonatal specific gravities and volumes.[27] In 22 of the 23 recipients who received tacrolimus during pregnancy (25 of 29 pregnancies), consecutive serum trough levels of tacrolimus during pregnancy (at several times) were available, and the mean trough level was calculated. The pathological degree of acute rejection (the rejection activity index) was assessed according to the Banff classification.[28]

This study was approved by the ethics committee of the Osaka City University Graduate School of Medicine (no. 1856) and was conducted in accordance with the Declaration of Helsinki of 1996. Informed consent was obtained from the participants. No patient was excluded from the study because informed consent could not be obtained.

TABLE 1. Indications for LDLT

Disease	Patients (n)
Congenital biliary atresia	14
Acute hepatic failure	9
Primary sclerosing cholangitis	2
Autoimmune hepatitis	1
Hepatitis B virus	1
Budd-Chiari syndrome	1
Familial amyloid polyneuropathy	1
Hepatocellular carcinoma	1

Statistics

To assess the relationships between complication rates during pregnancy and pregnancy outcomes and the age at pregnancy and interval from LDLT to pregnancy, receiver operating characteristic (ROC) curves were constructed. In addition, areas under the receiver operating characteristic curve (AUCs) with 95% confidence intervals (CIs) were calculated. The optimal age and interval cutoff values were determined with Youden's index (sensitivity + specificity − 1). Categorical variables were compared with the chi-square test or Fisher's exact test as appropriate. The Student t test was used to analyze differences in ages. A P value < 0.05 was considered significant. All statistical data were generated with JMP 9.0 (SAS Institute, Cary, NC).

RESULTS

Recipient Characteristics

The study participants were 30 LT recipients who had 38 pregnancies (Fig. 1). The recipients underwent LDLT at 11 institutions. The indications for LDLT included congenital biliary atresia (14 recipients), acute liver failure (9 recipients), primary sclerosing cholangitis (2 recipients), autoimmune hepatitis (1 recipient), liver cirrhosis caused by hepatitis B virus (1 recipient), Budd-Chiari syndrome (1 recipient), familial amyloid polyneuropathy (1 recipient), and hepatocellular carcinoma (1 recipient; Table 1). The age of the recipients at the time of LDLT ranged from 4 to 38 years. The age at which pregnancy was diagnosed ranged from 22 to 41 years (mean = 30.3 years). The time from LDLT to the diagnosis of pregnancy ranged from 356 to 6798 days (median = 1751 days).

At the diagnosis of pregnancy, tacrolimus was being administered to 23 recipients (27 pregnancies); cyclosporine was being administered to 2 recipients (2 pregnancies); a combination of tacrolimus and steroids was being administered to 2 recipients (2 pregnancies); a combination of cyclosporine and sirolimus was being administered to 1 recipient (1 pregnancy); and a combination of tacrolimus, steroids, and mycophenolate mofetil (MMF) was being administered to 1 recipient (1 pregnancy). The mean trough level of tacrolimus at the diagnosis of pregnancy was 4.5 ng/mL (range = 0.9-10.0 ng/mL), and the mean trough level during

TABLE 2. Interval From LDLT to Pregnancy and Delivery Outcomes

Outcome	Total	Interval		P Value
		<3 Years	≥3 Years	
Age at pregnancy (years)*	27 (22-41)	35 (24-41)	29 (22-40)	0.0014
Indications for LT (n)				0.327
Congenital biliary atresia	16	3	13	
Acute hepatic failure	12	4	8	
Primary sclerosing cholangitis	1	1	0	
Other	6	2	4	
Complications during pregnancy [n (%)]†				
Spontaneous abortion	1 (2.9)	0	1 (4.0)	>0.999
Fetal death	3 (8.6)	2 (20.0)	1 (4.0)	0.190
Fetal growth restriction	7 (20)	5 (50.0)	2 (8.0)	0.0120
Liver dysfunction	4 (11.4)	2 (20.0)	2 (8.0)	0.561
Pregnancy-induced hypertension	6 (17.1)	5 (50.0)	1 (4.0)	0.0040
Delivery outcomes [n (%)]‡				
Preterm delivery	10 (32.3)	4 (50.0)	6 (26.1)	0.381
Cesarean delivery	12 (38.7)	4 (50.0)	8 (34.8)	0.676
Low birth weight (<2500 g)	12 (38.7)	5 (62.5)	7 (30.4)	0.206
Extremely low birth weight (<1500 g)	4 (12.9)	3 (37.5)	1 (4.3)	0.0432
Birth defects	2 (6.5)	1 (12.5)	1 (4.3)	0.456

NOTE: There were 35 pregnancies in 27 recipients (3 pregnancies in 3 recipients ended by artificial abortions were excluded from the analysis).
*The data are reported as medians and ranges.
†There were 10 pregnancies in the <3-year group and 25 pregnancies in the ≥3-year group.
‡There were 8 pregnancies in the <3-year group and 23 pregnancies in the ≥3-year group (4 pregnancies in 4 recipients ending in a spontaneous abortion or fetal death were excluded from the analysis).

pregnancy was 4.5 ng/mL (range = 1.5-10.0 ng/mL). No immunosuppressive drugs were administered during 3 pregnancies at the time of the pregnancy diagnosis because of auxiliary partial orthotopic LT (1 pregnancy in 1 recipient) or the discontinuation of drugs after LDLT in childhood (2 pregnancies in 1 recipient). The serum creatinine levels at the diagnosis of pregnancy were available for 32 pregnancies (24 recipients), and they were within the reference range.

Pregnancy Outcomes

Thirty-eight pregnancies in 30 recipients resulted in 31 live births (81.6%) for 25 recipients, 3 artificial abortions for 3 recipients, 1 spontaneous abortion for 1 recipient, and 3 fetal deaths for 3 recipients (Fig. 1). Artificial abortions were performed in the first trimester because of MMF use in 1 pregnancy (1 recipient), sirolimus use in 1 pregnancy (1 recipient), and a short time after LDLT (356 days) in 1 pregnancy (1 recipient).

Obstetric Complications

After the exclusion of the 3 artificial abortions in 3 recipients, there were 35 pregnancies in 27 recipients: a spontaneous abortion occurred during 1 pregnancy (2.9%) in 1 recipient, and fetal death occurred during 3 pregnancies (8.6%) in 3 recipients as previously described (Table 2). Pregnancy-induced hypertension developed during 6 pregnancies (17.1%) in 5 recipients, fetal growth restriction developed during 7 pregnancies (20.0%) in 6 recipients, and ileus developed during 1 pregnancy in 1 recipient. Liver dysfunction [elevated serum activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and/or gamma-glutamyl transpeptidase (γ-GTP)] was detected during 4 pregnancies in 4 recipients. Acute rejection, diagnosed by liver biopsy (rejection activity index = 2) and laboratory test results, occurred in 2 of these 4 recipients; an increased dose of cyclosporine and steroid pulse therapy was given to 1 recipient, and an increased dose of tacrolimus was administered to 1 recipient. Other obstetric complications such as gestational diabetes, infections, placental abruption, and thromboembolic disorders did not occur in any recipient. Two recipients did not receive immunosuppressive drugs, and for the one who underwent auxiliary partial orthotopic LT, fetal death occurred because of umbilical cord coiling. In another patient (2 pregnancies), no complications developed during pregnancy.

In 1 of the 8 recipients who were pregnant twice, the second pregnancy resulted in a spontaneous abortion (at 7 weeks of gestation), although the first pregnancy was uneventful. Another recipient had pregnancy-induced hypertension in both the first and second pregnancies; fetal death ended the first pregnancy (at 25 weeks), and fetal growth restriction occurred during the second pregnancy.

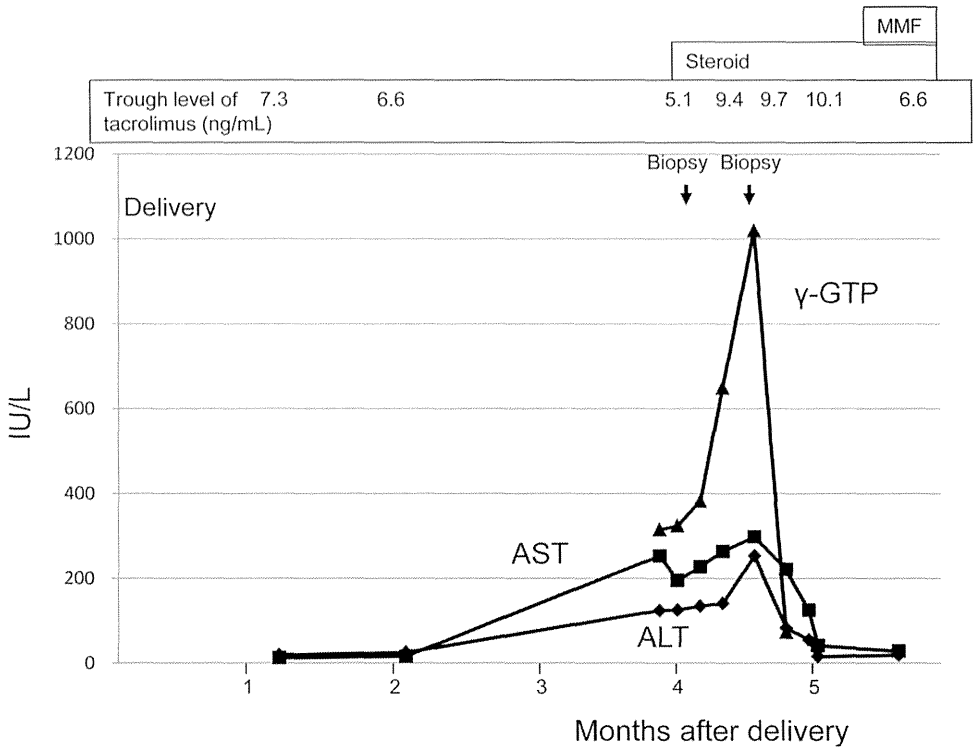

Figure 2. Clinical course of recipients suffering acute rejection after delivery. Acute rejection was diagnosed with a second liver biopsy (rejection activity index = 4).

Delivery Outcomes

There were 31 pregnancies in 27 recipients, and preterm delivery (<37 weeks) occurred for 10 of these pregnancies (32.3%) in 10 recipients. Cesarean delivery was performed for 12 pregnancies (38.7%) in 12 recipients because of pregnancy-induced hypertension (6 pregnancies in 6 recipients), hypotonic contraction during labor (1 pregnancy in 1 recipient), transient bradycardia of the fetus (1 pregnancy in 1 recipient), ileus (1 pregnancy in 1 recipient), previous multiple abdominal operations (1 pregnancy in 1 recipient), previous cesarean delivery (1 pregnancy in 1 recipient), and the recipient's will (1 pregnancy in 1 recipient).

After delivery, liver dysfunction (elevated serum activities of AST, ALT, and/or γ-GTP) occurred during 4 pregnancies (4 recipients), and acute rejection, diagnosed by liver biopsy (rejection activity index = 2-4), occurred within 4 months of LDLT in 3 of these 4 recipients. For acute rejection, steroid pulse therapy was administered to 2 recipients, and a steroid and MMF were added to tacrolimus therapy for 1 recipient (Fig. 2). The recipients' liver function improved with these treatments. In 1 recipient, artificial respiration was necessary because of acute respiratory distress syndrome after delivery, and renal dysfunction persisted after recovery. Puerperal fever developed in 1 recipient. The pregnancy-induced hypertension improved after delivery in all recipients who had hypertension during pregnancy. In 1 recipient, retransplantation was performed because of the recurrence of primary sclerosing cholangitis 5 years after delivery.

There were 31 live births, and neonatal asphyxia occurred in 1 neonate. Twelve neonates were born with low birth weights (<2500 g), and 4 of the 12 low-birth-weight neonates were born with extremely low birth weights (<1500 g). Although intracranial bleeding developed after delivery in 1 neonate with an extremely low birth weight, the condition improved without complications.

One neonate had tetralogy of Fallot, and 1 neonate had hypospadias.

Risk Factors for Obstetric Complications, Delivery Outcomes, and Birth Defects

Relationships between the mean trough level of tacrolimus and obstetric complications, delivery outcomes, and birth defects were not found.

Relationships between the age at the diagnosis of pregnancy and complications during pregnancy were studied with ROC curves. The AUC was 0.784 (95% CI = 0.613-0.905) for pregnancy-induced hypertension (Fig. 3A). The optimal cutoff value was 33 years (sensivitity = 83.3%, specificity = 69.0%). No significant relationship was found between the age at pregnancy and other complications such as spontaneous abortion, fetal death, fetal growth restriction, and liver dysfunction. The incidence of pregnancy-induced hypertension in recipients who were 33 years old or older at the diagnosis of pregnancy was significantly

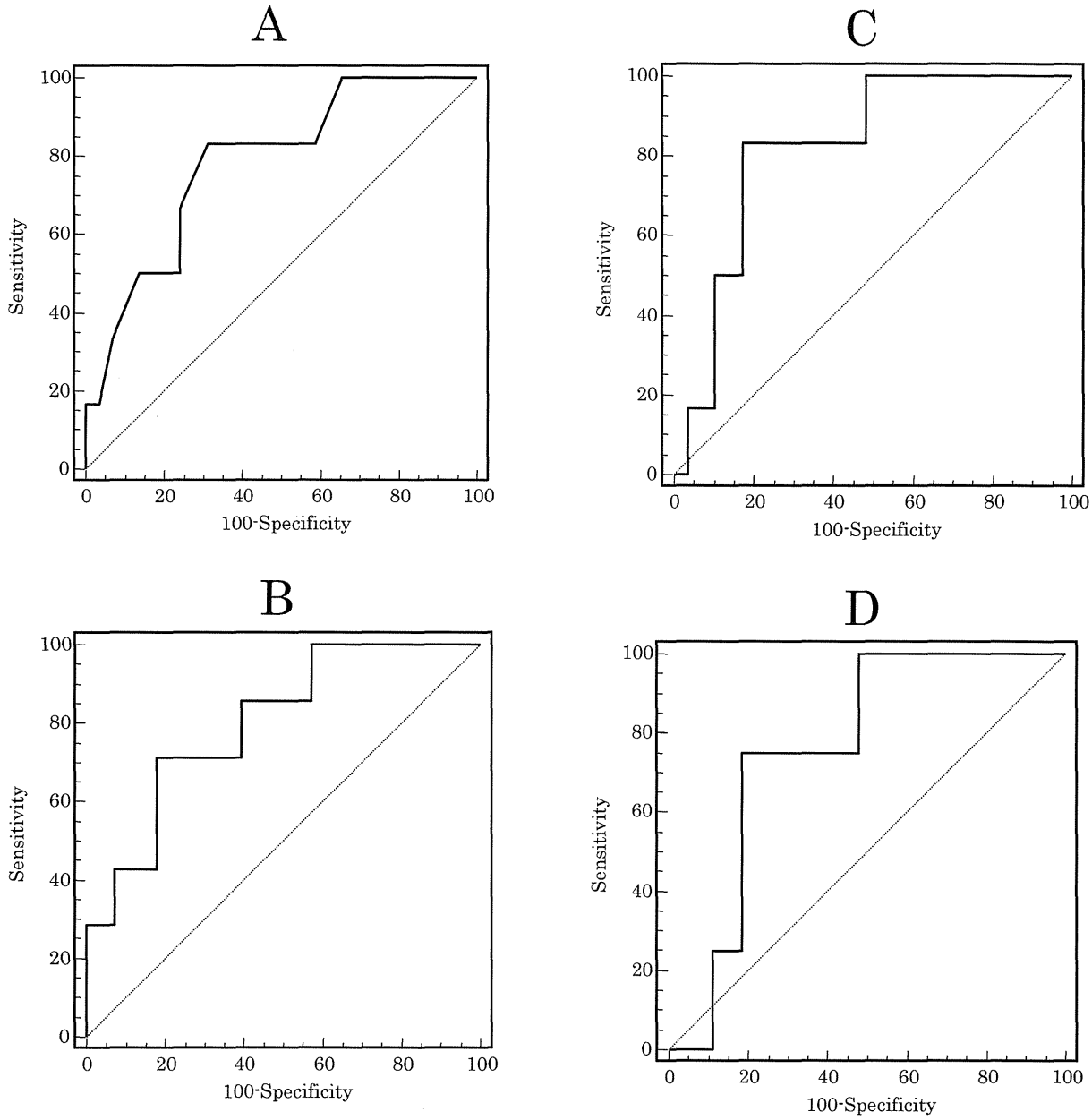

Figure 3. ROC curves for pregnant recipients: (A) age at the diagnosis of pregnancy and pregnancy-induced hypertension, (B) interval from LT to pregnancy and fetal growth restriction, (C) interval from LT to pregnancy and pregnancy-induced hypertension, and (D) interval from LT to pregnancy and extremely low birth weight.

higher than the incidence in recipients who were less than 33 years old at the diagnosis of pregnancy (*P* value = 0.0278 according to Fisher's exact test).

Relationships between the interval from LDLT to pregnancy and delivery outcomes were studied with ROC curves. The AUC was 0.801 (95% CI = 0.632-0.916) for fetal growth restriction (Fig. 3B). The optimal cutoff value was 1096 days (sensitivity = 71.4%, specificity = 82.1%). The AUC was 0.822 (95% CI = 0.656-0.930) for pregnancy-induced hypertension (Fig. 3C). The optimal cutoff value was 1096 days (sensitivity = 83.3%, specificity = 82.8%). The AUC was 0.759 (95% CI = 0.573-0.893) for extremely low birth weight (Fig. 3D). The optimal cutoff value was 1096 days (sensitivity = 75.0, specificity = 81.5%). No significant relationship was found between the interval and other factors, including spontaneous abortion, fetal death, liver dysfunction, and preterm delivery.

The obstetric complications and delivery outcomes were compared for 10 pregnancies for which the interval from LT to pregnancy was <3 years (the early group) and 25 pregnancies for which this interval was ≥3 years (the late group) because the optimal cutoff value was 1096 days according to the analysis using ROC curves (Table 2). The 3 pregnancies for which

artificial abortions were performed in the first trimester were excluded from this comparison. The mean age at pregnancy was significantly higher for the early group versus the late group. The proportions of recipients with fetal growth restriction and pregnancy-induced hypertension were significantly higher in the early group versus the late group. The proportion of neonates with extremely low birth weight was significantly higher in the early group versus the late group.

The incidence of pregnancy-induced hypertension in recipients in the early group who were 33 years old or older at the diagnosis of pregnancy (5/8 pregnancies or 62.5%) was significantly higher than the incidence in recipients in the late group who were less than 33 years old at the diagnosis of pregnancy (1/19 pregnancies or 5.3%, $P = 0.0037$) and the incidence in recipients in the late group who were 33 years old or older at the diagnosis of pregnancy (0/6 pregnancies, $P = 0.031$); the incidence of pregnancy-induced hypertension was highest in recipients in the early group who were 33 years old or older at the diagnosis of pregnancy (interval from LDLT to pregnancy < 3 years).

DISCUSSION

An increased risk of complications, including prematurity, low birth weight, pregnancy-induced hypertension, renal dysfunction, and cesarean delivery, has been reported in previous studies of pregnancy in LT recipients (most patients have undergone cadaveric LT).[1-24]

In this study, pregnancy-induced hypertension developed during 6 pregnancies (17.1%) in 5 recipients. Shiozaki et al.[29] reported that pregnancy-induced hypertension was present in 1.2% of pregnancies (2802/241,292) in the Japan Society of Obstetrics and Genecology database. The incidence of pregnancy-induced hypertension seems to be higher in LDLT recipients versus the general population. Several studies have reported that pregnancy-induced hypertension is common among LT recipients (11%-43%).[1,3-6,10,11,13,17,20,23,24] The incidence of pregnancy-induced hypertension in LDLT recipients (17.1%) was similar to the incidence in cadaveric LT recipients. On the other hand, pregnancy-induced hypertension did not occur in 1 recipient (2 pregnancies) who did not receive immunosuppressive drugs during pregnancy. This complication has been shown to occur more frequently in LT recipients with renal dysfunction.[11,12] Although no relationship between the mean trough levels of tacrolimus and pregnancy-induced hypertension was observed in this study, underlying renal dysfunction[11] and the vasoconstrictive effects of calcineurin inhibitors may affect hypertension. In addition, it is necessary to pay attention when the recipient's age at the diagnosis of pregnancy is ≥33 years.

In this study, a spontaneous abortion ended 1 pregnancy (1 recipient), and fetal death ended 3 pregnancies (3 recipients). Coffin et al.[23] reported that infants of LT recipients had a 3-fold risk of complications, most notably fetal death (6% versus 2% in controls). Among 241 pregnancies in LT recipients described in the National Transplantation Pregnancy Registry in 2008,[3] 19.2% and 2.1% ended in spontaneous abortions and stillbirths, respectively. The maternal and fetal conditions might affect the rates of spontaneous abortion and fetal death. Another adverse fetal outcome noted in this study was fetal growth restriction in 7 pregnancies (20.0%). The incidence of complications appears to be higher in these individuals versus the general population.[23] However, the mechanisms underlying the high incidences of spontaneous abortion, fetal death, and fetal growth restriction are unclear.

Several previous studies have reported a high incidence of preterm delivery (14%-53%).[1,3-6,8-10,13,14,17,18,20,23,24] In this study, preterm delivery (<37 weeks) occurred in 10 pregnancies (32.3%). The proportion of preterm deliveries seemed to be high because the database of the Japan Society of Obstetrics and Genecology indicated that the rate of threatened premature delivery was 2.34%.[30] Preterm delivery might be related to maternal conditions such as hypertension and fetal conditions such as fetal growth restriction.

Several previous studies have shown that cesarean delivery is more common among transplant recipients.[4-6,10,13,15-17,20,23,24] In this study, cesarean delivery was performed for 12 of 31 pregnancies (38.7%). The indications for cesarean delivery included pregnancy-induced hypertension, hypotonic contraction during labor, transient bradycardia, ileus, multiple previous abdominal operations, previous cesarean delivery, and the recipient's will. Thus, it is likely that the high rate of cesarean delivery was attributable to pregnancy complications rather than LT itself.

Acute rejection is an important problem during and after pregnancy because rejection may induce graft loss. In fact, the National Transplantation Pregnancy Registry (2006) reported that 7% of pregnancies were complicated by acute rejection, and 8% of individuals lost their grafts within 2 years of delivery.[1] Other studies have reported that rejection rates during pregnancy are 0% to 17%.[2-6,9,10,13,15-17,20,23] It has been reported that rejection episodes up to 3 months after delivery are a risk factor for graft loss after delivery.[5,7] Kainz et al.[31] reported that rejection was followed by preeclampsia, renal impairment, and infection. In this study, acute rejection occurred in 2 recipients during pregnancy and in 3 recipients after delivery (within 4 months of delivery), although these patients had no renal dysfunction. All recipients were successfully treated with an increased dose of tacrolimus and/or the addition of corticosteroids or MMF, and graft loss did not occur. Thus, adequate treatment for acute rejection can prevent graft loss, although close follow-up of pregnant recipients is necessary even after delivery, especially when the recipients have renal dysfunction.

Congenital malformations in live-born neonates have been reported to occur in 3% of the

nontransplant population.[32] In transplant recipients, the incidence of congenital malformations has been reported to be 4% with corticosteroids,[32] 7% with azathioprine,[32] 3% with cyclosporine,[33] and 4% with tacrolimus.[14] Kainz et al.[31] reported that 4 neonates presented with malformations among 100 pregnancies in which the mother was treated with tacrolimus. In the present series, most recipients received tacrolimus-based therapy, and 2 of the 31 neonates (6.4%) had congenital malformations (tetralogy of Fallot and hypospadias). A higher incidence of structural malformations was observed with MMF exposure during pregnancy.[34] This agent is classified as pregnancy category D (there is positive evidence of fatal risk to humans, but potential benefits may warrant the use of the drug in pregnant women despite the potential risk; there is evidence of fetal risk).[35] No structural defects have been reported with early-pregnancy sirolimus exposure to date. In this study, artificial abortions were performed in 2 recipients to whom MMF or sirolimus was administered. Calcineurin inhibitors are classified as pregnancy category C (animal reproductive studies have shown an adverse effect on the fetus or are lacking, and there are no adequate and well-controlled studies in humans, but the potential benefits may warrant the use of the drug in pregnant women despite the potential risks; fetal risk cannot be ruled out).[35] Thus, calcineurin inhibitor–based therapy, including cyclosporine and tacrolimus, is favorable for pregnant recipients.

Although there is no established optimal interval between LT and pregnancy, a report from the National Transplantation Pregnancy Registry and the American Society of Transplantation recommended that LT recipients wait a minimum of 1 year before conception to stabilize graft function and immunosuppressant dosage. Christopher et al.[16] reported that pregnancies occurring within 1 year of LT had an increased incidence of prematurity, low birth weight, and acute rejection in comparison with those occurring more than 1 year after LT. Nagy et al.[15] reported that the risk of complications during pregnancy is low when liver LT recipients become pregnant more than 2 years after LT because the recipients have stable and normal hepatic function and normal renal function, and immunosuppressive therapy is at a maintenance dosage. The results of the National Transplantation Pregnancy Registry (2008) showed that the incidence of very-low-birth-weight neonates in pregnancies within 2 years of LT was higher than the incidence in pregnancies more than 5 years after LT.[3] A higher incidence of rejection was also reported for recipients who were pregnant 1 to 2 years after LT. These results indicate better outcomes for recipients and infants with pregnancies occurring at least 2 years after LT. In this study, the incidences of fetal growth restriction, pregnancy-induced hypertension, and neonates with extremely low birth weights were significantly higher in the early group (<3 years after LDLT) versus the late group (≥3 years after LDLT). In addition, the incidence of pregnancy-induced hypertension was higher for recipients who were 33 years old or older at the diagnosis of pregnancy versus recipients who were less than 33 years old. Thus, it is necessary to pay careful attention to complications during pregnancy when a recipient becomes pregnant within 3 years of LDLT, particularly if the age at the diagnosis of pregnancy is ≥33 years.

The pregnancy outcomes of LDLT recipients were similar to those of cadaveric LT recipients. Although most pregnancy outcomes are favorable, special attention should be given to obstetric complications such as pregnancy-induced hypertension, spontaneous abortion, fetal death, fetal growth restriction, preterm delivery, cesarean delivery, and acute rejection. It is difficult to draw definitive conclusions from this study because the number of recipients in this study was too small, and this survey might not reflect all pregnant recipients. Thus, it is necessary to analyze the outcomes after pregnancy in larger studies with prospective registration to establish and improve the clinical management of pregnancy in LT recipients.

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Reply

We thank Dr Li and colleagues for their interest in our study.

There are data[1] supporting race as a risk factor for stroke and mortality after carotid endarterectomy, the risk being higher in persons of black race compared with white. The risk of complications for other races is unclear. Although it may be premature to generalise these findings to a mixed vascular surgery population and cardiac complications, it would have been interesting to assess the association between race and cardiac outcome. Unfortunately, data regarding race are not available in the study population.

Preoperative anaemia and blood loss are well-accepted risk factors for cardiac events after vascular surgery[2]. We adjusted for preoperative anaemia in multivariable analysis. However, blood loss is an intraoperative event and is therefore impossible to incorporate in preoperative cardiac risk stratification, which is the focus of our study. Furthermore, the amount of perioperative blood loss is unlikely to be influenced by the presence or absence of diabetes mellitus, making it unlikely as a confounding factor.

As pointed out by Li et al, intraoperative hypotension and tachycardia are undoubtedly influential on the risk of ischaemic myocardial injury. However, as stated above, preoperative cardiac risk assessment will have to rely on data available preoperatively. Therefore we chose not to include data on intraoperative haemodynamics.

Routine troponin measurements were performed three times a week during admission (or whenever clinically indicated). We agree with Li et al that this may have led to an underestimation of the risk of cardiac events. However, this effect is likely to be equally present in diabetics and non-diabetics and is therefore unlikely to limit the validity of the study.

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APRV in patients with atelectasis after liver transplantation

Atelectasis frequently occurs after living donor liver transplantation (LDLT)[1] and it is a risk factor for hypoxaemia and pneumonia. Airway pressure release ventilation (APRV), a mode providing two levels of airway pressure (P_{high} and P_{low}) during two set time periods (T_{high} and T_{low}), is one method that can be used to treat atelectasis. As far as we know, no studies have evaluated the impact of APRV on atelectasis and the hepatic blood-flow after LDLT.

After obtaining institutional ethics approval (013-0199), we compared the outcomes of patients who were ventilated with APRV after LDLT between January and December 2008. During this study period, APRV was used in patients who were more than 12 years old, with atelectasis confirmed on a chest X-ray within two days of LDLT. For each APRV patient we chose a similar historical control patient who was ventilated by synchronised intermittent mandatory ventilation (SIMV) after LDLT between October 2003 and December 2007. The ventilator settings and level of sedation were adjusted so that the PaO_2 was >100 mmHg, the $PaCO_2$ was 40±5 mmHg and the Richmond Agitation Sedation Scale was between -3 and 0, during either SIMV or APRV ventilation. The exclusion criteria included: 1) reoperation, 2) bilateral thoracentesis and 3) intolerance to APRV for at least 12 hours.

The weaning method consisted of continuous positive airway pressure or continuous positive airway pressure with pressure support in both groups, and the endotracheal tube was removed when the patients met all the following criteria: 1) stable liver function, 2) no haemodynamic instability, 3) PaO_2 to FiO_2 ratio of >200, 4) positive end-expiratory pressure of <5 cmH_2O and 5) pressure support of <5 cmH_2O.

During the study period, nine patients were treated with APRV (mean age=46.0 ± standard deviation 13, 4 male/5 female, body mass index=25.9±3.5, Model for End-Stage Liver Disease score=18.7±11.9 and duration of surgery=949.1±156.1 minutes) and they were compared to 27 historical controls subjects who had similar characteristics. The average APRV settings were P_{high} of 14.1±3.6 cmH_2O, P_{low} of 2.1± 2.7 cmH_2O, T_{high} of 5.2±2.9 seconds, T_{low} of 1.1±0.3 seconds, with a mean airway pressure (MAP) of 13.6±4.7 cmH_2O. The atelectasis score was significantly better after

Table 1
The extent of atelectasis and postoperative course

	Control Group (n=27)	APRV Group (n=9)	*P* value
Atelectasis			
Radiological atelectasis score			
1 POD	2.2±1.2	2.5±1.4	0.07
7 POD	3.2±2.0	0.4±0.7	<0.01
7 POD (A/W ratio (%))	16.1±9.1	3.1±2.8	<0.01
Postoperative course (P/F)			
1 POD	302.6±62.0	280.0±60.0	>0.05
5 POD	230.7±67.0	312.0±54.3	<0.01
10 POD	272.7±89.0	379.1±49.0	<0.01
Acute rejection (within 30 POD)	7	2	1.00
Vascular complications	2	1	0.55
Pneumonia (within 21 POD)	3	0	0.53
Mechanical ventilation (days)	5.1±4.2	4.6±2.3	0.60
ICU stay (days)	8.3±7.6	7.0±3.3	0.77
1 year mortality, no. (%)	1 (3.7)	1 (12.5)	0.41
2 year mortality, no. (%)	3 (11.1)	1 (12.5)	1.00
Hospital stay (days)	42.3±16.3	37.3±27.3	0.46

Data are expressed as the mean ± SD or number. APRV=airway pressure release ventilation, POD=postoperative day, A/W=ratio of atelectatic area/whole lung area on CT thorax, P/F=ratio of PaO_2 to FiO_2.

APRV compared to that after SIMV in the control on the seventh postoperative day (Table 1). Although the PaO_2 to FiO_2 ratios in the APRV were greater than those observed in the control, no significant differences were found between the two groups regarding the postoperative course (Table 1). APRV did not appear to induce significant changes in the portal vein blood-flow (949.1±570.6 ml/minute before APRV compared to 1110.0±367.2, 1025.9±482.4 and 1113.6±319.6 ml/minute; P=0.73 after 12, 24 and 36 hours of APRV, respectively). The resistive indexes (a reflection of increased hepatic vascular resistance) on Doppler ultrasonography also did not change significantly (baseline 0.8±0.1 compared to 0.7±4.5, 0.8±4.6 and 0.8±2.3 after 12, 24 and 36 hours of APRV; P=0.51). The hepatic vein blood-flow remained triphasic pattern throughout the study period.

In this study, APRV improved atelectasis in patients after LDLT without compromising hepatic blood-flow. The P_{high} titrated in this study differed from the higher P_{high} titration (>14 cmH_2O) previously reported when APRV was used for patients with acute respiratory distress syndrome[3]. During positive pressure mechanical ventilation, hepatic perfusion can be affected by the MAP[4]. We therefore paid special attention to the following three points in order to avoid excessive MAP. First, we set up the initial MAP of APRV using the MAP obtained during SIMV prior to changing to APRV. Consequently, our MAP (13.9 cmH_2O) was similar to that reported by Saner et al, who studied the use of high positive end-expiratory pressure strategies after LDLT[5]. Second, we tried to preserve spontaneous breathing during APRV, which is important in maintaining hepatic perfusion[4]. Third, we set a relatively long T_{low} and short T_{high} during APRV in our patients.

In conclusion, the present study demonstrated that judicious use of APRV could improve atelectasis without compromising hepatic blood-flow after LDLT. An adequately powered randomised controlled trial is needed to confirm whether routine use of APRV can improve patient-centred outcomes, including length of intensive care and hospital stay after LDLT.

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Benefit of intermittent pneumatic compression of lower limbs in reducing venous thromboembolism in hospitalised patients: interactions between risk and effectiveness

Venous thromboembolism (VTE) is an important, preventable cause of morbidity and mortality in hospitalised patients[1,2]. Our recent analysis of the Australian and New Zealand Intensive Care Society Centre for Outcomes and Resource Evaluation showed that acute pulmonary embolism accounted for 0.9% of all emergency intensive care admissions and over 20% of these patients required mechanical ventilation, 4.2% had a cardiac arrest prior to intensive care admission and the associated mortality was high (14.8%)[1]. Furthermore, omission of early mechanical or pharmacological thromboprophylaxis in critically ill patients was associated with an increased risk of both crude and adjusted mortality[3], particularly substantial in patients who had severe critical illness.

Use of thromboprophylaxis in many institutions has improved in the past decade; however, recent evidence suggested that many hospitalised patients remained not treated with early thromboprophylaxis when it was indicated. This may be, in part, due to the concern that pharmacologic thromboprophylaxis may increase risk of bleeding. Our recent work showed that many critically ill patients may have an increased risk of in vitro thrombotic tendency[4], and VTE can still occur in patients who have a mild to moderate degree of acquired coagulopathy[5]. Perhaps the best thromboprophylaxis strategy for patients who are at high risk of developing VTE and, at the same time, at risk of bleeding or with acquired coagulopathy may be mechanical thromboprophylaxis. Our recent meta-analysis showed that intermittent pneumatic compression of the lower limbs was indeed useful in preventing VTE in hospitalised patients[6]. It was more effective than no thromboprophylaxis in reducing VTE, more effective than thromboembolic deterrent stockings in reducing deep vein thrombosis and appeared to be as effective as pharmacological thrombo-

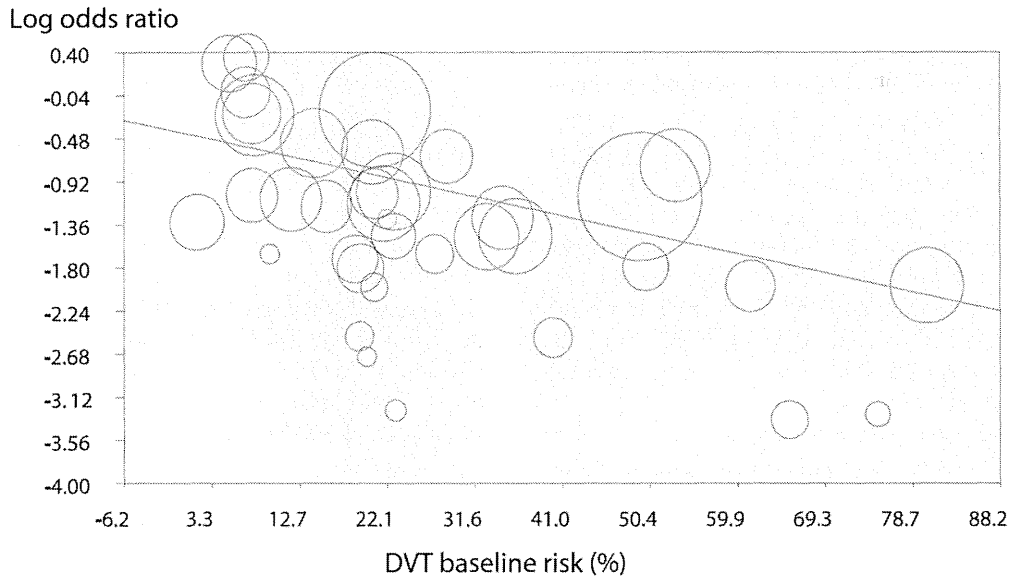

Figure 1: The protective effect of intermittent pneumatic compression on risk of deep vein thrombosis was stronger with increasing risk of baseline risk of deep vein thrombosis. Size of the marker is directly proportional to the size of the trial. Slope of meta-regression=-0.02, 95% confidence interval -0.03 to -0.01; P <0.01. DVT=deep vein thrombosis.

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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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See Editorial on Page 255

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

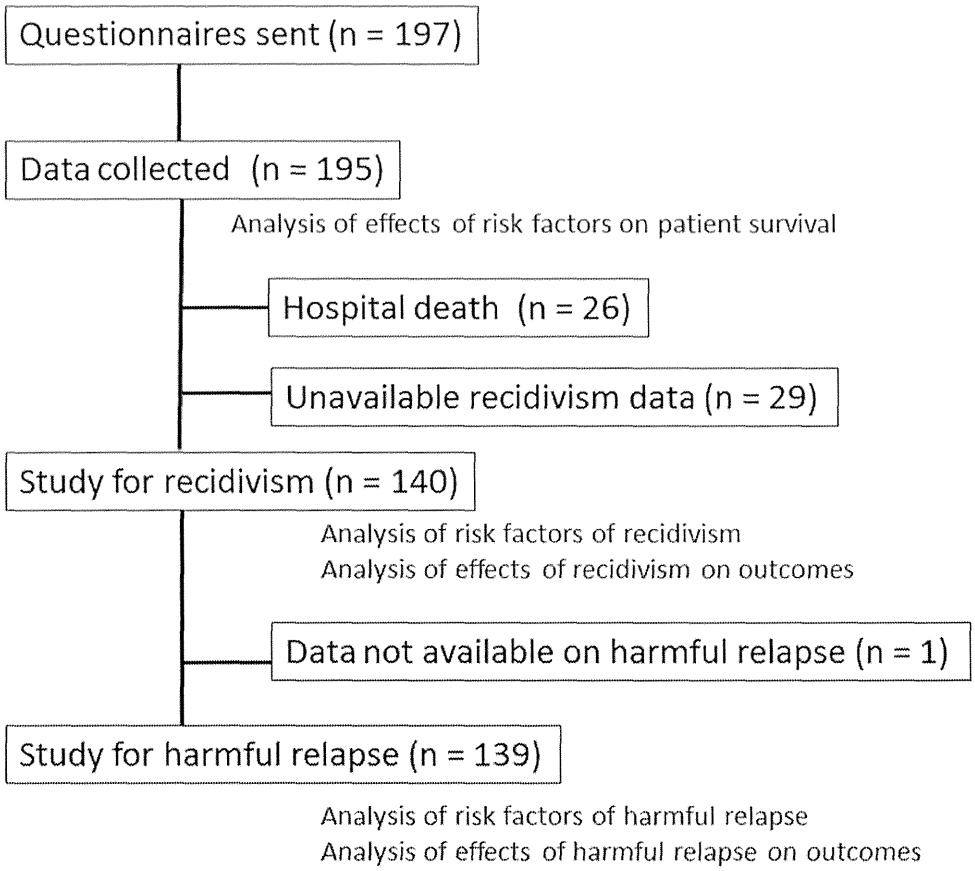

Figure 1. Patient enrollment and inclusion in our analysis. Questionnaires were sent to 38 centers for 197 patients. Clinical data were collected for 195 patients from 36 centers, and risk factors for patient survival were analyzed for these patients. Risk factors for recidivism and the impact of recidivism 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