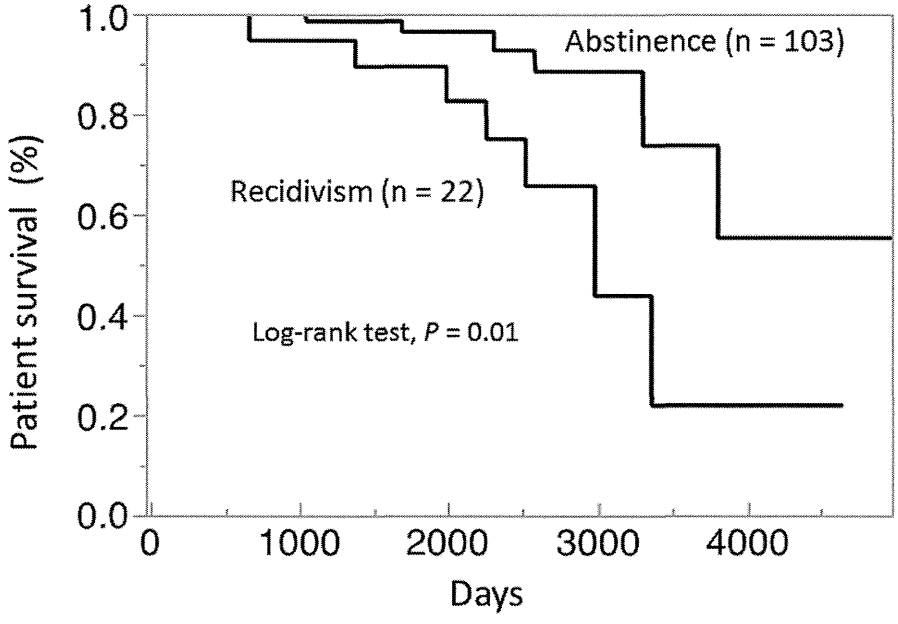

Numbers at risk	0 years	1 year	3 years	5 years	7 years	10 years
Recidivism	22	22	19	14	7	2
Abstinence	103	103	70	42	25	5

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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REFERENCES

1. Japanese Liver Transplantation Society. Liver transplantation in Japan—registry by the Japanese Liver Transplantation Society [in Japanese]. Ishoku 2010;46:524-536.
2. Mackie J, Groves K, Hoyle A, Garcia C, Garcia R, Gunson B, Neuberger J. Orthotopic liver transplantation for alcoholic liver disease: a retrospective analysis of survival, recidivism, and risk factors predisposing to recidivism. Liver Transpl 2001;7:418-427.
3. Bird GL, O'Grady JG, Harvey FA, Calne RY, Williams R. Liver transplantation in patients with alcohol cirrhosis: selection criteria and rates of survival and relapse. BMJ 1990;301:15-17.
4. Pfitzmann R, Schwenzer J, Rayes N, Seehofer D, Neuhaus R, Nüssler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl 2007;13:197-205.
5. Dew MA, DiMartini AF, Steel J, De Vito Dabbs A, Myaskovsky L, Unruh M, Greenhouse J. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. Liver Transpl 2008;14:159-172.
6. Bravata DM, Keeffe EB, Owens DK. Quality of life, employment, and alcohol consumption after liver transplantation. Curr Opin Organ Transplant 2001;6:130-141.
7. Kawaguchi Y, Sugawara Y, Yamashiki N, Kaneko J, Tamura S, Aoki T, et al. Role of 6-month abstinence rule in living donor liver transplantation for patients with alcoholic liver disease. Hepatol Res 2013;43:1169-1174.
8. Shawcross DL, O'Grady JG. The 6-month abstinence rule in liver transplantation. Lancet 2010;376:216-217.
9. Jauhar S, Talwalkar JA, Schneekloth T, Jowsey S, Wiesner RH, Menon KV. Analysis of factors that predict alcohol relapse following liver transplantation. Liver Transpl 2004;10:408-411.
10. Kelly M, Chick J, Gribble R, Gleeson M, Holton M, Winstanley J, et al. Predictors of relapse to harmful alcohol after orthotopic liver transplantation. Alcohol Alcohol 2006;41:278-283.
11. DiMartini A, Day N, Dew MA, Javed L, Fitzgerald MG, Jain A, et al. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. Liver Transpl 2006;12:813-820.
12. Tandon P, Goodman KJ, Ma MM, Wong WW, Mason AL, Meeberg G, et al. A shorter duration of pretransplant abstinence predicts problem drinking after liver transplantation. Am J Gastroenterol 2009;104:1700-1706.
13. De Gottardi A, Spahr L, Gelez P, Morard I, Mentha G, Guillaud O, et al. A simple score for predicting alcohol relapse after liver transplantation: results from 387 patients over 15 years. Arch Intern Med 2007;167:1183-1188.
14. Yates WR, Booth BM, Reed DA, Brown K, Masterson BJ. Descriptive and predictive validity of a high-risk alcoholism relapse model. J Stud Alcohol 1993;54:645-651.
15. Schmeding M, Heidenhain C, Neuhaus R, Neuhaus P, Neumann UP. Liver transplantation for alcohol-related cirrhosis: a single centre long-term clinical and histological follow-up. Dig Dis Sci 2011;56:236-243.
16. Cuadrado A, Fábrega E, Casafont F, Pons-Romero F. Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcohol liver disease. Liver Transpl 2005;11:420-426.
17. Webb K, Shepherd L, Day E, Masterton G, Neuberger J. Transplantation for alcoholic liver disease: report of a consensus meeting. Liver Transpl 2006;12:301-305.
18. Burra P, Senzolo M, Adam R, Delvart V, Karam V, Germani G, Neuberger J; for ELITA and ELTR Liver Transplant Centers. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant 2010;10:138-148.
19. Lim JK, Keeffe EB. Liver transplantation for alcoholic liver disease: current concepts and length of sobriety. Liver Transpl 2004;10(suppl 2):S31-S38.
20. Gish RG, Lee A, Brooks L, Leung J, Lau JY, Moore DH II. Long-term follow-up of patients diagnosed with alcohol dependence or alcohol abuse who were evaluated for liver transplantation. Liver Transpl 2001;7:581-587.

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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References

1. Brown HA, Sullivan MC, Gusberg RG, Dardik A, Sosa JA, Indes JE. Race as a predictor of morbidity, mortality, and neurologic events after carotid endarterectomy. J Vasc Surg 2013; 57:1325-1330.
2. Valentijn TM, Hoeks SE, Martienus KA, Bakker EJ, van de Luijtgaarden KM, Verhagen HJ et al. Impact of haemoglobin concentration on cardiovascular outcome after vascular surgery: A retrospective observational cohort study. Eur J Anaesthesiol 2013; 30:664-670.

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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References

1. Golfieri R, Giampalma E, Morselli Labate AM, d'Arienzo P, Jovine E, Grazi GL et al. Pulmonary complications of liver transplantation: radiological appearance and statistical evaluation of risk factors in 300 cases. Eur Radiol 2000; 10:1169-1183.
2. Richter LK, Ingwersen U, Thode S, Jakobsen S. Mask physiotherapy in patients after heart surgery: a controlled study. Intensive Care Med 1995; 21:469-474.
3. Varpula T, Valta P, Niemi R, Takkunen O, Hynynen M, Pettila VV. Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. Acta Anaesthesiol Scand 2004; 48:722-731.
4. Hering R, Bolten JC, Kreyer S, Berg A, Wrigge H, Zinserling J et al. Spontaneous breathing during airway pressure release ventilation in experimental lung injury: effects on hepatic blood flow. Intensive Care Med 2008; 34:523-527.
5. Saner FH, Olde Damink SW, Pavlakovic G, van den Broek MA, Sotiropoulos GC, Radtke A et al. Positive end-expiratory pressure induces liver congestion in living donor liver transplant patients: myth or fact. Transplantation 2008; 85:1863-1866.

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-

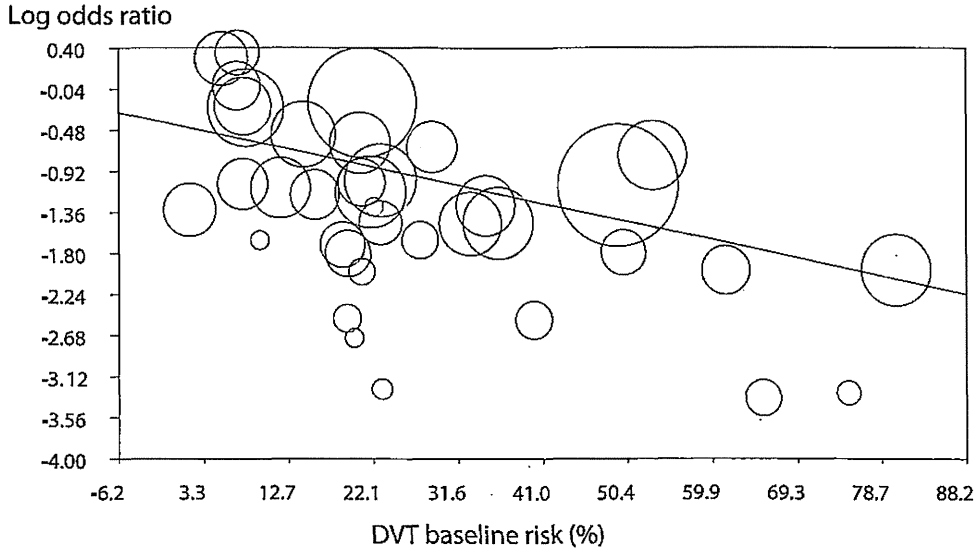

Figure 1: The protective effect of intermittent pneumatic compression on risk of deep vein thrombosis was stronger with increasing risk of baseline risk of deep vein thrombosis. Size of the marker is directly proportional to the size of the trial. Slope of meta-regression=-0.02, 95% confidence interval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

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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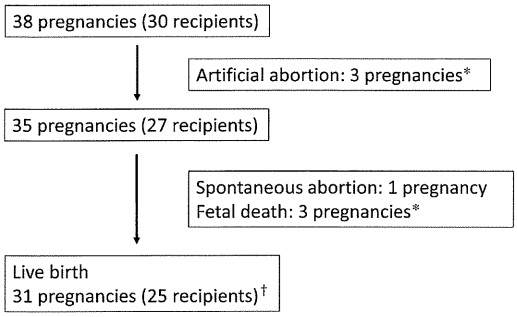

Figure 1. Subjects of this study. *In one recipient, artificial abortion was performed at the first pregnancy, and the second pregnancy was resulted in fetal death. †Six recipients had live births twice.

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.

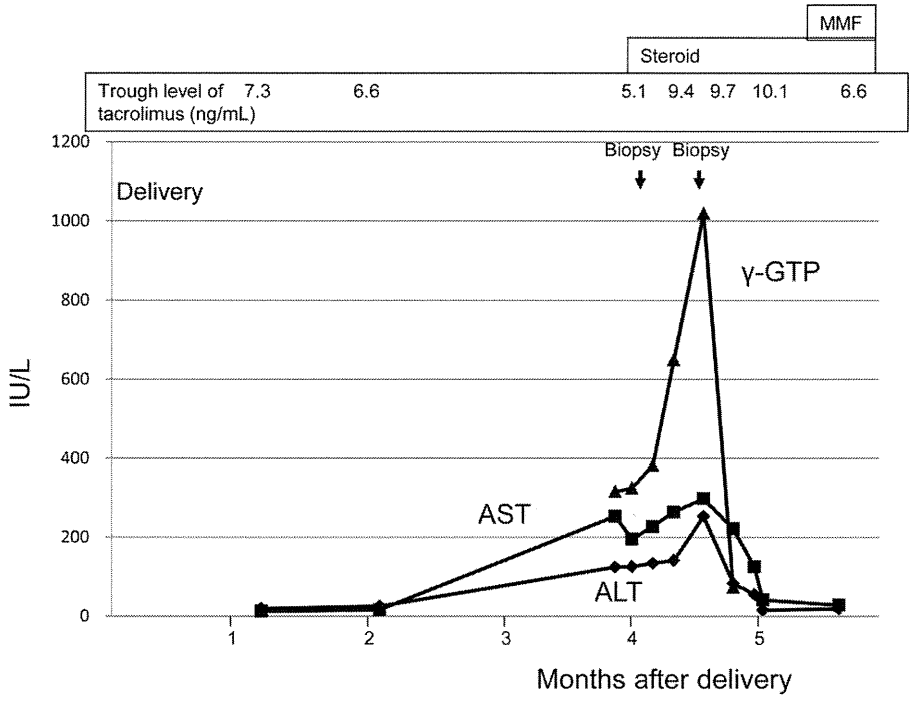

Figure 2. Clinical course of recipients suffering acute rejection after delivery. Acute rejection was diagnosed with a second liver biopsy (rejection activity index = 4).

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

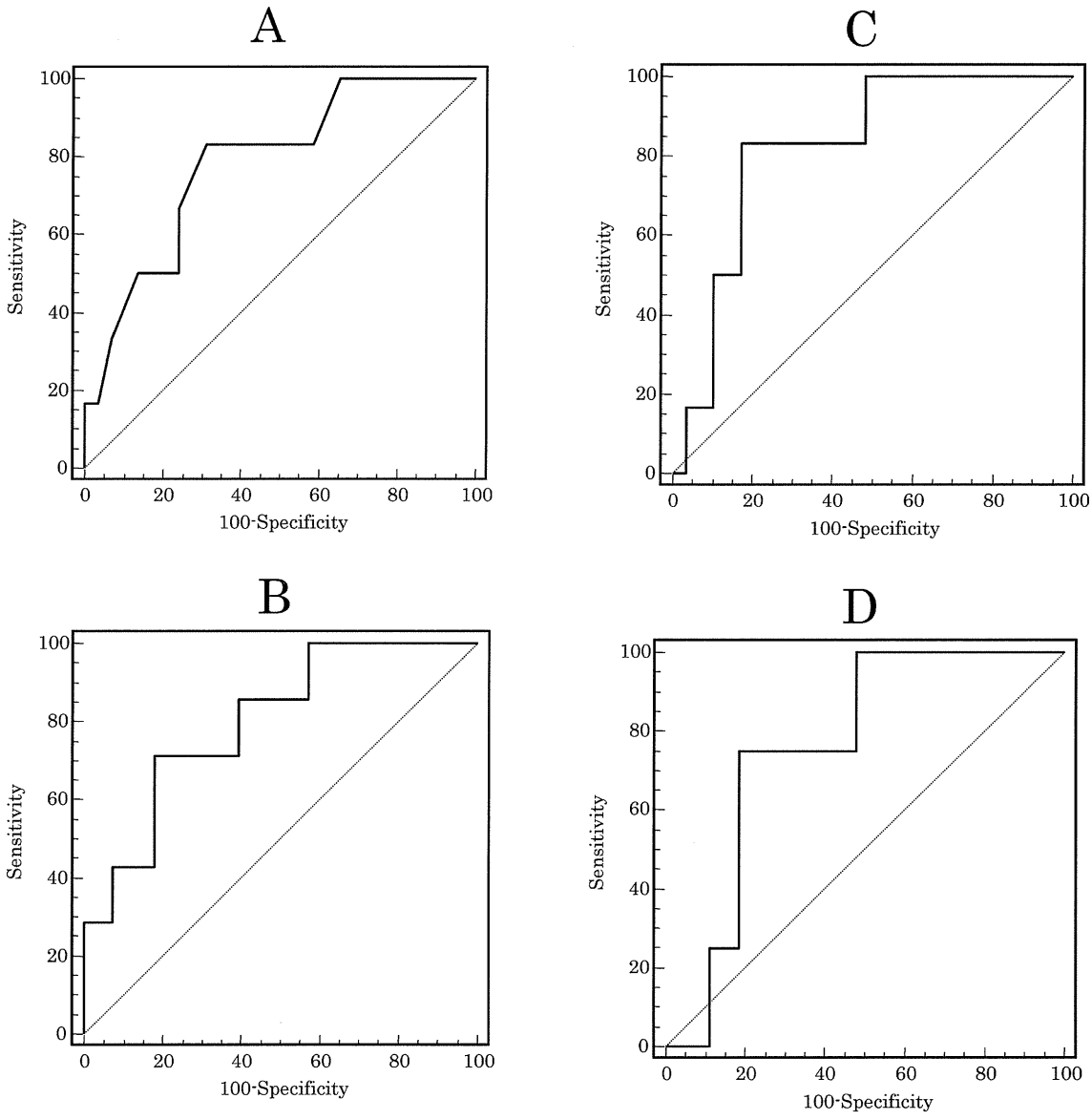

Figure 3. ROC curves for pregnant recipients: (A) age at the diagnosis of pregnancy and pregnancy-induced hypertension, (B) interval from LT to pregnancy and fetal growth restriction, (C) interval from LT to pregnancy and pregnancy-induced hypertension, and (D) interval from LT to pregnancy and extremely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

1. Armenti VT, Daller JA, Constantinescu S, Silva P, Radomski JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry: outcomes of pregnancy after transplantation. Clin Transpl 2006:57-70.
2. Coscia LA, Constantinescu S, Moritz MJ, Radomski JS, Gaughan WJ, McGrory CH, Armenti VT; for National Transplantation Pregnancy Registry. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2007:29-42.
3. Coscia LA, Constantinescu S, Moritz MJ, Frank AM, Ramirez CB, Doria C, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2008:89-105.
4. Coscia LA, Constantinescu S, Moritz MJ, Frank A, Ramirez CB, Maley WL, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2009:103-122.
5. Coscia LA, Constantinescu S, Moritz MJ, Frank AM, Ramirez CB, Maley WR, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2010:65-85.

6. Scantlebury V, Gordon R, Tzakis A, Koneru B, Bowman J, Mazzaferro V, et al. Childbearing after liver transplantation. Transplantation 1990;49:317-321.
7. Radomski JS, Ahlswede BA, Jarrell BE, Mannion J, Cater J, Moritz MJ, Armenti VT. Outcomes of 500 pregnancies in 335 female kidney, liver, and heart transplant recipients. Transplant Proc 1995;27:1089-1090.
8. Jain A, Venkataramanan R, Fung JJ, Gartner JC, Lever J, Balan V, et al. Pregnancy after liver transplantation under tacrolimus. Transplantation 1997;64:559-565.
9. Patapis P, Irani S, Mirza DF, Gunson BK, Lupo L, Mayer AD, et al. Outcome of graft function and pregnancy following liver transplantation. Transplant Proc 1997;29: 1565-1566.
10. Wu A, Nashan B, Messner U, Schmidt HH, Guenther HH, Niesert S, Pichmayr R. Outcome of 22 successful pregnancies after liver transplantation. Clin Transplant 1998;12:454-464.
11. Casele HL, Laifer SA. Association of pregnancy complications and choice of immunosuppressant in liver transplant patients. Transplantation 1998;65:581-583.
12. Carr DB, Larson AM, Schmucker BC, Brateng DA, Carithers RL Jr, Easterling TR. Maternal hemodynamics and pregnancy outcome in women with prior orthotopic liver transplantation. Liver Transpl 2000;6:213-221.
13. Raakow R, Neuhaus R, Büscher U, Schmidt S, Rayes N, Glanemann M, Neuhaus P. Parenthood following liver transplantation. Transplant Proc 2001;33:1450-1452.
14. Jain AB, Reyes J, Marcos A, Mazariegos G, Eghtesad B, Fontes PA, et al. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. Transplantation 2003;76: 827-832.
15. Nagy S, Bush MC, Berkowitz R, Fishbein TM, Gomez-Lobo V. Pregnancy outcome in liver transplant recipients. Obstet Gynecol 2003;102:121-128.
16. Christopher V, Al-Chalabi T, Richardson PD, Muiesan P, Rela M, Heaton ND, et al. Pregnancy outcome after liver transplantation: a single-center experience of 71 pregnancies in 45 recipients. Liver Transpl 2006;12:1138-1143.
17. Dei Malatesta MF, Rossi M, Rocca B, Iappelli M, Giorno MP, Berloco P, Cortesini R. Pregnancy after liver transplantation: report of 8 new cases and review of the literature. Transpl Immunol 2006;15:297-302.
18. Sibanda N, Briggs JD, Davison JM, Johnson RJ, Rudge CJ. Pregnancy after organ transplantation: a report from the UK Transplant Pregnancy Registry. Transplantation 2007;83:1301-1307.
19. Masuyama H, Matsuda M, Shimizu K, Segawa T, Hiramatsu Y. Pregnancy after living-related liver transplantation associated with severe preeclampsia and a review of the literature. Arch Gynecol Obstet 2010;281:423-425.
20. Jabiry-Zieniewicz Z, Szpotanska-Sikorska M, Pietrzak B, Kociszewska-Najman B, Foroncewicz B, Mucha K, et al. Pregnancy outcomes among female recipients after liver transplantation: further experience. Transplant Proc 2011;43:3043-3047.
21. Parhar KS, Gibson PS, Coffin CS. Pregnancy following liver transplantation: review of outcomes and recommendations for management. Can J Gastroenterol 2012;26: 621-626.
22. Blume C, Sensoy A, Gross MM, Guenter HH, Haller H, Manns MP, et al. A comparison of the outcome of pregnancies after liver and kidney transplantation. Transplantation 2013;95:222-227.
23. Coffin CS, Shaheen AA, Burak KW, Myers RP. Pregnancy outcomes among liver transplant recipients in the United States: a nationwide case-control analysis. Liver Transpl 2010;16:56-63.
24. Deshpande NA, James NT, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Cameron AM, et al. Pregnancy outcomes of liver transplant recipients: a systemic review and meta-analysis. Liver Transpl 2012;18:621-629.
25. Japanese Liver Transplantation Society. Liver transplantation in Japan: registry by the Japanese Liver Transplantation Society. Ishoku 2012;47:416-432.
26. ACOG Committee on Practice Bulletins–Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol 2002;99:159-167.
27. Shinozuka N, Okai T, Kohzuma S, Mukubo M, Shih CT, Maeda T, et al. Formulas for fetal weight estimation by ultrasound measurements based on neonatal specific gravities and volumes. Am J Obstet Gynecol 1987;157: 1140-1145.
28. Banff scheme for grading liver allograft rejection: an international consensus document. Hepatology 1997;25: 658-663.
29. Shiozaki A, Matsuda Y, Satoh S, Saito S. Comparison of risk factors for gestational hypertension and preeclampsia in Japanese singleton pregnancies. J Obstet Gynaecol Res 2013;39:492-499.
30. Shiozaki A, Matsuda Y, Hayashi K, Satoh S, Saito S. Comparison of risk factors for major obstetric complications between Western countries and Japan: a case-cohort study. J Obstet Gynaecol Res 2011;37:1447-1454.
31. Kainz A, Harabacz I, Cowlrick IS, Gadgil SD, Hagiwara D. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. Transplantation 2000;70:1718-1721.
32. Armenti VT, Moritz MJ, Davison JM. Drug safety issues in pregnancy following transplantation and immunosuppression: effects and outcomes. Drug Saf 1998;19:219-232.
33. Lamarque V, Leleu MF, Monka C, Krupp P. Analysis of 629 pregnancy outcomes in transplant recipients treated with Sandimmun. Transplant Proc 1997;29:2480.
34. Sifontis NM, Coscia LA, Constantinescu S, Lavelanet AF, Moritz MJ, Armenti VT. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation 2006;82:1698-1702.
35. University of Washington. FDA pregnancy categories. http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf. Accessed January 2014.

Cyst Infection of Intraductal Papillary Mucinous Neoplasms of the Pancreas: Management of a Rare Complication

Report of 2 Cases

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Abstract: The purpose of this study was to describe the cyst infection of intraductal papillary mucinous neoplasm in 2 patients. The patients were 62- and 74-year-old men. The initial symptom was acute febrile abdominal pain. Laboratory tests revealed severe infection (C-reactive protein concentrations were 23.3 μg/mL in patient 1 and 22.3 μg/mL in patient 2) and multilocular cystic masses (the diameters were 70 mm in patient 1 and 50 mm in patient 2) at the pancreatic head that involved peripancreatic vessels were demonstrated by computed tomography. Laboratory and radiographic findings were markedly improved by endoscopic transpapillary drainage. The enteric bacteria were detected in the drainage specimens. Curative resection was achieved, and histological findings indicated a carcinoma in situ in patient 1 and an invasive carcinoma in patient 2. Neither hyperamylasemia nor histological fat necrosis, frequently observed in acute pancreatitis, was evident. Both patients were free from recurrence after surgery (17 months in patient 1, and 18 months in patient 2). Cyst infection is an unknown complication of intraductal papillary mucinous neoplasm. Transpapillary drainage is highly recommended as an initial intervention. It is difficult to distinguish between cyst infection and unresectable invasive carcinoma with imaging modalities; however, surgical intervention after drainage may contribute to long-term survival.

Key Words: intraductal papillary mucinous neoplasms, cyst infection, transpapillary drainage

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Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a common pancreatic tumor that is characterized by the intraductal and papillary proliferation of neoplastic cells and the production of thick fluid.[1] Since it was originally described in the 1980s by Ohashi et al,[2] a large number of studies have been performed to establish the etiology of this tumor. Intraductal papillary mucinous neoplasms are classified as main-duct or branch-duct types depending on the location of the lesion.[3] They are also subdivided into 4 types (gastric, intestinal, pancreaticobiliary, and oncocytic) based on morphological features.[4] Although a number of studies have investigated the use of imaging modalities or cytogenetic analysis of tissue and fluid samples obtained by endoscopy to estimate tumor grade, IPMN staging is still subject to debate.[5,6] In general, surgical intervention is highly recommended for patients with main duct tumors or large branch-duct tumors with mural nodules.[7] In addition, patients who have IPMN-related symptoms are generally considered to be candidates for surgical resection.[8] Acute pancreatitis (AP), caused by large amounts of mucin, has been recognized as a major complication of IPMN, and the incidence of AP in the largest surgical series published to date varied from 12% to 67%.[9] Sendai guidelines recommend surgical resection in patients with branch-duct IPMN and clinical symptoms, including AP.[3] In contrast with the relatively high frequency of AP coexistent with IPMNs, reports of cyst infection associated with IPMN are rare. We report our experience with 2 patients with IPMN who developed sepsis due to cyst infection, which is a rare but notable complication of IPMN. Herein, we discuss the diagnosis, initial treatment, and management strategy for IPMN associated with cyst infection, which may represent an unknown complication of IPMN.

PATIENT 1

A 62-year-old man was admitted to a local clinic complaining of epigastralgia with fever. He was treated by administration of antibiotics without relief of symptoms. The patient was then referred to our hospital for further intervention. He had been abusing alcohol (360 mL of distilled spirits per day) for 40 years and had diabetes mellitus, hypertension, and benign prostatic hypertrophy. There was no history of AP. Blood tests revealed a marked inflammatory response: 18,660 white blood cells/μL and 23.3 μg/mL C-reactive protein (CRP). All of the tumor markers that we examined were within reference range. Serum pancreatic amylase values were within normal limits, but elastase 1 was elevated to 640 ng/dL. A computed tomography (CT) scan revealed a multilocular cystic tumor 70 mm in diameter at the head and the uncinate process of the pancreas. The tumor involved peripancreatic vessels, including the celiac artery, the superior mesenteric artery, and the portal vein (PV) (Figs. 1A, B, and D). Transpapillary nasopancreatic drainage tube, 7F in diameter, was inserted to cyst immediately after admission to our hospital. Cannulation was not difficult, because the orifice of the duodenal papilla was markedly dilated by copious amounts of mucin (Fig. 1G). The patient defervesced 3 days after drainage. The amount of drainage fluid was 170 mL at day 1 and decreased to 32 mL at day 3 after procedure. The drainage tube was removed at 9 days after drainage. *Enterococcus faecalis* and *Escherichia coli* were detected in the pus discharge. Cytological examination of the drained fluid revealed mucin-producing papillary clusters with mild atypia and positive immunoreactivity for MUC2 and NUC5AC. Both laboratory and imaging findings

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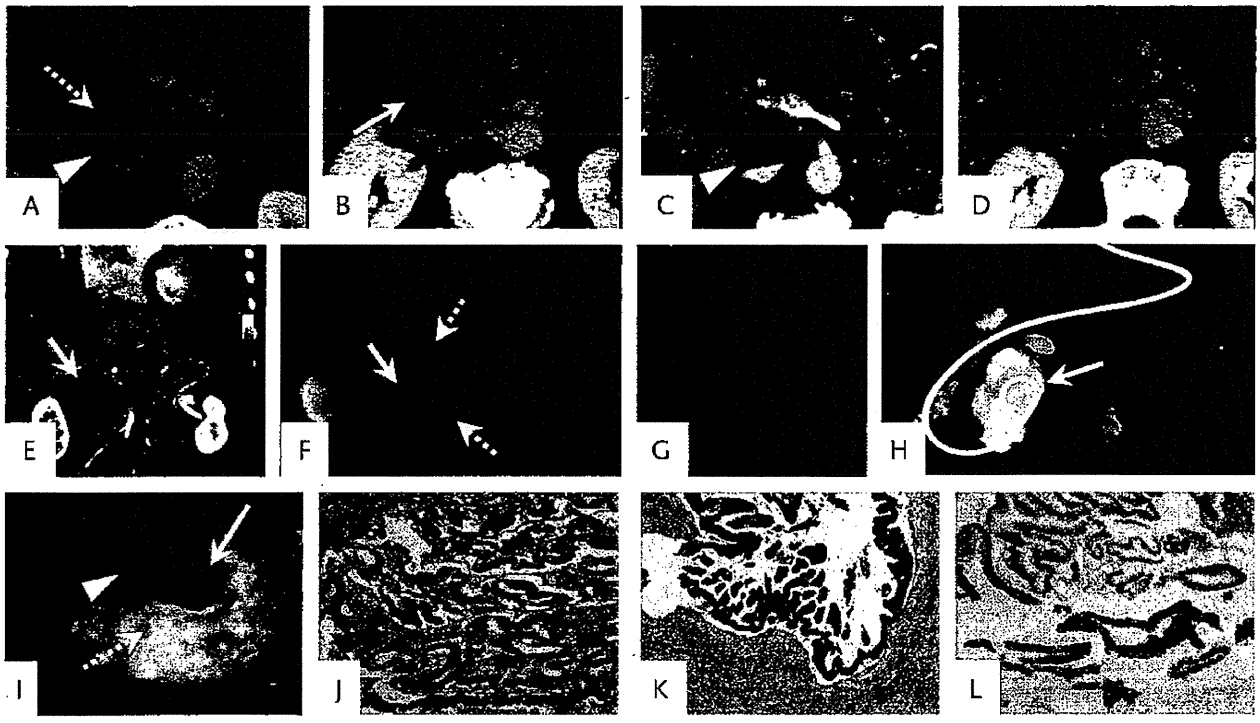

FIGURE 1. Imaging findings and resected specimen of patient 1. Computed tomography images of patient 1 before (A and B) and after (C and D) transpapillary cyst drainage are shown in the top panel; cystic lesions of the pancreas head composed of ventral (arrow) and dorsal part (dashed arrow). Both lesions 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

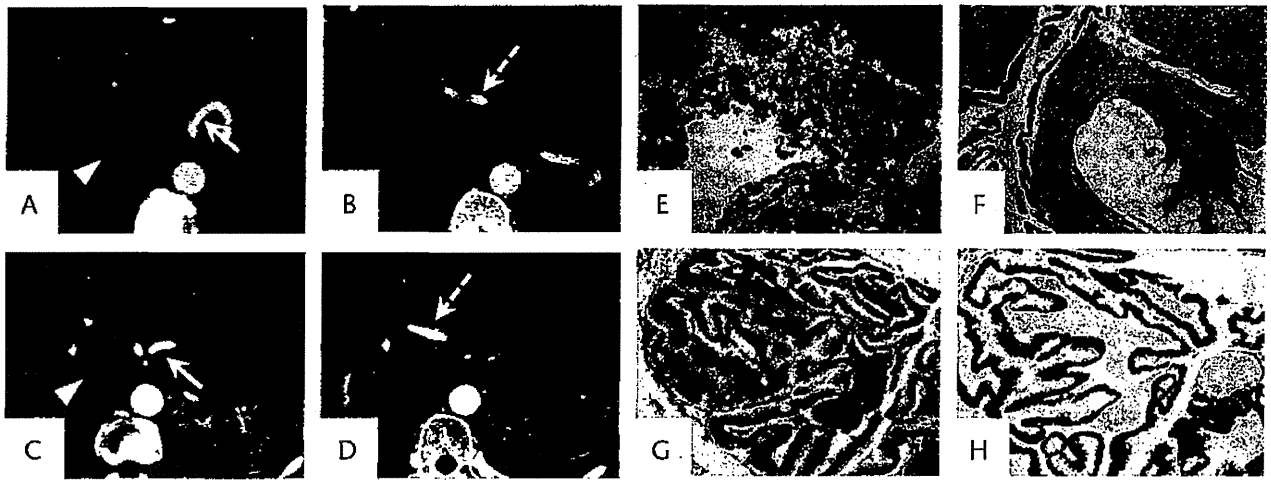

FIGURE 2. Imaging findings and resected specimen of patient 2. Computed tomography scan of patient 2 before (A and B) and after (C and D) transpapillary cyst drainage. A multilocular cystic lesion involving the SPA (solid arrow) and the common hepatic artery (dashed arrow) was observed at the pancreas 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.

REFERENCES

1. Adsay NV, Kloppel G, Fukushima N, et al. Intraductalneoplasms of the pancreas. In: Bosman F, Carneiro F, Hruban RH, et al, eds. *WHO Classification of Tumours of the Digestive System*. 4th ed. Lyon, France: IRAC; 2010:304–313.
2. Ohashi K, Murakami Y, Maruyama M, et al. Four cases of mucous secreting pancreatic cancer. [in Japanese, with English abstract]. *Prog Digest Endosc*. 1982;20:348–351.
3. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology*. 2006;6:17–32.
4. Furukawa T, Kloppel G, Volkan Adsay N, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. *Virchows Arch*. 2005;447:794–799.
5. Schmidt CM, White PB, Waters JA, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. *Ann Surg*. 2007;246:644–651; discussion 51–54.
6. Kawai M, Uchiyama K, Tani M, et al. Clinicopathological features of malignant intraductal papillary mucinous tumors of the pancreas: the differential diagnosis from benign entities. *Arch Surg*. 2004;139:188–192.
7. Salvia R, Fernandez-del Castillo C, Bassi C, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. *Ann Surg*. 2004;239:678–685; discussion 85–87.
8. Sugiyama M, Izumisato Y, Abe N, et al. Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. *Br J Surg*. 2003;90:1244–1249.
9. McGrath K, Slivka A. Diagnosis and management of intraductal papillary mucinous neoplasia. *Nat Clin Pract Gastroenterol Hepatol*. 2005;2:316–322.
10. Pelletier AL, Hammel P, Rebours V, et al. Acute pancreatitis in patients operated on for intraductal papillary mucinous neoplasms of the pancreas: frequency, severity, and clinicopathologic correlations. *Pancreas*. 2010;39:658–661.
11. Tsutsumi K, Ohtsuka T, Oda Y, et al. A history of acute pancreatitis in intraductal papillary mucinous neoplasms of the pancreas is a potential predictive factor for malignant papillary subtype. *Pancreatology*. 2010;10:707–712.
12. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101:2379–2400.
13. Lerch MM, Stier A, Wahnschaffe U, et al. Pancreatic pseudocysts: observation, endoscopic drainage, or resection? *Deutsch Arzteblatt Int*. 2009;106:614–621.
14. Luiten EJ, Hop WC, Endtz HP, et al. Prognostic importance of gram-negative intestinal colonization preceding pancreatic infection in severe acute pancreatitis. Results of a controlled clinical trial of selective decontamination. *Intensive Care Med*. 1998;24:438–445.

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Waiting list mortality of patients with primary biliary cirrhosis in the Japanese transplant allocation system

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Abstract
Background The present study aimed to evaluate etiology-based differences in the risk of waiting list mortality, and to compare the current Japanese transplant allocation system with the Child–Turcotte–Pugh (CTP) and the Model for End-Stage Liver Disease (MELD) scoring systems with regard to the risk of waiting list mortality in patients with primary biliary cirrhosis (PBC).
Methods Using data derived from all adult candidates for deceased donor liver transplantation in Japan from 1997 to 2011, we assessed factors associated with waiting list mortality by the Cox proportional hazards model. The waiting list mortality risk of PBC patients was further estimated with adjustment for each scoring system.
Results Of the 1056 patients meeting the inclusion criteria, 743 were not on the list at the end of study period; waiting list mortality was 58.1 % in this group. In multivariate analysis, increasing age and PBC were significantly associated with an increased risk of waiting list mortality. In comparison with patients with hepatitis C virus (HCV) infection, PBC patients were at 79 % increased risk and had a shorter median survival time by approximately 8 months. The relative hazard of PBC patients was statistically significant with adjustment for CTP score and medical point score, which was the priority for ranking candidates in the Japanese allocation system. However, it lost significance with adjustment for MELD score. Stratification by MELD score indicated a comparable waiting list survival time between patients with PBC and HCV.

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