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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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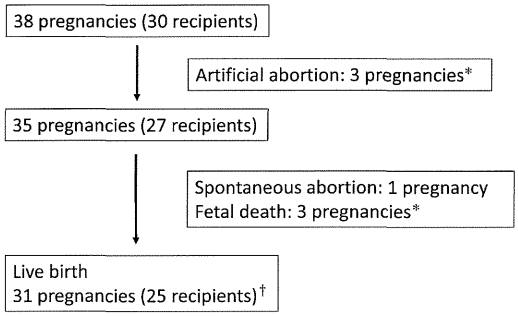


Figure 1. Subjects of this study. *In one recipient, artificial abortion was performed at the first pregnancy, and the second pregnancy was resulted in fetal death. †Six recipients had live births twice.

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.

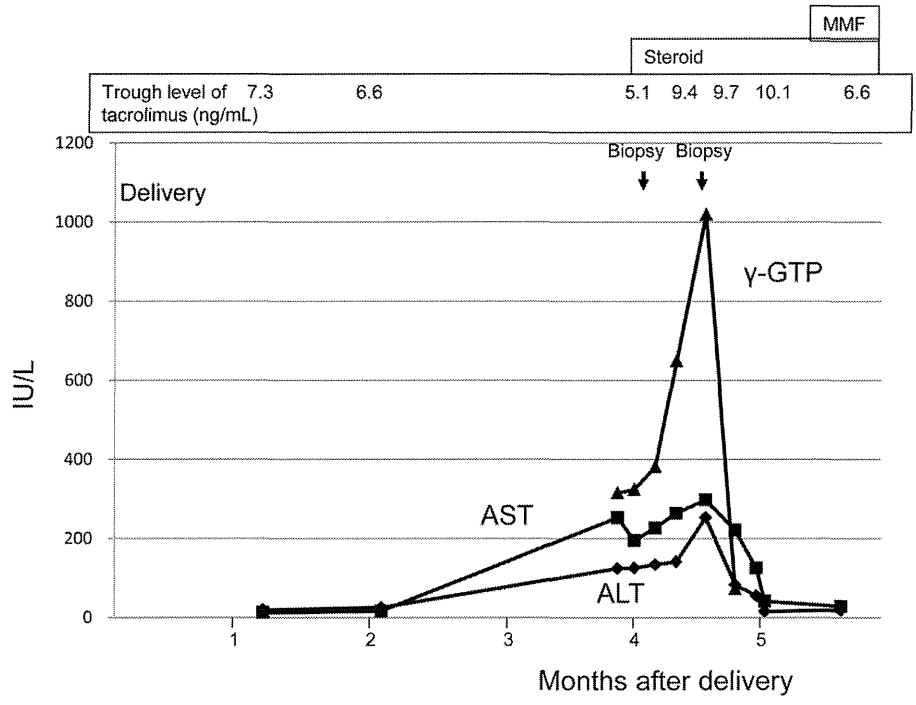


Figure 2. Clinical course of recipients suffering acute rejection after delivery. Acute rejection was diagnosed with a second liver biopsy (rejection activity index = 4).

## 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

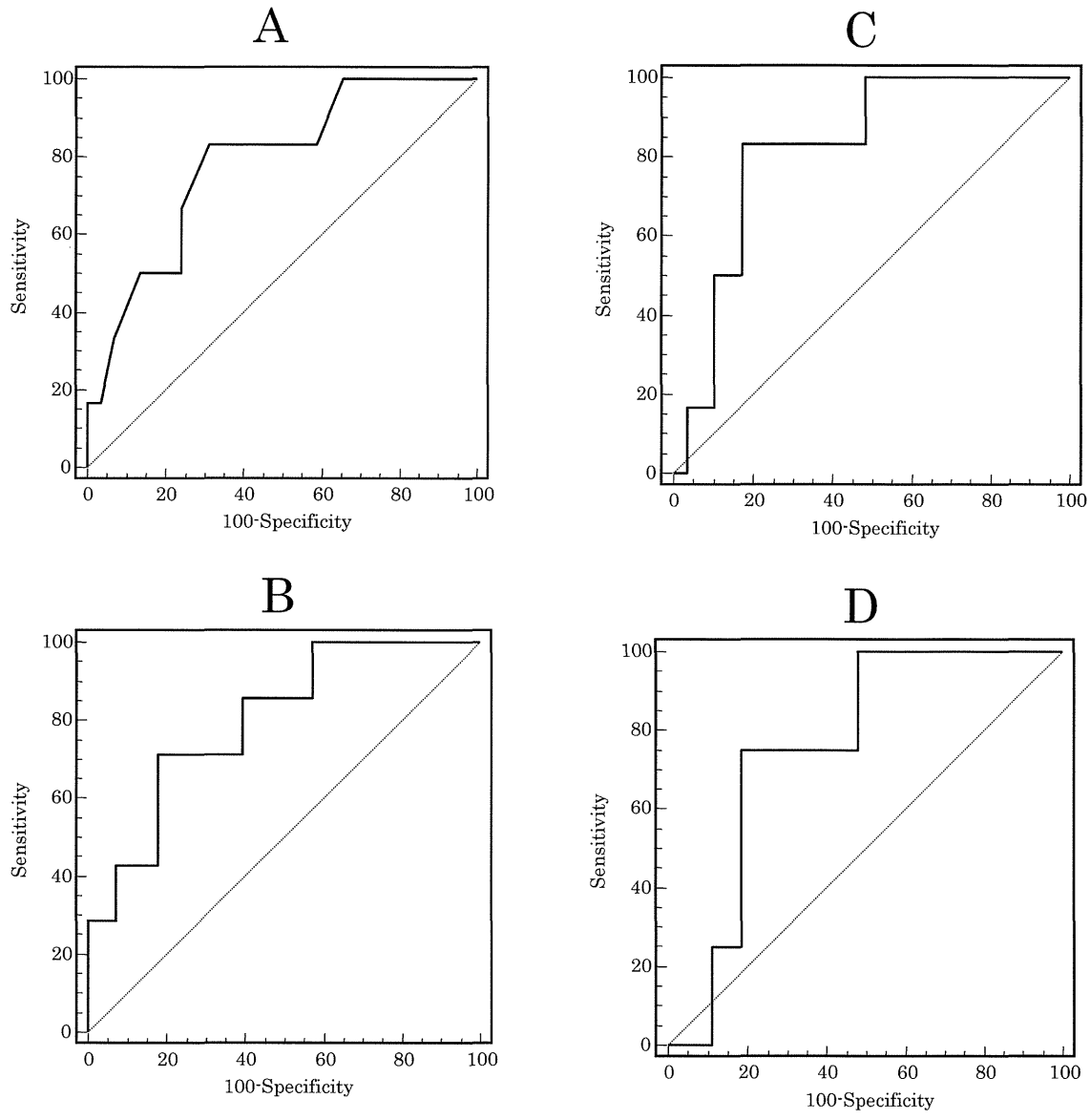


Figure 3. ROC curves for pregnant recipients: (A) age at the diagnosis of pregnancy and pregnancy-induced hypertension, (B) interval from LT to pregnancy and fetal growth restriction, (C) interval from LT to pregnancy and pregnancy-induced hypertension, and (D) interval from LT to pregnancy and extremely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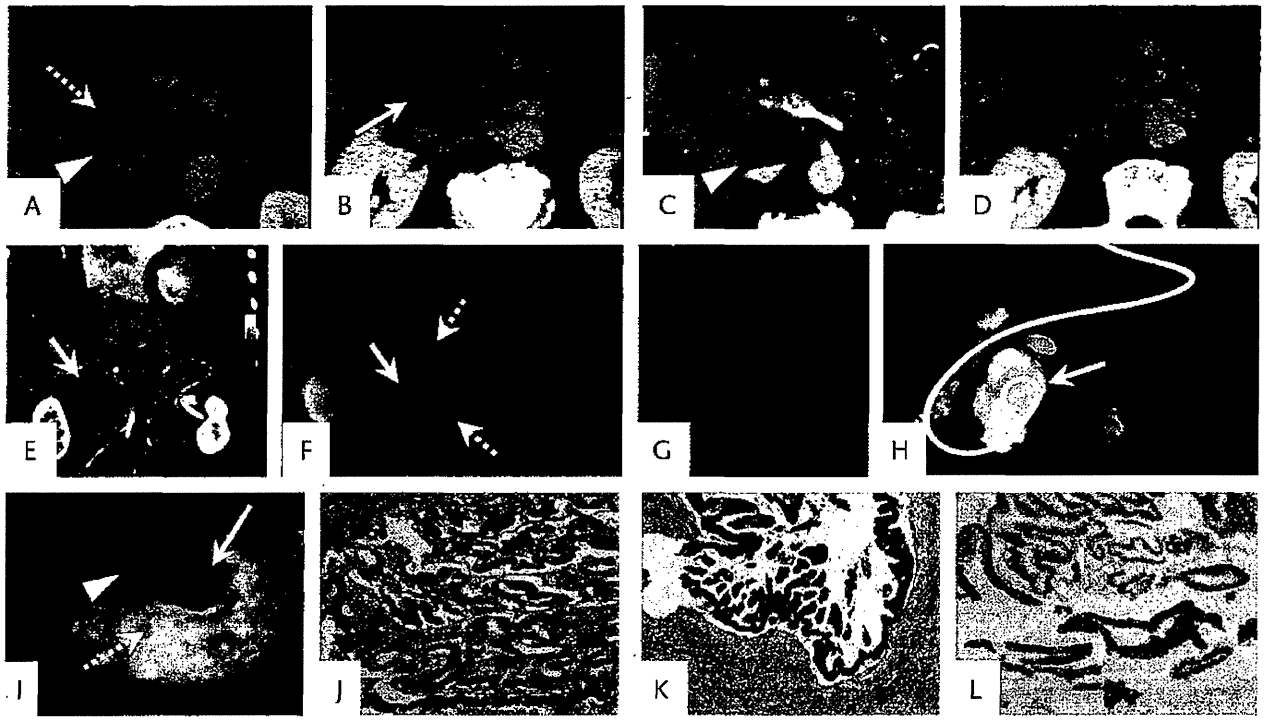


FIGURE 1. Imaging findings and resected specimen of patient 1. Computed tomography images of patient 1 before (A and B) and after (C and D) transpapillary cyst drainage are shown in the top panel; cystic lesions of the pancreas head composed of ventral (arrow) and dorsal part (dashed arrow). Both lesions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

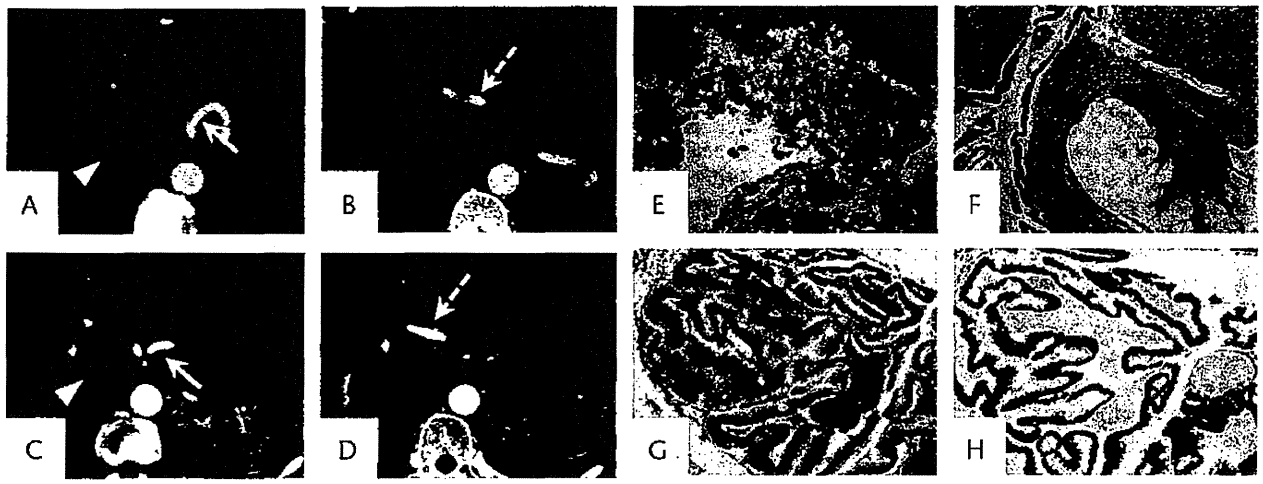


**FIGURE 2.** Imaging findings and resected specimen of patient 2. Computed tomography scan of patient 2 before (A and B) and after (C and D) transpapillary cyst drainage. A multilocular cystic lesion involving the SPA (solid arrow) and the common hepatic artery (dashed arrow) was observed at the pancreas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

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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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*Conclusions* PBC patients are at high risk of waiting list mortality in the current allocation system. MELD-based allocation could reduce this risk.

**Keywords:** Child–Turcotte–Pugh · Liver transplantation · Model for End-Stage Liver Disease

## Introduction

Liver transplantation is the only curative treatment option with excellent long-term results in patients with end-stage liver diseases. At present, the number of patients waiting to undergo liver transplantation is increasing in Japan, as well as in both Europe and the United States. However, many patients are dying on the waiting list because of the donor organ shortage. For example, recent waiting list mortality was reported as being 22.8 % in the United States [1]. Management of liver transplant waiting lists is aimed at minimizing waiting list deaths by prioritization of those with a higher mortality risk, and by ensuring allocation of available organs to these patients. Therefore, prioritization and allocation decisions require the accurate prediction of the survival probability of patients.

The indications for liver transplantation include a wide variety of liver diseases, including viral hepatitis, autoimmune hepatitis, cholestatic disease, metabolic disorders, and hepatic neoplasms. Because each type of liver disease has disease-specific therapeutic options and associated risk of complications, liver disease etiology can influence the patient's natural disease course and risk of death. Moreover, disease-specific clinical tools are widely used to determine prognosis in patients with primary biliary cirrhosis (PBC) [2, 3] and primary sclerosing cholangitis [4]. However, it is uncertain whether patients waiting for liver transplantation have a disease-specific risk for waiting list mortality, and whether the ability of the currently used allocation system to assess the urgency of transplantation could be generalized to every patient with heterogeneous etiology.

By consensus, a disease severity index used to allocate liver donor organs should be able to predict the probability of death in patients with end-stage liver diseases of heterogeneous etiology. In the United States, where a large number of patients are registered for liver transplantation, the Child–Turcotte–Pugh (CTP) score [5] was initially applied to assess the severity of liver disease in the United Network for Organ Sharing (UNOS) allocation algorithms, because of its simplicity and recognized ability to assess prognosis in patients with heterogeneous chronic liver disease. Subsequently, a number of studies have demonstrated the accuracy of the Model of End-Stage Liver Disease (MELD) score [6] in predicting short-term mortality risk in patients with end-stage liver disease [7–9]. Since February 2002, the MELD score has therefore been used as a UNOS criterion for allocating organs to patients waiting for liver transplantation [10].

On the other hand, in the countries with a small number of registrations for liver transplantation, a system of prioritization based on a detailed clinical review, which includes CTP score, MELD score, and other disease-specific prognostic scores, as well as patients' demographics, laboratory data, and disease histories, by a small number of expert clinicians is likely to be used to judge disease severity and potential mortality accurately. This clinical judgment-based prioritization of patients awaiting liver transplantation was initiated in October 1997 in Japan and, at present, little information is available concerning the prognostic ability of this allocation system.

The aims of the present retrospective study were: (1) to clarify the disease-specific risk for waiting list mortality in patients waiting for liver transplantation; and (2) to compare the current system of waiting list prioritization and organ allocation in Japan with the MELD and CTP scoring systems with regard to the risk in PBC patients, who have the highest risk of waiting list mortality.

## Patients and methods

### Patients and liver allocation policy in Japan

This was a nationwide retrospective cohort study. We used the Japan Organ Transplant Network (JOT)/the Assessment Committee of Indication for Transplantation database to identify all patients listed for deceased donor liver transplantation in Japan between October 15, 1997 and August 31, 2011. We excluded patients who were less than 18 years of age because they had a spectrum of primary diagnoses substantially different from those of patients older than 18 years. We also excluded patients listed for retransplantation to ensure that all observations represented unique individuals. Finally, we excluded patients who were diagnosed with acute liver failure because these patients rarely have chronic liver disease and are assigned the highest priority.

For JOT registration, the demographic, clinical, and laboratory data including CTP score, MELD score, or disease-specific prognostic score of all candidates are reviewed, and each candidate is assigned a clinical priority by the Assessment Committee of Indication for Transplantation (four physicians, five surgeons, and one pediatrician). The priority of candidates is represented by a medical point system, in which points are awarded according to estimated survival: 9 points for estimated survival <30 days, 6 points for <180 days, 3 points for

<360 days, and 1 point for ≥360 days. In patients with hepatocellular carcinoma, the points were determined only by the degree of hepatic decompensation. Additional points are awarded according to ABO blood group compatibility: 1.5 points for an identical blood group and 1 point for a compatible blood group. Patients with higher total points have a higher priority for donor liver allocation. For patients with identical points, waiting time is a liver allocation measure.

Age of the patient, blood type, etiology of liver disease, and medical point at listing were available for all the patients. Detailed demographic, clinical, laboratory data, including CTP score and MELD score at the time of listing, were available only in patients registered since June 22, 2006. The CTP score uses two clinical variables (ascites and encephalopathy), and three laboratory parameters (serum bilirubin and albumin levels and prothrombin time). Each variable is assigned a score from 1 to 3, with the aggregate score representing the CTP score [5]. Although the original CTP score used different criteria for total bilirubin level between patients with cholestatic disease and those with other etiologies, the criteria for the CTP score in the current Japanese allocation system did not change according to the etiology of liver disease. The MELD score was calculated using the most recent version of the formula documented on the UNOS website [11]: $9.57 \times \log_e$(creatinine mg/dL) $+ 3.78 \times \log_e$(bilirubin mg/dL) $+ 11.2 \times \log_e$(international normalized ratio [INR]) + 6.43, rounded to the nearest integer. Liver disease etiology was not incorporated in this version of the formula. Laboratory values less than 1.0 were set to 1.0 and the maximum serum creatinine was set to 4.0 mg/dL. The serum creatinine was set to 4.0 mg/dL if the patients had received dialysis at least twice within the week prior to the serum creatinine test. The MELD score was not capped at a score of 40. In PBC patients, the spontaneous survival predicted by the updated Mayo model was calculated as described previously [3].

### Outcome

The patients' follow-up ended on 30 September 2011. The primary endpoint "waiting list mortality" or "waiting list death" was a combination of death and removal from the waiting list because the patient became too sick for transplantation or was otherwise medically unsuitable. We considered patients who were removed from the transplant list on account of clinical deterioration to be equivalent to patients who died, because these chronic liver diseases are almost uniformly fatal in the short term without transplantation. All other outcomes were censored, with the most common censoring events being transplantation or list removal due to an improvement in the patient's condition resulting in the patient no longer requiring transplantation.

### Statistical analysis

Cox proportional hazards ratios (HRs) with 95 % confidence intervals (CI) for waiting list mortality were estimated with univariate models using age, gender, blood type, etiology of liver disease, as well as multivariate models using age and etiology of liver disease. To compare patients' characteristics between chronic hepatitis C virus (HCV) infection and PBC, we used the Mann–Whitney *U* test for numerical variables or the chi-square test for categorical variables. The HRs with 95 % CI for waiting list mortality of PBC patients were adjusted for each disease severity index, such as medical point, CTP score, and MELD score by bivariate Cox proportional hazards models. The rates of survival were estimated by the Kaplan–Meier method, and compared by log-rank test. All analyses were conducted using IBM SPSS version 19 (IBM SPSS, Chicago, IL, USA). A P value below 0.05 was considered to be statistically significant.

## Results

### Patient characteristics and outcome

A total of 1,407 patients were listed for deceased donor liver transplantation through the JOT registry during the study period. Of these patients, 1,295 (92.0 %) were aged ≥18 years. The etiology of liver disease in these subjects is shown in Table 1. The most prevalent diagnoses in patients ≥18 years were HCV infection (254 of 1,295, 19.6 %), hepatitis B virus infection (157 of 1,295, 12.1 %), and PBC (156 of 1,295, 12.0 %), and these accounted for 43.7 % of all patients ≥18 years. Of 1,295 patients, 239 were excluded from the study: 142 for acute liver failure and 97 for repeat liver transplant. Thus, a total of 1,056 patients formed the study cohort. In the study cohort, 64 % of patients were men and the median age of all patients was 51 years (range, 18–69 years). At listing, 78 patients were registered at medical point 1, 297 at point 3, 682 at point 6, and 29 at point 9. A flow diagram of the patient outcomes is shown in Fig. 1. At the end of study period, 313 patients were still listed and 743 had been removed from the list, with 267 removed for liver transplantation, 378 for death, and 98 for other reasons, including 54 who were too sick, 11 for improvement in their condition, and 33 for an unknown reason. Of the 267 patients who received liver transplantation, only 81 cases were able to receive deceased donation in Japan, and this accounted for 10.9 % of all patients removed from the list. Waiting list mortality, a combination of death and becoming too sick for transplantation, accounted for 58.1 % of all the patients removed from the list.

Factors associated with waiting list mortality

In univariate analysis, age, biliary atresia, PBC, hepatocellular carcinoma, metabolic diseases, polycystic diseases, and vascular diseases showed statistically significant association with waiting-list mortality. In multivariate analysis, age (HR 1.04; 95 % CI 1.03–1.05, $P < 0.001$), PBC (HR 1.79; 95 % CI 1.34–2.39, $P < 0.001$), and polycystic diseases (HR 0.27; 95 % CI 0.10–0.73, $P = 0.01$) were independently associated with waiting list mortality (Table 2). Hence, PBC patients had a 79 % higher risk of waiting list mortality compared with HCV patients with adjustment for age.

**Table 1** Etiology of liver disease

| | Total ($n$ = 1,407) | ≥18 years ($n$ = 1,295) | <18 years ($n$ = 112) |
|---|---|---|---|
| Cholestatic diseases | 381 | 325 | 56 |
| BA | 93 | 48 | 46 |
| PBC | 156 | 156 | 0 |
| PSC | 105 | 99 | 6 |
| Caroli disease | 8 | 7 | 1 |
| Others | 18 | 15 | 3 |
| Hepatocellular diseases | 567 | 565 | 2 |
| HCV | 254 | 254 | 0 |
| HBV | 157 | 157 | 0 |
| HCV and HBV | 8 | 8 | 0 |
| Alcoholic | 48 | 48 | 0 |
| AIH | 22 | 22 | 0 |
| NASH | 25 | 25 | 0 |
| Cryptogenic cirrhosis | 53 | 51 | 2 |
| HCC | 76 | 76 | 0 |
| Acute liver failure | 163 | 142 | 21 |
| Graft failure | 121 | 97 | 24 |
| Vascular disease | 12 | 12 | 0 |
| Metabolic disease | 62 | 53 | 9 |
| Polycystic disease | 24 | 24 | 0 |
| Others | 1 | 1 | 0 |

*AIH* autoimmune hepatitis, *BA* biliary atresia, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *NASH* non-alcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

Waiting list mortality of PBC patients

The Kaplan–Meier waiting list survival curves for all PBC and HCV patients are shown in Fig. 2. The 1- and 2-year survival probabilities in HCV patients were 63 and 49 %, respectively (median 631 days, 95 % CI 355–907 days), whereas those in PBC patients were 51 and 33 %, respectively (median 392 days, 95 % CI 283–500 days); the differences between them represented a statistically significant difference (log-rank test, $P < 0.001$). Detailed demographic and clinical characteristics were available in 189 of 254 HCV patients and 81 of 156 PBC patients who were registered after June 2006. A comparison of the characteristics of patients with PBC and HCV is shown in Table 3. In comparison with HCV patients, PBC patients were younger and predominantly female. Patients with PBC had significantly higher platelet counts and serum bilirubin values, and lower INR and serum creatinine values. Neither the CTP score nor the medical point at listing was different between the groups. Conversely, the MELD score at listing was significantly higher in patients with PBC than in those with HCV. In addition, the median of the updated Mayo risk score was 9.4 in the PBC patients, and this predicted 1- and 2-year spontaneous survival rates of 74 and 54 %, respectively.

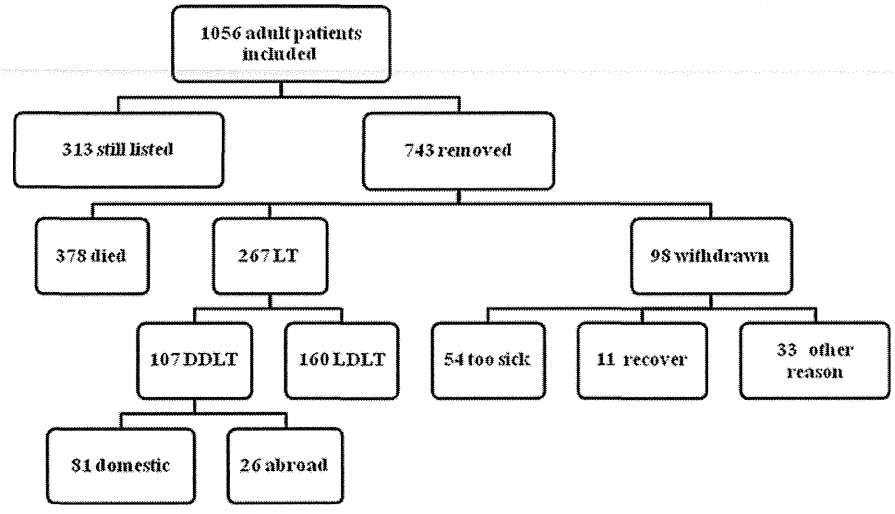


**Fig. 1** Flow diagram of patient outcomes. *DDLT* deceased donor liver transplantation, *LDLT* living donor liver transplantation, *LT* liver transplantation

**Table 2** Univariate and multivariate analysis of variables associated with waiting list mortality

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95 % CI | *P* value | HR | 95 % CI | *P* value |
| Age (per year of age) | 1.04 | 1.03–1.05 | <0.001 | 1.04 | 1.03–1.05 | <0.001 |
| Male gender | 0.93 | 0.77–1.13 | 0.48 | | | |
| Blood type | | | | | | |
| A | 1.00 | Reference | | | | |
| B | 1.07 | 0.83–1.43 | 0.61 | | | |
| O | 1.13 | 0.90–1.43 | 0.29 | | | |
| AB | 1.26 | 0.90–1.77 | 0.17 | | | |
| Etiology | | | | | | |
| HCV | 1.00 | Reference | | | | |
| BA | 0.40 | 0.22–0.72 | 0.002 | | | |
| PBC | 1.62 | 1.21–2.16 | 0.001 | 1.79 | 1.34–2.39 | <0.001 |
| PSC | 0.79 | 0.54–1.17 | 0.24 | | | |
| HBV | 0.77 | 0.56–1.05 | 0.10 | | | |
| Alcohol | 0.95 | 0.59–1.53 | 0.83 | | | |
| AIH | 0.77 | 0.34–1.74 | 0.52 | | | |
| NASH | 1.11 | 0.76–1.63 | 0.59 | | | |
| HCC | 1.46 | 1.05–2.05 | 0.003 | | | |
| Metabolic disease | 0.40 | 0.22–0.75 | 0.004 | | | |
| Polycystic disease | 0.26 | 0.10–0.70 | 0.008 | 0.27 | 0.10–0.73 | 0.01 |
| Vascular disease | 0.009 | 0.01–0.67 | 0.002 | | | |
| Others | 0.70 | 0.34–1.43 | 0.33 | | | |

*AIH* autoimmune hepatitis, *BA* biliary atresia, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HR* hazard ratio, *NASH* non-alcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

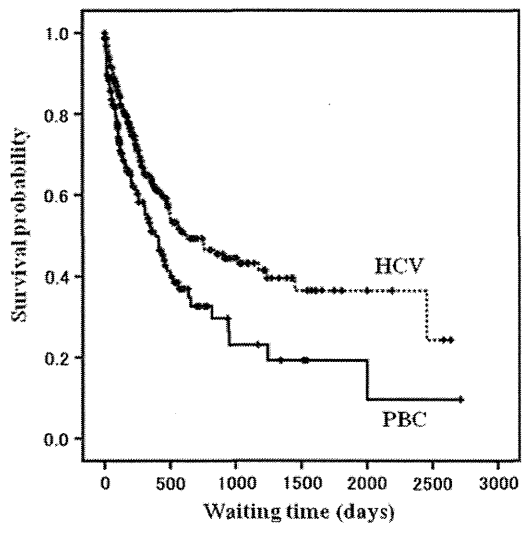


**Fig. 2** Kaplan–Meier curves comparing the cumulative waiting list survival probability of patients with chronic hepatitis C (HCV, $n = 254$) and primary biliary cirrhosis (PBC, $n = 156$)

**Table 3** Comparison of patient characteristics between HCV and PBC

| Variable | HCV ($n = 189$) | PBC ($n = 81$) | *P* value |
|---|---|---|---|
| Age (years) | 55 (29–69) | 52 (27–69) | 0.02[a] |
| Gender (male/female) | 143/46 | 15/66 | <0.001[b] |
| Platelet count ($\times 10^4/\mu L$) | 6.0 (1.7–49.0) | 10.2 (2.2–42.3) | <0.001[a] |
| Albumin (g/dL) | 2.8 (1.8–4.4) | 2.8 (1.4–4.2) | 0.96[a] |
| Total bilirubin (mg/dL) | 2.7 (0.4–39.8) | 7.2 (0.7–41.2) | <0.001[a] |
| Creatinine (mg/dL) | 0.78 (0.4–7.4) | 0.67 (0.37–2.83) | <0.001[a] |
| Prothrombin time (%) | 54.7 (11.0–103.0) | 62.2 (16.0–120.0) | 0.001[a] |
| INR | 1.51 (0.98–6.24) | 1.32 (0.91–4.31) | 0.001[a] |
| MELD score | 15 (7–52) | 17.5 (8–39) | 0.002[a] |
| CTP score | 10 (6–15) | 10 (5–15) | 0.27[a] |
| Medical point (1, 3/6, 9) | 54/135 | 22/59 | 0.81[b] |

Data are shown as median (range). Data were available for patients who were listed after June 22, 2006

*CTP* Child–Turcotte–Pugh, *HCV* hepatitis C virus, *INR* international normalized ratio, *MELD* model of end-stage liver disease, *PBC* primary biliary cirrhosis

[a] Mann–Whitney *U* test

[b] Chi-square test

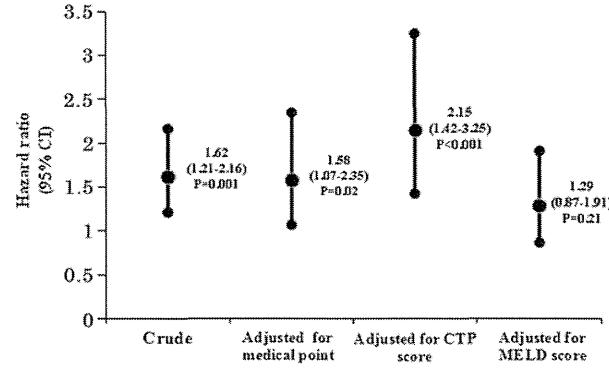


**Fig. 3** Adjusted risk of waiting list mortality for patients with primary biliary cirrhosis compared with patients with chronic hepatitis C

To examine which disease severity index was able to assess the risk of PBC patients accurately, we estimated their relative hazards with adjustment for each index. We did not estimate age-adjusted relative hazard because age was not included in the allocation measures. Figure 3 indicates the crude and disease severity index-adjusted HR for waiting list mortality of PBC patients with reference to HCV patients. In univariate analysis, PBC patients were at 62 % (HR 1.62; 95 % CI 1.21–2.16, $P = 0.001$) increased risk of waiting list mortality

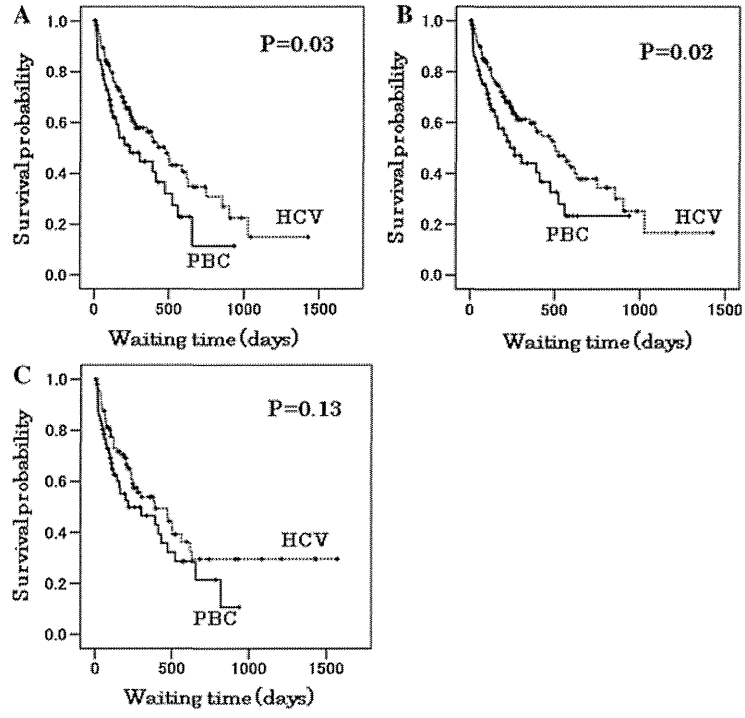


**Fig. 4** Kaplan–Meier curves comparing the cumulative waiting list survival probability of patients with chronic hepatitis C (HCV) and primary biliary cirrhosis (PBC). Patients stratified medical point = 6 (**a**), and Child–Turcotte–Pugh score ≥10 (**b**), and Model of End-Stage Liver Disease (MELD) score ≥15 (**c**)

compared with HCV patients. In bivariate analysis, the medical point-adjusted HR of waiting list mortality of PBC patients was significantly higher than that of HCV patients (HR 1.58; 95 % CI 1.07–2.35, $P = 0.02$). The CTP score-adjusted HR also showed a significantly increased risk of waiting -list mortality in PBC patients (HR 2.15; 95 % CI 1.42–3.25, $P < 0.001$). However, the MELD score-adjusted HR did not show a statistically significant risk of waiting list mortality in PBC patients (HR 1.29; 95 % CI 0.87–1.91, $P = 0.21$).

Waiting list survival of patients with HCV and PBC was compared with stratification by each of the disease severity indices (Fig. 4). Patients with medical point 6, for which most PBC and HCV patients were registered, showed a significantly shorter waiting list survival for PBC patients than of HCV patients (median 261 vs. 503 days, $P = 0.02$). In patients with CTP score ≥10, the score classified as C, the shorter waiting list survival of PBC patients was also significant (median 235 vs. 475 days, $P = 0.03$). On the other hand, when they were selected by MELD ≥15, the score indicating patients who can be expected to achieve improved survival with liver transplantation [12], there was no significant difference in the waiting list survival rate between them ($P = 0.13$).

## Discussion

The result of this study clearly indicated that the most common reason for removal from the waiting list in Japan was "waiting list death", which was a combination of death and becoming too sick for transplantation. The waiting list death included 58.1 % of all the patients removed from the list. In the United States, a recent report indicated that waiting list death was the reason for removal from the list in 25.9 % of adult patients [1]. Although this report included patients with acute liver failure and re-transplantation, high waiting list mortality in Japan was evident. Thus, the high mortality rate on the liver transplant waiting list is a major challenge in Japan. Moreover, severe donor organ shortage in Japan should contribute to the high waiting list mortality [13]; an improved organ allocation policy will be necessary to cause a decrease in waiting list death.

In this study, we found that PBC patients had a significantly higher risk of waiting list mortality compared with patients with other etiologies in the JOT registry. Since PBC is currently the third most common diagnosis in the JOT registry for liver transplantation, poor waiting list survival of PBC patients would contribute to the high waiting list mortality in Japan. PBC is a cholestatic liver disease that causes bile duct deterioration and progresses slowly to a terminal phase characterized by hyperbilirubinemia, signs of decompensated cirrhosis, ascites, and variceal bleeding. Only one type of medical therapy, involving the use of ursodeoxycholic acid (UDCA), is now widely recognized to improve the prognosis of PBC patients. Many studies have shown that UDCA therapy not only improves biochemical indices, but also delays histologic progression and improves survival without transplantation [14–16]. However, evidence has also accumulated that the

favorable effect of UDCA therapy is limited to patients with early-stage disease. In histologically advanced patients or biochemical non-responders, the transplant-free survival rate of UDCA-treated patients was not different from spontaneous survival [16, 17]. This means that PBC patients have no effective medical therapeutic option to prolong their survival when they have progressed to end-stage liver disease, and liver transplantation remains the only hope of a cure [18, 19]. PBC patients in our cohort also showed a consistently poor survival of a median period of 392 days.

The reason why PBC patients have a higher risk for waiting list mortality compared with patients with other etiologies of chronic liver disease is not clearly understood. Interestingly, PBC patients were younger, and their INR and serum creatinine levels were lower than for HCV patients at registration. This indicated that neither age nor liver and renal function at registration alone caused poor waiting list survival of PBC patients; the registration of PBC patients was not later than that for HCV patients. The rate of disease progression and lethal complications might be involved in their short waiting list survival rate. Moreover, the actual waiting list survival rate in PBC patients was not greater than the updated Mayo score-predicted spontaneous survival rate. This observation indicated that the PBC patients on the waiting list were refractory to the medical therapy and their waiting list survival suddenly deteriorated. Further analyses, particularly on the cause of death, are required to clarify the pathophysiology of PBC patients who have progressed to end-stage liver disease.

In general, deceased donor livers are allocated for transplantation on the basis of "sickest first", i.e., those who are more likely to die without a liver transplantation are assigned the highest priority. Therefore, the disease severity index used in the liver allocation system should consider the urgency of PBC patients for liver transplantation. However, our results have clarified the inability of the currently used Japanese allocation system to identify the risk of PBC patients. The medical point-adjusted HR of PBC patients revealed that they were at 58 % increased risk of waiting list mortality compared with HCV patients. In addition, the CTP score-adjusted HR showed that PBC patients were at 115 % increased risk for waiting list mortality. Thus, it is not only the current allocation system but also the CTP score-based allocation that cannot capture the risk for waiting list mortality in PBC patients. On the other hand, we found that the MELD score-adjusted HR of PBC patients lost statistical significance, and stratification by MELD score revealed comparable survival curves between patients with PBC and HCV. These results indicated that PBC patients had a similar risk of waiting list mortality compared with patients with other etiologies when they were stratified by MELD score. At the time of registration, the patients with HCV and PBC had different characteristics; however, only the MELD score accurately evaluated their disease severity, and therefore, MELD-based allocation would adequately assign priority to the patients according to their risk of waiting list mortality. Thus, our results demonstrated that the MELD score was superior to both the current Japanese allocation and CTP score-based allocation for ranking patients in the JOT registry by their risk of waiting list mortality.

In addition, patients should be re-evaluated according to their chronological change of hepatic failure to improve allocation. However, most patients with chronic liver disease were waiting at medical point 6 as an upper limit, because the highest priority at medical point 9 was generally awarded to the patients with acute liver failure or early graft failure in the current Japanese allocation system. Therefore, the current allocation system did not completely reflect the chronological change in the degree of liver failure. Thus, the MELD score, which was expressed numerically as a continuous variable with a wide dynamic range in the evaluation of hepatic decompensation, would have an advantage over the medical point system for assessing the chronological change in patients' risk of death.

In conclusion, this study demonstrated that patients with PBC, the third most common indication for liver transplantation in Japan, have a high risk for waiting list mortality in the current Japanese allocation system. The allocation system should be changed to accurately prioritize the patients with a higher mortality risk; MELD-based allocation would be suitable for this purpose and could reduce the waiting list mortality of PBC patients.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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