Limitations

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

How Can We Decrease Relapse?

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

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

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ORIGINAL ARTICLE

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

Takehisa Ueno · Motoshi Wada · Ken Hoshino · Shinji Uemoto · Tomoaki Taguchi · Hiroyuki Furukawa · Masahiro Fukuzawa

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

Keywords Intestinal transplant · Pediatric transplant · Japanese registry

T. Ueno (✉)
Department of Pediatric Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: ueno@pedsurg.med.osaka-u.ac.jp

M. Wada
Department of Pediatric Surgery, Tohoku University School of Medicine, Sendai, Japan

K. Hoshino
Department of Surgery, Keio University Graduate School of Medicine, Tokyo, Japan

S. Uemoto
Department of HBP Surgery and Transplantation, Kyoto University, Kyoto, Japan

T. Taguchi
Department of Pediatric Surgery, Kyusyu University School of Medicine, Fukuoka, Japan

H. Furukawa
Department of Gastroenterologic and General Surgery, Asahikawa Medical University, Asahikawa, Japan

M. Fukuzawa
Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan

Introduction

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

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

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

Methods

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

Results

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

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

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

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

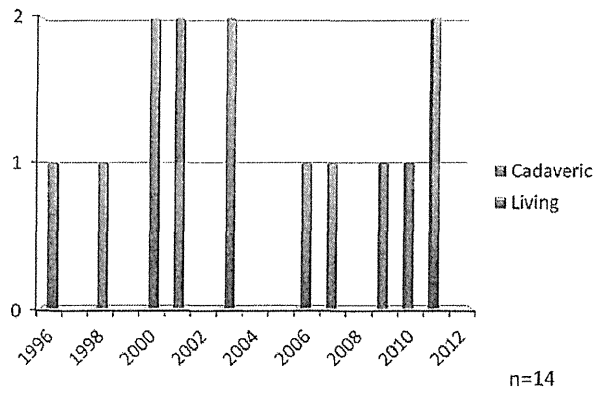

Fig. 1 Number of intestinal transplants by year

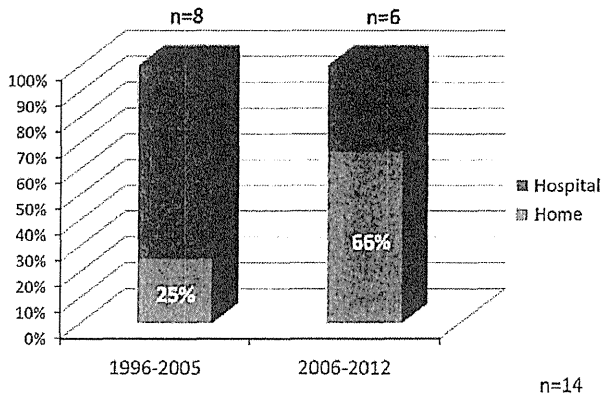

Fig. 2 Pre-transplant patient status

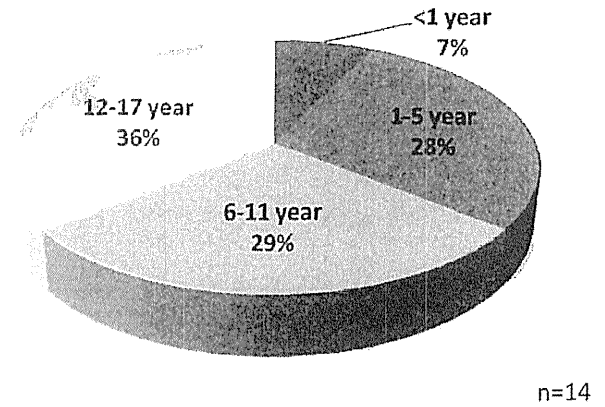

Fig. 3 Recipient age at transplant

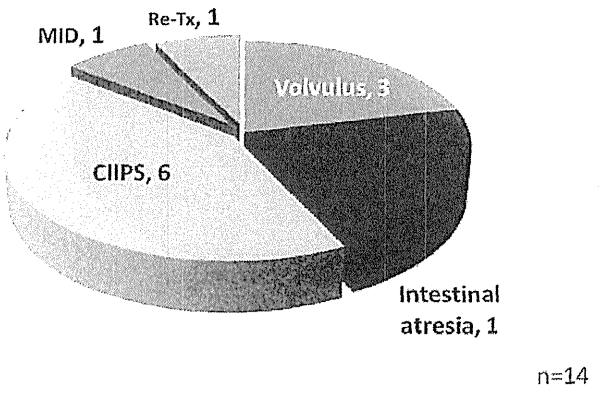

Fig. 4 Cause of intestinal failure *NEC* necrotizing enterocolitis, *CIIPS* chronic idiopathic intestinal pseudo-obstruction syndrome, *MID* microvillus inclusion disease, *Re-Tx* Re-transplant

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

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

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

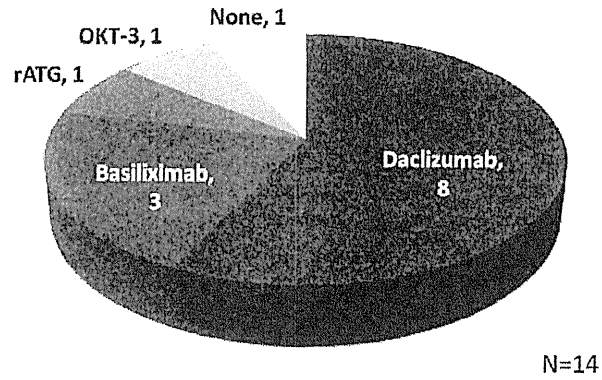

Fig. 5 Induction immunosuppression therapy *rATG* rabbit anti-thymus globulin, *OKT-3* anti-CD3 monoclonal antibody

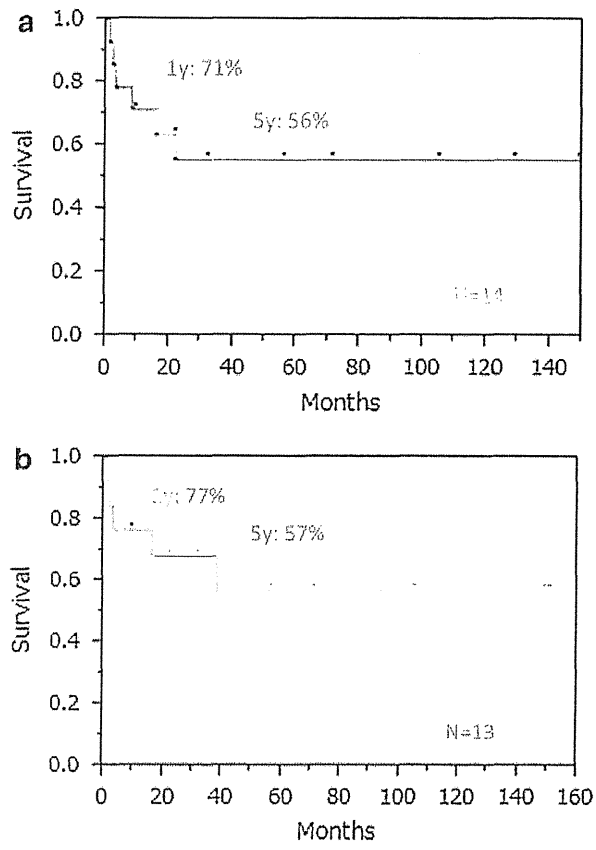

Fig. 6 Overall graft (**a**) and patient (**b**) survival

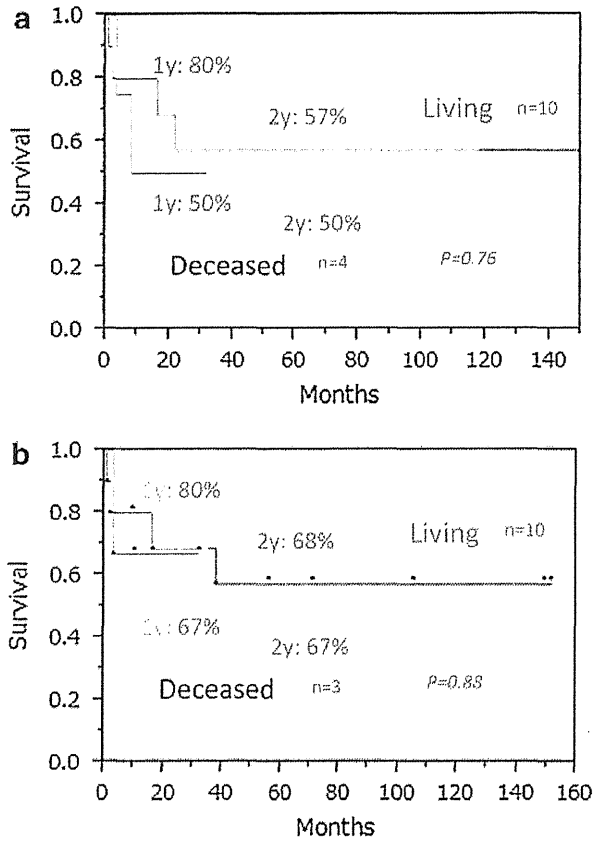

Fig. 7 Graft (a) and patient (b) survival according to graft type

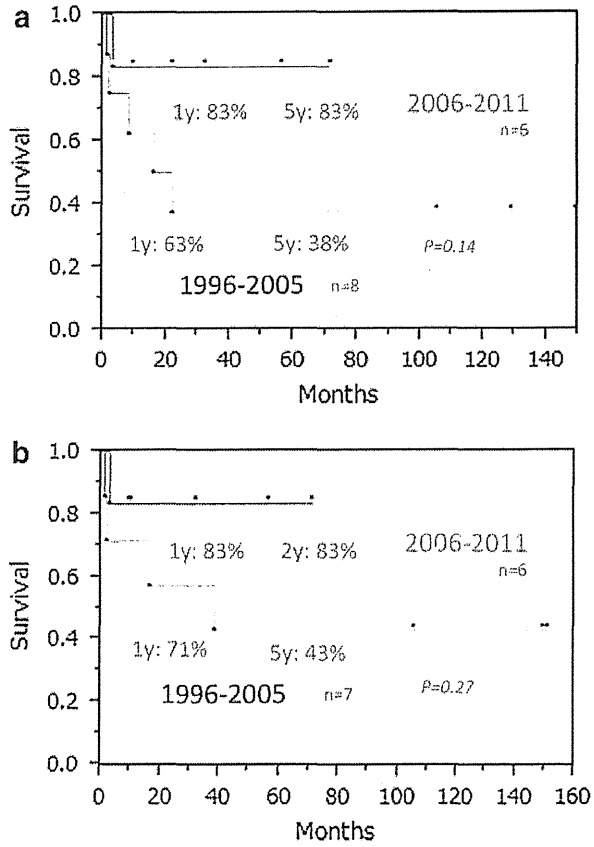

Fig. 8 Graft (a) and patient (b) survival by era

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

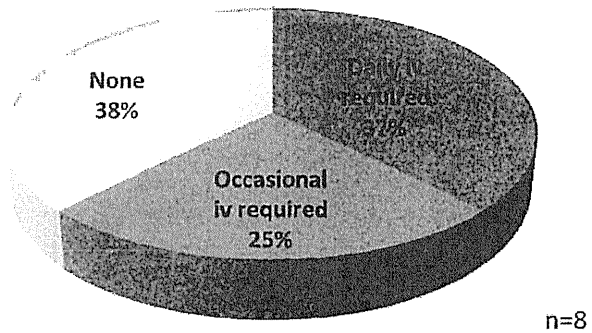

Fig. 9 Intravenous (IV) fluid requirement after intestinal transplantation

Discussion

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

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

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

complications, some children develop end-stage intestinal failure.

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

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LIVER TRANSPLANTATION 20:576–583, 2014

ORIGINAL ARTICLE

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

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

Department of [1]Hepato-Biliary-Pancreatic Surgery and [2]Obstetrics and Gynecology, Osaka City University Graduate School of Medicine, Osaka, Japan; [3]Department of Hepato-Biliary-Pancreatic Surgery and Transplantation, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [4]Division of Gastroenterological and General Surgery, Department of Surgery, Asahikawa Medical University, Asahikawa, Japan; and [5]Division of Health Sciences, Graduate School of Medicine, Osaka University, Osaka, Japan

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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Address reprint requests to Shoji Kubo, M.D., Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-Ku, Osaka 545-8585, Japan. E-mail: m7696493@msic.med.osaka-cu.ac.jp

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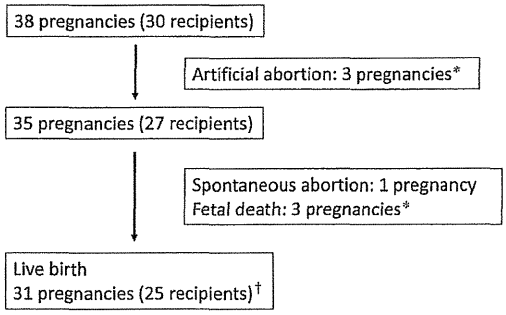

Figure 1. Subjects of this study. *In one recipient, artificial abortion was performed at the first pregnancy, and the second pregnancy was resulted in fetal death. †Six recipients had live births twice.

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.

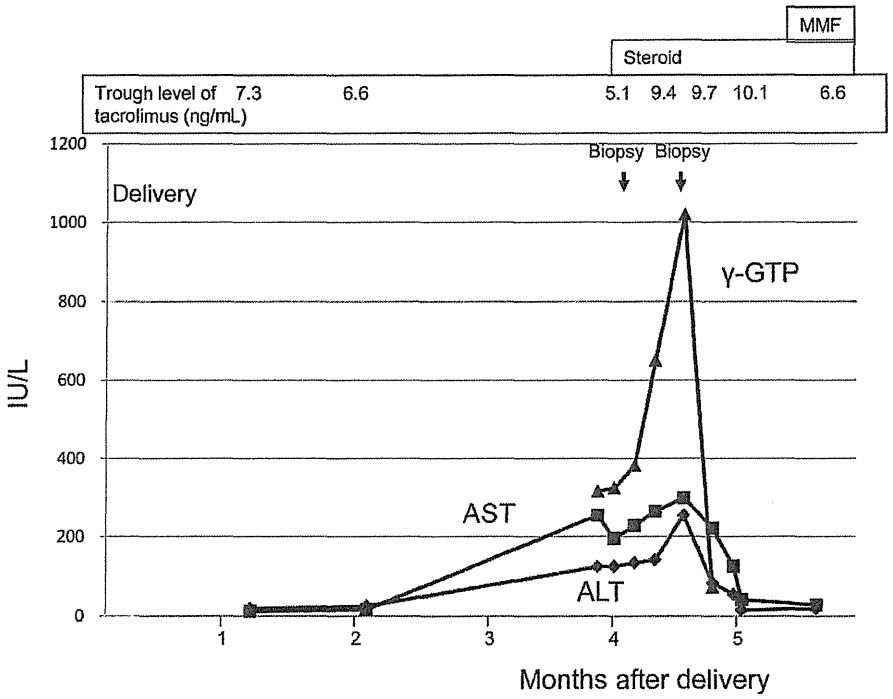

Figure 2. Clinical course of recipients suffering acute rejection after delivery. Acute rejection was diagnosed with a second liver biopsy (rejection activity index = 4).

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

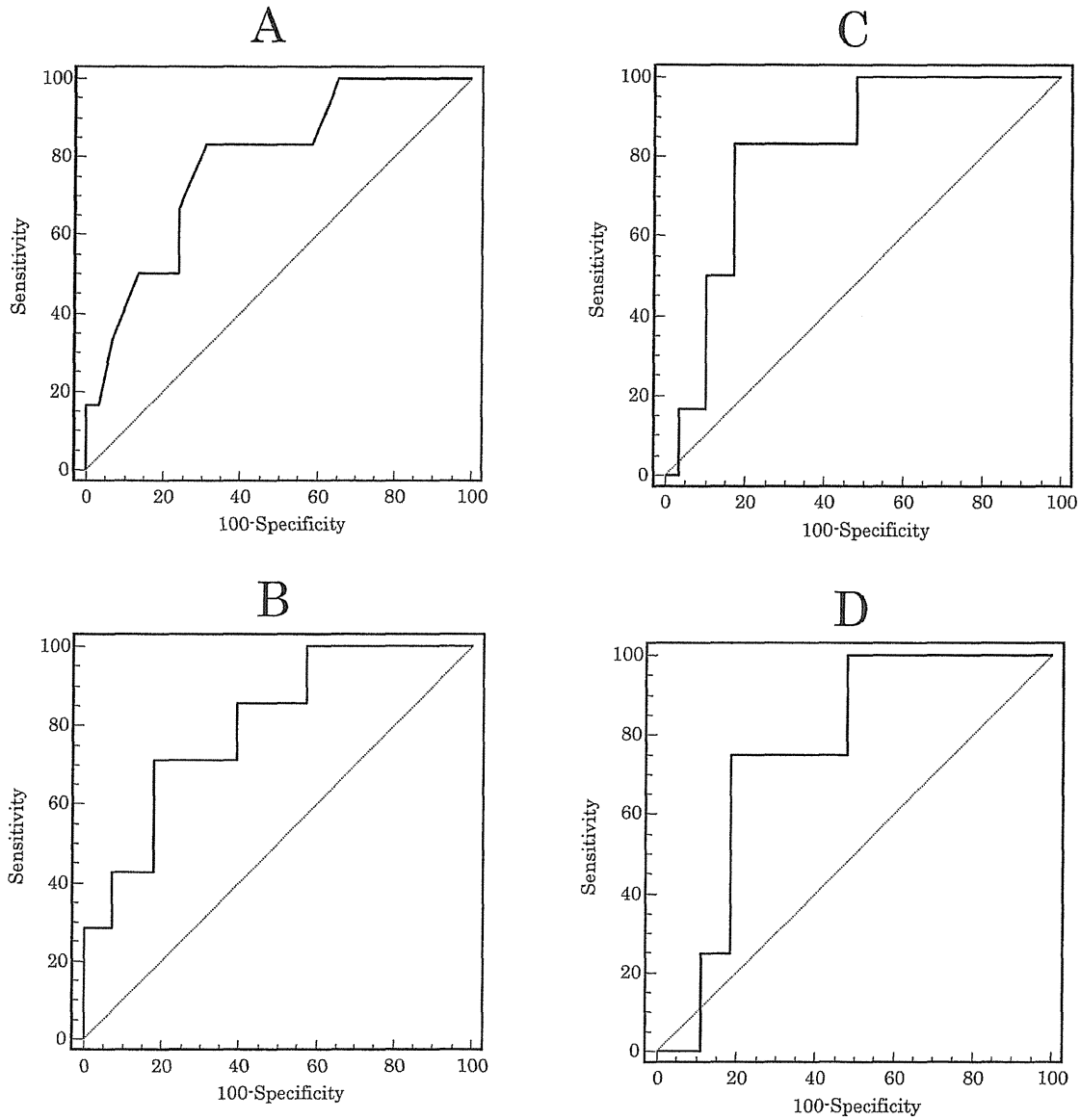

Figure 3. ROC curves for pregnant recipients: (A) age at the diagnosis of pregnancy and pregnancy-induced hypertension, (B) interval from LT to pregnancy and fetal growth restriction, (C) interval from LT to pregnancy and pregnancy-induced hypertension, and (D) interval from LT to pregnancy and extremely 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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Waiting list mortality of patients with primary biliary cirrhosis in the Japanese transplant allocation system

Takuya Genda · Takafumi Ichida · Shotaro Sakisaka · Michio Sata · Eiji Tanaka · Ayano Inui · Hiroto Egawa · Kouji Umeshita · Hiroyuki Furukawa · Seiji Kawasaki · Yukihiro Inomata

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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.

The Assessment Committee of Indication for Transplantation: T. Ichida, S. Sakisaka, M. Sata, E. Tanaka, A. Inui, H. Egawa, K. Umeshita, H. Furukawa, S. Kawasaki, Y. Inomata.

T. Genda (✉) · T. Ichida
Department of Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital, 1129 Nagaoka Izunokuni-shi, Shizuoka 410-2295, Japan
e-mail: genda@rice.ocn.ne.jp

S. Sakisaka
Department of Gastroenterology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

M. Sata
Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan

E. Tanaka
Department of Medicine, Shinshu University School of Medicine, Matsumoto, Japan

A. Inui
Division of Hepatology and Gastroenterology, Department of Pediatrics, Eastern Yokohama Hospital, Yokohama, Japan

H. Egawa
Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan

K. Umeshita
Department of Surgery, Osaka University Graduate School of Medicine, Suita, Japan

H. Furukawa
Department of Gastroentrologic and General Surgery, Asahikawa Medical University, Asahikawa, Japan

S. Kawasaki
Department of Hepatobiliary-Pancreatic Surgery, Juntendo University School of Medicine, Tokyo, Japan

Y. Inomata
Department of Transplantation and Pediatric Surgery, Postgraduate School of Medical Science, Kumamoto University, Kumamoto, Japan

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]: $9.57 \times \log_e(\text{creatinine mg/dL}) + 3.78 \times \log_e(\text{bilirubin mg/dL}) + 11.2 \times \log_e(\text{international normalized ratio [INR]}) + 6.43$, 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.

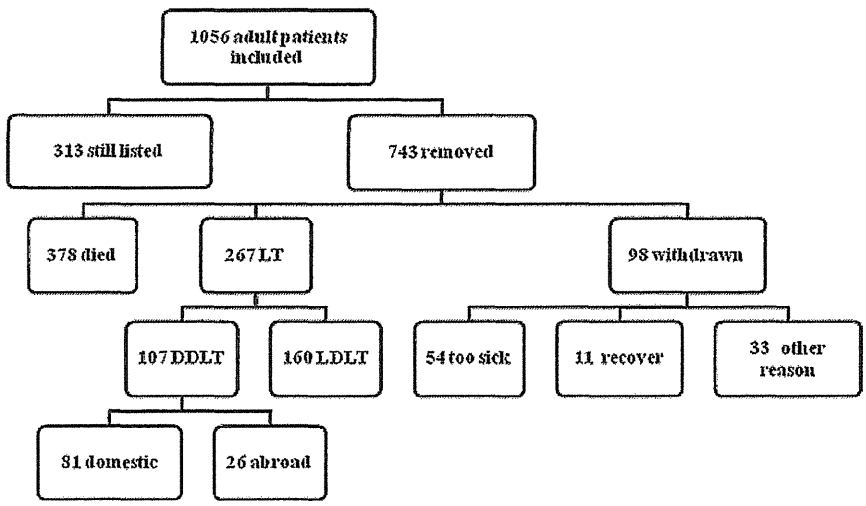

Fig. 1 Flow diagram of patient outcomes. *DDLT* deceased donor liver transplantation, *LDLT* living donor liver transplantation, *LT* liver transplantation