Table 1 Comparison of the data among patients carrying CC allele and CA allele at rs1127354

rs1127354	CC ($n = 43$)	CA ($n = 20$)	*P*-value
Pretransplantation factor			
Recipient's age (years), mean ± SD	57 ± 1	56 ± 2	n.s
Recipient's sex (male / female), *n*	24 / 19	14 / 6	n.s
Recipient's BMI ($kg \cdot m^{-2}$), mean ± SD	24.9 ± 0.62	24.0 ± 0.88	n.s
Donor's age (y), mean ± SD	33 ± 2	34 ± 2	n.s
Donor's sex (male / female), *n*	31 / 12	12 / 8	n.s
Donor's BMI ($kg \cdot m^{-2}$), mean ± SD	23.3 ± 0.61	21.3 ± 0.89	n.s
Pretransplant Hb level (g/dL), mean ± SD	10.9 ± 0.36	11.2 ± 0.48	n.s
MELD score, mean ± SD	10.3 ± 0.79	10.8 ± 1.1	n.s
Operative factor			
Operative time (min), mean ± SD	793 ± 31	839 ± 44	n.s
Simultaneous splenectomy (yes/no), *n*	28 / 15	13 / 7	n.s
Intraoperative bleeding (mL), mean ± SD	5752 ± 891	6105 ± 1260	n.s
GV/SLV (%), mean ± SD	40.5 ± 1.4	42.3 ± 2.0	n.s
Post-transplantation factor			
Bile duct complication (yes / no), *n*	40 / 3	16 / 4	n.s
Pretreatment viral load (logIU/mL), mean ± SD	6.2 ± 0.1	6.6 ± 0.2	0.02
Pathological activity score, mean ± SD	1.3 ± 0.12	1.4 ± 0.16	n.s
Pathological fibrosis score, mean ± SD	1.1 ± 0.20	0.88 ± 0.28	n.s
Immunospressive agents (CyA / FK), *n*	21 / 22	15 / 5	n.s
Total dose of RBV during the first 4 weeks (mg), mean ± SD	8882 ± 703	8755 ± 1034	n.s
Pretreatment Hb level (g/dL), mean ± SD	12.3 ± 0.27	11.9 ± 0.40	n.s

BMI, body mass index; CyA, cyclosporine; FK, tacrolimus; GV, graft volume; Hb, hemoglobin; MELD, model for end-stage liver disease; n.s, not significant; SLV, standard liver volume.

−1.59 g/dL; $P = 0.81$, respectively, Fig. 1c). The ITPA genetic polymorphism did not correlate with PEG-IFN/RBV-induced anemia after LT.

ITPA genotype and RBV dosage

The dosage of PEG-IFNα2b and RBV were adjusted for each individual so as not to cause any side effects, including anemia. If the ITPA minor allele was able to protect post-transplant patients from RBV-related hemolytic anemia, the RBV dosage could be increased in recipients carrying the CA allele. As described in Table 1, total dose of RBV administered during the first 4 weeks were similar in each group (8882 mg vs. 8875 mg, $P = 0.787$). It was possible to increase the RBV dosage in 16 recipients (40%) carrying the CC allele and eight recipients (40%) carrying the CA allele ($P = 1.00$; Fig. 2a). Twelve patients carrying the CC allele and four carrying the CA allele had their RBV dosage decreased because of anemia ($P = 0.409$; Fig. 2b).

Ochi *et al.*[9] reported that there was marginal correlation between ITPA genetic polymorphism and the outcome of PEG-IFN/RBV therapy, probably because of the dose reduction of RBV in patients showing severe anemia. In patients enrolled in the current study, the therapeutic effects between recipients carrying the CC and those carrying the CA allele were not significantly different; with a VR of 68.9% and 72.7% ($P = 0.746$; Fig. 3a), respectively. The SVR for these two groups was 38.9% and 42.7% ($P = 0.768$, Fig. 3b), respectively.

Efficacy of splenectomy

We performed simultaneous splenectomy at transplantation for HCV-related liver diseases to prevent PEG-IFN/RBV therapy-induced blood cytopenia. Univariate analysis showed that splenectomy was significantly related to a Hb level less than 10 g/dL after 4 weeks (Table 2). Therefore, to prove the efficacy of splenectomy against treatment-induced anemia, the incidence of anemia and RBV dose reduction were compared between 41 recipients who had undergone spontaneous splenectomy (Spx group) and 22 recipients who had not undergone splenectomy (Non-Spx group). Although the incidence of Hb decline greater than 3 g/dL was not significantly different between the two groups (2.4 *vs.* 4.5%, $P = 0.649$; Fig. 4a), the Spx group showed a

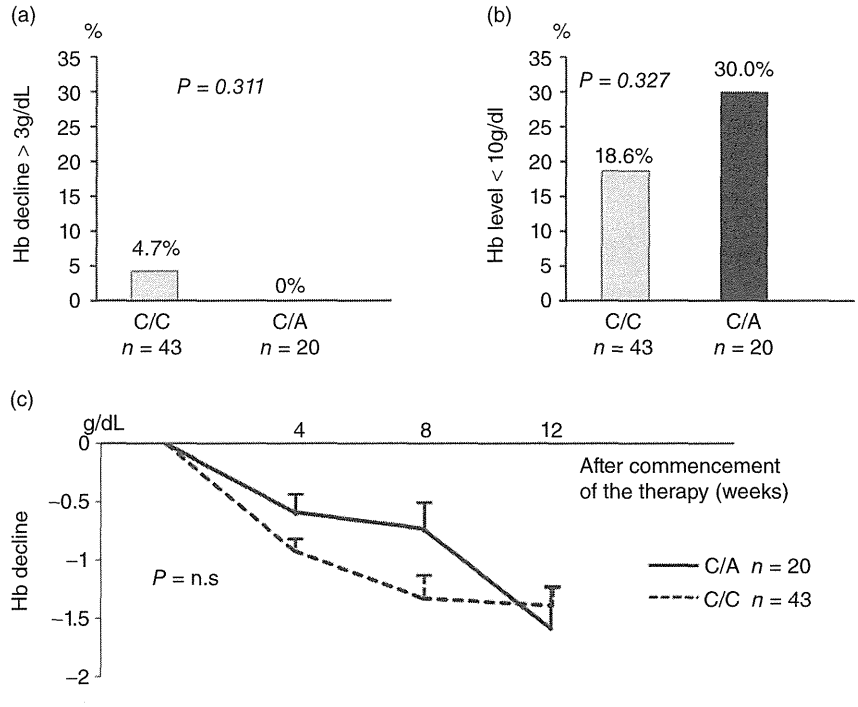

Figure 1 Inosine triphosphate pyrophosphatase (ITPA) genetic polymorphism and pegylated-interferon/ribavirin (PEG-IFN/RBV)-related anemia after liver transplantation (LT). (a) Hemoglobin (Hb) decline greater than 3 g/dL at 4 weeks after the commencement of therapy was found in 4.7% of CC allele carriers and in none of the CA allele carriers. (b) hemoglobin (Hb) levels less than 10 g/dL at 4 weeks were found in 18.6% of CC allele carriers and in 30.0% of CA allele carriers. (c) Hb decline at 4, 8, and 12 weeks after commencement of the therapy were compared. There was no statistical difference in the progression of anemia during the treatment between two groups. (—): C/A $n = 20$; (----): C/C $n = 43$.

significantly lower incidence of Hb levels lower than 10 g/dL compared with the Non-Spx group (14.6 *vs.* 36.4%, $P < 0.05$; Fig. 4b). Additionally, the RBV dosage tended to be increased more often in the Spx group than in the Non-Spx group (46.3 *vs.* 22.7%, $P = 0.09$; Fig. 4c); and at the same time was not reduced because of anemia (19.5 *vs.* 36.4%, $P = 0.09$; Fig. 4d), though there was no statistical difference.

The incidence of treatment-induced anemia between those carrying the CC and CA alleles among the non-Spx group was evaluated. Of the 22 recipients in the non-Spx group, 15 carried the CC allele and seven carried the CA allele. Although there was no significant difference because of the small numbers involved, a Hb decline greater than 3 g/dL and Hb levels less than 10 g/dL at 4 weeks were found more often in recipients carrying

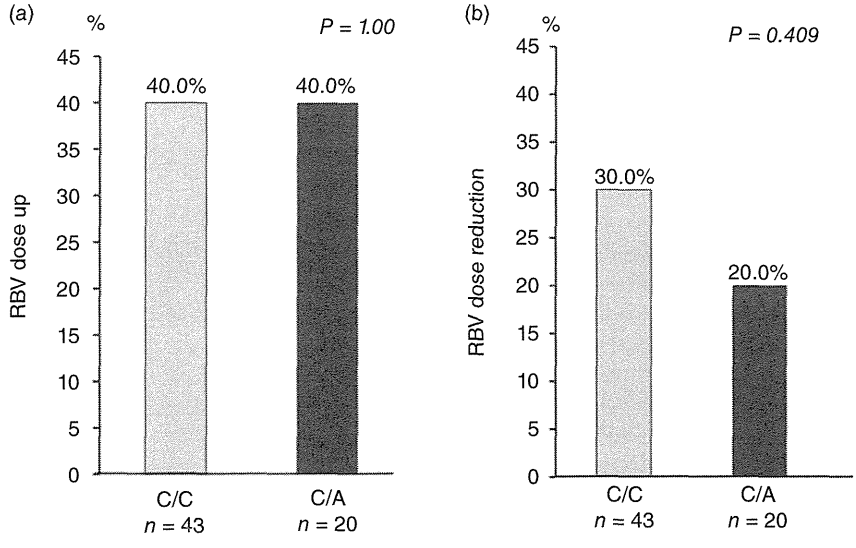

Figure 2 Inosine triphosphate pyrophosphatase (ITPA) genetic polymorphism and ribavirin (RBV) dosage. (a) The dosage of RBV was increased in 40% of each genotype group. (b) RBV dose reduction due to anemia was found in 30% of those carrying the CC allele and 20% of those carrying the CA allele.

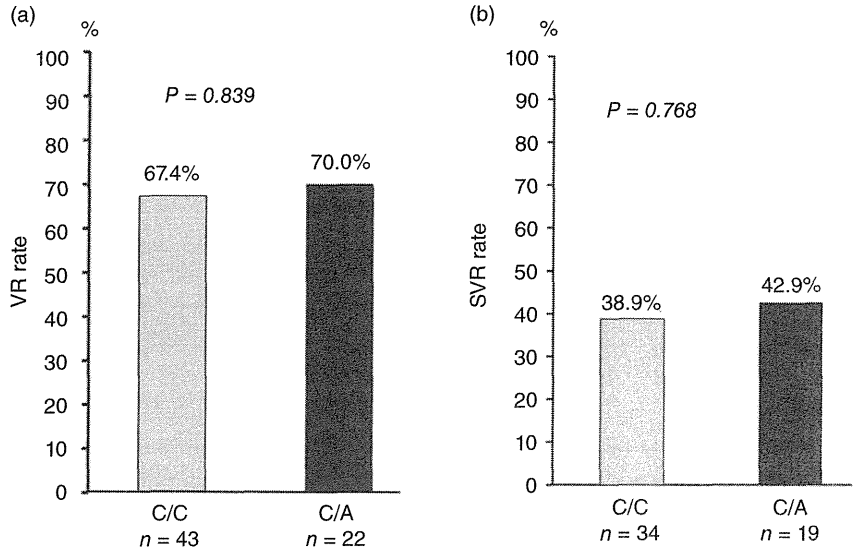

Figure 3 Inosine triphosphate pyrophosphatase (ITPA) genetic polymorphism and virological response. (a) Cirological response (VR) between the two genotypes was 68.9% and 72.7%. (b) The incidence of the sustained virological response (SVR) was 38.9% and 42.9%.

the CC allele (6.6 *vs.* 0% and 60 *vs.* 28.6%, respectively; Fig. 5a,b). In addition, tolerance to RBV seemed better in recipients carrying the CA allele. The dosage of RBV was able to be increased in 15.4% of those carrying the CC allele and in 42.9% of those carrying CA (Fig. 5c). At the same time, RBV dose reduction due to anemia was found in 46.7% of those carrying the CC allele and in 28.6% of those with the CA allele (Fig. 5d).

Table 2 Comparison of the data among patients whose Hb level < 10 g/dL and ≥10 g/dL at 4 weeks

Hb level at 4 weeks	Hb ≥ 10 g/dL (n = 49)	Hb < 10 g/dL (n = 14)	P-value
Pretransplantation factor			
Recipient's age (year), mean ± SD	56 ± 1	58 ± 2	n.s
Recipient's sex (male/female), n	32 / 17	6 / 8	n.s
Recipient's BMI (kg · m^{-2}), mean ± SD	24.6 ± 0.6	24.5 ± 1.3	n.s
Donor's age (year), mean ± SD	33 ± 2	34 ± 4	n.s
Donor's sex (male/female), n	33 / 16	10 / 4	n.s
Donor's BMI (kg · m^{-2}), mean ± SD	23.0 ± 0.6	21.5 ± 1.2	n.s
Pretransplant Hb level (g/dL), mean ± SD	11.2 ± 0.32	9.9 ± 0.68	n.s
MELD score, mean ± SD	10.2 ± 0.73	10.9 ± 1.2	n.s
Operative factor			
Operative time (min), mean ± SD	823 ± 29	730 ± 63	n.s
Simultaneous splenectomy (yes/no), n	35 / 14	6 / 8	0.04
Intraoperative bleeding (mL), mean ± SD	5721 ± 786	5332 ± 1260	n.s
GV / SLV (%), mean ± SD	40.2 ± 1.0	44.5 ± 2.3	n.s
Post-transplantation factor			
Bile duct complication (yes/no), n	40 / 3	16 / 4	n.s
Pretreatment viral load (logIU/mL), mean ± SD	6.2 ± 0.1	6.7 ± 0.2	0.03
Pathological activity score, mean ± SD	1.3 ± 0.11	1.2 ± 0.22	n.s
Pathological fibrosis score, mean ± SD	0.9 ± 0.19	1.2 ± 0.38	n.s
Immunospressive agents (CyA / FK)	25 / 24	11 / 3	n.s
Total dose of RBV during the first 4 weeks (mg), mean ± SD	9282 ± 633	7000 ± 1294	n.s
Pretreatment Hb level (g/dL), mean ± SD	12.7 ± 0.21	10.4 ± 0.40	<0.0001

BMI, body mass index; CyA, cyclosporine; FK, tacrolimus; GV, graft volume; Hb, hemoglobin; MELD, model for end-stage liver disease; n.s, not significant; RBV, ribavirin; SLV, standard liver volume.

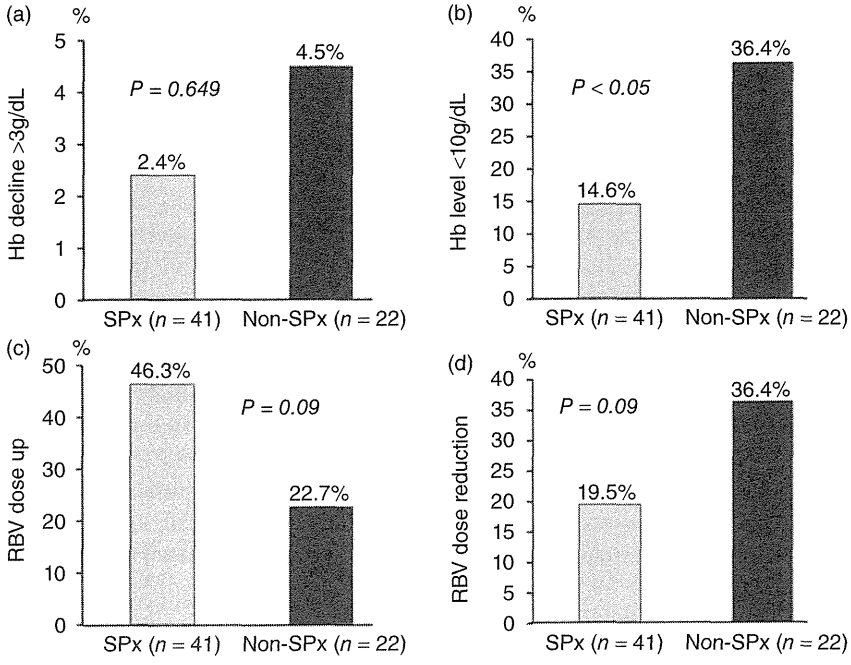

Figure 4 The efficacy of splenectomy for anaemia and ribavirin (RBV) tolerance. (a) The incidence of a hemoglobin (Hb) decline greater than 3 g/dL at 4 weeks was evident in 2.4% of recipients who had simultaneous splenectomy at liver transplantation (LT) (Spx group) and 4.5% of recipients were not subjected to a splenectomy (non-Spx group). (b) The incidence of Hb level less than 10 g/dL at 4 weeks was significantly lower in the Spx (14.6%) as compared with the non-Spx group (36.4%). (c) The dosage of RBV tended to increase more often in the Spx group (46.3%) than in the non-Spx group (22.7%). (d) RBV dose reduction due to anemia tended to be less frequent in the Spx group (19.5%) than in the non-Spx group (36.4%).

DISCUSSION

HCV-RELATED LIVER DISEASES are the main reason for liver transplantation worldwide.[1] The post-transplant prognosis for HCV is worse than with other diseases because of the recurrence of hepatitis C[11]. Although PEG-IFN/RBV is the only standardized anti-HCV therapy after LT, the outcome is poor with less than 30% of cases exhibiting a SVR. This is likely because of immunosuppressive agents used and severe side

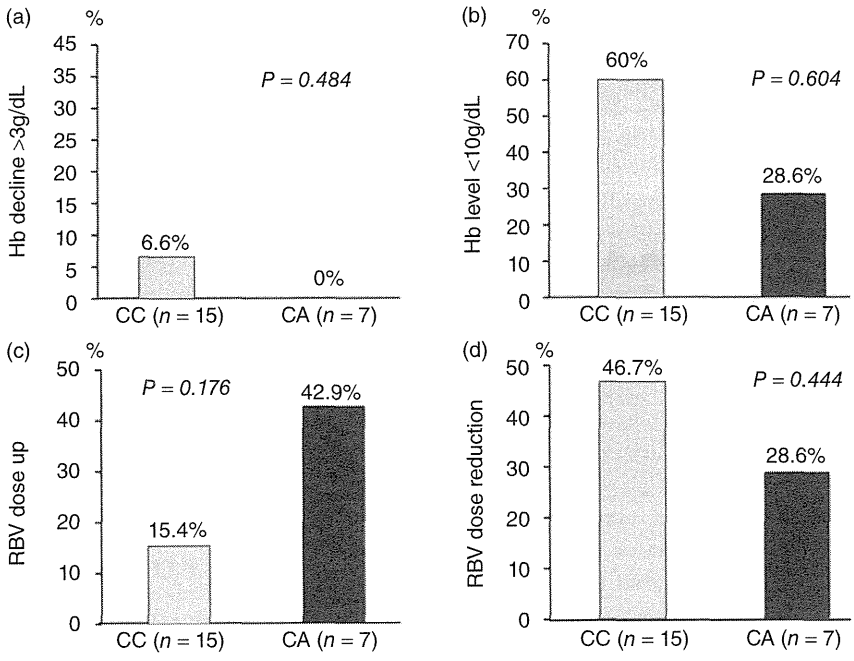

Figure 5 Inosine triphosphate pyrophosphatase (ITPA) genotypes and anemia among non-Spx group. (a) The incidence of hemoglobin (Hb) decline at 4 weeks was higher in CC allele carriers compared with CA allele carriers (6.6 *vs.* 0%). (b) The incidence of Hb levels less than 10 g/dL at 4 weeks was higher in the CC allele carriers (60 *vs.* 28.6%). (c) The dosage of RBV could be increased more often in CA allele carriers than in CC allele carriers (42.9 *vs.* 15.4%). (d) RBV dose reduction due to anemia was found more often in CC allele carriers than in CA allele carriers (46.7 *vs.* 28.6%).

effects, including anemia.[2] Treatment-induced anemia is an important issue in Japan where erythropoietin-replacement therapy is seldom performed. The ITPA genetic polymorphism was recently reported to be associated with PEG-IFN/RBV-induced anemia in chronic hepatitis C patients.[7,9,10] However, the correlation between this genetic polymorphism and post-transplant PEG-IFN/RBV induced anemia has never been examined until now.

We have made many attempts to prevent side effects, such as minimal dose of PEG-IFN/RBV at therapy commencement followed by dose adjustment in a stepwise manner.[6] In the current study, we hypothesized that the CA allele at rs1127354 correlated to post-transplant PEG-IFN/RBV therapy-induced anemia, and that those who carried the CA allele could tolerate a full dose of PEG-IFN/RBV without reduction.

Among the 63 recipients enrolled in this study, the CA allele was found in 20 (31.7%) patients, a frequency corresponding to previous reports regarding Japanese people.[8] Contrary to the hypothesis, the ITPA genetic polymorphism did not correlate with treatment-induced anemia after LT as shown in Figures 1 and 2. The incidence of Hb decline greater than 3 g/dL was relatively low, whereas the numbers of patients with Hb levels less than 10 g/dL were high at 4 weeks of post-transplant PEG-IFN/RBV therapy compared with those in previous reports for chronic hepatitis C patients.[7,10] In the current study, Hb decline was found in 4.7% of individuals in the CC group and none in the CA group, whereas this was 47.6–48.7% and 0.8–4.5%, respectively, in chronic hepatitis C patients.[7,10] In contrast, a Hb level below 10 g/dL was found in 18.6% and 30.0% in the CC and CA groups, respectively, and in 9.3–15.9% and 0.0–0.8% of chronic hepatitis C patients.[7,10] These findings may reflect that post-transplant patients are originally subject to severe anemia with or without PEG-IFN/RBV treatment and that our stepwise manner protocol in PEG-IFN/RBV therapy prevents the progression of anemia.

Ochi *et al.*[9] demonstrated that the ITPA genetic polymorphism correlated not only with anemia but with treatment efficacy. In the present study, however, the VR was not different between the two genotypes. It can be assumed that this was because of similar RBV tolerance, although another possibility is that the difference for each pretreatment viral load (6.2 *vs.* 6.6 logIU/mL) affected the efficacy of the ITPA minor genotype. It was recently reported that treatment-related anemia would possibly be associated with a greater occurrence of VR[12]. The correlation of the ITPA genetic polymorphism or anemia with the efficacy of PEG-IFN/RBV therapy requires further investigation.

Another strategy against the side effects of post-transplant PEG-IFN/RBV therapy at our institute is simultaneous splenectomy at LT[5]. Splenectomy is known to be effective and safe in combination with PEG-IFN/RBV therapy for thrombocytopenic patients with HCV-related cirrhosis,[13–15] but its efficacy in alleviating anemia is yet to be demonstrated. In the guidelines for the treatment of chronic hepatitis and cirrhosis due to HCV in Japan,[16] a splenectomy is recommended for patients with a platelet count less than 50 000/mm^3. Kishi *et al.*[17] described that a splenectomy was effective for treating leukocytopaenia, thrombocytopenia, but not for anemia in post-transplant recurrent HCV patients. In fact, there was no difference in pretreatment Hb levels between the Spx and non-Spx groups (12.0 *vs.* 12.4 g/dL, $P = 0.39$; data not shown) in the present study. However, the incidence of Hb levels less than 10 g/dL after treatment was significantly lower in the Spx group as compared with the non-Spx group, which shows the efficacy of a splenectomy for treatment-induced anemia after LT. At the same time, the ITPA genetic polymorphism tended to be associated with treatment-induced anemia and RBV tolerance in the non-Spx group only, similar to chronic hepatitis C patients. Conversely, it could be said that a splenectomy prevents PEG-IFN/RBV-related anemia regardless of the ITPA genetic polymorphism. However, neither splenectomy nor other factors that were suggested to be significantly associated with anemia by univariate analysis was shown to be associated with Hb level <10g/dl at 4 weeks after commencement of the therapy by multiple logistic regression (data not shown). The proof of the efficacy of splenectomy in preventing PEG-IFN/RBV induced anemia needs further investigation.

In conclusion, this is the first report regarding the relationship of the ITPA genetic polymorphism and anemia caused by post-transplant PEG-IFN/RBV therapy in recurrent HCV. The ITPA genetic polymorphism does not correlate with treatment-induced anemia after LT.

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Risk Factors That Increase Mortality After Living Donor Liver Transplantation

Tomoharu Yoshizumi,[1,2,3] Ken Shirabe,[2] Akinobu Taketomi,[2] Hideaki Uchiyama,[2] Noboru Harada,[2] Hideki Ijichi,[2] Masanori Yoshimatsu,[2] Toru Ikegami,[2] Yuji Soejima,[2] and Yoshihiko Maehara[2]

Background. Female liver to male recipient is a well-accepted risk factor for graft loss in cadaveric liver transplantation. However, gender matching is infeasible because of an insufficient number of available donors. No studies have been performed on the role of gender in the field of living donor liver transplantation. This report investigates the effect of gender mismatch on the outcome of living donor liver transplantation.

Methods. A total of 335 patients and donors were classified into four groups according to the following gender combinations: male donor to male recipient group (n=104), male donor to female recipient group (n=120), female donor to male recipient (FM) group (n=59), and female donor to female recipient group (n=52). Patient and graft survival were compared among the groups. We performed a multivariable analysis to identify the factors associated with patient mortality.

Results. The 1-, 3-, 5-, and 10-year patient survival rates in the FM group were 80.6%, 66.8%, 61.8%, and 47.7%, respectively. The FM group showed significantly shorter patient survival compared with the other three groups. Independent risk factors for patient mortality were: FM group (P=0.006), pretransplant diabetes mellitus (P=0.001), and a model for end-stage liver disease score more than or equal to 20 (P=0.004).

Conclusions. Male recipients of transplants from female donors, pretransplant diabetes mellitus, and a model for end-stage liver disease score more than or equal to 20 have poor survival rates.

Keywords: Donor, Gender, Transplantation, Mismatch.

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The role of gender in the transplantation of body parts such as the kidney, lung, bone marrow, and heart has been extensively studied (*1–4*). In general, today's solid organ donors cannot be matched by gender because of a disparity between supply and demand (*5*). Some reports indicate that gender mismatch has an impact on graft failure, specifically in male recipients of female livers in cadaveric liver transplantation (LT) (*6–8*). Marsman et al. reported that female recipients had a higher incidence of early rejection within 6 months of LT compared with male recipients. They also found decreased graft survival rate in male recipients of female livers (*9*). In contrast, Lehner et al. (*10*) recently reported no significant differences in patient survival in gender-mismatched LT in a single-center database of 1355 recipients.

Donor age, high model for end-stage liver disease (MELD) score, graft size, and portal hypertension are risk factors for graft failure after living donor liver transplantation (LDLT) for patients with chronic liver failure (*11*). Standard liver volume is proportional to body surface area (*12*). Therefore, the difference in body size between males and females sometimes results in a small-for-size graft (SFSG) in males who receive livers from female donors. Data show poor LDLT outcomes with a graft-weight to recipient-weight ratio of less than 0.8 (*13*). Despite this difference between cadaveric LT and LDLT, there are no studies on gender and LDLT. Therefore, the aim of this study was to clarify the effect of gender mismatch on LDLT outcomes.

RESULTS

Table 1 shows a comparison of variables among the four groups classified by gender combination. The distribution of the primary diagnosis was markedly skewed because of the presence of diseases such as hepatitis C (HCV), primary biliary cirrhosis, and primary sclerosing cholangitis (PSC). Operation time and blood loss were greater in the female donor to male recipient (FM) group than in the other three groups. More left lobe was used in the male donor to male

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[1] Department of Surgery and Multidisciplinary Treatment, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
[2] Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
[3] Address correspondence to: Tomoharu Yoshizumi, M.D., Department of Surgery and Multidisciplinary Treatment, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Fukuoka 812-8582, Japan.
E-mail: yosizumi@surg2.med.kyushu-u.ac.jp

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TABLE 1. Comparison of variables between the groups classified by gender combination

Variables	MM group (n=104)	FF group (n=52)	MF group (n=120)	FM group (n=59)	*P*
Recipient variables					
Age, yr (range)	52.5 (19–69)	49.4 (18–71)	52.7 (18–73)	49.9 (23–68)	NS
Primary diagnosis					<0.001
Liver cirrhosis					
Hepatitis C (HCC)	61 (49)	18 (15)	41 (33)	27 (17)	
Hepatitis B (HCC)	12 (10)	1 (1)	9 (7)	6 (5)	
Non-B non-C (HCC)	5 (2)	3 (1)	3 (2)	6 (2)	
Alcohol (HCC)	6 (4)	2 (0)	1 (0)	3 (2)	
Fulminant hepatic failure (FHF)	11	7	25	7	
Primary biliary cirrhosis	3	10	31	1	
Primary sclerosing cholangitis	4	1	1	5	
Biliary atresia	1	3	1	1	
Others	1	7	8	3	
Body mass index (kg/m^2)	23.6±3.0	22.4±3.7	23.0±3.6	23.9±3.7	0.08
MELD score	14.0±7.0	15.4±8.5	15.5±8.4	15.6±8.2	NS
Pretransplant DM (yes/no)	24/80	0/52	15/105	12/47	0.001
Operation time (min)	834±174	765±136	751±139	866±209	<0.001
Blood loss (mL)	6498±6940	4936±5296	4617±5006	8676±7884	0.001
Donor/graft variables					
Graft (left/right/posterior)	72/31/1	28/24/0	95/22/3	15/43/1	<0.001
GW-SLW ratio (%)	40.9±8.2	40.9±9.7	44.2±9.0	40.7±7.1	0.01
GW-BW ratio (%)	0.77±0.16	0.82±0.03	0.88±0.02	0.76±0.02	<0.001
ABO (identical/compatible/incompatible)	84/16/3	39/11/2	82/27/10	39/18/2	NS
Consanguinity (yes/no)	100/4	50/2	97/23	33/26	<0.001
Age, yr (range)	31.7 (20–62)	35.9 (20–58)	36.9 (20–65)	40.2 (22–60)	<0.001
Body mass index (kg/m^2)	22.6±3.1	21.4±2.8	22.9±2.6	21.3±2.3	0.001
Operation time (min)	458±80	426±58	443±67	437±76	0.07
Cold ischemic time (min)	86±59	87±61	66±35	122±69	<0.001
Warm ischemic time (min)	41±12	39±13	37±9	45±11	0.001
Blood loss (mL)	582±340	470±288	630±505	531±442	NS

DM, diabetes mellitus; GW, graft weight; SLW, standard liver weight calculated by 706.2×body surface area+2.4; MM, male donor to male recipient; FF, female donor to female recipient; MF, male donor to female recipient; FM, female donor to male recipient; NS, not significant; HCC, hepatocellular carcinoma; FHF, fulminant hepatic failure; MELD, model for end-stage liver disease; BW, body weight.

recipient (MM) and male donor to female recipient (MF) groups compared with the other two groups. Nevertheless, the ratio of graft weight (GW) to standard liver weight (SLW) and the ratio of GW to body weight were higher in the MF group than in the other three groups. LDLT between spouses was included in the FM and MF groups, reducing consanguinity between donors and recipients. Donors in the MM group were younger than those in the other three groups. Cold and warm ischemic times were longest in the FM LDLT group. Most such cases involve the use of a right lobe graft, which requires hepatic vein reconstruction.

In our series, 80 patients died after LDLT. Hepatocellular carcinoma (HCC) recurrence occurred in 14 patients, sepsis in 13 patients, HCV recurrence in 9 patients, graft failure in 9 patients, bleeding in 8 patients, de novo malignancy in 7 patients, chronic rejection in 4 patients, multiple organ failure in 4 patients, fungal infection in 3 patients, and other conditions in 9 patients. There was no difference in cause of death among the groups. Furthermore, 23 patients died in the FM group. Nine patients died of surgery-related causes (sepsis in five, graft failure in one, multiple organ failure in one, abdominal bleeding in one, and fungal infection in one). The other 14 patients died of medical reasons (HCC recurrence in 4, chronic rejection in 3, HCV recurrence in 2, PSC recurrence in 1, hemangioendothelioma recurrence in 1, fungal infection in 1, adult T-cell leukemia in 1, and subcapsular hemorrhage of the hepatic graft secondary to liver biopsy in 1).

Figure 1 shows the overall patient and graft survival rates among the four groups. The 1-, 3-, 5-, and 10-year patient survival rates in the MM group were 87.0%, 77.7%, 76.2%, and 70.2%, respectively. Those in the female donor to female recipient (FF) group were 94.0%, 84.6%, 81.6%, and 81.6%, respectively. Those in the MF group were 83.3%, 83.3%, 81.7%, and 75.4%, respectively. Those in the FM group were 80.6%, 66.8%, 61.8%, and 47.7%, respectively. The FM group had significantly worse patient survival rates compared with the FF ($P<0.01$), MF ($P<0.01$), and MM ($P<0.05$) groups.

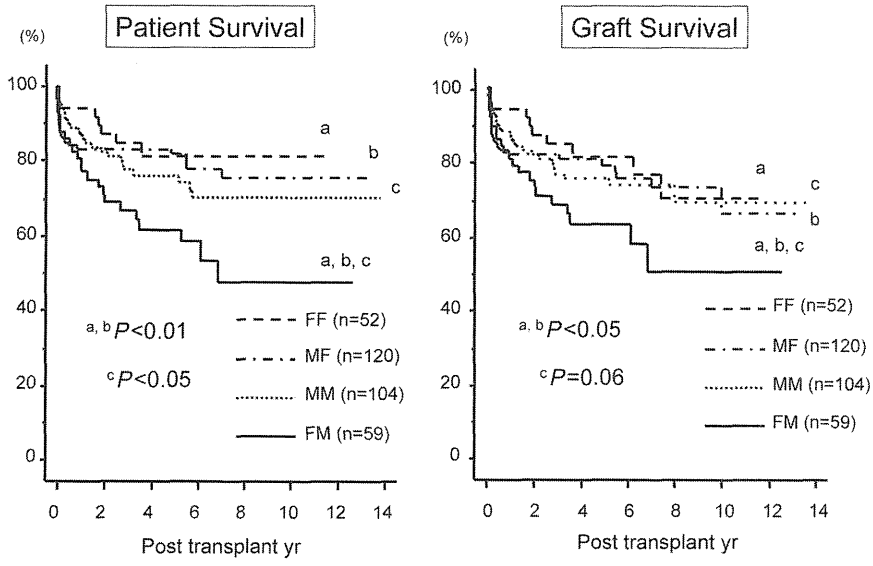

FIGURE 1. Patient and graft survival after LDLT among the four groups defined according to gender combination. The FM group had significantly worse patient survival rates compared with the FF (a, $P<0.01$), MF (b, $P<0.01$), and MM (c, $P<0.05$) groups. The FM group had significantly worse graft survival rates compared with the FF (a, $P<0.05$) and MF (b, $P<0.05$) groups. FM, female donor to male recipient; FF, female donor to female recipient; MF, male donor to female recipient; MM, male donor to male recipient; LDLT, living donor liver transplantation.

The 1-, 3-, 5-, and 10-year graft survival rates in the MM group were 86.2%, 76.9%, 75.5%, and 65.4%, respectively. Those in the FF group were 94.1%, 84.7%, 81.6%, and 70.4%, respectively. Those in the MF group were 81.2%, 81.2%, 78.4%, and 65.8%, respectively. Those in the FM group were 80.9%, 67.0%, 62.0%, and 47.1%, respectively. The FM group had significantly worse graft survival rates compared with the FF ($P<0.02$) and MF ($P<0.05$) groups.

Univariable analysis revealed the following risk factors for patient mortality after LDLT: MELD score more than or equal to 20; the presence of pretransplant diabetes mellitus (DM); absence of consanguinity between the donor and recipient; and inclusion in the FM group (Table 2). The following variables had P values of less than 0.10: donor age more than 60 years and liver failure without HCC. A multivariable analysis including these variables revealed that the FM group ($P=0.006$), the presence of DM ($P=0.001$), and a MELD score more than or equal to 20 ($P=0.004$) were independent risk factors for patient mortality after LDLT (Table 3). Figure 2 shows the overall patient survival rate according to each risk factor.

DISCUSSION

This is the first report on the impact of gender and LDLT outcomes. That a multivariable analysis identified organ donation from a female to a male recipient as an independent risk factor for patient mortality after LDLT is of interest. Because the male–female difference in body size is believed to be a factor in lower survival rates, we performed a subgroup analysis in the FM group according to the GW-SLW ratio. Patients were classified into two subgroups: those with a GW-SLW ratio of less than 40% (n=26) and those with a GW-SLW ratio of more than or equal to 40% (n=33). Findings showed no significant differences between the subgroups (data not shown). Recipient age and primary diagnosis, such as HCV or fulminant hepatic failure, also had no effect on outcomes (data not shown). Biliary issues (type of reconstruction and stricture), which are likely important and related to infection complications, were assessed in the univariable analysis. They did not affect outcomes either (Table 2).

When using a right lobe graft, complicated reconstruction of the middle hepatic vein (MHV) is necessary (*12*). Therefore, the FM group had the highest operation time, cold ischemic time, and recipient blood loss (Table 1). The prevalence of a complicated operation for right lobe graft might have affected outcomes in this study. The patency rate of these reconstructed veins confirmed by Doppler echo 7 days after LDLT was 80%. The frequency of SFSG syndrome in each group was assessed. A total of 30 of 120 cases using a right hepatic graft developed SFSG syndrome. Among them, 10 were in the MF group (47.6%), 12 were in the FM group (27.9%), 5 were in the FF group (20.8%), and 3 were in the MM group (9.7%). The difference was significant ($P=0.02$); however, the frequency rate of SFSG syndrome was more in the MF group than in the other three groups.

In this study, the prevalence of DM, which is a well-accepted risk factor for mortality in cadaveric LT (*14*), differed between males and females (Table 1). Furthermore, the presence of DM was an independent risk factor for mortality.

In the FM group, 44% of recipients received grafts from nonconsanguineous donors (spouses). Univariable analysis revealed that a lack of consanguinity between donor and recipient was a risk factor for mortality, although the frequency of acute cellular rejection did not differ among the four groups. Therefore, it is not clear how consanguinity affected outcomes in this study.

Although Marino et al. (*15*) reported that livers from female donors yielded poorer results even in female recipients, perhaps because of a gender-related immunologic factor or sex hormones, this study confirmed that the FF group had the best patient survival (Fig. 1). It also showed that having a female donor was not a risk factor for survival.

Outcomes from this study are somewhat consistent with those of prior reports on cadaveric LT (*6, 8*). The increased risk of graft failure in male recipients of female livers may be related to the lack of estrogen and/or progesterone in male recipients (*16*). Furthermore, the human liver has gender-related differences, such as increased hepatic content of microsomal oxidative enzymes in males and different

TABLE 2. Risk factors for patient survival after LDLT: univariable analysis

Variables	Patient survival 1 yr	3 yr	5 yr	P
Recipient variables				
Age (%)				
≥60 yr (n=84)	85.4	75.4	73.4	NS
<60 yr (n=251)	85.7	79.5	77.0	
Etiology (%)				
HCV (n=147)	87.7	77.5	75.3	NS
Others (n=188)	84.0	79.4	76.9	
HCC (%)				
No (n=180)	80.5	74.7	73.0	0.077
Yes (n=155)	91.7	83.2	80.0	
MELD score (%)				
≥20 (n=72)	72.2	65.7	63.3	0.003
<20 (n=258)	89.1	82.4	80.0	
Diabetes mellitus (%)				
Yes (n=51)	70.9	63.9	61.0	0.005
No (n=284)	88.3	81.3	79.0	
Bile duct reconstruction (%)				
Roux-en-Y (n=81)	82.3	76.6	74.9	NS
Duct to duct (n=251)	87.0	79.6	76.9	
Bile duct stenosis (%)				
Yes (n=71)	94.3	83.6	80.3	NS
No (n=262)	83.8	78.0	75.9	
Donor/graft variables				
Age (%)				
≥60 yr (n=6)	66.7	66.7	66.7	0.089
<60 yr (n=329)	86.0	78.9	76.5	
Graft (%)				
Left lobe (n=210)	84.2	80.0	77.9	NS
Others (n=125)	88.2	76.4	73.4	
GW-SLW ratio (%)				
≤35 (n=68)	83.4	77.7	75.4	NS
>35 (n=264)	86.1	78.8	76.3	
Donor-recipient matching				
ABO incompatible (%)				
Yes (n=17)	86.2	86.2	86.2	NS
No (n=318)	85.5	78.3	75.9	
Consanguinity (%)				
No (n=55)	80.9	68.6	68.6	0.030
Yes (n=280)	86.6	80.6	77.8	
Donor-recipient gender (%)				
Mismatch (n=179)	82.4	77.6	74.9	NS
Match (n=156)	89.3	79.9	78.0	
FM group (%)				
Yes (n=59)	80.6	66.8	61.8	0.002
No (n=276)	86.7	81.3	79.5	

LDLT, living donor liver transplantation; GW, graft weight; SLW, standard liver weight calculated by 706.2×body surface area+2.4; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NS, not significant; MELD, model for end-stage liver disease; FM, female donor to male recipient.

TABLE 3. Risk factors for patient survival after LDLT: multivariable analysis

Variables	Odds ratio	95% CI	P
FM group			
Yes vs. No	2.10	1.24–3.57	0.006
Diabetes mellitus			
Yes vs. No	2.76	1.56–4.88	0.001
MELD score			
≥20 vs. <20	2.12	1.27–3.53	0.004
Donor age (yr)			
≥60 vs. <60	2.79	0.85–9.17	0.09
HCC			
No vs. yes	1.54	0.90–2.64	0.11
Consanguinity			
No vs. yes	1.37	0.77–2.43	0.28

LDLT, living donor liver transplantation; CI, confidence interval; FM, female donor to male recipient; MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma.

numbers of estrogen and androgen receptors on hepatocytes between males and females (*7*).

In a rodent hepatectomy model, serum estrogen levels and the number of estrogen hepatic receptors increased concomitantly with liver regeneration (*17*). Kahn et al. (*18*) also demonstrated a reduction in the number of estrogen receptors in the livers of gender-mismatched recipients 10 days after transplantation. Thus, it is possible that the poor outcome in the FM group was caused by reduced serum estrogen levels in the male recipients and a lower number of estrogen receptors in the female organ. Further long-term study is warranted to clarify how hormonal factors affect the outcome of LT.

Because of the shortage of donor organs, the gender of donors is not routinely used as a selection criterion for LDLT (*19*). Although LDLT allows for elective planning of the procedure, which may enable selection of the most suitable donor from among the candidates (*19*), it is important to be mindful of hormonal and/or immunological differences between the genders to improve LDLT outcomes. At the same time, we need to remember that a multiplicity of donor and recipient factors influence posttransplant outcomes (*20*). For these reasons, further study in this area is called for before any changes in clinical decision-making based on findings in this report.

In conclusion, male recipients who received transplants from female donors had the worst survival among the four donor-recipient groups. Being a male recipient receiving a transplant from a female donor was an independent risk factor for patient mortality after LDLT. Further study is warranted to clarify the mechanism of this outcome.

MATERIALS AND METHODS

Patients

A total of 335 adult patients (172 women and 163 men) who had undergone LDLT because of end-stage liver disease at Kyushu University Hospital between May 1997 and March 2011 were enrolled in the trial; seven retransplanted cases were included. The cause of liver disease (women/men) was hepatitis C (59/88), fulminant hepatic failure (32/18), primary biliary cirrho-

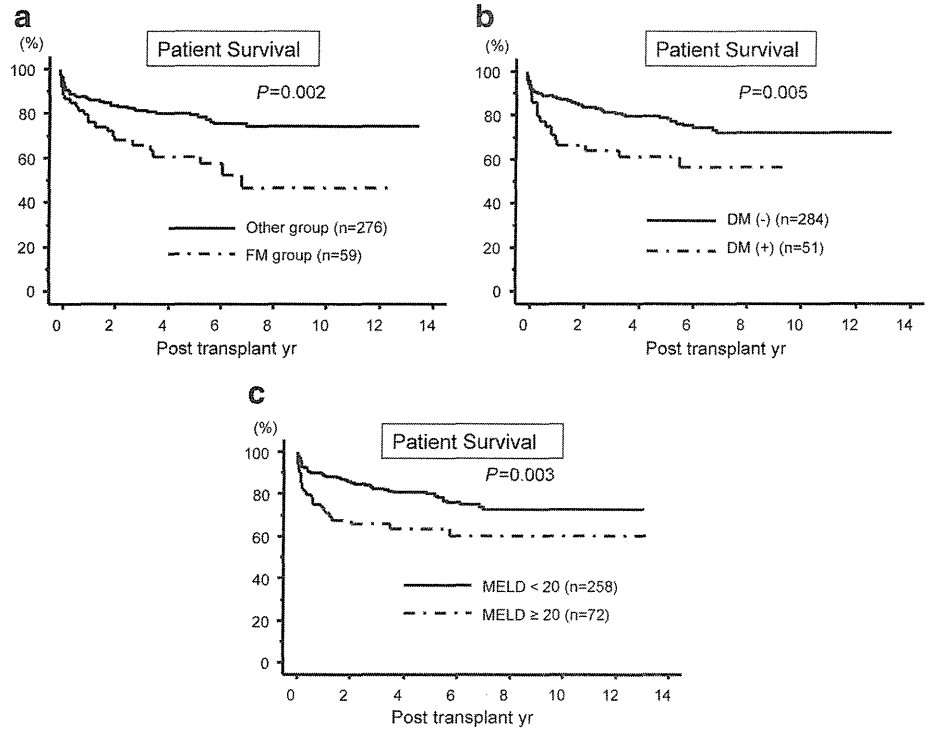

FIGURE 2. (a) Patient survival after LDLT between the two groups according to gender combination. The 1-, 3-, 5-, and 10-year patient survival rates in the FM group were 80.6%, 66.8%, 61.8%, and 47.7%, respectively, and those in the other combination groups were 86.7%, 81.3%, 79.5%, and 74.5%, respectively. The FM group had significantly worse patient survival rates compared with the other combination group (P=0.002). (b) Patient survival after LDLT between the two groups according to pretransplant DM. The 1-, 3-, 5-, and 10-year patient survival rates in the DM (+) group were 70.9%, 63.9%, 61.0%, and 56.6%, respectively. Those in the DM (−) group were 88.3%, 81.3%, 79.0%, and 72.3%, respectively. The DM (+) group had significantly worse patient survival rates compared with the DM (−) group (P=0.005). (c) Patient survival after LDLT between the two groups according to pretransplant MELD. The 1-, 3-, 5-, and 10-year patient survival rates in the MELD score more than or equal to 20 group were 72.2%, 65.7%, 63.3%, and 60.1%, respectively. Those in the MELD score less than 20 group were 89.1%, 82.4%, 80.0%, and 72.7%, respectively. The MELD score more than or equal to 20 group had significantly worse patient and graft survival rates compared with the MELD score less than 20 group (P=0.003). LDLT, living donor liver transplantation; FM, female donor to male recipient; DM, diabetes mellitus; MELD, model for end-stage liver disease.

sis (41/4), hepatitis B (10/18), cryptogenic (6/11), PSC (2/9), alcohol abuse (3/9), biliary atresia (4/2), and others (15/4) (Table 1).

Donor and Graft Selection

Donors were selected from among candidates who hoped to be living donors (*11, 12*). Consequently, 335 donors (111 women and 224 men) were enrolled. The relationships between donors and recipients were as follows: son (n=141), daughter (n=47), brother (n=36), wife (n=25), sister (n=20), husband (n=21), mother (n=10), father (n=10), nephew (n=7), son-in-law (n=3), cousin (n=2), father-in-law (n=2), and others (n=11). The graft types included left lobe with caudate lobe graft (n=194), right lobe graft without the MHV (n=117), right lobe graft with MHV (n=3), left lobe graft (n=16), and posterior segment graft (n=5). Donors were required to be spouses or within the third degree of consanguinity with recipients and to be between 20 and 65 years of age. For a donor who was not within the third degree of consanguinity, individual approval was obtained from the ethics committee of Kyushu University Hospital. Good Samaritan organ donations were not used.

We used three-dimensional computed tomography for volumetric analysis and delineation of vascular anatomy. The SLW of recipients was calculated according to the formula of Urata (*11, 12*). GW was predicted by computed tomographic volumetric analysis. The decision about graft type for the recipients was based on the preoperatively predicted GW to SLW (GW-SLW) ratio. A left lobe graft was used when the preoperatively predicted GW-SLW ratio was more than 35%.

Postoperative Management

Graft harvesting technique, recipient surgery, and perioperative management of the recipients, including immunosuppression regimens, have been previously described (*11, 12, 21*). Bile ducts were reconstructed using the Roux-en-Y (n=81) or duct-to-duct (n=251) techniques. Bile ducts were not reconstructed in two cases because of intraoperative bleeding. We initiated immunosuppression with a protocol based on tacrolimus (Prograf; Astellas Pharma Inc., Tokyo, Japan) or cyclosporine A (Neoral; Novartis Pharma K.K., Tokyo, Japan).

All patients had monthly follow-ups, and the median follow-up period was 1377 days, with 369 days and 2186 days as the 25th and 75th percentiles, respectively. Patient survival was defined as the time period between LDLT and patient death.

Impact of Recipient and Donor Gender

The 335 patients and donors were classified into four groups according to the donor-recipient gender combinations as follows: MM group (n=104), MF group (n=120), FM group (n=59), and FF group (n=52). The 1-, 3-, 5-, and 10-year patient and graft survival rates were compared among the

groups. Univariable and multivariable analyses were performed to identify the factors associated with patient mortality after the LDLT.

Statistical Analysis

The significance of differences among four groups was determined by one-factor analysis of variance. Cox regression analysis was applied to the univariable and multivariable analyses. Survival was calculated by the Kaplan-Meier product-limited method, and differences in survival between two groups or among all four groups were then compared using the log-rank test. Data were expressed as mean±standard deviation. All statistical analyses were performed using StatView 5.0 software (SAS Institute, Inc., Cary, NC). A P value of less than 0.05 was considered significant.

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ORIGINAL ARTICLE

The long-term outcomes of patients with hepatocellular carcinoma after living donor liver transplantation: a comparison of right and left lobe grafts

Akinobu Taketomi · Ken Shirabe · Takeo Toshima · Kazutoyo Morita · Naotaka Hashimoto · Hiroto Kayashima · Tohru Ikegami · Tomoharu Yoshizumi · Yuji Soejima · Yoshihko Maehara

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Abstract
Purpose The feasibility of living donor liver transplantation (LDLT) using left lobe (LL) grafts has been demonstrated. However, the long-term outcome of the hepatocellular carcinoma (HCC) patients with LL grafts has not been elucidated. The aim of this study was to analyze the long-term outcomes after LDLT for HCC according to the graft type.
Methods A retrospective analysis was performed evaluating the outcomes of LL graft recipients ($n = 82$) versus recipients of RL grafts ($n = 46$). The analysis endpoints were the overall and recurrence-free survival after LDLT. The demographics of both recipients and donors, and the tumor characteristics associated with the graft type were also analyzed.
Results The graft volume (436 ± 74 g), as well as the graft volume-standard liver volume rate (38.3 ± 6.2%) of the LL graft group were significantly decreased as compared to those of the RL graft group (569 ± 82 g, 46.3 ± 6.7%; $p < 0.01$). The 1-, 3-, 5- and 7-year overall survival rates of the LL graft group were 88.2, 80.2, 75.7 and 72.4%, respectively, which were not significantly different compared to those of the RL graft group (95.4, 87.3, 87.3 and 87.3%). The recurrence-free survival rates of the LL graft group (89.1% at 1 year, 78.8% at 3 years, 75.8% at 5 years and 70.3% at 7 years) were similar to those of the RL graft group (88.6, 88.6, 88.6 and 88.6%). The mean peak postoperative total bilirubin levels and duration of hospital stay after surgery for the LL grafting donors were significantly decreased as compared to those of the RL grafting donors ($p < 0.01$). The rate of severe complications (over Clavien's IIIa) associated with LL graft procurement was 6.2%, which was lower than that in the RL graft group (15.6%).
Conclusions The long-term outcomes in the HCC patients with LL grafts were similar to those of patients receiving RL grafts, and the outcomes of the donors of LL grafts were more favorable. Therefore, LL grafts should be considered when selecting LDLT for HCC to ensure donor safety.

Keywords Surgery · Hepatocellular carcinoma · Recurrence · Living donor liver transplantation · Graft type

Abbreviations

AFP	Alpha-fetoprotein
CL	Caudate lobe
CT	Computed tomography
DCP	Des-gamma-carboxy prothrombin
DDLT	Deceased donor liver transplantation
GRWR	Graft-recipient weight ratio
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
LDLT	Living donor liver transplantation
LL	Left lobe
LT	Liver transplantation
MMF	Mycophenolate mofetil
RL	Right lobe
RV	Remnant liver volume
SLV	Standard liver volume
TLV	Total liver volume

A. Taketomi (✉) · K. Shirabe · T. Toshima · K. Morita · N. Hashimoto · H. Kayashima · T. Ikegami · T. Yoshizumi · Y. Soejima · Y. Maehara
Department of Surgery and Science,
Graduate School of Medicine, Kyushu University,
3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
e-mail: taketomi@surg2.med.kyushu-u.ac.jp

Introduction

Living donor liver transplantation (LDLT) is currently the treatment of choice for unresectable hepatocellular carcinoma (HCC; 1, 2). A large survey of 49 centers in Japan including a total of 653 patients with HCC has been reported [1]. A postoperative pathological study showed that the 5-year disease-free survival of those who met ($n = 325$) and exceeded ($n = 272$) the Milan criteria were 95.3 and 66.4%, respectively. Therefore, LDLT for patients with HCC within the Milan criteria can also achieve an acceptable outcome comparable to the outcome for deceased donor liver transplantation (DDLT) for HCC. Some DDLT centers have expanded the selection criteria, like up-to seven criteria, because of concerns that the Milan criteria are too stringent [2, 3]. The expanded criteria are also proposed by some LDLT high-volume centers in Japan [4–6]. Tumor markers, such as alpha-fetoprotein (AFP) or des-gamma-carboxy prothrombin (DCP), in addition to the tumor size and the number of tumors, are useful to properly rate the candidate without decreasing the long-term survival after liver transplantation (LT). Therefore, LDLT has been established as a treatment choice for HCC.

Living donor liver transplantation using right lobe (RL) grafts has gained widespread acceptance, whereas the use of left lobe (LL) grafts for adults has been severely limited because of their size limitation. On the other hand, some centers have limited LDLT between adults to LL grafting, arguing that RL donation involves unacceptable risks [7]. Donor selection criteria have been established based on graft liver volume (GV) and the remnant liver volume (RV) of the donor, as calculated using three-dimensional computed tomography (CT), and the LL is considered to be the first choice for the graft [8].

There is a potential risk for HCC after LDLT due to the rapid liver regeneration that occurs in the immediate post-LDLT period, which could lead to cancer progression in these patients, which in turn, could lead to early or multiple-site recurrence [9]. However, the long-term outcome of the HCC patients treated with LL grafts has not yet been elucidated.

The aim of this study was to compare the long-term and recurrence-free survival rates between recipients of LL and RL grafts.

Patients and methods

Three hundred forty-six LDLT procedures for HCC were performed at Kyushu University Hospital, Fukuoka, Japan, from July 1995 and November 2009, after prior approval from the Ethics and Indications Committee of Kyushu University. One hundred twenty-eight adult-to-adult LDLT for HCC were included in this study. The selection criteria for the HCC patients were [10] no modality except LDLT available to cure the patients with HCC and end-stage liver disease, [4] no extra-hepatic metastasis, [1] no major vascular infiltration, such as the portal vein or hepatic vein, which ensures that there was no restriction on the tumor size or the number of tumors.

The transplant procedures for both the donors and recipients have been described previously [11–13]. The immunosuppressive regimen was a combination of a calcineurin inhibitor (tacrolimus or cyclosporine) and steroids, with or without mycophenolate mofetil (MMF). Basiliximab (20 mg) was given intravenously within 6 h after graft reperfusion and on postoperative day 4. A steroid injection was given intraoperatively (methylprednisolone 1 g) and tapered to zero by day 7. Maintenance immunosuppression therapy was conducted with low-dose tacrolimus or cyclosporine from postoperative day 7.

Donor evaluation and selection

The general selection criteria for grafts in adult-to-adult LDLT based on volumetric analysis have been described previously [8]. Briefly, the LL is initially considered for the graft and is generally used. The RL is chosen if the estimated LL with the caudate lobe (CL) volume of the donor is less than 35% of the SLV of the recipient. The person will be excluded as a donor candidate if the RV is less than 35% of the total liver volume (TLV). A biopsy of the donor liver is performed if the CT or ultrasonography study shows the possibility of steatosis, or if the donor's body mass index is greater than 25.

Patient follow-up

The clinical follow-up of patients who underwent HCC followed a strict protocol, which did not change during the study period. The patients were seen bi-weekly for the first month and then monthly for 6 months. The patients underwent ultrasound and enhanced CT examinations at 6 month intervals. Hepatic angiography, bone scintigraphy, or a thoracic CT examination was also performed if there was deterioration in the graft function, or an increase in the AFP or DCP level was noted. The mean follow-up period of the RL and LL graft groups was 3.63 and 3.52 years, respectively.

Statistical analysis

All statistical analyses were performed using the StatView® 5.0 software package (Abacus Concepts, Berkeley, CA, USA). The continuous variables were compared using the Mann–Whitney U test. All variables were expressed as

the means ± SD. The categorical data were compared using the Chi-square test. A logistic regression analysis was performed to identify the independent variables for postoperative complications. The differences were considered to be significant if $p < 0.05$.

Results

Recipients and tumor characteristics according to the graft type

The clinical parameters of the recipients were compared between the two groups according to the graft type (Table 1). Males were predominant in the RL group. The mean age of the LL group was significantly higher than that in the RL group ($p < 0.05$). The rate of patients with a Child-Pugh classification of "C" in the RL group was significantly higher than that in the LL group ($p < 0.05$). The graft volume (436 ± 74 g), as well as the graft volume-standard liver volume rate (38.3 ± 6.2%), of the LL graft group was significantly lower than that in the RL graft group (569 ± 82 g, 46.3 ± 6.7%; $p < 0.01$). Although the duration of surgery of the RL graft group was significantly longer than that of the LL graft group, the intraoperative blood loss was similar in the two groups. The mean length of warm and cold ischemia in the RL group (44 ± 12, 125 ± 66 min) was significantly longer than those of the LL group (38 ± 12, 57 ± 26 min). No difference was found between the two groups with regard to the hepatitis C virus (HCV) infection rate, alpha-fetoprotein (AFP) and DCP levels, number of tumors, maximum tumor size, TNM stage, and Milan classification. There were also no differences in the histological tumor differentiation and vascular invasion between the groups.

Table 1 Recipient and tumor characteristics according to the graft type

Factors	RL graft ($n = 46$)	LL graft ($n = 82$)	p value
Gender			
male (%)	73.9	53.7	0.0242
Age (years)[a]	54.6 ± 6.8	58.7 ± 7.9	0.0034
Hepatitis			
HCV/non-HCV	32/14	63/19	0.3673
Child-Pugh classification			
A/B/C	1/14/31	8/37/37	0.0341
GV (g)[a]	569 ± 82	436 ± 74	<0.0001
GV/SLV (%)[a]	46.3 ± 6.7	38.3 ± 6.2	<0.0001
Length of operation (min)[a]	903 ± 199	772 ± 143	<0.0001
Intraoperative blood loss (ml)[a]	7027 ± 5541	8121 ± 25134	0.7717
Length of warm ischemia (min)[a]	44 ± 12	38 ± 12	0.0038
Length of cold ischemia (min)[a]	125 ± 66	57 ± 26	<0.0001
AFP (ng/ml)			
<300/≥300	40/6	66/16	0.3520
DCP (mAU/ml)			
<300/≥300	37/9	66/16	0.9942
Number of tumors			
≤3/>3	34/12	49/33	0.1075
Tumor size (cm)	2.2 ± 1.3	2.6 ± 1.3	0.1282
Type of HCC			
Initial/recurrent	31/15	54/28	0.8597
Stage			
I/II/III	8/14/21	8/25/45	0.3942
Milan criteria			
Yes/no	29/17	43/39	0.2459
Tumor differentiation (histological)			
Well/mod/por	3/28/14	8/48/26	0.8231
Vascular invasion (histological)			
Yes/no	20/26	33/49	0.7215

AFP alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *GV* graft volume, *GV/SLV* graft volume versus standard liver volume ratio, *HCV* hepatitis C virus

[a] Mean value ± standard deviation

Survival after LDLT according to the graft type

The 1-, 3-, 5- and 7-year overall survival rates of the LL graft group were 88.2, 80.2, 75.7 and 72.4%, respectively, which were not significantly different in comparison to those of the RL graft group (95.4, 87.3, 87.3 and 87.3%, Fig. 1a). The recurrence-free survival rates of the LL graft group (89.1% at 1 year, 78.8% at 3 years, 75.8% at 5 years and 70.3% at 7 years) were also similar to those of the RL graft group (88.6, 88.6, 88.6 and 88.6, Fig. 1b). Patients demonstrating scores beyond the Milan criteria tend to show worse outcomes with LDLT in comparison to DDLT [14], thus, the survival of patients classified beyond the Milan criteria in the current series were also compared based on the graft type. The 1-, 3-, and 5-year overall survival rates of the patients beyond the Milan criteria of the LL graft group ($n = 39$) were 81.7, 70.1 and 65.7%, respectively, which were not significantly different in comparison to those of the patients beyond the Milan criteria in the RL graft group ($n = 17$, 94.1, 73.9 and 73.9%, Fig. 2a). The recurrence-free survival rates of the patients beyond the Milan criteria in the LL graft group (78.7% at 1 year, 65.7% at 3 years and 61.0% at 5 years) were similar to those of the patients beyond the Milan criteria in the RL graft group (74.0, 74.0 and 74.0%, Fig. 2b).

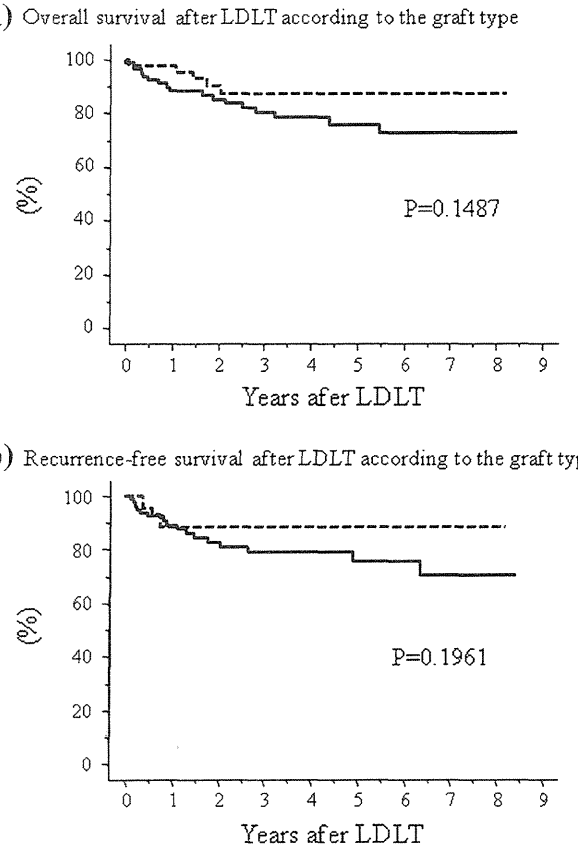

Fig. 1 The overall (**a**) or recurrence-free (**b**) survival after LDLT for 82 patients with LL grafts (*continuous line*) and 46 patients with RL grafts (*dotted line*)

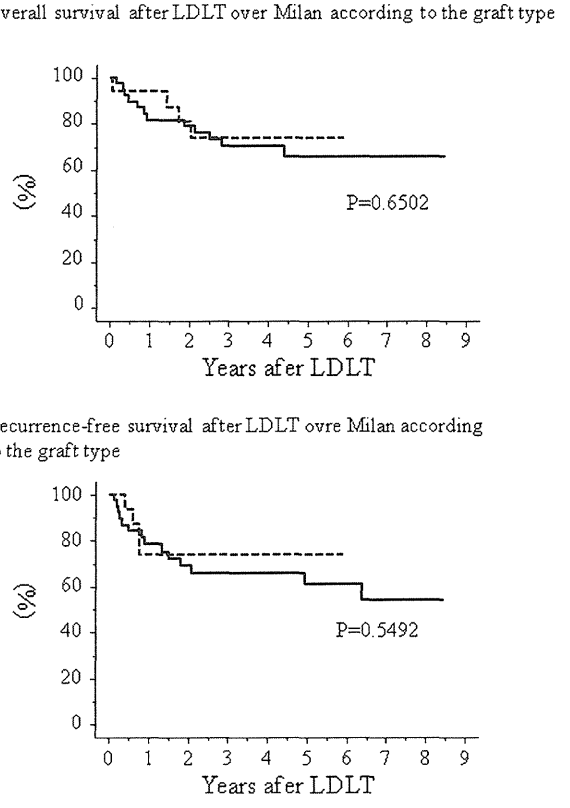

Fig. 2 The overall (**a**) or recurrence-free (**b**) survival after LDLT for 39 patients who were classified beyond the Milan criteria treated with LL grafts (*continuous line*) and 17 patients beyond the Milan criteria treated with RL grafts (*dotted line*)

Donor characteristics according to the graft type

The clinical parameters of the donors were compared between the two groups according to the graft type (Table 2). Males were predominant in the LL group. No difference was found in the duration of the operation and intraoperative blood loss between the groups. The RV ratio of the RL graft group (45.2 ± 6.3%) was significantly lower than that of the LL graft group (64.4 ± 6.2%, < 0.0001). The mean peak postoperative total bilirubin levels and duration of hospital stay after surgery of the LL grafting donors were significantly decreased as compared to those of the RL graft donors ($p < 0.01$). The rate of complications over Clavien's IIIa after the LL graft procurement was 6.2%, which was lower than that in the RL graft group (15.6%).

Table 2 The donor characteristics according to the graft type

Factors	RL graft ($n = 46$)	LL graft ($n = 82$)	p value
Gender (% male)	52.2	79.3	0.0014
Age (years)[a]	36.0 ± 11.0	32.4 ± 8.7	0.0448
Length of operation (min)[a]	445 ± 62	440 ± 73	0.7353
Intraoperative blood loss (ml)[a]	356 ± 305	370 ± 242	0.7807
RV ratio (%)[a]	45.2 ± 6.3	64.4 ± 6.2	<0.0001
Peak ALT (IU/l)[a]	679 ± 351	558 ± 246	0.0247
Peak TB (mg/dl)[a]	3.1 ± 1.6	2.3 ± 1.3	0.0015
Hospital stay (days)[a]	16.7 ± 9.3	11.1 ± 3.5	<0.0001
All complications	13 (28.3)	23 (28.0)	0.9796
Complications over Clavien's II	7 (15.6)	5 (6.2)	0.0856

ALT alanine aminotransferase, *LL* left lobe, *RL* right lobe, *RV* remnant liver volume, *TB* total bilirubin

[a] Mean ± standard deviation

Discussion

The factors involved in liver regeneration may stimulate the growth of occult tumors, thus leading to questions regarding the implications of the type of graft on the disease process and outcome. Donor selection criteria have been established based on the GV and the RV of the donor calculated using three-dimensional-CT, in which an LL graft is considered to be the first choice to ensure donor safety. However, the long-term outcome of the HCC

patients treated with LL grafts has not been elucidated. Thus, the aim of this study was to compare the long-term outcomes between the recipients of LL and RL grafts. Our results showed that the overall survival and recurrence-free survival rates of the LL graft group were similar to those of the RL graft group, although the graft volume of the LL graft group was significantly lower than that of the RL graft group. Furthermore, the overall survival and recurrence-free survival rates after LDLT of the patients beyond the Milan criteria were comparable between the two groups.

It has been unclear whether the rapid liver regeneration after LT can affect the recurrence of HCC. Interestingly, Shi et al. [15] reported experimental data about hepatectomy performed in rats with concomitant implantation of hepatoma cells in the remnant liver. The tumor volume and number increased significantly with the size of the partial hepatectomy, and the largest resections were also associated with increased hepatoma cell infiltration in the lungs. These findings suggest that the liver regeneration after partial hepatectomy may facilitate growth and malignant transformation of microscopic HCC. On the other hand, Hwang et al. [16] showed clinical data about the influence of the graft-recipient weight ratio (GRWR) to assess the risk of HCC recurrence during liver regeneration. The authors divided 181 LT recipients with HCC into four groups according to their GRWR: low GRWR (<0.8), mid GRWR (0.8–1.0), high GRWR (>1.0), and whole liver graft group (>1.5), and found no significant differences in the overall patient survival and recurrence-free survival among these four groups. Therefore, the question of whether liver regeneration influences HCC recurrence remains controversial.

There have been several reports comparing LDLT versus DDLT for HCC [14, 17, 18]. For example, Bhangui et al. [14] performed a comparative intention-to-treat analysis of the recurrence rates and survival outcomes after LDLT and DDLT in HCC patients. The authors reported that the recurrence rates in the two groups were similar (12.9 and 12.7%), and that there was a trend toward a longer time to recurrence after LDLT (38 ± 27 vs. 16 ± 13 months). Furthermore, the overall survival in the two groups was comparable on an intention-to-treat basis. In addition, the outcomes of the 312 HCC patients who underwent LT at 4 Korean institutions were evaluated [17]. A comparison of HCC recurrence curves did not reveal any statistically significant difference between LDLT and DDLT. The current study revealed that the overall survival and recurrence-free survival rates of the LL graft group were similar to those of the RL graft group. There were differences of about 10% in the GV/SLV and about 130 g for the graft volume between the LL and RL grafts, thus resulting in significant differences in the liver regeneration ratio after LDLT. Nonetheless, the type of graft did not affect the long-term outcome after LDLT for the HCC patients in our study. These findings might suggest that rapid liver regeneration does not affect the HCC recurrence after LT.

There have been at least 19 donor deaths associated with LDLT donation [19]. Extensive donor evaluation, detailed preoperative planning, and meticulous surgical technique are essential to minimize donor complications and to avoid donor death. LL grafting, which provides only 30–50% of the required liver volume, has been thought to be inadequate to sustain the metabolic demands of adult recipients. Furthermore, an at least 40–45% graft volume is usually required in the presence of severe portal hypertension. Subsequently, LDLT using RL grafts has gained widespread acceptance. However, the feasibility of LDLT using LL grafts between adults to ensure the safety of the donor has been demonstrated [11]. The current study showed that LL graft procurement was less invasive as compared to RL graft procurement, thus resulting in a lower rate of complications for the donors. LL grafts should therefore be considered more favorably when selecting donors in LDLT for HCC, since the long-term outcomes in the HCC patients with LL grafts were similar to those with RL grafts.

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Conflict of interest None of the authors has any conflict of interest.

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Acoustic radiation force impulse imaging predicts postoperative ascites resulting from curative hepatic resection for hepatocellular carcinoma

Noboru Harada, MD, PhD, Ken Shirabe, MD, PhD, Hideki Ijichi, MD, PhD, Rumi Matono, MD, Hideaki Uchiyama, MD, PhD, Tomoharu Yoshizumi, MD, PhD, Akinobu Taketomi, MD, PhD, Yuji Soejima, MD, PhD, *and* **Yoshihiko Maehara, MD, PhD,** *Fukuoka, Japan*

Background. *Measurement of liver stiffness using Virtual Touch Tissue Quantification (VTTQ) based on acoustic radiation force impulse imaging reflects the degree of hepatic fibrosis and reserve. This prospective study investigated how well the VTTQ value predicts the development of postoperative complications before curative hepatic resection for hepatocellular carcinoma (HCC).*
Methods. *The study enrolled 50 consecutive patients between February 2009 and October 2010 whose preoperative VTTQ values were determined before they underwent curative hepatic resection for HCC. We assessed the relationship between postoperative complications and VTTQ values.*
Results. *The study included 41 (82%) patients with chronic hepatitis and 9 (18%) with nonviral cirrhosis. The mean VTTQ value was 1.60 (m/sec), which correlated with the fibrosis stage (*P = *.0058). The VTTQ value was the only variable correlated with postoperative ascites that did not respond to pharmacologic treatment and required invasive management. Univariate and subsequent multivariate analyses revealed that the preoperative VTTQ value was the only independent risk factor for predicting the development of postoperative ascites (cutoff, 1.68 cm/sec;* P = *.007; odds ratio, 76.481). The area under the receiver operating characteristic curve for the diagnosis of postoperative ascites using VTTQ values was 0.90, whereas those using the aspartate transaminase-to-platelet ratio index and indocyanine green retention rate at 15 minutes values were 0.68 and 0.55, respectively.*
Conclusion. *These data suggest that the VTTQ value is a reliable surrogate marker for predicting postoperative ascites before curative hepatic resection for HCC. (Surgery 2012;151:837-43.)*

From the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

IMPROVEMENTS IN PERIOPERATIVE INTENSIVE CARE AND REFINEMENTS IN OPERATIVE TECHNIQUES have decreases the rates of death and complications following hepatic resection.[1-4] Nevertheless, because many patients still develop liver cirrhosis or other chronic liver disease, complications such as postoperative ascites may follow hepatic resection surgery. Despite evaluating preoperative hepatic function by Child-Pugh grading and imaging, postoperative ascites can complicate markedly liver failure in patients with cirrhotic and compromised liver function. Once postoperative ascites develops, the prognosis worsens, and patients become susceptible to complications such as bacterial peritonitis, hepatic hydrothorax, hyponatremia, and hepatorenal syndrome, which can lead to liver failure.[5] Postoperative ascites is believed to be among the most common manifestations of portal hypertension in patients with cirrhosis.[5] An increased resistance to portal flow at the sinusoidal level leads to the development of sinusoidal portal hypertension and the backward transmission of this increased pressure into splanchnic capillaries. As a result, the excess fluid preferentially localizes in the peritoneal cavity as ascites.[5]

Moreover, liver stiffness commonly results from hepatic fibrosis and portal hypertension.[6] Therefore, we reasoned that it was important to investigate preoperative liver stiffness to predict postoperative complications such as ascites before hepatic resection. Such careful preoperative

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Reprint requests: Ken Shirabe, MD, PhD, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: kshirabe@surg2.med.kyushu-u.ac.

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evaluation of liver stiffness combined with liver function tests and refined operative techniques have decreased the incidence of postoperative complications such as ascites.[1-4]

Acoustic radiation force impulse (ARFI) elastography was reported recently to show very good accuracy for the assessment of liver fibrosis and has been considered superior to other noninvasive methods such as transient elastography and liver biopsy.[7,8] ARFI-based Virtual Touch Tissue Quantification (VTTQ) measurement exploits the phenomena whereby lesser displacement magnitudes are present in cirrhotic liver tissue compared with those in noncirrhotic liver tissue, whereas the elastic shear waves of transient elastography are emitted from the vibrator attached to the ultrasound transducer probe, and the velocity of such waves through the liver can be determined as liver stiffness.[9]

The aim of this study was to investigate if liver stiffness measurement by ARFI can predict postoperative complications, especially postoperative ascites that does not respond to pharmacologic treatment and requires invasive management.

PATIENTS AND METHODS

Patients. In this pilot study, 50 consecutive patients who were eligible for curative hepatic resection for hepatocellular carcinoma (HCC) were enrolled prospectively between February 2009 and October 2010 at Kyushu University Hospital, Japan. We excluded patients who underwent operation because of other conditions or were scored as Child-Pugh class C. Thirty-four patients expressed the hepatitis C virus antibody (HCVAb), 5 were positive for hepatitis B virus surface antigen (HBsAg), 2 were positive for both HCVAb and HBsAg, and 9 were negative for both HCVAb and HBsAg. The Model for End-Stage Liver Disease (MELD) score was calculated using the following formula[10]: MELD = $9.57 \times \log_e$ (creatinine mg/dL) + $3.78 \times \log_e$ (bilirubin mg/dL) + $11.20 \times \log_e$ (International Normalized Ratio) + 6.43. Postoperative complications were defined using the Clavien classification.[11] Postoperative ascites was defined as diuretic-resistant ascites classified as Clavien grade IIIA (requiring invasive management with local anesthesia) or greater.[12] This classification selection included ascites requiring paracentesis for a tense abdomen or spontaneous bacterial peritonitis, or requiring the closure of operative wounds and drainage sites owing to leakage of ascites after removal of the abdominal drains. Our postoperative ascites management includes diuretic agents such as furosemide given if water or sodium restriction or potassium canrenoate alone were ineffective in controlling ascites. The dosage of furosemide was started at a ratio of 20 mg of furosemide per 100 mg of potassium canrenoate. The abdominal drains were left in place for ≥3 days and then removed. The thoracic tube was removed when the amount of discharge decreased to <200 mL/d. Any symptomatic fluid collection in the chest or abdominal cavity was drained percutaneously under ultrasonographic guidance. Posthepatectomy liver failure was defined as a postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased International Normalized Ratio and concomitant hyperbilirubinemia on or after postoperative day 5 according to the definition of the International Study Group of Liver Suergery.[13] We obtained written informed consent from all patients. Our Institutional Review Board approved the study protocol, which conformed to the 1975 Helsinki Declaration.

Liver stiffness. Liver stiffness was measured by the VTTQ system within 1 week before operation. The VTTQ system was installed on an ACUSON model S2000 ultrasound system (Siemens Medical Solutions, Inc., Ultrasound Division, Issaquah, WA). Surgeons trained by Siemens Medical Solutions, Inc., operated the instrument. The VTTQ system utilizes an acoustic push pulse to generate shear waves that pass through the liver parenchyma orthogonal to the acoustic push pulse, through a user-placed region of interest. When detection pulses interact with a passing shear wave, they reveal the location of the wave at a specific time, allowing calculation of the shear wave speed. This absolute numeric value relates to the stiffness of the tissue within the region of interest.[9,14,15] Results are expressed in meters per second. We performed 7 successive measurements on each patient several days before operation and acquired histologic specimens during operations. We performed 350 measurements on right lobe, except for the tumor and vessels, in 50 patients. The VTTQ measurements of the right liver lobe were performed by placing the ultrasonic probe on the right intercostal space. We calculated the median value of all measurements and the standard deviation (SD) of the VTTQ measurements for each patient.

Surrogate serum markers. Blood samples obtained from all the patients during the VTTQ measurements were examined in the same laboratory. The following clinical parameters were determined: Platelet count, serum aspartate aminotransferase