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ERRATUM

Anonymity and Live-Donor Transplantation: An ELPAT View: Erratum

In the February 27, 2013 issue of *Transplantation* in the article by Mamode et al, "Anonymity and Live-Donor Transplantation: An ELPAT View" the author Frank Dor should have been listed as Frank J.M.F. Dor.

REFERENCE

Mamode N, Lennerling A, Citterio F, et al. Anonymity and live-donor transplantation: an ELPAT view. *Transplantation.* 2013; 95: 536.

Rendezvous Ductoplasty for Biliary Anastomotic Stricture After Living-Donor Liver Transplantation

Shohei Yoshiya, Ken Shirabe, Yoshihiro Matsumoto, Tetsuo Ikeda, Yuji Soejima, Tomoharu Yoshizumi Hideaki Uchiyama, Toru Ikegami, Norifumi Harimoto, and Yoshihiko Maehara

Background. Biliary anastomotic stricture (BAS) after living-donor liver transplantation (LDLT) is difficult to manage. We used rendezvous ductoplasty (RD) to treat BAS after LDLT.

Methods. We retrospectively analyzed 53 patients with BAS after adult-to-adult LDLT with duct-to-duct biliary reconstruction.

Results. BAS was classified according to endoscopic retrograde cholangiography findings after normal-pressure contrast injection: type I (n=32) in which the stricture was visualized; type II (n=13) in which the common hepatic duct and graft intrahepatic ducts were visualized, but the stricture was not visualized; or type III (n=8) in which the stricture and graft intrahepatic ducts were not visualized. In right lobe grafts, types II and III occurred more frequently than type I (P=0.0023). Type I had significantly shorter cold ischemic time (76±11 vs. 118±12 min; P=0.0155) and warm ischemic time (38±2 vs. 49±3 min; P=0.0069) than types II and III. The number of attempts to pass the guidewire through the stricture was significantly lower in type I (1.2±0.2 attempts) than type II (2.2±0.2 attempts; P=0.0018) or type III (2.8±0.3 attempts; P<0.0001). The treatment success rate was 78.1% for type I, 38.5% for type II, and 50.0% for type III (P=0.0282). RD was the first successful treatment in a higher proportion of types II and III patients than type I patients (66.7% vs. 6.3%; P<0.0001). Cumulative treatment success rates were not significantly different between the RD and the non-RD groups (P=0.0920).

Conclusions. RD was a useful treatment for difficult cases of BAS after LDLT and achieved successful outcomes.

Keywords: Living-donor liver transplantation, Biliary anastomotic stricture, ERC, PTC.

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Living-donor liver transplantation (LDLT) is one of the treatment options for end-stage liver disease, especially in countries with a shortage of deceased donors. Duct-to-duct biliary reconstruction, which preserves biliary function, is now preferred over hepaticojejunostomy (*1–4*). Biliary complications, including biliary anastomotic stricture (BAS), are the most common complications after LDLT and have been reported to occur in 19% of LDLT patients (*5, 6*). BAS treatment is difficult and requires frequent and prolonged hospitalizations, resulting in loss of quality of life (*2*).

Currently, many institutes manage BAS via the endoscopic transpapillary approach, but this approach has a failure rate of more than 40% (*7*). The percutaneous transhepatic approach may be used as second-line treatment (*4, 8, 9*). Surgery may be considered when other modalities have failed and may include conversion from duct-to-duct anastomosis to hepaticojejunostomy. However, surgical treatment carries a risk of related complications (*10*), and a nonsurgical approach is therefore preferable when reasonable results can be expected.

We performed rendezvous ductoplasty (RD; Fig. 1) in patients with BAS who were difficult to manage. The aims of this study were to classify BAS, to evaluate the difficulty of treatment according to BAS type, and to evaluate the usefulness of RD for treating BAS.

RESULTS

BAS Classification

To evaluate the difficulty of passing a guidewire through the stricture, we classified BAS into three types according to cholangiography findings after normal-pressure contrast injection. In type I, the common hepatic duct, stricture, and graft intrahepatic ducts were visualized (Fig. 2A). In type II, the common hepatic duct and graft intrahepatic ducts were visualized, but the area of the stricture was not visualized (Fig. 2B). In type III, the common hepatic duct was visualized,

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S.Y. participated in the research design, data analysis, and writing of the paper. K.S., T. Ikeda, and Y. Maehara contributed to the discussion and reviewed the article. T.Y., T. Ikegami, H.U., and Y.S. participated in the research design. N.H. and Y. Matsumoto participated in the data collection.

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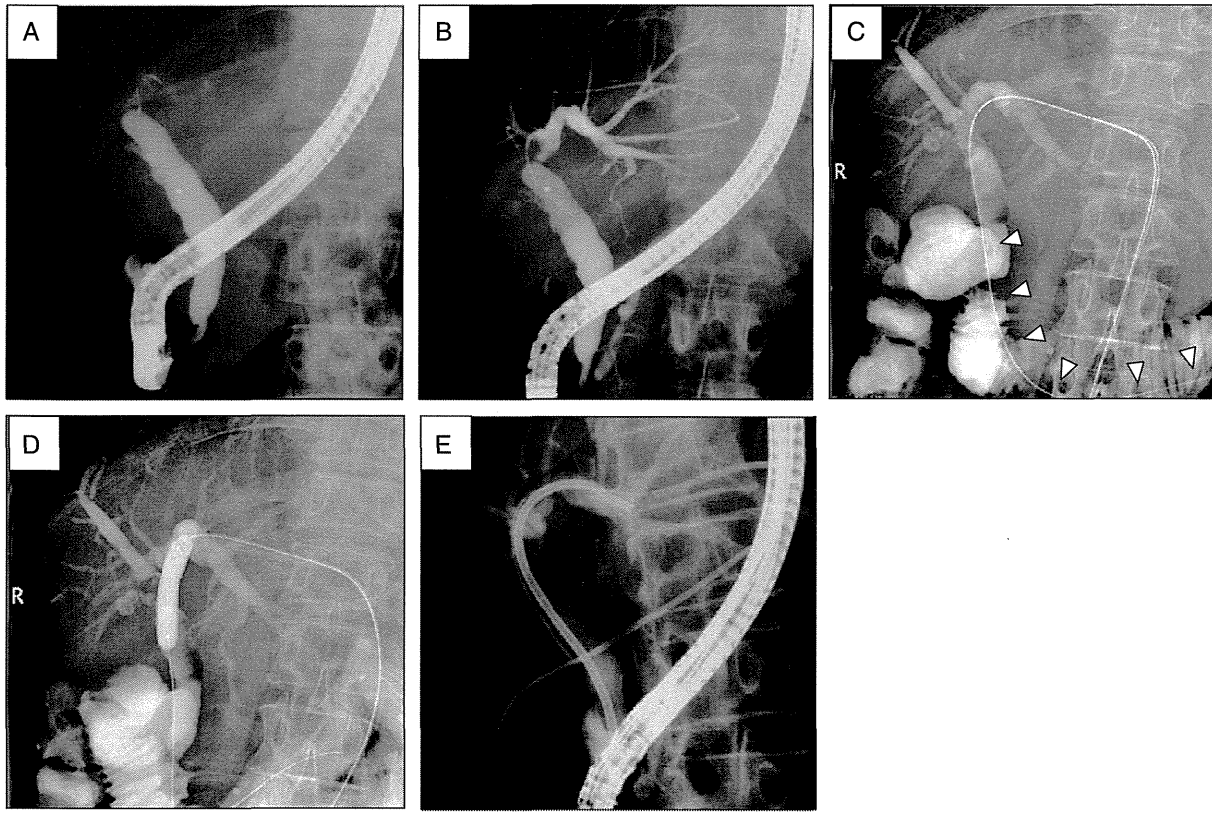

FIGURE 1. RD procedure. A, endoscopic access in the prone position. B, percutaneous transhepatic access under fluoroscopic guidance with endoscopic contrast agent injection. C, guidewire is passed from the percutaneous transhepatic side through the stricture and the ampulla of Vater. D, E, balloon dilatation followed by stent placement using the endoscope. RD, rendezvous ductoplasty.

but the area of the stricture and the graft intrahepatic ducts were not visualized (Fig. 2C).

Clinical Characteristics in the Three Types of BAS

Analysis of variance showed a significant association between graft type and BAS type. Among patients with type I BAS, 24 had left lobe (LL) grafts, 8 had right lobe (RL) grafts, and none had posterior segment (PS) grafts; among patients with type II BAS, 4 had LL grafts, 8 had RL grafts, and 1 had a PS graft; and among patients with type III BAS, 3 had LL grafts, 3 had RL grafts, and 2 had PS grafts (P=0.0079). There were significant differences among types I to III in cold ischemic time (76±11 vs. 131±16 vs. 98±20 min; P=0.0240) and warm ischemic time (38±2 vs. 54±3 vs. 40±4 min; P=0.0015). In addition, Tukey–Kramer's tests revealed significant differences between types I and II in cold ischemic time (P=0.0011) and warm ischemic time (P=0.0431). Multivariate analyses comparing types I and II showed that warm ischemic time was an independent risk factor for type II (odds ratio, 1.17; 95% confidence interval, 0.70–0.96; P=0.0030). Multivariate analyses comparing types I and III showed that an RL graft was an independent risk factor for type III compared with an LL graft (odds ratio, 5.00; 95% confidence interval, 1.01–29.24; P=0.0491). There were no significant differences among BAS types in the rates of hepatitis C virus infection (P=0.5933) or other recipient factors, donor factors, operative factors, or postoperative factors (Table 1).

Evaluation of Difficulty of Treatment in the Three Types of BAS

We evaluated the difficulty of treatment in the three types of BAS using two factors: the number of attempts to pass the guidewire through the stricture and the rate of successful completion of treatment. The number of attempts to pass the guidewire was significantly lower in type I than type II (1.2±0.2 vs. 2.2±0.2 attempts; P=0.0018) or type III (1.2±0.2 vs. 2.8±0.3 attempts; P<0.0001), but there was no significant difference in the number of attempts between types II and III (Table 1). The rate of successful treatment was 78.1% in type I, 38.5% in type II, and 50.0% in type III (P=0.0282).

First Successful Treatment Modality in Each Type of BAS

We analyzed the first successful treatment modality in each type of BAS. Overall, we performed endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), and RD in 66.0% (n=35), 3.8% (n=2), and 30.2% (n=16) of cases, respectively (Fig. 3A). In type I, we performed ERC, PTC, and RD in 87.4% (n=28), 6.3% (n=2), and 6.3% (n=2) of cases, respectively (Fig. 3B). In type II, we

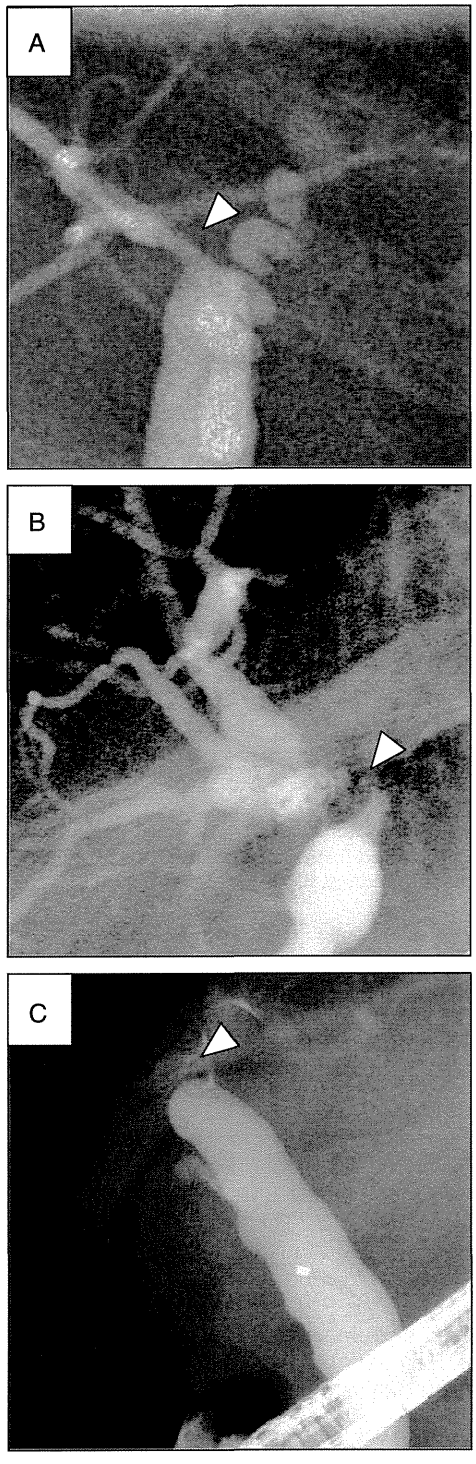

FIGURE 2. Three types of BAS according to cholangiography findings. A, type I, with the narrow stricture visualized. B, type II, with the common hepatic duct and graft intrahepatic ducts visualized, but the stricture not visualized. C, type III, with the stricture and the donor intrahepatic ducts not visualized. Arrowheads indicate the stricture site. BAS, biliary anastomotic stricture.

performed ERC, PTC, and RD in 46.2% (n=6), 0% (n=0), and 53.8% (n=7) of cases, respectively (Fig. 3C). In type III, we performed ERC, PTC, and RD in 12.5% (n=1), 0% (n=0), and 87.5% (n=7) of cases, respectively (Fig. 3D). The rate of RD was significantly higher in types II and III than type I (66.7% vs. 6.3%; $P<0.0001$).

Comparison of Cumulative Treatment Success Rates between the RD and the Non-RD Groups

To evaluate the usefulness of RD, we divided patients into two groups: an RD group (n=16) and a non-RD group (n=37). The 1- and 4-year cumulative treatment success rates were 26.7% and 87.6%, respectively, in the RD group and 51.3% and 89.0%, respectively, in the non-RD group (Fig. 4). The cumulative success rates were not significantly different between the two groups ($P=0.0920$). None of the 53 patients with BAS underwent surgical treatment.

DISCUSSION

Although efforts to prevent BAS have decreased the frequency of this complication, from 14.5% to 32.5% of patients who receive LDLT still develop BAS (*1, 3, 11–13*). Development of BAS is related to various factors, such as the fragile vascular networks in the biliary tree, ischemia-reperfusion injury, age-related changes, fibrous scar formation as part of the normal healing process, tiny or multiple bile duct orifices, and immunologic reactions (*1, 12, 14, 15*). We focused on careful dissection of the peribiliary tissues to preserve maximal vascular integrity of the recipient's bile duct and achieved a BAS rate of 14.5%, which is lower than the rate of 32.5% reported in the literature (*1, 16*). However, other factors causing BAS have not been overcome, and BAS is still thought to be an inevitable complication after LDLT.

In this study, BAS was classified into three types according to cholangiography findings, and the difficulty of treating each type was evaluated. Lee et al. (*13*) reported that stricture morphology was a significant factor ($P<0.0001$) in the success rate of primary endoscopic management. Kato et al. (*2*) reported that cholangiography findings were related to the risk of failure of stent deployment. However, no studies have reported on the difficulty of treatment according to BAS type.

The current study found that graft type, cold ischemic time, and warm ischemic time were associated with BAS type after LDLT. Previous studies reported that the incidence of BAS was higher in RL grafts than LL grafts because of the anatomy of the right bile duct (*3, 15, 17–19*). Graft stumps tend to be more horizontal in PS grafts than RL grafts. Interestingly, there were no cases of type I BAS in patients with PS grafts in this study, which suggests that both bile duct size and the biliary anastomotic angle have an effect on BAS type. Although cold ischemic time was not significantly associated with BAS in our series, it is thought to induce postreperfusion endothelial damage, resulting in impaired perfusion (*1*). Warm ischemic time has also been reported to be a risk factor for BAS after LDLT because of its impact on graft microcirculation (*12, 20*). We therefore assumed an association between the microcirculation around the biliary tree and BAS type. Other reported risk factors for BAS, such as hepatic artery flow (*21*) and biliary leakage (*1, 15, 22*), were not significantly associated with BAS type in this series.

TABLE 1. Patient characteristics by type of BAS after LDLT

	Type I (n=32)	Type II (n=13)	Type III (n=8)	*P*
Recipient factors				
Age, yr	57.1 ± 1.5	56.3 ± 2.3	57.9 ± 2.9	0.9109
Gender, male (%)	19 (59.4)	9 (69.2)	3 (37.5)	0.3544
MELD score, points	14.9 ± 0.0	18.2 ± 1.4	16.3 ± 1.8	0.1409
Hepatitis C virus infection (%)	21 (65.6)	7 (53.9)	6 (75.0)	0.5933
Donor factors				
ABO-incompatible graft (%)	1 (3.1)	1 (7.7)	1 (12.5)	0.5477
Graft type (LL/RL/PS)	24/8/0	4/8/1	3/3/2	0.0079[a]
GV/SLV (%)	40.1 ± 1.2	45.5 ± 1.9	39.7 ± 2.4	0.0740
Operative factors				
Operation time, min	750 ± 31	848 ± 49	785 ± 62	0.2458
Cold ischemic time, min	76 ± 11	131 ± 16	98 ± 20	0.0240[a]
Warm ischemic time, min	38 ± 2	54 ± 3	40 ± 4	0.0015[a]
Operative blood loss, L	6.12 ± 1.21	5.76 ± 1.89	4.19 ± 2.41	0.7680
HAF at closure, mL/min	90 ± 9	91 ± 15	96 ± 19	0.9586
No. donor bile ducts (1/2/3)	25/6/1	11/2/0	7/1/0	0.8640
Bile ductoplasty (%)	9 (28.1)	4 (30.8)	2 (25.0)	0.9594
Postoperative factors				
Bile leakage (%)	4 (12.5)	3 (23.1)	2 (25.0)	0.5666
Time to biliary stricture, yr	0.95 ± 0.16	0.68 ± 0.26	0.87 ± 0.33	0.6700
Difficulty of treatment				
No. attempts	1.2 ± 0.2	2.2 ± 0.2	2.8 ± 0.3	<0.0001[a]
Treatment success rate (%)	25 (78.1)	5 (38.5)	4 (50.0)	0.0282[a]

[a] $P<0.05$.

BAS, biliary anastomotic stricture; GV, graft volume; HAF, hepatic artery flow; LDLT, living-donor liver transplantation; LL, left lobe graft; MELD, model for end-stage liver disease; PS, posterior segment; RL, right lobe; SLV, standard liver volume.

Because the current first-line therapy for BAS is endoscopic balloon dilatation and stent placement, passage of a guidewire through the stricture is critical (*2, 8, 13*). The success rate of primary endoscopic treatment is 40% to 90% (*6*), and percutaneous treatment may be performed as second-line therapy if endoscopic treatment has failed (*4, 8, 9*). However, it is difficult to access the intrahepatic duct using ultrasonography if it is not dilated. Giampalma et al. (*23*) reported a percutaneous treatment failure rate of 10% (5 of 48). When both endoscopic and percutaneous treatments have failed, surgical therapy is usually unavoidable (*10*).

When performing RD, we were easily able to access nondilated intrahepatic ducts after visualizing them with endoscopic contrast agent injection. We therefore assume that it is easier to treat BAS using RD than PTC. We were able to apply sufficient force to both ends of guidewire, via the patient's mouth and the transhepatic route, to enable us to align the stricture and place stents. Use of RD therefore avoided the need for external stents, which would have reduced quality of life. The duration of treatment tended to be shorter in the non-RD group than the RD group, but cumulative treatment success rates were not significantly different between the RD and the non-RD groups (P=0.0920). None of our patients required hepaticojejunostomy or repeat transplantation. These results indicate the importance of successful initial treatment of BAS after LDLT.

The main limitations of this study are its retrospective nature, possible biases due to the learning curves for surgical techniques, and possible biases in patient selection for RD. However, the indications for LDLT and our graft selection criteria were consistent. Another limitation is the relatively small number of cases. Although our findings support the use of RD for BAS after LDLT with duct-to-duct biliary reconstruction, they do not provide definitive evidence of the usefulness of BAS, because it was not possible to make direct comparisons between RD and control treatments. Further analysis of a larger number of patients in a multicenter study, such as a randomized controlled trial, is necessary to confirm our findings.

In conclusion, ERC findings predicted the difficulty of treatment of BAS after LDLT with duct-to-duct reconstruction. Most cases of BAS were successfully treated with endoscopic therapy, and RD was a useful treatment modality for more difficult cases. We therefore advocate using RD as second-line therapy instead of percutaneous transhepatic approach.

MATERIALS AND METHODS

Patients

Between June 2001 and July 2012, 289 LDLTs with duct-to-duct biliary reconstruction were performed at Kyushu University Hospital (Fukuoka, Japan). Fifty-three (18.3%) of these patients developed BAS and were included in this study.

Donor Surgery

The surgical techniques for graft harvesting have previously been described (*24*). From 2005, we performed minimal dissection around the bile duct to preserve the blood supply. Before 2005, we performed more extensive

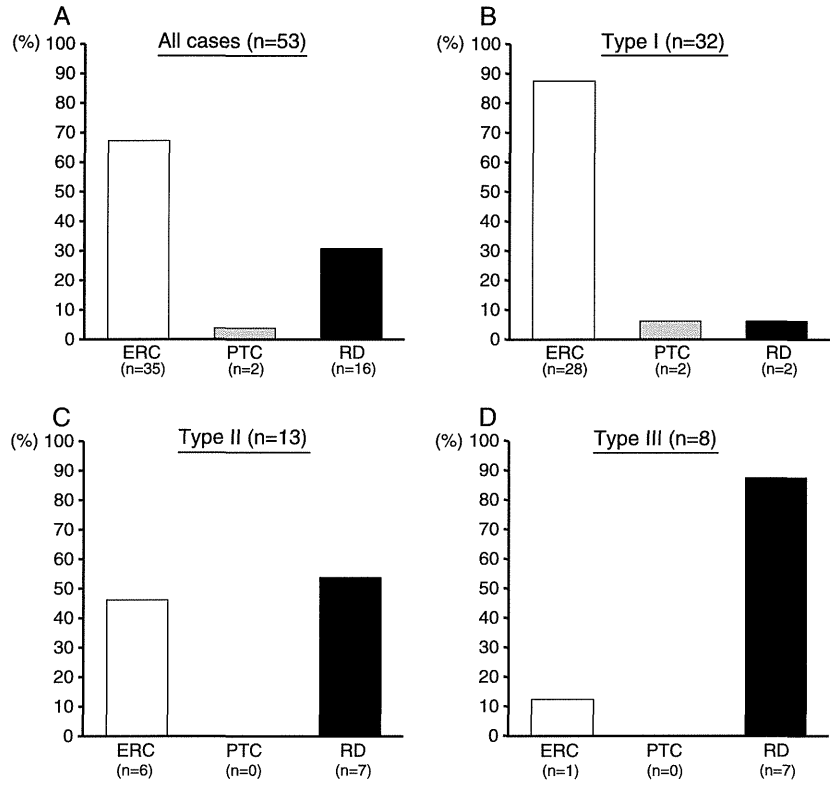

FIGURE 3. First successful treatment modalities in each type of BAS: (A) all cases, (B) type I cases, (C) type II cases, and (D) type III cases. BAS, biliary anastomotic stricture; ERC, endoscopic retrograde cholangiography; PTC, percutaneous transhepatic cholangiography; RD, rendezvous ductoplasty.

dissection of the tissues surrounding the bile duct. After complete parenchymal transection, we performed intraoperative fluorocholangiography to examine the anatomical details of the biliary ducts and determine the location and angle for hepatic duct transection. Intraoperative fluorocholangiography was performed with a portable C-arm unit (Arcadis Avantic; Siemens, Berlin, Germany) from 2005 and with a static X-ray film unit before 2005. Ductoplasty was sometimes performed during the cold phase if multiple bile ducts were located close together in the graft.

Recipient Surgery

We introduced duct-to-duct biliary reconstruction in 2001 (*25*). From April 2006, we used the minimal hilar dissection technique (*1, 16*) to preserve maximal vascular integrity of the recipient biliary tree. Before April 2005, we dissected the peribiliary connective tissues to isolate the common bile duct. After portal and arterial reconstruction, biliary reconstruction was performed as follows. Interrupted 6-0 absorbable monofilament sutures were placed over a straight silicone external stent tube (2.0–3.0 mm retrograde transhepatic biliary drainage tube; Sumitomo Bakelite, Tokyo, Japan) with the knots outside the lumen. The silicone stent tube was anchored at the biliary anastomosis and passed through the anterior wall of the recipient's common bile duct. Intraoperative fluorocholangiography was performed to confirm that there were no biliary strictures or leakages. The stent tube was removed in a two-step process under fluoroscopic guidance at least 3 months after surgery, as previously described (*26*). We have not changed our procedure since 2006.

Diagnosis and Treatment of BAS

Biliary stricture was suspected when a patient developed elevated liver enzyme levels or symptoms such as jaundice, itching, or fever. BAS was confirmed by direct imaging techniques such as ERC. The time of onset of BAS was defined as the day of diagnosis on imaging findings, and the completion of treatment was defined as the day a stent-free state was achieved (free passage of injected contrast agent and good drainage from the intrahepatic duct on cholangiography). When BAS was diagnosed, endoscopic treatment was attempted first. If several attempts to pass the guidewire through the stricture failed, RD was performed. Biliary stents were changed endoscopically every

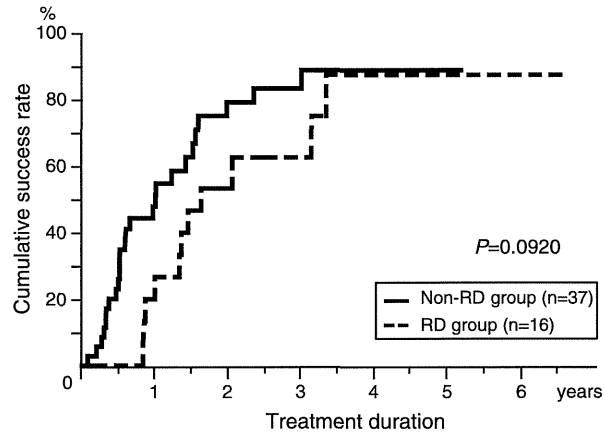

FIGURE 4. Cumulative 1- and 4-year treatment success rates were 26.7% and 87.6%, respectively, in the RD group (n=16) and 51.3% and 89.0%, respectively, in the non-RD group (n=37; *P*=0.0920). RD, rendezvous ductoplasty.

3 to 6 months, at which time the BAS was reevaluated. Stenting was continued until the stricture had resolved.

Endoscopic Transpapillary Approach Procedure

Our endoscopic transpapillary approach procedure was as follows. Under conscious sedation, the patient was placed prone and the ampulla of Vater was cannulated. Contrast agent was injected through the cannula to show the common hepatic duct and the graft intrahepatic ducts. If the graft intrahepatic ducts were not visible, we used balloon occlusion to increase the pressure of the contrast injection. We then tried to pass the guidewire through the stricture followed by balloon dilatation and stent placement.

RD Procedure

RD was performed as follows (Fig. 1). First, endoscopic access was obtained in the prone position. The patient was then placed supine, keeping the endoscope in position, and percutaneous transhepatic access was obtained under fluoroscopic guidance. If the intrahepatic ducts could not be visualized (type III), we used balloon occlusion to increase the pressure of the contrast agent injection. The guidewire from the percutaneous transhepatic side was passed through the stricture and through the ampulla of Vater. We then performed balloon dilatation before or after the guidewire was withdrawn through the mouth using the endoscope followed by stent placement as for the endoscopic transpapillary approach. If the guidewire could not be passed through the stricture during the RD procedure, we placed a temporary external drainage stent via the percutaneous transhepatic route to reduce duct edema. During subsequent RD sessions, we inserted the guidewire via the external drainage route and then attempted to pass it through the stricture. After RD, we usually removed the balloon via the percutaneous transhepatic route. We did not experience any cases of clinical bile leakage or biliary peritonitis.

Statistical Analysis

All statistical analyses were performed using SAS software (JMP 9.0.1; SAS Institute, Cary, NC). Multiple comparisons were performed using analysis of variance and Tukey–Kramer tests. Cumulative treatment success rates were analyzed using the Kaplan–Meier method and compared using the log-rank test. All variables are expressed as mean±standard deviation. $P<0.05$ was considered statistically significant.

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ORIGINAL ARTICLE

A high MELD score, combined with the presence of hepatitis C, is associated with a poor prognosis in living donor liver transplantation

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Abstract
Purpose The feasibility of performing living donor liver transplantation (LDLT) for patients with high end-stage liver disease (MELD) scores needs to be assessed.
Methods A total of 357 patients who underwent LDLT were included in this analysis.
Results Overall, 46 patients had high MELD scores ($\geq$25) and their graft survival was similar to that in patients with low MELD scores (<25; $n = 311$; $p = 0.395$). However, among patients with high MELD scores, a multivariate analysis showed that the presence of hepatitis C ($p = 0.013$) and LDLT in Era-I ($p = 0.036$) was significantly associated with a poorer prognosis. Among patients with hepatitis C ($n = 155$), the 5-year graft survival rate was significantly lower in patients with high MELD scores (33.7 %, $p < 0.001$) than in patients with low MELD scores. The 5-year graft survival rate was significantly lower in patients in Era-I ($n = 119$) compared with those in Era-II/III when stratified by low (73.0 vs. 82.5 %, $p = 0.040$) and high (55.0 vs. 86.1 %, $p = 0.023$) MELD scores. Among the patients with high MELD scores, those with hepatitis C and LDLT in Era-I had the worst 5-year graft survival rate (14.3, $p < 0.001$).
Conclusion The graft outcomes in patients with high MELD scores and the presence of hepatitis C were found to be particularly poor.

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Keywords Living donor liver transplantation · Hepatitis C · Model for end-stage liver disease · Learning curve

Abbreviations

GRWR	Graft recipient weight ratio
GV	Graft volume
GW	Graft weight
LDLT	Living donor liver transplantation
MELD	Model for end-stage liver disease
PVF	Portal venous flow
PVP	Portal venous pressure
SLV	Standard liver volume

Introduction

The model for end-stage liver disease (MELD) was originally developed as a scoring system to assess the severity of terminal liver diseases. Therefore, it is often used as part of the criteria for allocating deceased donor livers [1, 2]. Previous studies have shown that the MELD system might also predict graft outcomes after deceased donor liver transplantation (DDLT), although this possibility is still widely debated [3–5].

Partial grafts are always used in living donor liver transplantation (LDLT), but might be too small to fulfill the recipient's metabolic needs [6]. Therefore, the pre-transplant disease severity, as represented by a high MELD score, might be an important determinant of the graft outcome [7]. The technical advances in LDLT in the last decade have dramatically improved the overall graft outcomes after LDLT [8–10]. The Toronto group recently reported that LDLT could provide excellent graft outcomes, even in patients with high MELD scores [11].

However, the impact of high MELD scores on the outcome of LDLT has not been fully elucidated, and is hotly debated [7–11]. Moreover, there has so far been no subgroup analyses of patients with high MELD scores aimed at elucidating the factors associated with the graft outcomes after LDLT.

Therefore, the aims of this study were to evaluate the overall impact of the MELD score on the graft outcomes in LDLT, and to identify clinically relevant prognostic factors in patients with high MELD scores.

Materials and methods

Patients

We retrospectively analyzed our prospective database of all adult-to-adult LDLTs performed since May 1997 ($n = 357$). The recipients included 172 males (48.2 %), and the mean age of the recipients was 51.6 ± 11.6 years. Hepatitis C infection was present in 155 (43.4 %) patients, and hepatocellular carcinoma was present in 156 (43.8 %). The primary liver diseases included liver cirrhosis ($n = 216$; hepatitis C, $n = 153$; hepatitis B, $n = 40$), cholestatic liver diseases ($n = 78$), acute liver or graft failure ($n = 54$; including hepatitis B, $n = 17$; hepatitis C, $n = 2$; hepatic artery thrombosis, $n = 1$; graft congestion, $n = 1$; primary graft failure, $n = 1$) and others ($n = 8$). A major shunt vessel was defined as a portosystemic shunt with a caliber >10 mm.

The donors included 231 males (64.8 %), and the mean age of the donors was 35.9 ± 11.1 years. Seventeen (4.8 %) donors were blood-type incompatible donors. The graft types included left lobe ($n = 223$, 62.6 %), right lobe ($n = 128$, 35.8 %) and posterior segment ($n = 6$, 1.7 %) grafts. The mean graft volume (GV), graft volume/standard liver volume (GV/SLV) ratio and graft recipient weight ratio (GRWR) were 479 ± 106 g, 41.7 ± 8.5 % and 0.81 ± 0.19. All of the LDLTs were performed after obtaining full informed consents from all patients and approval from the Liver Transplantation Committee of Kyushu University. The mean follow-up time was 4.8 ± 3.2 years.

MELD score

The pretransplant total bilirubin levels, creatinine levels and prothrombin time international normalized ratio (PT-INR) were used to calculate the medical MELD score without the additional MELD points [1]. A high MELD score is not a contraindication for LDLT at our center.

Graft selection and surgical procedures

The grafts were selected as described previously [12]. Left lobe grafts were considered to be the primary graft type if the desired GV/SLV was >35 %. Right lobe grafts were considered if the simulated GV/SLV of the left lobe graft was <35 % and the donor's remnant liver volume was >35 %.

The surgical procedures used are described elsewhere [12]. Briefly, the procured graft was perfused ex situ using University of Wisconsin solution (Viaspan™, DuPont Inc., Wilmington, DE). Splenectomy was performed to control the portal venous pressure after reperfusion or to treat thrombocytopenia before introducing interferon treatment for recurrent hepatitis C, if indicated [13].

Immunosuppression and anti-viral treatment for hepatitis C

The immunosuppression protocol consisted of tacrolimus or cyclosporine with mycophenolate mofetil and steroids [12]. The antiviral treatment for hepatitis C consisted of pegylated interferon α2a or 2b plus ribavirin [14].

Assessment of outcomes after LDLT

The endpoint of this study was graft loss, including patient death or re-transplantation. Deaths caused by infection, cardiovascular diseases or recurrent hepatocellular carcinoma were included as graft loss. However, deaths caused by de novo malignancies or accidents were censored.

Transplant era

The total cohort of 357 patients was divided into three groups of equal numbers of consecutively treated patients, Era-I ($n = 119$) consisted of patients 1–119 who were treated between May 1997 and February 2004, Era-II ($n = 119$) consisted of patients 120–238 who were treated between March 2004 and January 2008 and Era-III ($n = 119$) consisted of patients 239–357 who were treated since February 2009.

Statistical analysis

The values are expressed as the mean ± standard deviation or as n (%). Variables were analyzed using the χ^2 tests for categorical variables and the Mann–Whitney U test for continuous variables. The univariate and multivariate survival analyses were performed using the Kaplan–Meier method with the log-rank test and Cox proportional hazards model, respectively. Values of $p < 0.05$ were considered to be statistically significant.

Results

Surgical and postoperative outcomes

The 1- and 5-year cumulative graft survival rates were 87.1 and 78.2 %, respectively. The recipient and donor graft variables, and post-transplant characteristics, are summarized in Table 1.

MELD score and graft survival

A number of patients with MELD scores of <5, 5–9, 10–14, 15–19, 20–24 and ≥25 were 0 (0.0 %), 41 (11.5 %), 108 (30.3 %), 94 (26.3 %), 68 (19.1 %) and 46 (12.8 %), respectively (Fig. 1a). The median and the mean MELD scores were 16 and 17.1 ± 6.9, respectively. The 5-year graft survival rates in the patients with MELD scores of <5 ($n = 148$), 5–25 ($n = 163$) and ≥25 ($n = 46$) were 79.9, 78.2 and 72.1 %, respectively ($p = 0.395$, Fig. 1b).

Characteristics of patients with high MELD scores

The patients were categorized into those with high (≥25, $n = 46$) or low (<25, $n = 311$) MELD scores. Patients with high MELD scores had significantly higher total bilirubin levels (20.8 ± 11.40 vs. 6.0 ± 7.0 mg/dl, $p < 0.001$), prolonged PT-INR (2.54 ± 1/17 vs. 1.48 ± 0.27, $p < 0.001$) and higher creatinine levels (0.8 ± 0.5 vs. 1.3 ± 1.4, $p < 0.001$). After LDLT, the incidence of cytomegalovirus infection (43.4 vs. 23.0 %, $p = 0.003$), bacterial sepsis (28.2 vs. 12.1 %, $p = 0.003$) and the peak total bilirubin levels

Table 1 Patient characteristics stratified by MELD score

Variables	MELD score		*p* value
	Low (<25, $n = 311$)	High (≥25, $n = 46$)	
MELD score	15.2 ± 4.6	30.1 ± 5.6	<0.001
Total bilirubin before LDLT	6.0 ± 7.0	20.8 ± 11.40	<0.001
PT-INR before LDLT	1.48 ± 0.27	2.54 ± 1.17	<0.001
Creatinine before LDLT (mg/dl)	0.8 ± 0.5	1.3 ± 1.4	<0.001
Donor age (years)	35.9 ± 11.4	35.6 ± 9.5	0.809
Donor gender, male	203 (65.5)	28 (60.9)	0.540
Incompatible blood type	17 (5.5)	0 (0.0)	0.104
Left lobe graft	198 (63.8)	25 (54.3)	0.795
GV (g)	478 ± 102	489 ± 127	0.481
GV/SLV ratio (%)	41.6 ± 8.4	42.3 ± 9.6	0.598
GRWR (%)	0.81 ± 0.19	0.83 ± 0.19	0.382
Recipient age (years)	52.2 ± 11.5	47.9 ± 12.2	0.230
Recipient gender, male	149 (48.1)	23 (50.0)	0.806
Hepatocellular carcinoma	153 (49.3)	3 (6.5)	<0.001
Hepatitis C	142 (45.5)	13 (28.3)	0.028
Cold ischemic time (min)	86.9 ± 54.9	95.2 ± 57.9	0.351
Warm ischemic time (min)	39.9 ± 11.9	39.0 ± 8.1	0.594
Hepatic arterial flow (ml/min)	106 ± 68	119 ± 56	0.231
Portal venous flow (l/min)	1.62 ± 0.65	1.54 ± 0.62	0.403
PVP at the closure (mmHg)	16.8 ± 4.4	17.2 ± 4.9	0.636
Major shunt vessels	62 (13.8)	6 (13.1)	0.266
Length of operation (min)	797 ± 174	796 ± 217	0.946
Intraoperative blood loss (l)	7.1 ± 15.4	7.2 ± 8.1	0.960
Acute cellular rejection	46 (14.9)	10 (21.7)	0.238
Hepatic artery thrombosis	6 (1.9)	1 (2.2)	0.918
Portal venous thrombosis	8 (2.6)	1 (2.2)	0.864
Cytomegalovirus infection	70 (23.0)	20 (43.4)	0.003
Pneumonia	36 (11.9)	10 (21.7)	0.067
Bacterial sepsis	37 (12.1)	13 (28.2)	0.003
Peak total bilirubin (mg/dl)	11.6 ± 9.7	17.3 ± 8.7	<0.001
Peak ascites output (l/day)	1.2 ± 1.4	1.3 ± 1.1	0.63

GRWR graft recipient weight ratio, *GV* graft volume, *LDLT* living donor liver transplantation, *MELD* model for end-stage liver disease, *POD* postoperative day, *PT-INR* prothrombin time international normalized ratio, *PVP* portal venous pressure, *SLV* standard liver volume

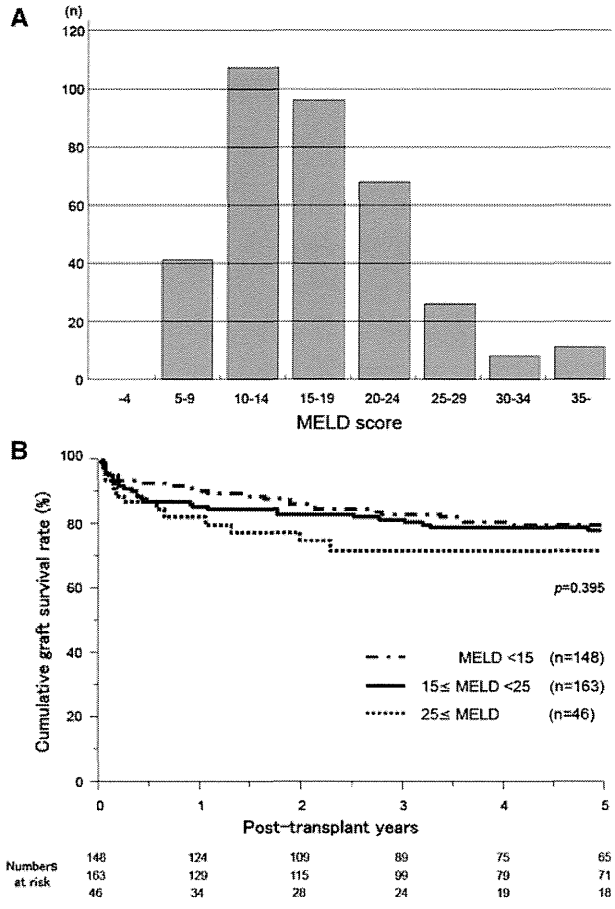

Fig. 1 Distribution of MELD scores (**a**), and the cumulative graft survival according to the MELD score (**b**)

(17.3 ± 8.7 vs. 11.6 ± 9.7, $p < 0.001$) were significantly higher in patients with high MELD scores.

We next evaluated the factors associated with graft loss among the patients with high MELD scores (≥25, $n = 46$). The univariate analysis showed that Era-I ($n = 119$, $p = 0.023$), recipient gender (male, $p = 0.045$), hepatitis C (positive, $p < 0.001$) and the presence of major shunt vessels (yes, $p = 0.010$) were significantly associated with early graft loss (Table 2). The multivariate analysis of these four factors showed that hepatitis C infection (yes, odds ratio 4.9, 95 % confidence interval 1.5–17.8, $p = 0.013$) and LDLT during Era-I (yes, odds ratio 4.0, 95 % confidence interval 1.2–15.8, $p = 0.036$) were independently associated with graft loss (Table 3).

Hepatitis C positive patients

The patients with hepatitis C were classified into four groups based on the MELD scores: <15 ($n = 82$), 15–19 ($n = 39$), 20–24 ($n = 21$) and ≥25 ($n = 13$). The 5-year graft survival rates in these four groups were 78.9, 80.0, 75.6 and 33.7 %, respectively. Patients with hepatitis C and MELD scores ≥25 had significantly worse graft outcomes compared with the other three groups ($p < 0.001$, Fig. 2a).

Among the patients without hepatitis C infection ($n = 202$), the 5-year survival rates in patients with low

Table 2 Results of the univariate analysis of graft mortality in patients with high (≥25) MELD scores

Variables	*n*	Graft survival rate (%)		
		1-year	5-year	*p* value
Era-I (first 1/3 cases)				
Yes	21	70.0	55.0	0.023
No	25	91.8	86.1	
Recipient gender, male				
Yes	23	77.3	54.1	0.045
No	23	86.5	86.5	
Emergency LDLT				
Yes	26	83.8	83.8	0.147
No	20	80.0	58.4	
Hepatitis C				
Yes	13	61.5	33.7	<0.001
No	33	90.4	86.6	
Donor age ≥40 years				
Yes	16	81.2	54.5	0.096
No	30	82.4	82.4	
Donor gender, male				
Yes	28	80.9	80.9	0.217
No	18	83.3	59.2	
Left lobe graft				
Yes	25	78.6	78.6	0.427
No	21	85.7	62.9	
GV/SLV <40 %				
Yes	21	88.0	84.1	0.623
No	25	91.7	72.4	
GRWR <0.8				
Yes	19	68.4	68.4	0.424
No	27	92.1	74.5	
Major shunt vessels				
Yes	6	50.0	33.3	0.010
No	40	84.1	77.9	
Splenectomy				
Yes	11	81.8	68.2	0.930
No	35	82.0	71.9	
Duct-to-duct				
Yes	16	75.0	66.8	0.686
No	43	90.1	80.8	

GRWR graft recipient weight ratio, *GV* graft volume, *LTLT* living donor liver transplantation, *MELD* model for end-stage liver disease, *SLV* standard liver volume

Table 3 Results of the multivariate analysis of graft mortality in patients with high (≥25) MELD scores

95 % confidence interval				
Variables	Odds ratio	Lower	Upper	*p* value
Hepatitis C	4.9	1.5	17.8	0.013
Era-I (first 1/3 cases)	4.0	1.2	15.8	0.036
Major shunt vessels	3.3	0.9	11.9	0.061
Recipient gender, male	3.1	0.8	12.2	0.106

MELD model for end-stage liver disease

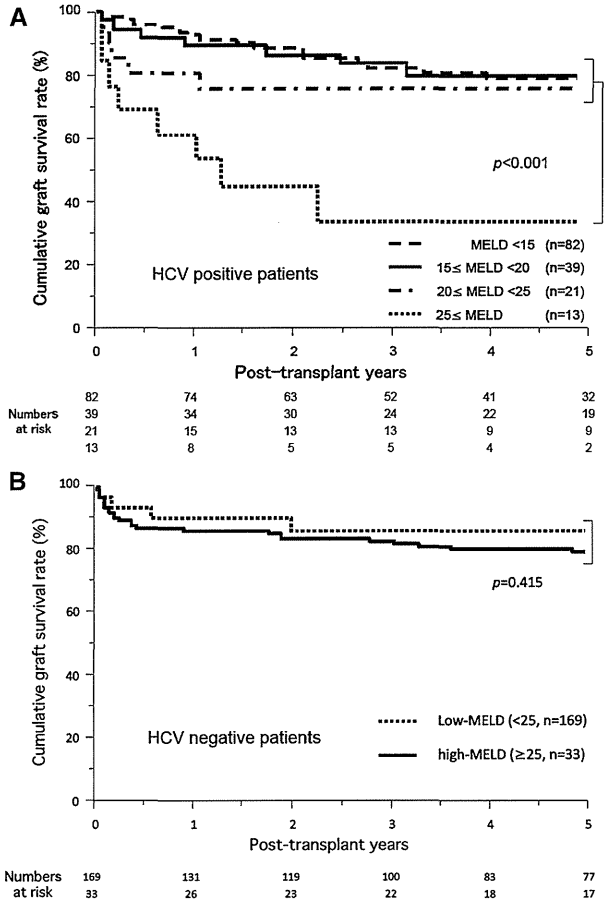

Fig. 2 Cumulative graft survival in patients with (**a**) or without (**b**) hepatitis C according to the MELD score

(<25, $n = 169$) and high (≥25, $n = 33$) MELD scores were 86.6 and 79.6 %, respectively ($p = 0.415$, Fig. 2b). Even when we excluded hepatitis C-negative patients with acute liver or graft failure from the analysis, the 5-year graft survival rates were comparable between those with low (<25, $n = 143$) and high (≥25, $n = 10$) MELD scores (81.5 and 80.0 %, respectively, $p = 0.926$). Therefore, hepatitis C was only associated with poor graft survival among the patients with high MELD scores.

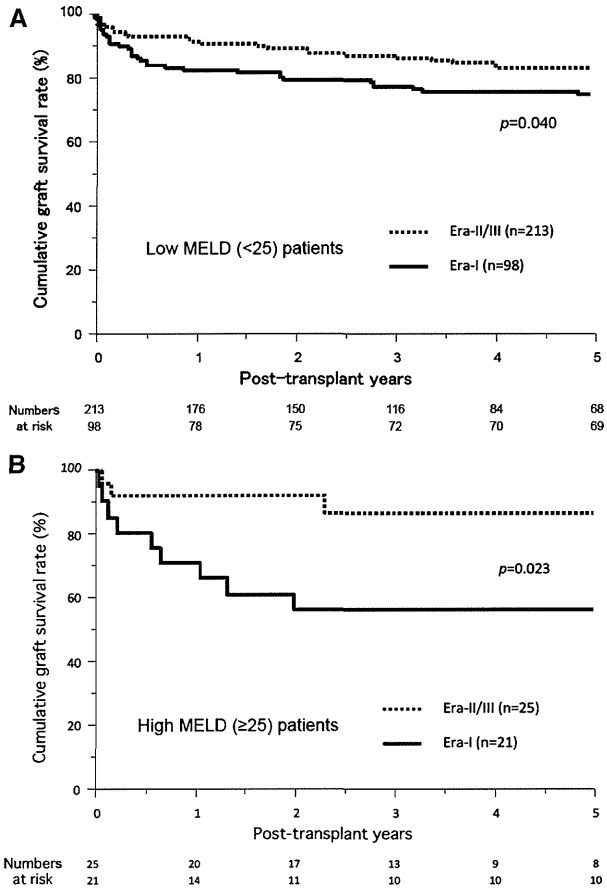

Fig. 3 Cumulative 5-year graft survival rate following LDLTs in Era-I (May 1997–February 2004) or Era-II/III (March 2004 onwards) in patients with low (**a**) or high (**b**) MELD scores

Transplant era and graft survival

The cumulative 5-year graft survival rate was compared between patients undergoing LDLT in Era-I or Era-II/III, and was stratified by high ($n = 46$) or low ($n = 311$) MELD scores. Among the patients with low MELD scores (Fig. 3a), the 5-year graft survival rate was significantly lower in patients who underwent LDLT in Era-I ($n = 98$), compared with Era-II/II ($n = 213$), with rates of 73.0 and 82.5 %, respectively ($p = 0.040$). The 5-year graft survival rate in patients with high MELD scores (Fig. 3b) was also significantly lower in the patients who underwent LDLT in Era-I ($n = 21$) than in Era-II/II ($n = 25$), with rates of 55.0 and 86.1 %, respectively ($p = 0.023$).

Effects of hepatitis C in combination with the transplant era

Patients with high MELD scores (≥25) were categorized into three groups according to the combination of time of

LDLT and hepatitis C status as follows: (1) LDLT in Era-II/III and absence of hepatitis C; (2) either LDLR in Era-I or the presence of hepatitis C; and (3) LDLT in Era-I and the presence of hepatitis C. The 5-year graft survival rates of these three groups of patients were 94.4, 72.6 and 14.3 %, respectively. Patients in group 3 (LDLT in Era-I and the presence of hepatitis C) had a significantly worse prognosis than those in the other two groups ($p < 0.001$). Among the patients with hepatitis C and high MELD scores who underwent LDLT in Era-I ($n = 7$), the causes of graft loss included graft dysfunction because of sepsis and multiple organ failure ($n = 3$), recurrent hepatitis C ($n = 2$) and recurrent hepatocellular carcinoma ($n = 1$). On the other hand, among patients with hepatitis C and high MELD scores who underwent LDLT in Era-II/III ($n = 6$), only one graft was lost because of recurrent hepatitis C. Although three out of the six (50 %) grafts in this group had aggressive recurrent hepatitis C, two patients underwent interferon treatment resulting in a viral response. Moreover, no grafts in patients with high MELD scores were lost as a result of septic complications in patients who underwent LDLT in Era-II/III (Fig. 4).

Discussion

The findings of the current study can be summarized as follows: first, the overall graft survival was not significantly different between patients with high or low MELD scores. Second, among patients with high MELD scores (≥25), the presence of hepatitis C and LDLT in Era-I (May 1997–February 2004) were significantly associated with a poor prognosis.

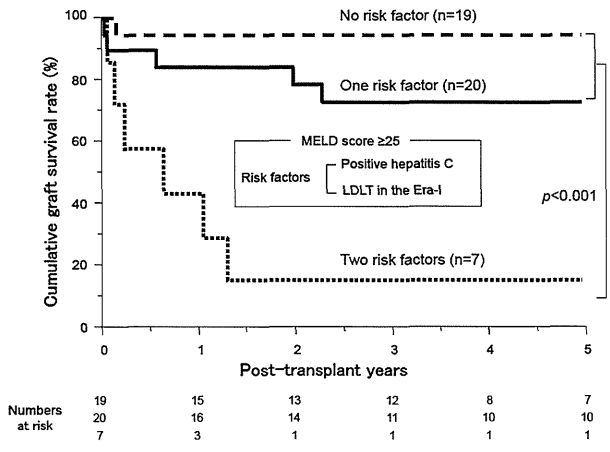

Fig. 4 Cumulative graft survival in three groups of patients with high MELD scores (≥25) stratified according to the time of LDLT and hepatitis C status: (1) LDLT in Era-II/II and the absence of hepatitis C ($n = 19$); (2) either LDLT in Era-I or the presence of hepatitis C ($n = 20$); and (3) LDLT in Era-I and the presence of hepatitis C ($n = 7$)

Regarding the overall general impact of high MELD scores, the current results appear to be convincing because it is generally accepted that surgical outcomes are largely influenced by the pre-surgical conditions [15]. However, the findings are reasonable considering the patient characteristics and transplant era, since the majority of patients had moderate MELD scores (median: 16, mean: 17) and most transplants were performed after 2000. On the other hand, the Kyoto group [10] analyzed 576 adult-to-adult cases since 1993, with a mean MELD score of 20, and found that patients with high MELD scores had an increased risk of graft loss (odds ratio 1.65). Their results are also reasonable, because their patients generally had higher MELD scores, and transplantation was done before 2000, before the introduction of major refinements in surgical techniques for adult-to-adult LDLT [16]. Marubashi et al. [7] reported similar results in their initial 39 cases with a higher mean MELD score of 22. In contrast, the Toronto group [11] recently reported a negative impact of the MELD score on graft outcomes. They analyzed more recent LDLTs since 2002 ($n = 271$); the mean MELD score of their patients was 17. Therefore, we would anticipate that our outcomes would be similar to those reported by the Toronto group. By taking into account these findings, it could be concluded that a high MELD score does not negatively affect the overall graft outcomes of patients undergoing LDLT in recent years, and with the application of the recent refinements in LDLT.

The negative effect of a high MELD score on graft outcomes in patients with hepatitis C patients is a particularly important finding. The difference in survival between patients with higher and lower MELD scores among those with hepatitis C became prominent within 3 months of LDLT, and the gap gradually increased with time, reaching 40 % 2 years after LDLT. The high risk of graft loss associated with a high MELD score and hepatitis C continues until 2 years after transplantation. This conflicts with the belief that the pre-transplant disease severity only affects graft outcomes in the very early post-transplant course, namely in the first 2–3 months after LDLT [10, 17]. In our patients, five out of 13 (38.5 %) with high MELD scores had aggressive recurrent hepatitis C, defined as cholestatic or fibrosing hepatitis C [14]. The incidence of aggressive hepatitis C was higher in patients with high MELD scores than in patients with low MELD scores (5/13 vs. 16/142, $p = 0.006$). Because there were no significant differences in the donor age, graft volume, immunosuppression protocol or viral load between patients with high or low MELD scores, the difference in the rate of aggressive hepatitis C might be attributed to the disease. However, there have so far been no reports describing an

association between the disease severity and progression of aggressive fibrosis. Retortillo et al. [18] reported that partial live donor grafts showed earlier fibrotic progression compared with deceased whole-liver transplants. Furthermore, Honda et al. [19] reported that hepatitis C virus actively infects and replicates in rapidly dividing hepatocytes via the activation of hepatocyte growth factors. A possible explanation for this could be that the metabolic demands on partial grafts are increased to a greater extent in sicker patients after LDLT, resulting in an increased activation of growth factors and active replication of hepatitis C virus.

Regarding the impact of center experience in performing LDLT, a combination of multiple surgical and non-surgical factors could explain the improved outcomes, as previously reported in the A2ALL study [20, 21]. That study showed a significant improvement in graft outcome after the first 15–20 cases, which was attributed to improvements in patient selection, perioperative management and surgical techniques. However, it should be noted that both A2ALL and non-A2ALL centers in the USA had extensive experience in performing deceased donor liver transplantation before starting LDLT. This differs from the clinical experience in Eastern countries. At our institutes, many surgical and non-surgical refinements have been introduced over the last 15 years [22]. The main surgical refinements include recipient high hilar dissection [23], controlling portal hypertension by splenectomy [24] and aggressive reconstruction of the middle hepatic vein tributaries [25]. Non-surgical refinements include three-dimensional anatomical and volumetric analysis [26], recipient risk evaluation [27] and the application of early enteral nutrition [28].

The managing strategies for recurrent hepatitis C have also been changed with increasing clinical experience. It has long been difficult to differentiate between acute rejection and early recurrent hepatitis C, and bolus doses of steroids were used to prevent possible rejection, resulting in the development of aggressive hepatitis C, as in other centers [29]. Currently, we treat patients with hepatitis C with a higher but more stable immunosuppression regimen to avoid acute rejection, which require bolus steroids for treatment. The incidence of acute rejection following bolus steroid administration has decreased significantly since Era-II (9/119 vs. 5/238 in Era-I, $p = 0.012$). This was largely due to the administration of interferon, which allowed for higher rates of biochemical and viral responses [14].

The relationship between PVP and the presence of major shunt vessels seems to be mutually related. Advanced liver disease causes an increased PVP, resulting in the creation of major shunts, which then reciprocally decrease the PVP. Moreover, the PVP after reperfusion is determined by the graft compliance, PV inflow and the regenerative activity of the graft [9]. Therefore, we believe that the development of major shunt vessels is one of the significant factors reflecting the hepatic disease severity, and thus the MELD scores [22]. The current results showing the significance of major shunt vessels implied that a deteriorated recipient condition had a significant impact on the short-term graft outcomes. However, the PVP had no significant impact in the current series, possibly because a higher PVP was intentionally controlled by splenectomy [13]. A lack of PVP modulation might have resulted in a finding that the PVP was a significant indicator for inferior graft survival.

The significant weakness of this study might be the learning curve bias. Since 2004, we have introduced many surgical and non-surgical refinements in LDLT, including splenectomy for high PVP [13], the introduction of a vessel sealing system [13], aggressive reconstruction of the middle hepatic tributaries in right lobe LDLT [25], the introduction of early enteral nutrition for preventing septic complication [28] and tailored antiviral treatment for recurrent hepatitis C [14]. However, our data showed that the accumulation of experiences significantly improved the outcomes in difficult cases.

In conclusion, the graft outcomes in patients with high MELD scores and the presence of hepatitis C were particularly poor. In patients with these risk factors, LDLT should be performed at experienced centers and/or by experienced surgeons.

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Conflict of interest No financial or other conflict of interest exists with the authors.

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Liver Regeneration and Venous Collateral Formation in the Right Lobe Living-Donor Remnant: Segmental Volumetric Analysis and Three-Dimensional Visualization

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Background. In left lobe (LL) living-donor liver transplantation (LDLT), hepatic venous congestion (HVC) caused by ligation of the middle hepatic vein tributaries is unavoidable in the right lobe (RL) donor remnant.
Methods. To clarify the impact of HVC on liver regeneration and venous collateral formation (VCF), we used three-dimensional computed tomography to examine the volumes of total/segmental liver and HVC and the degree of VCF; preoperative data were compared with data obtained on postoperative day (POD) 35 in 13 LL LDLT donors.
Results. On POD 35, the congestion rate decreased from 32.5% to 1.6% and the total liver regeneration rate was 81.7%. Preoperatively, the anterior sector-to-RL volume ratio was significantly lower, and the posterior sector-to-RL volume ratio was significantly higher than postoperatively (56.7% vs. 52.9%, $P<0.01$, and 36.9% vs. 41.5%, $P<0.01$, respectively). There was no correlation between degree of HVC and liver regeneration. Obvious VCF was found in five (38.5%) cases. The RL and posterior sector volume per square meter of body surface area in the VCF group were significantly lower than that in the non-VCF group (412 cm^3/m^2 vs. 492 cm^3/m^2, $P<0.01$, and 140 cm^3/m^2 vs. 190 cm^3/m^2, $P<0.01$, respectively). The preoperative congestion rate and liver regeneration rate were not significantly different between the groups.
Conclusions. Reconstruction of the middle hepatic vein tributaries in the RL donor remnant might not be necessary in LL LDLT, because the HVC improved dramatically by POD 35 regardless of the development of VCF.

Keywords: Congestion, Hepatic vein, Left lobe graft, Living-donor liver transplantation, Reconstruction.

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Since the first study in 1989, living-donor liver transplantation (LDLT) has been widely accepted worldwide as the treatment of choice for end-stage liver failure (*1*). Although the use of the right lobe (RL) as a graft has been increasingly successful, the problem of donor safety exists. In LDLT, it was reported that the incidence of donor complications based on 1841 donors in Japan was significantly higher in donors of the RL than in donors of the left lobe (LL) and the left lateral segment (*2*). In addition, operative mortality for RL donors was estimated to be as high as 0.5%–1.0% (*3*). We have previously reported that LL LDLT was a feasible treatment modality for ensuring minimal mortality and morbidity in donors (*4*) and that the number of biliary complications was significantly lower in LL LDLT than in RL LDLT (*5*). Donor safety is the highest priority in LDLT. Therefore, to minimize the risk to donors, LL LDLT may be an ideal option in LDLT. However, because the grafts usually include the middle hepatic vein (MHV) to improve the venous drainage in LL LDLT, hepatic venous congestion (HVC) in the right anterior sector caused by deprivation of drainage from the MHV tributaries is unavoidable in the RL donor remnant; this can lead to territories with outflow obstruction bearing the risk of insufficient liver regeneration (*6, 7*).

In the preoperative evaluation of donor livers, HVC estimates are based on three-dimensional computed tomography (3D-CT). In RL LDLT, the operative decision for the reconstruction of the MHV tributaries on the recipient side depends on the degree of HVC. However, there is no consensus with regard to the optimal reconstruction strategy on the donor side in LL LDLT. Although it has been reported that drainage of the anterior sector might be

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dependent on intrahepatic venous collaterals between the MHV tributaries and the right hepatic vein (RHV) in the later postoperative phase (*8*), it is unclear how much anastomosis would develop postoperatively. Furthermore, it is still not clear as to how the HVC would influence liver regeneration and venous collateral formation (VCF) in the later postoperative phase.

The purpose of the present study was to better understand liver regeneration and VCF in the RL donor remnant in LL LDLT. We assessed total and segmental donor liver regeneration by comparing 3D-CT data obtained preoperatively with that obtained on postoperative day (POD) 35. We also determined the degree of VCF on POD 35 and examined how the HVC had influenced liver regeneration and VCF.

RESULTS

Preoperative and Postoperative Right Lobe Volume, Hepatic Venous Congestion Volume, Congestion Rate, and Liver Regeneration Rate

The mean (SD) preoperative 3D-CT estimated volumes of the whole liver, the RL, and the HVC were 1207 (40) cm^3 (range, 1029–1491), 801 (126) cm^3 (range, 593–1070), and 260 (81) cm^3 (range, 84–414), respectively. The mean (SD) postoperative volumes of the RL remnant and the actual congestion on POD 35 were 986 (135) cm^3 (range, 765–1232) and 15 (12) cm^3 (range, 0–34), respectively. The mean (SD) congestion rate decreased from 32.5% (10.7%) (range, 14.2%–59.4%) to 1.6% (1.3%) (range, 0.0%–3.4%) on POD 35. The mean (SD) liver regeneration rate on POD 35 was 81.7% (5.8%) (range, 70.1%–92.8%) (Table 1). There was no correlation between the preoperative congestion rate and the liver regeneration rate.

Comparison Between the Moderate and Severe Hepatic Venous Congestion Groups

Among the 13 LL LDLT donors, there were five (38.5%) cases in the moderate HVC group and eight (61.5%) cases in the severe HVC group. There was no significant difference in the rate of complications greater than Clavien grade 1 between these two groups (20.0% vs. 25.0%, *P* value is not significant [NS]); in addition, the liver regeneration rate on POD 35 did not differ significantly between the groups (83.8% vs. 80.4%, *P* value is NS). Postoperative liver function tests such as serum aspartate aminotransferase, alanine aminotransferase, total bilirubin, and prothrombin time were not significantly different between the two groups (Fig. 1A–D).

Preoperative and Postoperative Right Lobe Donor Volume: Segmental Volumetric Analysis

The mean (SD) preoperative estimated volumes of the anterior sector and the posterior sectors of the RL were 450 (71) cm^3 (range, 362–569) and 297 (81) cm^3 (range, 168–429), respectively. The mean (SD) volume ratio of the anterior sector to the RL was 56.7% (8.2%) (range, 44.0%–72.1%), and the mean (SD) volume ratio of the posterior sector to the RL was 36.9% (7.4%) (range, 23.1%–50.6%). The mean (SD) preoperative estimated volumes and mean (SD) segment-to-RL volume ratios were as follows: 163 (66) cm^3 (range, 108–357) and 20.5% (6.9%) (range, 11.9%–37.9%) in segment V, 286 (58) cm^3 (range, 212–400) and 36.2% (7.3%) (range, 22.5%–48.5%) in segment VIII, 129 (60) cm^3 (range, 46–229) and 16.3% (7.1%) (range, 5.9%–28.4%) in segment VI, and 168 (66) cm^3 (range, 92–277) and 20.6% (6.2%) (range, 11.5%–32.7%) in segment VII, respectively. The mean (SD) estimated volumes of the

TABLE 1. Summary of each liver parameter before and after surgery

	Preoperative	Postoperative (POD 35)
Whole liver volume, mean (SD), cm^3	1207 (40)	—
RL volume, mean (SD), cm^3	801 (126)	986 (135)
HVC volume, mean (SD), cm^3	260 (81)	15 (12)
Congestion rate,[a] mean (SD), %	32.5 (10.7)	1.6 (1.3)
Regeneration rate,[b] mean (SD), %	—	81.7 (5.8)
Segmental liver volume, mean (SD), cm^3		
Anterior sector	450 (71)	517 (73)
Segment V	163 (66)	172 (76)
Segment VIII	286 (58)	346 (60)
Posterior sector	297 (81)	413 (102)
Segment VI	129 (60)	175 (72)
Segment VII	168 (66)	238 (103)
Sector-to-RL volume ratio, mean (SD), %		
Anterior sector	56.7 (8.2)	52.9 (7.3)
Segment V	20.5 (6.9)	17.3 (6.5)
Segment VIII	36.2 (7.3)	35.6 (7.2)
Posterior sector	36.9 (7.4)	41.5 (6.9)
Segment VI	16.3 (7.1)	17.8 (7.2)
Segment VII	20.6 (6.2)	23.7 (8.2)

HVC, hepatic venous congestion; POD, postoperative day; RL, right lobe.
[a] Congestion rate (%) was calculated as HVC volume divided by RL volume.
[b] Regeneration rate (%) was calculated as postoperative RL volume on POD 35 divided by preoperative whole liver volume.

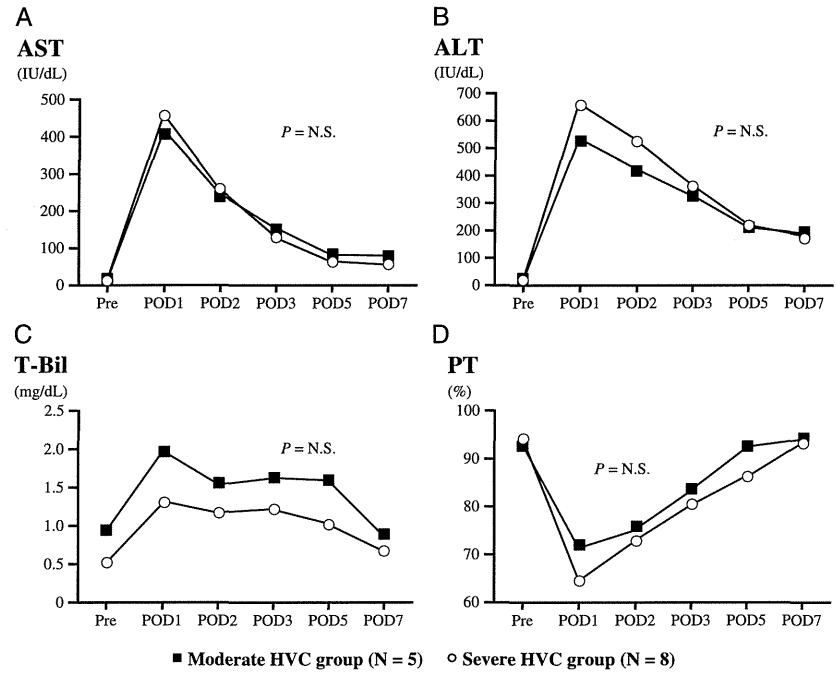

FIGURE 1. Postoperative serial change in liver function tests in the moderate and severe HVC groups. Postoperative liver function tests such as serum AST, ALT, T-Bil, and PT were not significantly different between the two groups. A, AST. B, ALT. C, T-Bil. D, PT. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HVC, hepatic venous congestion; NS, not significant; POD, postoperative day; PT, prothrombin time; T-Bil, total bilirubin.

anterior sector and the posterior sector on POD 35 were 517 (73) cm^3 (range, 396–650) and 413 (102) cm^3 (range, 238–573), respectively. On POD 35, the mean (SD) volume ratio for the anterior sector to the RL remnant and the posterior sector to the RL remnant was 52.9% (7.3%) (range, 38.6%–62.0%) and 41.5% (6.9%) (range, 31.1%–55.9%), respectively. The mean (SD) estimated volumes on POD 35 and mean (SD) segment-to-RL volume ratios were as follows: 172 (76) cm^3 (range, 112–390) and 17.3% (6.5%) (range, 10.9%–34.4%) in segment V, 346 (60) cm^3 (range, 260–445) and 35.6% (7.2%) (range, 22.9%–47.6%) in segment VIII, 175 (72) cm^3 (range, 54–300) and 17.8% (7.2%) (range, 4.8%–29.4%) in segment VI, and 238 (103) cm^3 (range, 124–407) and 23.7% (8.2%) (range, 14.0%–39.7%) in segment VII, respectively (Table 1).

On POD 35, the anterior sector did not atrophy but became enlarged, regardless of the degree of HVC, and of course, the posterior sector became enlarged. However, the ratio of the anterior sector volume to the RL volume on POD 35 was significantly lower, and the ratio of the posterior sector volume to the RL volume on POD 35 was significantly higher than preoperatively (56.7% vs. 52.9%, $P<0.01$, and 36.9% vs. 41.5%, $P<0.01$, respectively) (Fig. 2A, B). According to detailed segmental volumetric analysis, on POD 35, the ratio of segment V volume to the RL volume was significantly lower and the ratio of segment VII volume to the RL volume was significantly higher than preoperatively (20.5% vs. 17.3%, $P<0.05$, and 20.6% vs. 23.7%, $P<0.01$, respectively); however, there were no significant differences in this volume ratio for segments VIII and VI (36.2% vs. 35.6%, P value is NS, and 16.3% vs. 17.8%, P value is NS, respectively) (Fig. 2C–F).

Comparison Between the Venous Collateral Formation Group and the Non–Venous Collateral Formation Group

Among all 13 cases, obvious VCF between the MHV tributaries and the RHV was found in 5 (38.5%) cases (Fig. 3A–E), in which 1 (7.7%) case simultaneously developed intrahepatic venous anastomoses between the MHV tributaries and the inferior right hepatic vein (IRHV) (Fig. 3E). The comparison between the VCF group and the non-VCF group is summarized in Table 2. There was no significant difference in the rate of complications greater than Clavien grade 1 between the two groups (20.0% vs. 25.0%, P value is NS). Postoperative liver function tests were not significantly different between the two groups. Additionally, there was no significant difference in the preoperative congestion rate and the liver regeneration rate on POD 35 between the VCF and the non-VCF groups (35.9% vs. 30.4%, P value is NS, and 80.1% vs. 82.6%, P value is NS, respectively). The preoperative RL volume per square meter of body surface area (BSA) in the VCF group was significantly lower than that in the non-VCF group (412 cm^3/m^2 vs. 492 cm^3/m^2, $P<0.01$). Although the volume per square meter of BSA of the anterior sector was not significantly different between the VCF and non-VCF groups (250 cm^3/m^2 vs. 266 cm^3/m^2, P value is NS), the volume per square meter of BSA of the posterior sector was significantly lower

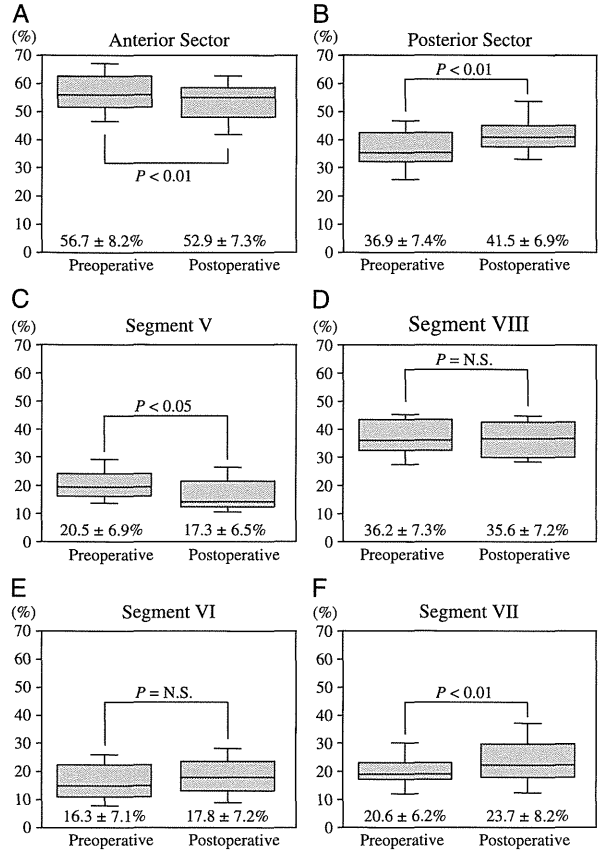

FIGURE 2. Comparison of preoperative and postoperative segmental liver-to-RL volume ratios. A, Anterior sector. B, Posterior sector. C, Segment V. D, Segment VIII. E, Segment VI. F, Segment VII. The postoperative anterior sector-to-RL volume ratio was significantly lower than preoperatively, and the postoperative posterior sector-to-RL volume ratio was significantly higher than preoperatively ($P<0.01$ and $P<0.01$, respectively). Postoperatively, the segment V-to-RL ratio was significantly lower, and the segment VII-to-RL ratio was significantly higher than preoperatively ($P<0.05$ and $P<0.01$, respectively). There were no significant differences in this ratio for segments VIII and VI, preoperatively and postoperatively. The liver segment-to-RL volume ratio is represented by box-and-whisker plots. The data (%) are shown as the mean value±standard deviation. The line in the box represents the median; the upper and lower lines of the box represent the 75th and 25th quartiles. The upper and lower lines outside of the box represent the 90th and 10th quartiles. NS, not significant; RL, right lobe.

in the VCF group than in the non-VCF group (140 cm^3/m^2 vs. 190 cm^3/m^2, $P<0.01$).

DISCUSSION

LDLT is an established procedure for the treatment of patients with end-stage liver disease, especially in Japan and other Asian countries, where deceased donors are not often available. In Western countries, LL LDLT has not generally been recognized as a feasible procedure because of the problem of graft size. The initial experience related to LL grafts demonstrated a higher incidence of small-for-size syndrome graft failure and recipient complications. Consequently, RL grafts have been used routinely at many centers (*9–11*). However, although the use of the RL as a graft has been increasingly successful, the problem of donor safety still exists. We have previously reported that the outcomes of LL LDLT were comparable with those of RL LDLT, although small-for-size syndrome occurred more often in LL LDLT. In addition, the overall donor morbidity rates were comparable between LL and RL, whereas postoperative liver function tests and hospital stay were significantly improved in LL donors (*12*). Donor safety should be the highest priority. Therefore, LL LDLT is considered the first choice in our institution.

In LL LDLT, the incidence of HVC in the right anterior sector caused by deprivation of drainage from the MHV tributaries is unavoidable. Left hepatectomy of the liver is a standard procedure in oncological liver surgery. Consequently, not much attention has been paid so far to the HVC of the remnant and reconstruction of the MHV tributaries is not usually performed. Indeed, even if transient liver dysfunction has occurred, HVC has been known to improve, with the liver returning to an almost normal level of function at POD 30 (*7*). In cases of HVC in the early postoperative phase, Doppler ultrasonography can show an absence of venous blood flow and reversed flow, indicating that the portal vein (PV) may be acting as a drainage vein owing to the presence of an acute hepatic outflow obstruction. However, by POD 7, Doppler ultrasonography can show a normal hepatopetal flow in the anterior PV (*13*). Therefore, in the later postoperative phase, drainage of the right anterior sector is believed to be dependent on the intrahepatic venous anastomoses between the MHV tributaries and the RHV (*8, 14*). Indeed, several reports have demonstrated that the collaterals can develop within several days after LDLT (*15, 16*). However, it is unclear as to how much anastomosis can develop postoperatively. Furthermore, it is still not clear as to how the HVC would influence liver regeneration and VCF in the later postoperative phase. Donor safety should be the highest priority as emphasized before. Death of donors can have a negative impact in various areas. After the death of a donor in New York in 2002, the frequency of LDLT was reduced by 51% in that city and by 21% in the United States as a whole (*17, 18*). Therefore, we find it difficult to understand such a phenomenon with regard to the RL donor remnant.

In liver transplant recipients receiving an RL graft, the reconstruction of the MHV tributaries has been performed using interposition grafts to prevent HVC. Cheng et al. (*19*) reported that there was no clinically significant difference in recipient outcome between the recipients who showed occlusion of the interposed graft and those recipients whose interposition grafts remained patent; however, graft regeneration was lower in the occluded group than that in the patent group. Whether the interposition grafts have remained patent is not considered to be clinically significant in the later postoperative phase, because the intrahepatic venous network between the MHV tributaries and the RHV is generally present (*8, 14*). However, this venous network has not been established yet in the early postoperative phase.

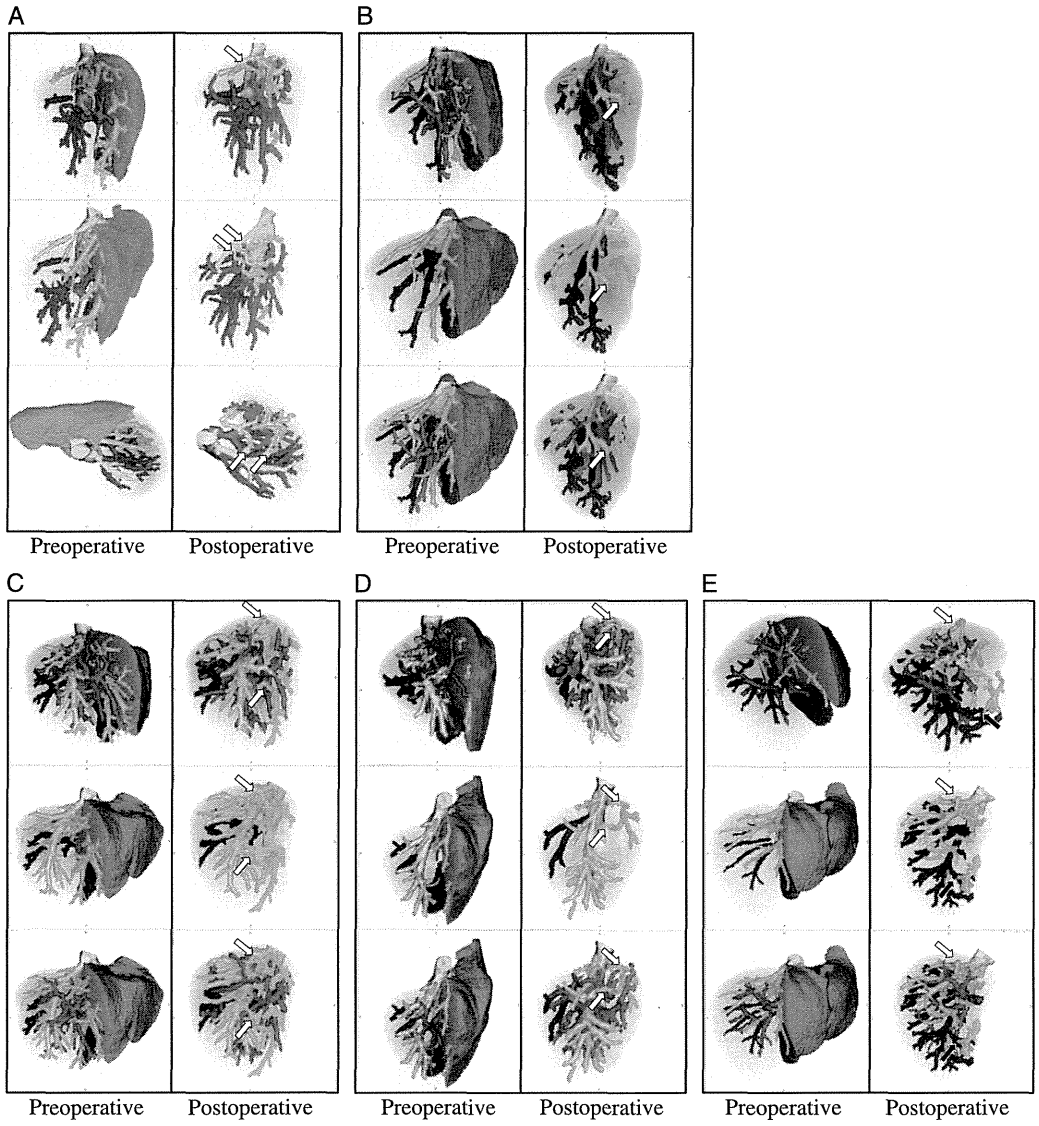

FIGURE 3. 3D-CT images of VCF visualization. Among all 13 cases, VCF between the MHV tributaries and the RHV (*white arrows*) was found in 5 cases (A–E). Of these cases, one simultaneously developed intrahepatic venous anastomoses between the MHV tributaries and the IRHV (*black arrows*) (E). The left and right sides of the figure represent preoperative and postoperative 3D-CT images, respectively. The RHV and IVC are colored aqua blue. The MHV tributaries, IRHV, and PV are colored yellow, red, and dark blue, respectively. 3D-CT, three-dimensional computed tomography; IRHV, inferior right hepatic vein; IVC, inferior vena cava; MHV, middle hepatic vein; PV, portal vein; RHV, right hepatic vein; VCF, venous collateral formation.

Therefore, to prevent liver dysfunction during this early period and eventual graft failure, the concept of the reconstruction of the MHV tributaries is an accepted modality (*8, 20*). We have previously reported that the MHV tributaries should be reconstructed in transplant recipients if the calculated HVC is more than 20% (*20*). However, there are no criteria for the reconstruction of the MHV tributaries in the RL remnant of donors in LL LDLT, and the reconstruction of the MHV tributaries has not usually been performed. The reasons for this are as follows: (1) the reconstruction procedure is difficult as it should be performed in situ and not on a back table; (2) it is necessary to create an additional wound to obtain the interposition graft; (3) because the imbalance between inflow and outflow can be mild in donors as compared with recipients (*21*), the impact of the congestion on the liver is believed to be mild in comparison to the impact on the recipients; (4) liver function will return to almost normal levels at POD 30 regardless of the degree of HVC (*7*); and (5) the collaterals between the ligated MHV tributaries and the RHV can develop within several days after LDLT (*15, 16*). However, it is still unclear as to the amount of intrahepatic venous