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SECTION 7. A NEW THERAPEUTIC STRATEGY ON PORTAL FLOW MODULATION THAT INCREASES DONOR SAFETY WITH GOOD RECIPIENT OUTCOMES

Toshimi Kaido,[1,3] Kohei Ogawa,[1] Yasuhiro Fujimoto,[1] Takashi Ito,[1] Koji Tomiyama,[1] Akira Mori,[1] Yasuhiro Ogura,[2] and Shinji Uemoto[1]

Abstract. The goal of this study was to examine whether the lower limit of the graft-to-recipient weight ratio (GRWR) can be safely reduced to make better use of the left lobe graft in adult-to-adult living donor liver transplantation in combination with portal pressure control. Beginning December 2007, the acceptable limit for GRWR was lowered to ≥0.7% and by April 2009, it was further lowered to ≥0.6%. A portal pressure control program targeting a final portal pressure <15 mm Hg was also introduced. The donor complication rate decreased from 13.8% to 9.3%. The overall survival of recipients with GRWR <0.8% did not differ from recipients with a GRWR ≥0.8%. In conclusion, the lower limit of the GRWR can be safely reduced to 0.6% using a left lobe graft in adult-to-adult living donor liver transplantation in combination with portal pressure control.

Keywords: Liver transplantation, Portal flow modulation, Graft-to-recipient weight ratio, Small-for-size graft.

Donor safety and favorable outcomes of recipients after liver transplantation (LT) are the most important priorities of living donor liver transplantation (LDLT). We recently established a new therapeutic strategy to satisfy both priorities. The strategy consists of grafting the left lobe first, decreasing the lower limit of the graft-to-recipient weight ratio (GRWR) and controlling portal pressure. The present short essay describes details and the value of our new strategy.

GRAFT SELECTION

One hundred ninety-two adult (age ≥18 years) patients underwent LDLT at Kyoto University Hospital between February 2008 and April 2012.

The incidence of all donor complications including donors for pediatric recipients is higher when using right (n=500, 44.2%), compared with left or extended lateral lobe grafts (n=762, 18.8%) (*P*<0.001) (*1*). Biliary complications are more frequent after right, than after left or extended lateral lobe grafts (12.2% vs. 4.9%, *P*<0.001). Thus, left lobe grafts are preferable because of lower complication rates and a larger remnant liver that ensures donor safety. However, the lower limit of GRWR and the risk of small-for-size syndrome are critical problems that need to be overcome when using left lobe grafts.

Eight hundred and ten adult recipients underwent LDLT at Kyoto University Hospital between February 1999 and March 2012. We have routinely applied the portal

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T.K. participated in research design, the writing of the paper, the performance of the research, and data analysis. K.O. participated in the performance of the research. Y.F. participated in the performance of the research. T.I. participated in the performance of the research. K.T. participated in research design, the performance of the research, and data analysis. A.M. participated in the performance of the research. Y.O. participated in the performance of the research. S.U. participated in research design and the performance of the research.

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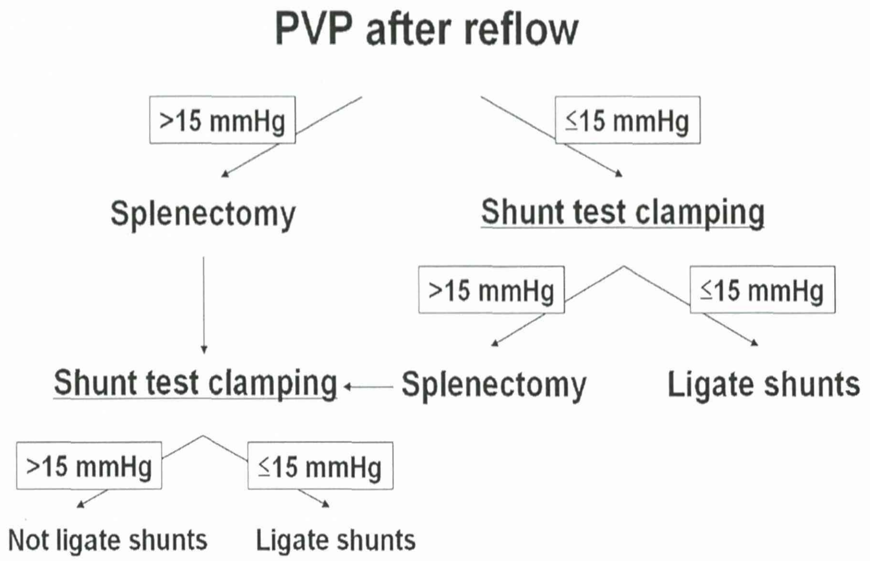

FIGURE 1. Current strategy for intentional portal pressure control.

pressure control program that targeted the final PVP to <15 mm Hg since 2008. Five hundred and fifty-two adult recipients and two hundred and fifty-eight adult recipients underwent LDLTs before and after application of our new strategy, respectively. Preoperative median Model for End-stage Liver Disease (MELD) scores before and after application of our new strategy were 19.2 and 21.0, respectively.

Our lower limit of GRWR had been 0.8% until November 2007 and then we gradually decreased it from ≥0.7% in December 2007 to ≥0.6% in April 2009 to preferentially select left, over right lobe grafts.

PORTAL FLOW MODULATION

We preliminarily analyzed overall survival in 100 consecutive patients who underwent adult-to-adult LDLT between April 2006 and March 2008 based on the final portal vein pressure (PVP). We found that overall survival rates were significantly higher in patients with final PVP ≤15 than >15 mm Hg (P=0.016). Based on these findings, we introduced a portal pressure control program that targeted the final PVP to <15 mm Hg to overcome small-for-size graft problems. We also have a policy of ligating large shunts including spleno-renal shunts to increase portal venous flow and to prevent the portal venous steal phenomenon from arising after LT when graft resistance increases during rejection. Figure 1 shows a flow chart for portal pressure control.

RECIPIENT OUTCOME OF NEW STRATEGY

We then validated the value of our new strategy. The ratio of left lobe grafts significantly increased to >50% especially after 2008 (Fig. 2). Donor complication rates (Clavien ≥ IIIa excluding wound infection) significantly decreased after the new strategy was introduced (Fig. 3). Final PVP and GRWR did not significantly correlate (*2*). Postoperative serum total bilirubin levels and average daily ascites output were significantly higher, and postoperative prothrombin time was significantly prolonged in patients with final PVP >15 than ≤15 mm Hg (*2*). Overall survival rates did not significantly differ between patients with GRWR ≥0.8% and <0.8% (3-year rates, 81% and 80%, respectively) after the new strategy was introduced (*3*).

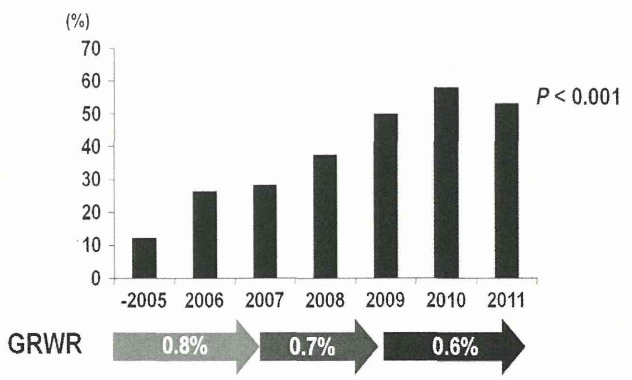

FIGURE 2. The ratio of left lobe graft.

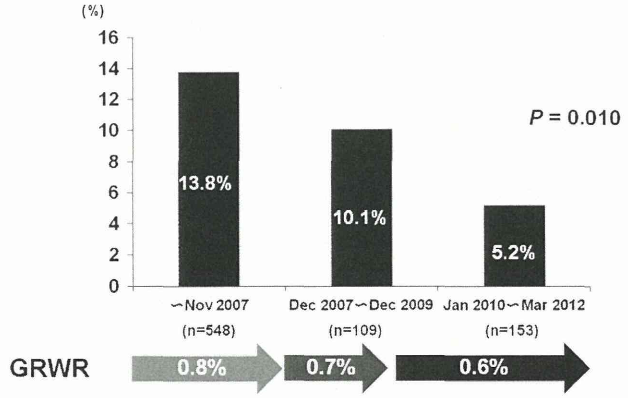

FIGURE 3. Donor complication rates.

CONCLUSION

In conclusion, our new strategy including portal pressure control increases donor safety and provides acceptable recipient outcomes.

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SECTION 8. MANAGEMENT OF PORTAL VENOUS COMPLICATIONS IN PEDIATRIC LIVING DONOR LIVER TRANSPLANTATION

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Abstract. Portal vein (PV) complications after living donor liver transplant (LDLT) have been a major concern in pediatric liver transplantation. The incidence of PV complications is more in pediatric (0%–33%) than in adult recipients. Early diagnosis and treatment of PV complications may ensure optimal graft function and good recipient survival. Small preoperation PV size (<4 mm) and slow portal flow (<10 cm/s) combined with lower hepatic artery resistance index (<0.65) are strong warning signs that may predict the development of post LDLT PV complications. Portal vein angioplasty/stenting is conventionally performed through the percutaneous transhepatic approach; however, this can also be performed through transjugular, trans-splenic, and intraoperative approaches. Depending on the situation, using optimal method is the key point to minimize complication (5%) and gain high success rate (80%). PV occlusion of greater than 1 year with cavernous transformation seems to be a factor causing technical failure. Good patency rate (100%) with self-expandable metallic stents was noted in long-term follow-up. In conclusion, PV stent placement is an effective, long-term treatment modality to manage PV complications after pediatric LDLT. Early diagnosis and treatment are essential to maximize the use of stent placement and achieve good success rates.

Keywords: Portal vein occlusion, Portal vein complication, Stent, Living donor liver transplantation, Pediatric liver transplantation.

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Living donor liver transplant (LDLT) is an optimal solution for the urgent demand for liver graft (*1*). Although portal vein (PV) abnormalities are rather uncommon and merely occur in 2% to 13% of transplant recipients, some devastating complications are troublesome and have been an imperative challenge for postoperative management (*2, 3*).

Risk Factors

There are certain factors that put recipients at the risk of developing PV complications. A PV with small diameter, history of preliver transplantation (LT) portal vein thrombosis (PVT), surgical shunt operation before LT, and splenectomy are known risk factors for the development of PVT in orthotopic LT (*4*). In the pediatric age group, the risk factors include preexisting portosystemic shunts with ensuing decreased PV flow, graft interposition, the age at first LT (children <1 year old), weight (<6 kg), and need for retransplantation (*5–7*). Chardot et al. reported that PV diameter, age and weight at transplantation, and emergency transplantation are significantly associated with PV complications in BA (*8*). In Chardot's biliary atresia (BA) series, most PVT occurred in the early stage (*5, 9*). Few reports focus on late-onset PVT with a long-term follow-up period.

Clinical Signs and Symptoms

Initially, most patients are asymptomatic and increased liver function tests are seldom. In late phase, obstruction of the PV contributes to thrombus or stenosis formation at the anastomosis site. The onset of ascites, variceal bleeding, splenomegaly, and pancytopenia are the typical clinical scenarios associated with PV stenosis. Although these symptoms could also be a result of occlusion of the hepatic vein, statistically, the PV bears a relatively higher tendency for occlusion.

Imaging Diagnosis

Early detection and diagnosis of any PV complication is essential for the prevention of late PV complication-related graft loss. Regular evaluation of PV flow by Doppler ultrasound is, thus, important (*10*). High-risk patients should be identified, and early signs of developing PVT must be sought to diagnose early PVT. Small PV size (<4 mm) and slow portal flow (<10 cm/sec) combined with lower hepatic artery resistance index (<0.65) are strong warning signs predicting the development of post-LDLT PV thrombosis in BA patients that require close monitoring (*11*). Jet flow phenomenon of portal flow and poststenotic dilatation of

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Clinical Transplantation

Hepatic arterial complications in adult living donor liver transplant recipients: a single-center experience of 673 cases

Iida T, Kaido T, Yagi S, Hori T, Uchida Y, Jobara K, Tanaka H, Sakamoto S, Kasahara M, Ogawa K, Ogura Y, Mori A, Uemoto S. Hepatic arterial complications in adult living donor liver transplant recipients: a single-center experience of 673 cases.

Abstract: Background: Hepatic arterial reconstruction during living donor liver transplantation (LDLT) is a very delicate and technically complicated procedure. Post-LDLT hepatic arterial complications are associated with significant morbidity and mortality.
Methods: We retrospectively analyzed the details of post-operative hepatic arterial complications in 673 consecutive adult LDLT recipients between January 1996 and September 2009.
Results: Hepatic arterial complications occurred in 43 of 673 adult recipients (6.4%) within a median of 13 post-transplant days (range, 1–63). These included hepatic artery thrombosis (including anastomotic stenosis) in 33 cases, anastomotic bleeding in seven cases, and rupture of anastomotic aneurysm in three cases. To treat these complications, surgical re-anastomosis was performed in 26 cases, while the other 17 cases underwent conservative therapies, including four angioplasties by interventional radiology. Biliary complications after hepatic arterial complications occurred in 17 cases. The overall survival rate after LDLT was significantly lower in the hepatic arterial complication group compared with that in the non-complication group (60.7% vs. 80.1% at one yr, 44.3% vs. 74.2% at five yr, respectively; $p < 0.001$). Multivariate analysis showed that the extra-anatomical anastomosis ($p = 0.011$) was the only independent risk factor for hepatic arterial complications.
Conclusion: Because hepatic arterial complications after LDLT are associated with poor patient survival, early diagnosis and immediate treatment are crucial. The anatomical anastomosis may be the first choice for the hepatic arterial reconstruction to the extent possible.

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Key words: hepatic arterial complications – hepatic arterial thrombosis – living donor liver transplantation

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Hepatic arterial reconstruction in liver transplantation (LT) is a crucial, yet delicate procedure. Particularly in living donor liver transplantation (LDLT), hepatic arterial reconstruction is an elaborate technique, as the hepatic artery of the graft in LDLT is smaller and narrower than that in deceased donor liver transplantation (DDLT).

Hepatic arterial complications are often associated with high graft loss and mortality rates if they occur in the early phase after LT and are left untreated. Hepatic arterial complications include hepatic artery thrombosis (HAT), hepatic arterial stenosis, bleeding from anastomotic sites, and rupture of hepatic artery aneurysms. Although there have been many reports regarding the surgical techniques for hepatic arterial reconstruction, the incidence and management of hepatic arterial complications, especially in adult LDLT, have not been fully elucidated.

In the present study, we retrospectively analyzed the incidence and treatment of hepatic arterial complications in 673 consecutive adult LDLT recipients in a single center.

Materials and methods

Our study population included 673 consecutive recipients (338 men, 335 women) who underwent LDLT at Kyoto University Hospital between January 1996 and September 2009. The median recipient age was 50 yr (range, 18–69 yr). Median Child-Pugh classification scores and model for end-stage liver disease (MELD) scores were 10 (range, 5–15) and 17 (range, 7–54), respectively.

This study was conducted in accordance with the Helsinki Declaration of 1975 following approval from our institutional review board. Biochemical patient data were collected in an automated fashion from the laboratory database, and clinical data were collected from electronic medical records.

The indications for LDLT in these patients included hepatocellular diseases such as hepatitis B or C virus-associated cirrhosis or alcoholic liver cirrhosis in 167 cases, hepatocellular carcinoma in 148 cases, progressive intrahepatic cholestatic diseases, including primary biliary cirrhosis and primary sclerosing cholangitis in 113 cases, re-transplantation due to graft loss in 32 cases, cryptogenic cirrhosis in 33 cases, fulminant hepatic failure in 73 cases, biliary atresia after Kasai's operation in 38 cases, autoimmune hepatitis in 14 cases, metabolic liver disease in 19 cases, and other causes in 36 cases.

The selection criteria for the donor and recipient, as well as surgical techniques for both donor and recipient operations, have been described in detail elsewhere (1). This study included eight domino LDLT cases. Six of the eight grafts were transplanted as a whole graft, and the other two grafts were transplanted to four patients as a split liver graft, two right lobe and two left lobe grafts. Graft types comprised 458 right lobes without the middle hepatic vein, 77 right lobes with the middle hepatic vein, 118 left lobes, eight posterior segments, six whole liver grafts, four extended lateral segments, and two lateral segments. The standard immunosuppression protocol consisted of tacrolimus and low-dose steroid. The median follow-up period was 41.4 months (range, 1–180 months).

Surgical techniques and post-operative management

In 641 cases, hepatic arterial reconstruction was performed between the hepatic arteries of the recipient and graft (anatomical reconstruction). Arterial reconstruction was performed under an optical field, with an approximately 10× (1–14.1×) zoom magnification using an operating microscope (VM900; Moller-Wedel GmbH, Wedel, Germany) in the beginning. Since 2000, it was made the transition from performed with microscope to surgical loupe with 4.5× magnification mainly.

However, depending on the situation which grafts and/or recipients' arteries were thin (<3 mm) and fragile, the extreme discrepancy of artery size existed, we selected the microscope reconstruction essentially.

Reconstruction was completed with interrupted sutures using 8-0 Prolene® or 9-0 Prolene® (blue monofilament, polypropylene, non-absorbable surgical suture; Ethicon Inc., Somerville, NJ, USA) (2).

In case of using a graft with two hepatic arteries, we aggressively performed the second hepatic artery reconstruction if backflow from the second artery was insufficient after the initial hepatic arterial reconstruction.

In our hospital, grafted hepatic arteries are usually reconstructed with recipient hepatic arteries (anatomical anastomosis). However, 30 of the 673 cases (4.5%) underwent extra-anatomical hepatic arterial anastomosis due to arterial injury, dissection, or size discrepancy. The extrahepatic arteries used included the gastroduodenal artery in 13 procedures, left gastric artery in 10, splenic artery in five, mesenteric artery of Roux-en-Y limb in one, and right gastric artery in one.

As routine management, all recipients underwent Doppler ultrasonography (D-US) twice a day for the first two wk and once a day thereafter until discharge. According to the intra-operative condition of the hepatic artery and the post-operative coagulation profile, anticoagulant therapy was initiated with intravenous heparin (120 U/kg/d) for the first week to keep the target level of APTT ranged 45–60 s approximately, followed by oral dipyridamole, with monitoring of the coagulation profile (2).

Definitions and therapies of hepatic arterial complications

The common hepatic arterial complications post-LDLT included HAT, anastomotic bleeding, anastomotic stenosis, and rupture of hepatic arterial aneurysms. HAT was diagnosed as loss or weakness of the hepatic artery signal on color D-US (pulsatility index [PI] = $[V\text{max} - V\text{min}]/V\text{mean}$; PI < 0.6 is considered a warning sign), with an onset within 30 d after LDLT (2).

CT angiography was always performed to diagnose HAT and other arterial complications, hepatic arterial angiography was not mandatory. Anastomotic stenosis was diagnosed by hepatic arterial angiography in addition to weakness of the hepatic artery signal on D-US. In this study, we defined that anastomotic stenosis was included as HAT.

As our policy regarding the treatment for hepatic arterial complications, a surgical repair is the first choice in the early phase (within 2 wk) after LT. Especially, emergency hemostasis and surgical repair required for anastomotic bleeding and rupture of anastomotic aneurysm cases.

For the HAT cases, which had the weakness of the hepatic artery flow by D-US and contrast-enhanced CT without liver dysfunction, sufficient intravenous fluid administration and conservative therapy (administration of heparin and/or urokinase) were selected firstly. On the other hand, for the patients with HAT, which have no hepatic artery signal with liver dysfunction, emergency surgical repair is indicated regardless of the timing of HAT onset.

Based on the weakness of the hepatic artery flow, angiography and angioplasty were performed in a limited number of cases with anastomotic stenosis, which occurred over two wk after LT. For the patients with biliary reconstruction using Roux-en-Y limb, we consider that immediate surgical repair is not mandatory, because development of collateral blood route toward the hepatic hilum may be expected in the recipients using Roux-en-Y limb biliary reconstruction in two wk later after LT.

However, it may be considerable to re-reconstruct the hepatic artery for the patients with a biliary reconstruction using a duct to duct fashion, more than two wk after LT. Although surgery was the first choice of therapy for hepatic arterial complications in most cases, angioplasty by interventional radiology (IVR) was simultaneously performed during diagnostic angiography in a limited number of cases with anastomotic stenosis, which occurred over two wk after LT. Conservative therapy for HAT or anastomotic stenosis was defined as continuous systemic administration of urokinase for more than 24 h over a day.

According to the occurrence of post-operative hepatic arterial complications, LDLT recipients in our study were divided into two groups: recipients with hepatic arterial complications (complication group; n = 43) and recipients without complications (non-complication group; n = 630). Recipient demographics and surgical data were compared between the two groups. Risk factors for hepatic arterial complications were analyzed by multivariate analysis.

Statistical analysis

Values are presented as mean ± SD unless otherwise indicated. Discontinuous data were analyzed by Mann–Whitney test, continuous data by Student's *t*-test, and categorical data by chi-square test. Overall survival was calculated using the Kaplan–Meier method and compared using log-rank test. Logistic regression analysis was used for multivariate analysis to assess predictive risk factors for post-operative hepatic arterial complications. Any variable identified as significant ($p < 0.1$) on univariate analysis was considered a candidate for multivariate analysis. Values of $p < 0.05$ were considered significant. All statistical calculations were carried out using SPSS 15.0 statistical software (Chicago, IL, USA).

Results

Post-operative hepatic arterial complications

Post-operative hepatic arterial complications occurred in 43 of the 673 adult recipients (6.4%). Of these, HAT occurred in 28 cases, anastomotic bleeding in seven cases, anastomotic stenosis in five cases, and rupture of anastomotic aneurysm in three cases. The median interval from LDLT to occurrence of hepatic arterial complications was 13 (1–63) d after transplant.

In detail, the median interval from LDLT was 13 d (2–44) in HAT, 5.5 d (1–19) in anastomotic bleeding, 29.5 d (13–63) in anastomotic stenosis, and 18 d (4–33) in rupture of anastomotic aneurysm.

According to graft types, hepatic arterial complication rate was 6.7% (36/535) in right lobe graft LT, 5.1% (6/118) in left lobe grafts, and 16.7% (1/6 cases) in whole liver LT, respectively (not significant). The complication rate was 5.1% (14/272 cases) under surgical loupe and 7.2% (29/401) under microscope ($p = 0.33$, NS).

Biliary complications after hepatic arterial complications occurred in 17 (39.5%) of the 43 cases. They consisted of seven biliary leakages, six liver abscesses, and four biliary stenoses.

Treatment of hepatic arterial complications

Surgical re-anastomosis was performed in 26 cases (16 HAT cases, seven anastomotic bleeding cases and three rupture of anastomotic aneurysm cases), while the other 17 cases (12 HAT cases, five anastomotic stenosis cases) underwent conservative therapies, including four angioplasties by IVR. No patients needed placement of an arterial stent or emergency re-transplantation due to hepatic arterial complications.

Risk factors for hepatic arterial complications

The backgrounds and characteristics of the complication and non-complication groups are shown in Table 1. Univariate analysis showed

Table 1. Background of two subgroups according to HA complications

	Complication group (n = 43)	Non-complication group (n = 630)	p Value
Gender	M 20, F 23	M 318, F 312	0.434
Age	49.6 (22–68)	50.6 (18–69)	0.332
Blood type match	Identical and compatible 36 Incompatible 7	Identical and compatible 542 Incompatible 88	0.653
Graft type	Right lobe 36, left 6 Whole 1	Right 499, left 112, posterior 8 Whole 5, extended lateral 4, lateral 2	0.671
Re-transplantation	2.3% (1/43)	4.9% (32/630)	0.715
HCC patient	30.2% (13/43)	21.4% (135/630)	0.181
Trans-arterial treatment	13.7% (6/43)	6.1% (39/630)	0.058
Operation time (min)	780 (450–1324)	737 (352–1404)	0.034
Blood loss (mL)	5700 (690–46 500)	4945 (250–92 910)	0.322
CIT (min)	79 (23–350)	83.5 (6–710)	0.413
WIT (min)	49.5 (26–81)	83.5 (17–175)	0.279
MELD score	20 (3–41)	17 (3–45)	0.286
Child-Pugh score	10 (7–13)	10 (2–14)	0.466
Mode of arterial reconstruction	Anatomical 37 Extra-anatomical 6	Anatomical 606 Extra-anatomical 24	0.012
Reconstructive procedure	L 14, M 29	L 258, M 372	0.336
Diameter of hepatic artery of grafts (mm)	3.0 (1–5)	3.5 (1.5–5)	0.329
Diameter of recipients' arteries (mm)	3.5 (1.8–6.0)	4.0 (2–6)	0.207
Intra-operative RCC transfusion	11 (0–127)	10 (0–148)	0.033
Intra-operative FFP transfusion	10 (0–70)	6 (0–140)	0.092
Intra-operative PC transfusion	15 (0–75)	10 (0–148)	0.047

L, surgical loupe; M, microscope; RCC, red cell concentrates; FFP, frozen fresh plasma; PC, platelet concentrates.

that prolonged operation time ($p = 0.030$), extra-anatomical anastomosis ($p = 0.012$), and massive intra-operative red cell transfusion ($p = 0.033$) were more frequently found in the complication group compared with the non-complication group (Table 1). Multivariate analysis revealed that extra-anatomical anastomosis ($p = 0.011$) was the only independent risk factor for hepatic arterial complications (Table 2).

Patient survival

The overall survival rate after LDLT was significantly lower in the complication group compared with that in the non-complication group (60.7% vs. 80.1% at one yr, 47.7% vs. 75.4% at three yr, 44.3% vs. 74.2% at five yr respectively; $p < 0.001$) (Fig. 1). Twenty-four patients died in the complication group.

Table 2. Risk factors for hepatic arterial complications

Variable	p Value	Odds ratio	95% confidence interval
Extra-anatomical anastomosis	0.011	3.429	1.327–8.866
Operation time	0.149	1.002	0.999–1.226
Intra-operative RCC transfusion	0.468	1.010	0.983–1.037
Intra-operative PC transfusion	0.509	1.009	0.967–1.016

In detail of the cause of death according to hepatic arterial complications, 15 of 24 cases died of HAT (graft failure four cases, sepsis 11 cases), three cases in anastomotic bleeding (graft failure two cases, sepsis one case), three cases in anastomotic stenosis (graft failure one case, sepsis one case, cerebrovascular diseases one case), and three cases in rupture of anastomotic aneurysm (graft failure three cases).

Discussion

We set out to determine the characteristics of hepatic arterial complications in 673 consecutive adult LDLT recipients, the largest single-center study of LDLT, as far as we know. In our study, the incidence of HAT was 4.2% in adult LDLT recipients, which is in line with previous reports (3, 4). Bekker et al. performed a systematic review of the incidence, outcome, and risk factors of early HAT after LT (3). They reported that the total incidence of early HAT in patients of all age groups was 4.4%, with an incidence of 8.3% in children and 2.9% in adults. The incidence of early HAT in studies reporting only on LDLT was 3.1%, while that on DDLT was 4.6%, with no statistical difference. In contrast, Salvalaggio et al. (4) demonstrated that the incidence of HAT in adult LDLT (3.5%) was significantly higher than that in DDLT (0.8%), due to the small

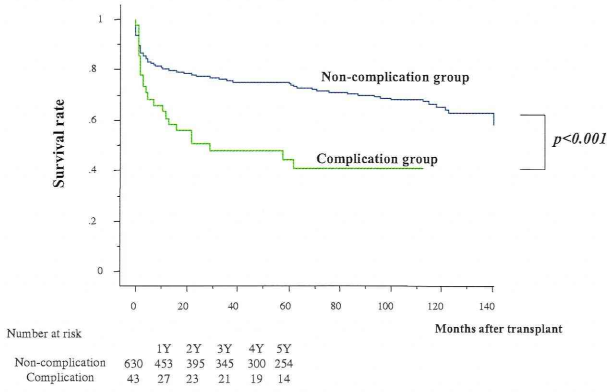

Fig. 1. Survival rates in patients with and without hepatic arterial complications. The overall survival rate after LDLT was significantly lower in the complication group compared with that in the non-complication group (60.7% vs. 80.1% at one yr, 47.7% vs. 75.4% at three yr, 44.3% vs. 74.2% at five yr respectively; $p < 0.001$).

diameter of the vessels and surgical complexity. Due to anatomical constraints, such as small vessel diameter and limited length of arteries in live-donor liver grafts, hepatic arterial reconstructions in LDLT are technically more complicated than those in DDLT.

Several reports have reported the risk factors for hepatic arterial complications after LT (6–11). While, as is well known, a narrow diameter of the hepatic artery makes the reconstructive procedure more difficult and complicated in both adult and pediatric LTs, microsurgical techniques can contribute to reduction of the incidence of hepatic arterial complications (5). Besides artery diameter, greater donor age (>60 yr) (6), prolonged cold ischemic time (7), prolonged warm ischemic time (8), prolonged operation time (8), the combination of a cytomegarovirus positive donor and negative recipient (8–10), ABO incompatibility (11), and Roux-en-Y biliary reconstruction (8) have been reported as risk factors for adult LT.

Our present study demonstrated that extra-anatomical anastomosis was the independent risk factor by multivariate analysis. In particular, extra-anatomical anastomosis is a very important surgical risk factor. Several studies demonstrated the usefulness of extra-anatomical reconstruction using other arteries, such as recipients' gastroduodenal artery (12), splenic artery (12, 13), and right gastroepiploic artery (12, 14), instead of unusable hepatic arteries. Besides these extrahepatic arteries, the condition of patients' vessels sometimes necessitates anastomosis using other arteries as well. For example, we reported successful use of a recipient's sigmoid artery in a pediatric recipient (15) and the mesenteric artery of a Roux-en-Y limb in an adult recipient (16) for hepatic arterial reconstruction.

However, the outcome of extra-anatomical anastomosis was unsatisfactory, due to the high complication rate. Uchiyama et al. (12) reported that approximately half of the patients with extra-anatomical anastomosis suffered anastomotic biliary strictures. According to our results, as much as possible, we try to reconstruct the hepatic artery by anatomical anastomosis fashion.

In present study, re-transplantation cases were 32 cases. Extra-anatomical anastomosis in re-transplantations was performed in seven cases and anatomical anastomosis in other transplantations in 25 cases. The rate of re-transplantation in extra-anatomical anastomosis cases were significantly higher than that in anatomical anastomosis cases (19.4% vs. 3.9%; $p = 0.001$).

However, the hepatic arterial complication occurred in only one case. There was no significant difference in the complication rates between complication and non-complication group.

Basically, re-transplant with extra-anatomical anastomosis was not the risk factor of the hepatic arterial complication. In spite of the high rate of extra-anatomical anastomosis in re-transplant cases, the hepatic arterial complication rate was low.

We speculated that this reason was the use of Roux-en-Y limb in biliary reconstruction in all re-transplantations, because the use of Roux-en-Y limb may contribute to develop the collateral blood route toward the hepatic hilum.

If extra-anatomical anastomosis is avoidable, the more careful check of the condition of arteries (the presences of dissection and arteriosclerosis) before the anastomosis and the tension of anastomosis are very important to prevent the arterial complications.

Because the development of collateral blood route toward the hepatic hilum can't be expected in the cases with a duct to duct biliary reconstruction, the extra-anatomical anastomosis was very careful for especially these patients.

For these difficult situations in high-risk cases, we sometimes filled hepatic hilum with the greater omentum. Additionally, the post-operative anticoagulant therapy and the Doppler US study should be initiated more aggressively and frequently than usual.

Regarding the treatment of hepatic arterial complications, we usually initiated the anticoagulant therapy with heparin and/or thrombolytic therapy with urokinase promptly in suspicious of HAT. Emergency operations for hemostasis and re-anastomosis are undoubtedly the treatment of choice for anastomotic bleeding and rupture of anastomotic aneurysms.

As the ideal treatment for HAT, anastomotic stenosis, and unruptured aneurysms, whether aggressive surgical operation or non-surgical therapies including IVR remains controversial. We have not experienced re-transplantation for HAT, although many reports demonstrated that more than a few recipients with HAT require re-transplantation (3, 4, 8). Prompt revascularization can contribute to the prevention of graft failure and loss following HAT. Meticulous post-transplant follow-up by D-US and laboratory data may contribute to the early detection of compromised hepatic arterial flow, including HAT. Some reports showed that revascularization by transluminal angioplasty (17), thrombolysis (18), and stent placement (19) using IVR was successful for anastomotic stenosis and unruptured aneurysm. Although IVR is a useful and non-invasive procedure, it should be cautioned that long-term patency of the vascular stent remains unknown. Moreover, balloon dilatation for hepatic arterial stenosis carries the potential risk of intimal injury and aneurysm formation (19). Additionally, performing surgical repair of the hepatic artery in case of a failure of such treatment is more difficult. Therefore, although hepatic artery angioplasty during IVR was performed in four of the patients with post-LDLT hepatic artery complications in our study group, surgical repair is, if possible, the first choice of treatment in our institute.

In conclusion, hepatic artery complications are the most critical and fatal complications of LDLT, followed by a moderate incidence of biliary complications. The anatomical anastomosis may be the first choice for the hepatic arterial reconstruction to the extent possible.

Authors' contributions

Study design: Iida T. Acquisition of data: Iida T, Yagi S, Hori T, Uchida Y, Jobara K, Tanaka H, Sakamoto S, Kasahara M, Ogawa K, Ogura Y. Analysis and interpretation: Taku Iida. Manuscript drafted by Taku Iida. Revision: Taku Iida, Shinji Uemoto. Statistical advice: Toshimi Kaido, Akira Mori.

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REVIEW ARTICLE

Perioperative nutritional therapy in liver transplantation

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Abstract Protein-energy malnutrition is frequently seen in patients with end-stage liver disease who undergo liver transplantation. This causes a deterioration of the patients' clinical condition and affects their post-transplantation survival. Accurate assessment of the nutritional status and adequate intervention are prerequisites for perioperative nutritional treatment. However, the metabolic abnormalities induced by liver failure make the traditional assessment of the nutritional status difficult. The methods that were recently developed for accurately assessing the nutritional status by body bioelectrical impedance may be implemented in pre-transplant management. Because preoperative malnutrition and the loss of skeletal muscle mass, called sarcopenia, have a significant negative impact on the post-transplantation outcome, it is essential to provide adequate nutritional support during all phases of liver transplantation. Oral nutrition is preferred, but tube enteral nutrition may be required to provide the necessary caloric intake. We herein discuss both bioelectrical impedance and the latest findings in the current perioperative nutritional interventions in liver transplant patients regarding synbiotics, micronutrients, branched-chain amino acid supplementation, the use of immune system modulating formulas, the fluid balance and the offering of nocturnal meals.

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Keywords Liver transplantation · Immunonutrition · Synbiotics · Nutritional intervention · Sarcopenia

Introduction

The liver orchestrates various physiological processes essential for a well-nourished state. It integrates several biochemical pathways of the metabolism of carbohydrates, fat, proteins and vitamins, as well as the secretion and excretion of bile and the transport of lipids, all of which are involved in muscle and protein metabolism [1–3].

Advances in post-transplantation care and the management of graft rejection have greatly improved the outcomes of patients after orthotopic liver transplantation (OLT). The clinical features of declining liver function tend to normalize following successful organ replacement, but preventing and treating malnutrition in these patients requires more attention [3–7].

Protein-energy malnutrition (PEM) is a common problem in patients with end-stage liver disease (ESLD) awaiting OLT [5, 7]. This applies to nearly every etiology of ESLD with the exception of fulminant hepatic failure. PEM is a risk factor for morbidity and mortality after liver transplantation (LT) [6, 7]. A patient's nutritional status can worsen rapidly during the post-operative period due to preoperative malnutrition, surgical stress, immunosuppressive therapy, post-interventional complications, post-operative protein catabolism and fasting periods [7, 8]. This suggests the need for early nutritional support with liver-adapted formulas containing additional carbohydrates, fat and proteins, especially branched-chain amino acids (BCAAs) [7, 8]. Even in non-cirrhotic and non-diabetic patients, hemihepatectomy results in moderate disturbances in glucose homeostasis, with increases in the