[12–15]. However, the value of pretransplantation BCAA supplementation remains unclear. The aim of the present study therefore was to examine pre- and perioperative predictors, including nutritional factors such as BCAA supplementation, for post-transplantation infectious complications so that a strategy could be established to improve short-term outcomes after LDLT.

Materials and methods

The present study retrospectively analyzed data from 100 consecutive adult patients (46 men and 54 women, ≥18 y old, age range 18–69 y, median age 56 y) who underwent LDLT at the Kyoto University Hospital from February 2008 through February 2010 after introducing the nutritional assessment described below. The Model for End-stage Liver Disease score was 19 (range 7–46). Thirty-two patients were ABO incompatible and 68 were identical or compatible. The indications for LT were hepatocellular carcinoma ($n = 33$), followed by hepatocellular diseases such as hepatitis B or C virus-associated liver cirrhosis ($n = 19$), progressive intrahepatic cholestatic diseases including primary biliary cirrhosis and primary sclerosing cholangitis ($n = 13$), fulminant hepatic failure ($n = 11$), and other causes ($n = 24$). The patients provided written informed consent before the start of the study, which was approved by the ethics committee of Kyoto University and conducted in accordance with the Declaration of Helsinki of 1975 as revised in 1996.

We introduced body composition analysis using multifrequency bioelectrical impedance with eight tactile electrodes (InBody 720; Biospace, Tokyo, Japan) in February 2008 for patients undergoing LT. Patients fast for at least 3 h and void immediately before starting the analysis. Various parameters are automatically measured, including body mass index, intra- and extracellular water levels, body fat mass, protein, and body cell mass (BCM), which is the sum of intracellular fluid and protein and a reliable parameter of nutritional status. The BCM is automatically calculated by the InBody 720 for each patient and displayed as a normal range (e.g., 23.0~28.1 kg). Low and high BCM values are below the lower limit and above the upper limit, respectively. Ten patients who could not undergo a preoperative InBody 720 examination because of emergency surgery were excluded from the BCM analysis.

Preoperative nutritional therapy was administered for about 2 wk before LDLT at the discretion of the surgeon or attending physician after admission to our department. The therapy consisted of a nutrient mixture enriched with BCAAs (Aminoleban EN; Otsuka Pharmaceutical Co., Tokyo, Japan) or BCAA nutrients (Livact; Ajinomoto Pharma Co., Tokyo, Japan) or no nutrient mixture. Thirty-seven patients received the preoperative BCAA-enriched nutrient mixture (100 g/d), 28 received the BCAA nutrients (12.45 g/d), and 35 received no nutritional therapy. Dietitians adjusted the type and amount of food for each patient to maintain a total caloric intake of 35 to 40 kcal/kg and a protein intake of 1.2 to 1.5 g/kg, including the BCAA nutrients, according to the guidelines of the European Society of Parenteral and Enteral Nutrition.

The selection criteria for the recipients and the surgical techniques for recipient operations have been described in detail elsewhere [16–18]. Immunosuppressive therapy usually consisted of tacrolimus or cyclosporine and low-dose steroids, as described elsewhere [18,19].

We examined the preoperative risk factors (including preoperative nutritional parameters) for post-transplantation sepsis, post-transplantation bacteremia, and in-hospital death from infection. Data on the following recipient variables for each patient were analyzed: age of recipient, gender, original disease underlying the need for LT, ABO compatibility, Child–Pugh classification, Model for End-stage Liver Disease score, graft type (right or left lobe), graft-recipient weight ratio, operative duration, operative blood loss, pretransplantation BCM, and preoperative nutritional therapy. We defined the conditions fulfilling the diagnostic criteria for the systemic inflammatory response syndrome with infections, including blood, urine, and pulmonary infection, as sepsis [20]. Infections were defined using the criteria proposed by the Centers for Disease Control and Prevention and based on reports of liver transplant patients [21]. The isolation of bacteria other than common skin contaminants from a single blood culture in the presence of clinical symptoms or of an infection was considered bacteremia. When caused by common skin contaminants, bacteremia was considered significant only if an organism was isolated from two blood cultures and clinical signs of infection were evident.

Statistical analysis

Categorical variables were compared using the chi-square test or the Fisher exact test where appropriate. Any variable identified as significant ($P < 0.05$) or with $P < 0.10$ in univariate analyses using the chi-square or Fisher exact test was considered a candidate for multivariate analysis using multiple logistic regression models. $P < 0.05$ was considered statistically significant. All data were statistically analyzed using JMP 5.0.1 (SAS Institute, Cary, NC, USA).

Results

Post-transplantation sepsis

Univariate analysis showed that an age younger than 60 y, a Model for End-stage Liver Disease score of at least 20, a low pretransplantation BCM, and the absence of preoperative supplementation with the BCAA-enriched nutrient mixture were of prognostic significance for post-transplantation sepsis (Table 1). Multivariate analysis showed that a low pretransplantation BCM ($P = 0.032$) and no preoperative BCAA-enriched nutrient supplementation ($P = 0.020$) were of independent prognostic significance for post-transplantation sepsis (Table 2).

Bacteremia

An age younger than 60 y, a Child–Pugh C classification, a perioperative blood loss of at least 10 L, and no preoperative BCAA-enriched supplementation were risk factors for bacteremia (Table 3). Multivariate analysis showed that a Child–Pugh C classification ($P = 0.002$) and a perioperative blood loss of at least 10 L ($P = 0.018$) were independent risk factors for post-transplantation bacteremia (Table 4).

Table 1
Univariate analysis of factors affecting post-transplantation sepsis

Variable	Incidence of event	*P*
Age (y)		0.001
<60 ($n = 68$)	72%	
≥60 ($n = 32$)	38%	
Gender		0.051
Male ($n = 46$)	52%	
Female ($n = 54$)	70%	
Original disease		0.460
HCC ($n = 34$)	50%	
HBV/HCV ($n = 19$)	68%	
PBC/PSC ($n = 20$)	70%	
FHF ($n = 8$)	75%	
Others ($n = 19$)	58%	
ABO blood type		0.166
Compatible ($n = 61$)	57%	
Incompatible ($n = 39$)	71%	
Child–Pugh class		0.112
A/B ($n = 39$)	51%	
C ($n = 61$)	67%	
MELD score		0.021
<20 ($n = 55$)	51%	
≥20 ($n = 45$)	73%	
GRWR (%)		0.163
<0.8 ($n = 28$)	50%	
≥0.8% ($n = 72$)	65%	
Graft		0.924
Right ($n = 57$)	61%	
Left ($n = 43$)	60%	
Operative time (h)		0.403
<12 ($n = 25$)	68%	
≥12 ($n = 75$)	59%	
Operative blood loss (L)		0.476
<10 ($n = 65$)	58%	
≥10 ($n = 35$)	66%	
Preoperative BCM		0.002
Low ($n = 24$)	83%	
Normal or high (n = 64)	48%	
Preoperative BCAA-enriched nutrient mixture		0.001
Present ($n = 37$)	38%	
Absent ($n = 63$)	73%	

BCAA, branched-chain amino acid; BCM, body cell mass; FHF, fulminant hepatic failure; GRWR, graft-to-recipient weight ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cirrhosis

Table 2
Multivariate analysis of factors affecting post-transplantation sepsis

Variable	OR	95% CI	P
Preoperative low BCM	4.633	1.493–17.701	0.032
Absence of preoperative BCAA-enriched nutrient mixture	3.201	1.202–7.849	0.020

BCAA, branched-chain amino acid; BCM, body cell mass; CI, confidence interval; OR, odds ratio

In-hospital death from infection

An age younger than 60 y, a Child–Pugh C classification, and a low preoperative BCM were significant risk factors for in-hospital death from infection (Table 5). Multivariate analysis showed that only a low preoperative BCM ($P = 0.004$) was an independent risk factor (Table 6).

Discussion

The present study examined the risk factors affecting three types of infectious complications after LDLT. We identified the independent risk factors as a Child–Pugh C classification, massive perioperative blood loss, a low pretransplantation BCM, and the absence of preoperative supplementation with a BCAA-enriched nutrient mixture. Decompensated liver cirrhosis, indicated by a Child–Pugh C classification, is usually accompanied by deteriorated immune function and nutritional status at the time of LT. Thus, a Child–Pugh C classification was undoubtedly a risk factor for postoperative infection, which is in line with the results of our previous report [22]. Massive perioperative bleeding is an established factor for postoperative complications of digestive surgery and LT, and massive blood loss is usually associated with massive blood transfusion. Homologous blood transfusion has adverse effects such as a risk of infection and graft-versus-host disease. This detrimental effect is supposed to be caused by a non-specific immunosuppression such as decreased CD4/CD8 ratios [23,24] and natural killer cell activity [25,26]. We recently

Table 4
Multivariate analysis of factors affecting post-transplantation bacteremia

Variable	OR	95% CI	P
Child–Pugh class C	4.253	1.731–11.294	0.001
Operative blood loss ≥10 L	2.983	1.229–7.541	0.018

CI, confidence interval; OR, odds ratio

Table 3
Univariate analysis of factors affecting post-transplantation bacteremia

Variable	Incidence of event	P
Age (y)		0.011
<60 (n = 68)	51%	
≥60 (n = 32)	25%	
Gender		0.470
Male (n = 46)	39%	
Female (n = 54)	46%	
Original disease		0.880
HCC (n = 34)	41%	
HBV/HCV (n = 19)	53%	
PBC/PSC (n = 20)	45%	
FHF (n = 8)	38%	
Others (n = 19)	37%	
ABO blood type		0.245
Compatible (n = 61)	39%	
Incompatible (n = 39)	52%	
Child–Pugh class		0.001
A/B (n = 39)	23%	
C (n = 61)	56%	
MELD score		0.059
<20 (n = 55)	35%	
≥20 (n = 45)	53%	
GRWR (%)		0.639
<0.8 (n = 28)	39%	
≥0.8 (n = 72)	44%	
Graft		0.309
Right (n = 57)	47%	
Left (n = 43)	33%	
Operative time (h)		0.726
<12 (n = 25)	40%	
≥12 (n = 75)	44%	
Operative blood loss (L)		0.012
<10 (n = 65)	34%	
≥10 (n = 35)	60%	
Preoperative BCM		0.093
Low (n = 24)	54%	
Normal or high (n = 64)	34%	
Preoperative BCAA-enriched nutrient mixture		0.015
Present (n = 37)	26%	
Absent (n = 63)	52%	

BCAA, branched-chain amino acid; BCM, body cell mass; FHF, fulminant hepatic failure; GRWR, graft-to-recipient weight ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cirrhosis

Table 5
Univariate analysis of factors affecting in-hospital death from infection

Variable	Incidence of event	P
Age (y)		0.017
<60 (n = 68)	19%	
≥60 (n = 32)	3%	
Gender		0.369
Male (n = 46)	17%	
Female (n = 54)	11%	
Original disease		0.462
HCC (n = 34)	6%	
HBV/HCV (n = 19)	21%	
PBC/PSC (n = 20)	20%	
FHF (n = 8)	13%	
Others (n = 19)	16%	
ABO blood type		0.684
Compatible (n = 61)	13%	
Incompatible (n = 39)	16%	
Child–Pugh class		0.030
A/B (n = 39)	5%	
C (n = 61)	20%	
MELD score		0.118
<20 (n = 55)	9%	
≥20 (n = 45)	20%	
GRWR (%)		0.192
<0.8 (n = 28)	7%	
≥0.8 (n = 72)	17%	
Graft		0.550
Right (n = 57)	16%	
Left (n = 43)	12%	
Operative time (h)		0.293
<12 (n = 25)	8%	
≥12 (n = 75)	16%	
Operative blood loss (L)		0.213
<10 (n = 65)	11%	
≥10 (n = 35)	20%	
Preoperative BCM		0.003
Low (n = 24)	29%	
Normal or high (n = 64)	5%	
Preoperative BCAA-enriched nutrient mixture		0.884
Present (n = 37)	14%	
Absent (n = 63)	15%	

BCAA, branched-chain amino acid; BCM, body cell mass; FHF, fulminant hepatic failure; GRWR, graft-to-recipient weight ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cirrhosis

Table 6
Multivariate analysis of factors affecting in-hospital death from infection

Variable	OR	95% CI	P
Preoperative low BCM	8.372	2.092–42.181	0.004

BCM, body cell mass; CI, confidence interval; OR, odds ratio

reported that a low pretransplantation BCM and the absence of preoperative BCAA-enriched supplementation are closely associated with postoperative sepsis [27]. The present findings supported not only our previous results but also demonstrated the powerful impact of pretransplantation nutritional conditions and preoperative treatment with a BCAA-enriched nutrient mixture on infectious complications.

The reason for the beneficial effects of pretransplantation BCAA supplementation remains unclear. One possible explanation is the improvement in pretransplantation nutritional status. Some nutritional parameters, such as prealbumin, total lymphocyte count, and the BCAA/tyrosine ratio, were significantly improved by a pretransplantation nutritional intervention including the BCAA-enriched nutrient mixture (unpublished data). Another possible reason is the improvement of the immune system. Bassit et al. [28] reported that BCAA supplementation improves the ability of peripheral blood mononuclear cells to proliferate in response to mitogens after long-distance intense exercise. García-de-Lorenzo et al. [29] reported that septic patients receiving a high-BCAA preparation showed a decreased mortality and improved nutritional parameters. In patients with advanced liver cirrhosis, Kakazu et al. [30] showed that increasing extracellular concentrations of BCAAs ex vivo improved the function of myeloid dendritic cells. Our results suggest that a preoperative BCAA-enriched supplementation can help to prevent postoperative sepsis through nutritional and immune improvements, although a randomized controlled study is required to confirm this hypothesis. Taken together with our findings demonstrating that the absence of post-transplantation enteral nutrition is a risk factor affecting in-hospital mortality after LT [1], perioperative nutritional treatment represents a promising strategy for improving short-term outcomes after LT.

Based on the present findings, we considered establishing an interventional strategy against these risk factors to prevent post-transplantation infectious complications. A Child–Pugh C classification is an indication for LT. In contrast, massive blood loss, pretransplantation low BCM, and the absence of preoperative BCAA-enriched supplementation are factors that can be altered to some extent. Blood loss can be decreased by more careful surgical maneuvering and the frequent application of hemostatic devices during the dissection of the liver from the surrounding ligaments and the inferior vena cava. The sum of intracellular fluid and body protein, BCM, is considered a highly reliable parameter of nutritional status. Especially for patients undergoing LT who usually have abundant extracellular fluid, such as edema and ascites, the BCM can assess their nutritional status more accurately than other nutritional parameters, including the body mass index and lean body mass. A low BCM in patients with cirrhosis suggests a decrease in skeletal muscle volume, which could interfere with early postoperative mobilization and result in pulmonary complications, including aspiration pneumonia and atelectasis. Therefore, we recently introduced a pretransplantation rehabilitation program to encourage early postoperative mobilization and avert pulmonary dysfunction. Because LDLT is an elective procedure that differs from deceased donor LT, a pretransplantation rehabilitation program can be implemented until the day of transplantation.

The prevalence of metabolic disorders, including the metabolic syndrome, in the LT population has recently attracted attention [31–33]. The prevalence of the metabolic syndrome in patients after LT is significantly higher than that estimated in the general population, and the metabolic syndrome is associated with an increased risk of major vascular events and long-term fibrosis progression. Therefore, the prevention of the metabolic syndrome after LT would also be a crucial objective of perioperative nutritional treatment.

Supplementation with a BCAA-enriched nutrient mixture is reportedly beneficial not only for patients with liver cirrhosis but also for patients undergoing hepatectomy [23–26]. However, the value of pretransplantation BCAA supplementation has remained unclear. Our results suggest that a preoperative BCAA-enriched supplementation can help to prevent postoperative sepsis, although a randomized controlled study is required to confirm this notion. Taken together with our findings demonstrating that the absence of post-transplantation enteral nutrition is a risk factor affecting in-hospital mortality after LT [1], perioperative nutritional treatment should be a promising strategy to improve short-term outcomes after LT.

Conclusion

Preoperative nutritional status, supplementation with a nutrient mixture enriched with BCAAs, and massive operative blood loss were closely associated with the occurrence of post-transplantation infectious complications. Perioperative management, including nutritional therapy, is needed to improve short-term outcomes after LT.

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Effects of Post-transplant Enteral Nutrition with an Immunomodulating Diet Containing Hydrolyzed Whey Peptide after Liver Transplantation

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Abstract

Background Complications due to infections, including bacteremia, often arise after liver transplantation (LT) and are the most frequent causes of in-hospital death. Hydrolyzed whey peptide (HWP), a protein complex derived from milk, has anti-inflammatory effects. The present study retrospectively analyzes the effects of early enteral nutrition with a new immunomodulating diet (IMD) enriched with HWP in patients after living-donor LT (LDLT).

Methods Data from 76 consecutive adult patients who underwent LDLT at our institute between September 2009 and March 2011 were retrospectively analyzed. The new IMD enriched with HWP and a conventional elemental diet were administered enterally to 40 (HWP group) and 36 (control group) patients, respectively, within the first 24 h after surgery.

Results The characteristics of patients and surgical parameters did not differ between the two groups. The incidence of bacteremia was significantly lower in the HWP (15%) than in the control group (47%) ($p = 0.002$). The in-hospital mortality due to infection was a little lower in the HWP group than in the control group, although there was no statistical difference ($p = 0.145$). The fasting blood glucose level at postoperative day 7 was significantly lower in the HWP group than in the control group ($p = 0.005$). The incidence of acute cellular rejection was similar between the two groups ($p = 0.858$).

Conclusion Early enteral nutrition with the new IMD enriched with HWP can prevent post-transplant bacteremia and post-transplant hyperglycemia without increasing the incidence of acute cellular rejection.

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Introduction

Protein-energy malnutrition is common in patients with end-stage liver disease requiring liver transplantation (LT) and is closely associated with a post-transplant risk of morbidity and mortality [1–5]. Complications due to infections, including bacteremia, often arise after LT and are the most frequent causes of in-hospital death [6]. Therefore, the prevention of post-transplant complications due to infections has a crucial role in improving short-term outcomes after LT.

The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines, published in 2006, recommend the early initiation of normal food intake or enteral feeding after organ transplantation as well as after gastrointestinal surgery [7]. These guidelines also recommend an immunomodulating formula (enriched with arginine, omega-3 fatty acids, and nucleotides), especially for patients with an obviously severe nutritional risk and those who underwent major surgery. In contrast to gastrointestinal surgery, little evidence supports the notion that early enteral nutrition is beneficial for patients after LT. We reported that the absence of postoperative enteral nutrition is an independent risk factor for in-hospital mortality after adult living-donor LT (LDLT) [6]. Moreover, our pilot prospective study showed that early enteral nutrition with a new immunomodulating diet (IMD) enriched with hydrolyzed whey peptide (HWP), a protein complex derived from milk, prevents post-transplant bacteremia and shortens the postoperative hospital stay [8].

The antioxidant, antihypertensive, antiviral, anti-inflammatory, and antibacterial effects of HWP should be beneficial [9]. Furthermore, the formula contains isomaltulose, a disaccharide composed of glucose and fructose with a glycosidic bond as the main carbohydrate substrate. Isomaltulose is often used instead of sugar in diets for patients with diabetes mellitus since it prevents postprandial hyperglycemia due to slow resolution. However, the clinical effect in patients after LT is unclear.

The present study retrospectively analyzed the effects of early enteral nutrition with a new IMD enriched with HWP on the incidence of infections and blood sugar levels in patients after LDLT.

Patients and methods

Patients

Seventy-six consecutive adult patients (male, $n = 33$; female, $n = 43$; median age = 53.5 (range = 15–67) years) who underwent LDLT at our institute between September 2009 and March 2011 were retrospectively analyzed in this study. The indications for LT were hepatocellular carcinoma in 20 patients; hepatocellular diseases such as hepatitis B or C virus-associated or alcoholic liver cirrhosis in 16; progressive intrahepatic cholestatic diseases, including primary biliary cirrhosis and primary sclerosing cholangitis in 13; fulminant hepatic failure in 9; and other causes, including alcoholic cirrhosis and biliary atresia after Kasai's operation in 18. The median model for end-stage liver disease (MELD) score was 19 (range = 6–48). The study was conducted in accordance with the Declaration of Helsinki following approval from our Institutional Review Board.

Surgical procedures and immunosuppressive treatments

Orthotopic LDLT was performed using a left-lobe graft for 42 patients and a right-lobe graft, including a posterior segment graft, for 34 patients. Surgical procedures for the donor and the recipient have been described elsewhere [10–12]. At the time of surgery, a tube jejunostomy was placed in the proximal jejunum using a 9-Fr enteral tube. Regarding compatibility, 20 and 56 patients were ABO-incompatible and ABO-identical or -compatible, respectively. The median graft-to-recipient body weight ratio (GRWR) was 0.83 (range = 0.53–1.27).

Immunosuppressive treatment usually consisted of tacrolimus or cyclosporine and low-dose steroids as described [12, 13]. All patients received a bolus injection of 10 mg/kg of steroid immediately after reflow during surgery. We then routinely administered 1, 0.5, and 0.3 mg/kg/day of intravenous steroid from postoperative days (POD) 1–3, 4–6, and 7, respectively, to ABO-identical or -compatible patients. Thereafter, we administered 0.3 mg/kg/day p.o. of steroid until POD 28 and 0.1 mg/kg/day until POD 90. For ABO-incompatible patients, we implemented a new protocol in 2009 consisting of preoperative anti-CD 20 antibody (Rituximab, 300 mg/body) with preoperative plasma exchange to lower the anti-AB antigen titer; perioperative mycophenolate mofetil from 7 days before LDLT (starting and maintenance doses of 500 and 1,000 mg/day, respectively); and continuous postoperative intraportal administration of steroids (125 mg/day) until POD 7 via a catheter intraoperatively positioned in the mesenteric vein, followed by the oral regimen described above until POD 90 [14, 15]. Therefore, both groups received the same doses of steroids. All patients received intravenous prophylaxis with ampicillin (0.5 g) and cefotaxime (0.5 g) twice daily for 3 days starting 30 min before surgery.

Blood glucose was controlled using exogenous insulin to avoid post-transplant hyperglycemia due to extant diabetes mellitus, impaired glucose tolerance, intra- and postoperative steroid challenge, or surgical diabetes. We administered continuous intravenous insulin using a sliding scale to maintain blood sugar between 100 and 160 mg/dl, at least until POD 14.

Enteral nutrition and study groups

We did not use total parenteral nutrition after LT since we removed the central venous catheter within 7 days of the procedure, subject to the status of the recipient, to prevent catheter-related fever. Therefore, we delivered nutrients mainly via the jejunal catheter and partly via the peripheral venous catheter until oral nutrition was started. An anesthesiologist positioned the central venous, peripheral venous, and Swan-Ganz catheters in all patients before surgery. We usually removed the central venous and Swan-Ganz catheters within 7 days of LT to prevent catheter-related infection.

Early enteral nutrition was started within the first 24 h after surgery through a tube jejunostomy. The starting total daily caloric intake of 10–15 kcal/kg until POD 3 was gradually increased to 25–35 kcal/kg. Forty patients (HWP group) received the new IMD enriched with HWP (MHN-02, MEIN®; Meiji Dairies Co., Tokyo, Japan) and 36 (control group) received a conventional elemental diet (Elental®, Ajinomoto Pharma Co., Tokyo, Japan), which was our standard nutrient mix until August 2009 according to the preferences of the surgeons. The initial infusion rate was 20 ml/h. If well tolerated, the enteral infusion rate was increased to 40 ml/h by POD 5. Oral nutrition was started after swallowing ability was confirmed, usually around POD 5. Dieticians calculated the daily amounts of protein

and carbohydrate required for each recipient and adjusted the speed of the enteral nutrition according to oral intake to make the total daily caloric intake in both groups similar. Enteral feeding was stopped when the patients could tolerate adequate oral intake containing solid food. This was usually between 10 and 14 days after LDLT. For synbiotics, all patients received both the enteral supplementation product enriched with glutamine, dietary fiber, and oligosaccharide (GFO®; Otsuka Pharmaceutical Factory, Tokushima, Japan) three times daily and a lactic fermented beverage containing 5×10^8/ml of *Lactobacillus casei* Shirota strain (Yakult 400®; Yakult Honsha Co., Tokyo, Japan) once a day via the feeding tube or orally until discharge. The new IMD enriched with HWP contains the following per 100 kcal: protein, 5.0 g; carbohydrate, 13.3 g (the main component is the disaccharide isomaltulose); and lipids, 2.8 g. Elental® contains per 100 kcal: protein, 4.4 g (the main components are L-glutamine, 0.644 g; L-serine, 0.386 g; and L-arginine hydrochloride, 0.375 g); carbohydrates, 21.1 g (the main component is the dextrin); and lipids, 0.17 g.

Analyzed parameters

The primary endpoint was the incidence of postoperative bacteremia during the first 30 postoperative days. We cultured blood samples from patients with a fever above 38°C or at the time of central venous catheter replacement. Infections were defined using the criteria proposed by the U.S. Centers for Disease Control and Prevention and based on previous findings of liver transplant patients [16]. Bacteremia was defined as the isolation of bacteria, other than common skin contaminants, from a single blood culture within 90 days after transplantation in the presence of clinical symptoms or signs of infection such as fever or tachycardia. Bacteremia caused by common skin contaminants was considered significant only if the organism was isolated from two blood cultures and accompanied by clinical signs of infection. Primary bacteremia was classified as being of unknown origin (no physical, radiological, or pathological evidence of a definite infection source) or related to an intravascular catheter infection. Secondary bacteremia was defined if the source was determined, that is, when an organism isolated from blood cultures was compatible with a related nosocomial infection at another infected site (urine, intra-abdominal abscess, bile, or peritoneal fluid; bronchoalveolar fluid or bronchial aspirate).

Secondary endpoints were in-hospital death due to infection, fasting blood glucose at POD 7, and an incidence of biopsy-proven acute cellular rejection. We defined infection-related death as death due to severe infection such as bacteremia.

Demographic data such as age, gender, underlying liver diseases; ABO compatibility; Child-Pugh classification; MELD score; preoperative nutritional parameters such as prealbumin, zinc level, and branched-chain amino acids/tyrosine ratio (BTR); and surgical data, including graft type, GRWR, surgical duration, and blood loss were compared between the two groups.

Statistical analysis

Data are presented as mean ± SD for continuous variables. Data were statistically analyzed by JMP 5.0.1 (SAS Institute, Cary, NC, USA). Discrete variables were compared using the χ^2 test. Continuous variables were nonparametrically analyzed using the Mann–Whitney U test. A p value < 0.05 was regarded as significant.

Results

Demographic and surgical data

Preoperative, demographic (age, gender, underlying disease, ABO compatibility, Child-Pugh classification, and MELD score), and nutritional parameters did not significantly differ between the two groups (Table 1). Operative time, blood loss, number of units of erythrocyte concentrates transfused, graft type, and GRWR also did not significantly differ between groups (Table 2).

Table 1 Demographic data of patients

	HWP ($n = 40$)	Control ($n = 36$)	p
Recipient age (years)	47.8 ± 14.8	53.2 ± 13.4	0.098
Gender (male/female)	19/21	14/22	0.494
Underlying disease			0.642
Hepatocellular carcinoma	8	12	
Hepatitis B/C-related cirrhosis	10	6	
Cholestatic disease	8	5	
Fulminant liver failure	4	5	
Other	10	8	
ABO compatibility			0.448
Identical/compatible	31	25	
Incompatible	9	11	
Child-Pugh classification			0.879
A, B/C	14/26	12/24	
MELD score	18.4 ± 9.6	19.8 ± 7.1	0.483
Prealbumin (mg/dl)	7.9 ± 4.9	7.2 ± 5.1	0.523
BTR	3.0 ± 1.5	2.7 ± 1.3	0.592
Zinc (μg/dl)	50.7 ± 17.1	46.4 ± 18.3	0.312

HWP hydrolyzed whey peptide, *MELD* median model for end-stage liver disease, *BTR* branched-chain amino acids/tyrosine ratio

Table 2 Surgical variables

	HWP ($n = 40$)	Control ($n = 36$)	p
Graft type			0.364
Left lobe	20	22	
Right lobe	20	14	
GRWR (%)	0.87 ± 0.21	0.84 ± 0.17	0.425
Surgical duration (min)	867 ± 181	850 ± 138	0.648
Blood loss (ml)	8267 ± 7704	11555 ± 8420	0.080

HWP hydrolyzed whey peptide, *GRWR* graft recipient weight ratio

Table 3 Primary and secondary endpoints

	HWP ($n = 40$)	Control ($n = 36$)	p
Bacteremia	6 (15%)	17 (47%)	0.002
In-hospital death due to infection	4 (10%)	8 (22%)	0.145
Fasting blood glucose at POD 7 (mg/dl)	125 ± 30	145 ± 36	0.005
Acute cellular rejection	5 (13%)	5 (14%)	0.858

HWP hydrolyzed whey peptide, *POD* postoperative day

Primary and secondary endpoints

Table 3 summarizes the outcomes of primary and secondary endpoints. The incidence of bacteremia was significantly lower in the HWP group than in the control group ($p = 0.002$). Six (15%) of 40 and 17 (47%) of 36 patients in the HWP and elemental diet (ED) groups, respectively, developed bacteremia. Of the six recipients in the HWP group who developed episodes of bacteremia, two and four had primary and secondary bacteremia, respectively. The sources of secondary bacteremia were cholangitis in two patients and a liver abscess and pneumonia in one each. The principal causative pathogens of bacteremia were methicillin-resistant *Staphylococcus aureus* (MRSA) in two patients and *Pseudomonas aeruginosa*, methicillin-resistant coagulase negative staphylococci (MRCNS), *Enterococcus*, and *Klebsiella* in one patient each. Among the 17 recipients with episodes of bacteremia in the control group, 10 and 7 had primary (including two that were catheter-related) and secondary bacteremia, respectively. The sources of the secondary bacteremia were cholangitis in three patients, pneumonia in two, and a liver abscess and bile leakage in one each. The principal causative pathogens of bacteremia were MRSA and *Enterococcus* in four patients each, *Pseudomonas aeruginosa* in three, MRCNS and *Klebsiella* in two patients each, and methicillin-sensitive *Staphylococcus aureus* and *Acinetobacter* in one each.

The in-hospital mortality due to infection was a little lower in the HWP group than in the control group, although there was no statistical difference ($p = 0.145$). Fasting blood glucose level at POD 7 was significantly lower in the HWP group ($p = 0.005$), but the incidence of acute cellular rejection was similar between the two groups ($p = 0.858$).

Discussion

Early postoperative enteral nutrition using a new IMD with HWP significantly reduced the incidence of post-transplant bacteremia in patients who underwent LDLT. These findings were in line with those of our recent prospective pilot study. We originally intended to perform a prospective randomized controlled study based on the pilot study [8]. However, because the new IMD with HWP lowered the incidence of post-transplant bacteremia, to conduct a prospective randomized controlled study would not have been ethical. Therefore, we retrospectively analyzed the results of 76 adult patients who underwent LDLT in our center.

The ESPEN guidelines for enteral nutrition after surgery, including organ transplantation, recommend starting enteral feeding within 24 h of surgery since several studies have shown that early enteral nutrition lowers the rate of postoperative complications due to infections and the duration of hospitalization [7]. These guidelines indicate early tube feeding for patients who cannot tolerate early oral nutrition or who are obviously malnourished at the time of surgery. Since most patients who undergo LT have poor nutrition, liver recipients comprise a good indication for early enteral nutrition. However, the effects of postoperative IMD have not been analyzed, especially after LDLT. We discovered here that early enteral nutrition using IMD reduced the incidence of bacterial infections after LT.

Plank et al. [17] reported that pre- and postoperative IMD in patients undergoing deceased-donor LT might help to hasten post-transplant recovery and reduce postoperative complications due to infections. They investigated the effects of an IMD during the waiting period and at 5 days after LT. We examined the effects of postoperative IMD only within 24 h of LDLT. Most LDLT recipients cannot consume sufficient food at POD 5. We usually administer an IMD via jejunostomy more than 14 days after LT when the anti-inflammatory properties of the diet might be more effective. Our findings are clinically significant because they showed that appropriate postoperative nutritional intervention can prevent bacteremia. Patients undergoing emergency LDLT for acute liver failure have little time to receive nutritional intervention. Therefore, early enteral

nutrition with a new IMD enriched with HWP could be a novel strategy with which to prevent post-transplant complications due to infections.

How the diet actually exerts such beneficial effects is unclear but we believe that the HWP is involved because its components include lactoferrin, β-lactoglobulin, α-lactalbumin, glycomacropeptide, and immunoglobulins that enhance the immune system [9].Furthermore, HWP also has antioxidant, antihypertensive, antiviral, anti-inflammatory, and antibacterial effects. One study has shown that HWP prevents the development of D-galactosamine-induced hepatitis and liver fibrosis by suppressing increases in plasma alanine and aspartate aminotransferase activities and increases of inflammatory cytokines, including IL-1β and IL-6 in a rat model [18]. We are presently investigating the molecular mechanisms involved in the anti-inflammatory effects of HWP.

Another other possible mechanism of the IMD is anti-hyperglycemia. Fasting blood sugar levels at POD 7 were significantly lower in the HWP group than that in the control group. One of the aims of the present study was to evaluate the effect of isomaltulose (the main carbohydrate substrate in the formula) on fasting blood sugar levels after LT. The considerable amount of steroid administered to the patients after LT as well as surgical diabetes and extant insulin resistance could easily cause postoperative hyperglycemia. On the other hand, early enteral nutrition was started within 24 h of surgery through tube jejunostomy, and if well tolerated, the enteral infusion rate was increased to 40 ml/h by postoperative POD 5. Moreover, oral nutrition was started after swallowing ability was confirmed, usually around POD 5. Therefore, we minimized the effects of factors other than enteral nutrition by measuring blood sugar levels only on POD 7. The daily median insulin requirements of the HWP and control groups on POD 7 were 24 (range = 12–72) and 36 (range = 12–96) U, respectively, and did not statistically differ between the two groups. Strictly speaking, the calorie intake in both groups might have differed, although dieticians calculated the daily requirements of protein and carbohydrate for each recipient and adjusted the speed of enteral nutrition according to oral intake. Nonetheless, this finding is notable because postoperative hyperglycemia is closely associated with postoperative complications in general surgery. In contrast, the role of hyperglycemia during the perioperative period in LT is not fully understood. Park et al. [19] reported that intraoperative hyperglycemia is independently associated with post-transplant infection at surgical sites. Steroids, immunosuppressants, and surgical diabetes cause hyperglycemia after LT. The disaccharide isomaltulose in the enteral formula might help maintain low blood sugar levels. If so, then isomaltulose has potential for wide application in perioperative care among patients with diabetes mellitus who undergo general surgery.

In conclusion, early enteral nutrition with an IMD enriched with HWP helps prevent post-transplant bacteremia and post-transplant hyperglycemia without an increase in the incidence of acute cellular rejection.

Conflict of interest The authors have no conflicts of interest or financial ties to disclose.

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LIVER TRANSPLANTATION 18:602-607, 2012

ORIGINAL ARTICLE

Standard Hepatic Vein Reconstruction With Patch Plasty Using the Native Portal Vein in Adult Living Donor Liver Transplantation

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An outflow obstruction of the hepatic vein is a critical complication after living donor liver transplantation (LDLT) and occasionally leads to hepatic failure. Here we introduce a simple method for preventing outflow obstructions by patch plasty in adult LDLT. Between September 2001 and May 2010, 468 adult LDLT procedures were performed at Kyoto University Hospital. We harvested each recipient's portal vein (PV) from the extirpated liver for a patch. We intended to re-form several orifices of the hepatic veins into a single, large orifice. The patch was attached to the anterior wall of the re-formed orifice on the bench. After we put in the liver graft, the procedure for the hepatic vein anastomosis to the inferior vena cava was simple enough that the warm ischemia time was reduced. Three of the 468 cases were diagnosed with an outflow obstruction. All 3 cases underwent hepatic vein reconstruction without patch plasty. In contrast, none of the 159 cases that underwent LDLT with patch plasty suffered from an outflow obstruction, regardless of the liver graft type. The procedure for hepatic vein plasty using a patch from the native PV is simple and elegant and results in excellent outcomes. We propose this as the standard procedure for hepatic vein reconstruction in adult LDLT. *Liver Transpl 18:602-607, 2012.* © 2012 AASLD.

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An outflow obstruction of the hepatic vein is a critical complication after liver transplantation.[1] Once it occurs, the liver graft is impaired by congestion, which results in jaundice, massive ascites, coagulopathy, and occasionally hepatic failure. Outflow obstructions after liver transplantation are caused by strictures and/or torsion on the anastomosis of the hepatic vein to the inferior vena cava (IVC).[2] The incidence has been reported to be 2% to 7% in living donor liver transplantation (LDLT).[3-5] Many procedures for the prevention of hepatic vein outflow obstructions have been reported.[6-19] Using the recipient's native portal vein (PV), we have managed to prevent outflow obstructions by simple patch plasty on the anterior wall of the hepatic vein. We collected patients' clinical data retrospectively, and here we introduce our simple method for hepatic vein reconstruction in adult LDLT and its excellent outcomes.

PATIENTS AND METHODS

Patients

Between September 2001 and May 2010, 468 adult LDLT procedures were performed at Kyoto University Hospital. The patient data are shown in Table 1. The

Abbreviations: EMS, self-expandable metallic stent; GRWR, graft-to-recipient weight ratio; IVC, inferior vena cava; LDLT, living donor liver transplantation; LEIV, left external iliac vein; LHV, left hepatic vein; LOV, left ovarian vein; MHV, middle hepatic vein; M/LHV, common trunk of middle and left hepatic veins; POD, postoperative day; PV, portal vein; RHV, right hepatic vein; UFV, umbilical fissure vein; V5, drainage vein of segment 5; V8, drainage vein of segment 8.

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TABLE 1. Recipient Demographics, Graft Types, and Survival Rates

	Total (n = 468)	Hepatic Vein Reconstruction: Without Patch Plasty (n = 309)	Hepatic Vein Reconstruction: With Patch Plasty (n = 159)	*P* value
Graft type (n)				
Left lobe with MHV	85	51	34	0.01*
Right lobe without MHV	299	205	94	
Right lobe with MHV	73	47	26	
Right lateral sector	11	6	5	
GRWR (%)†	1.06 ± 0.27	1.11 ± 0.27	0.95 ± 0.23	<0.001‡
Caliber of hepatic vein anastomosis (mm)†	30.0 ± 5.4§	29.3 ± 4.8‖	31.3 ± 6.3¶	0.01‡
Survival (%)				
1 year	81	80	81	0.53#
3 years	76	75	77	
5 years	73	72	77	

*Pearson test.
†The data are presented as means and standard deviations.
‡Wilcoxon test.
§n = 425.
‖n = 279.
¶n = 146.
#Log-rank test.

graft types were as follows: left lobe with the middle hepatic vein (MHV) (85 cases), right lobe without the MHV (299 cases), right lobe with the MHV (73 cases), and right lateral sector (11 cases). Our protocol for hepatic vein reconstruction changed over this time period. Before 2005, we performed only cavoplasty to make a large orifice without any patch.[3,20,21] We started to selectively use a patch on the anterior wall of the vein anastomosis for right lobe grafts with the MHV in January 2005, and we expanded the indications to all right lobe grafts in April 2006 and to all cases (including left lobe grafts) in July 2008. The protocol for selecting the liver graft type was also altered according to the expanded indications for the lower limit of the graft-to-recipient weight ratio (GRWR). To minimize the risks to healthy donors, we gradually decreased the lower GRWR limit to preferentially select a left lobe over a right lobe graft (from 0.7% in December 2007 to 0.6% in April 2009). We simultaneously managed to control the PV pressure of recipients to overcome small-for-size graft syndrome.[22,23] Consequently, the recent cases included a high proportion of left lobe grafts with low GRWRs.

The study protocol was approved by the ethics committee of Kyoto University Hospital and was performed in accordance with the ethical standards of the Declaration of Helsinki, which was established in 1964.

Hepatic Vein Plasty on the Bench

We always monitored the PV pressure of the recipient by inserting a catheter via a jejunal mesenteric vein during the operation.[22] If major collateral veins (eg, splenorenal shunts) had not developed with liver cirrhosis, the PV pressure was increased by test clamping of the PV trunk. We created a temporary portocaval shunt to prevent portal hypertension during the anhepatic period.

We harvested the recipient's PV from his liver after a total hepatectomy. We typically used the PV bifurcation and cut it longitudinally to make a wide patch. If we could not use the recipient's PV (eg, hepatocellular carcinoma at the hilus of the liver or PV thrombosis), we used another vein for the patch (eg, the donor's ovarian vein or inferior mesenteric vein or the recipient's inferior mesenteric vein). When the liver graft had several nearby but separated orifices of the major hepatic veins [eg, the MHV, left hepatic vein (LHV), and umbilical fissure vein (UFV) in a left lobe graft or the right hepatic vein (RHV) and drainage vein of segment 8 (V8) in a right lobe graft], we performed vein plasty by partial side-to-side suturing of these veins with 6-0 polypropylene stitches to turn them into a single orifice. The prominent septum between these veins had to be resected before suturing. We intended to prepare a single vein orifice for the anastomosis with a caliber as large as 30 mm. The patch was attached to the anterior wall of the hepatic vein by continuous sutures with 6-0 polypropylene stitches on the bench. An extremely wide patch was trimmed to a width of no less than 1 cm (Figs. 1 and 2).

For a right lobe graft without the MHV, we evaluated the drainage territory of each tributary of the MHV [ie, the drainage vein of segment 5 (V5) and V8] by computed tomography volumetry before transplantation. We planned to reconstruct each tributary to be more than 10% of the liver graft volume or to be larger than 5 mm in caliber. We used the donor's ovarian vein or

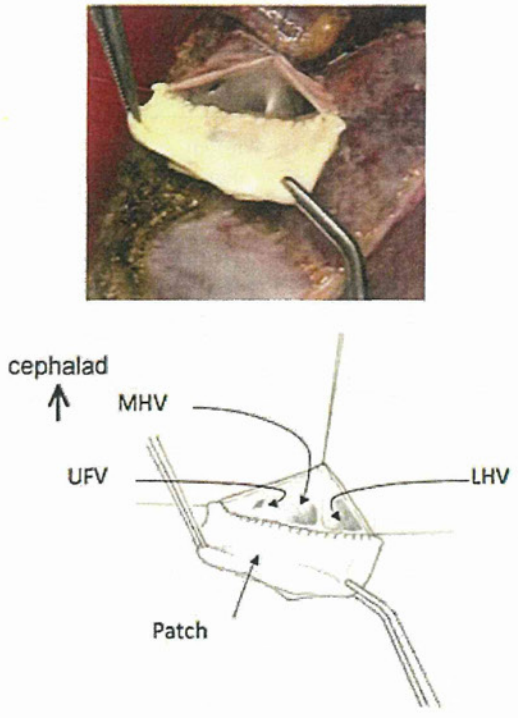

Figure 1. Patch plasty of the hepatic vein on the bench. For a left lobe graft with the MHV, a patch made from the recipient's PV was attached to the anterior wall of the cuff of the MHV and LHV.

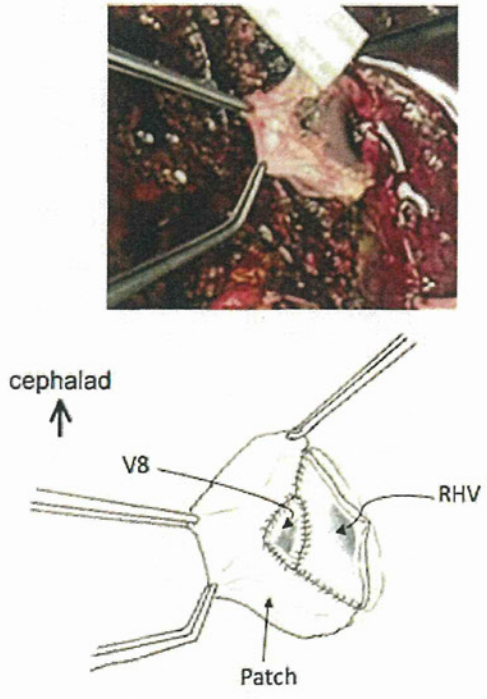

Figure 2. Patch plasty of the hepatic vein on the bench. For a right lobe graft without the MHV, after the separated RHV and V8 were sutured in a side-to-side fashion to make a single orifice, a patch was attached to the anterior wall of the RHV and V8.

inferior mesenteric vein, the recipient's left PV branch, or the external iliac vein to reconstruct the MHV tributary (Fig. 3). We reconstructed the inferior RHV according to the same criteria to prevent graft congestion.[24]

For a left lobe graft, the recipient's IVC was incised rightward from the stump of the MHV and LHV to make a large orifice. An end-to-side anastomosis between the graft's venous orifice with the patch and the recipient's cuff of the MHV and LHV was created with 5-0 polypropylene stitches.[20] For a right lobe graft, the recipient's IVC was incised caudally from the RHV stump, and a piece of the anterior wall was excised to make a large orifice. The graft's venous orifice with the patch was anastomosed with the recipient's enlarged RHV orifice.[21] Although a complicated reconstruction of hepatic veins on the bench (see Fig. 3) extended the anhepatic time as well as the cold ischemia time, the procedure for the hepatic vein anastomosis to the IVC was simple enough for the warm ischemia time to be reduced after we put in the liver graft. We carefully placed the liver graft in a suitable position so that the anastomosed vessels would not suffer from torsion or tension.

Diagnosis of Outflow Obstructions After LDLT

We routinely performed Doppler ultrasound twice per day after LDLT until postoperative day (POD) 14, then once per day until POD 28, and finally once per week until discharge. When any symptoms appeared (eg, the disappearance of the pulsatile waves of the hepatic vein, decreased PV flow on Doppler ultrasound, or increased ascites output), we performed dynamic computed tomography to evaluate any strictures or torsion of the hepatic vein anastomosis and parenchymal congestion.[24] Needle biopsy of the liver, when it could be performed safely without ascites, could be helpful for diagnosing outflow obstructions with findings of congestion, such as hemorrhaging around the central veins. When an outflow obstruction was suspected because of ultrasound, computed tomography, and biopsy findings, hepatic venography and manometry were performed to estimate the pressure gradient across the anastomosis site. When we diagnosed a stricture and an outflow obstruction with a pressure gradient greater than 3 mm Hg, the radiologist simultaneously performed balloon dilatation. When there was no improvement in the clinical symptoms within a few weeks, we performed venoplasty with repeated balloon dilatation or self-expandable metallic stent (EMS) placement.[25]

RESULTS

The mean caliber of the anastomosis orifice of the main hepatic vein was 30.0 ± 5.4 mm for 425 cases according to written data in the surgical records. The calibers of the anastomoses with and without patch plasty were 31.3 ± 6.3 (n = 146) and 29.3 ± 4.8 mm (n = 279), respectively ($P < 0.01$; Table 1).

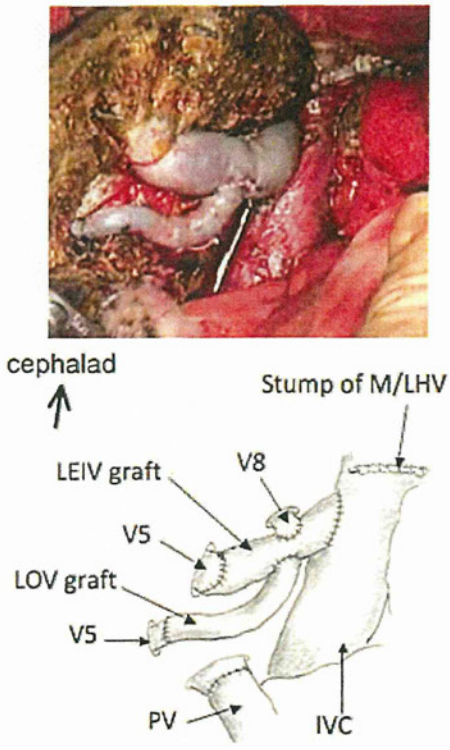

Figure 3. Simplification of hepatic vein reconstruction on the bench. For a right lobe graft without the MHV that had 2 orifices for V5 and 1 orifice from V8, the recipient's LEIV graft was interposed between the larger V5 orifice (upper) and the anterior wall of the RHV to prepare a single, large venous orifice for anastomosis. The recipient's LOV graft was interposed between the smaller V5 orifice (lower) and a newly opened side hole of the former vein graft. V8 was anastomosed to another newly opened side hole in the former vein graft. After the liver graft was put into the recipient, a single anastomosis for these tributaries was performed.

We definitively diagnosed outflow obstructions by venography and manometry in 3 of the 468 consecutive cases of adult LDLT (0.6%). All 3 cases underwent hepatic vein reconstruction without patch plasty for LDLT. Two of the 205 cases receiving a right lobe graft without the MHV were diagnosed with outflow obstructions on PODs 105 and 12. The calibers of the anastomosed RHVs of the liver grafts were 22 and 35 mm, respectively, at the time of LDLT. They were treated with balloon dilatation. Because the clinical symptoms of the latter case did not improve after balloon dilatation, venoplasty with EMS was performed (successfully) on POD 21. One of the 51 cases receiving a left lobe graft with the MHV was diagnosed with an outflow obstruction, and that patient was treated with balloon dilatation on POD 27. The caliber of the anastomosis orifice was 30 mm at the time of LDLT. These 3 patients who were treated for outflow obstructions were still alive 6.0, 3.5, and 3.6 years after the operation. In contrast, none of the 159 patients who underwent hepatic vein plasty with a patch on the anterior wall suffered from outflow obstructions, regardless of the liver graft type (Table 2).

TABLE 2. Incidence of Outflow Obstructions

	Hepatic Vein Reconstruction		
Graft Type	Without Patch Plasty	With Patch Plasty	Total
Left lobe with MHV	1/51	0/34	1/85
Right lobe without MHV	2/205	0/94	2/299
Right lobe with MHV	0/47	0/26	0/73
Right lateral sector	0/6	0/5	0/11
Total	3/309	0/159	3/468

NOTE: The data are presented as the number of patients with outflow obstructions divided by the total number of patients.

DISCUSSION

Outflow obstructions are some of the most serious complications after liver transplantation, and they occur more frequently with LDLT versus deceased donor liver transplantation because the anastomosis of the hepatic veins to the IVC is much narrower and more complicated than the anastomosis of the IVC to the IVC, and the liver graft is enlarged because of regeneration after transplantation.[1,26] Transplant surgeons have tried to prevent outflow obstructions in hepatic vein anastomoses by many procedures.[6-20]

Posttransplant outflow obstructions are more frequent in children, and children occasionally experience a later onset than adults.[27-31] It has been suggested that the regeneration of the liver graft and the narrower caliber of the recipient's IVC are responsible for outflow obstructions in children. We have to consider the anatomical alterations secondary to the regeneration of the liver graft after LDLT for not only pediatric recipients but also adult recipients.[2,32]

Once an outflow obstruction occurs, the function of the liver graft is rapidly impaired by congestion, and early treatment with interventional radiology (IVR) is necessary.[20,33] Because repeated balloon dilatation is not always effective, some cases require venoplasty with an EMS.[34,35] After EMS placement, the patient's condition must be controlled with anticoagulants for years. This situation is disadvantageous for posttransplant patients because many treatments (eg, liver biopsy for graft dysfunction, interferon therapy for recurrent hepatitis C, and biliary stenting for strictures) carry considerable risk of bleeding for patients undergoing anticoagulant therapy.

Many procedures have been reported for the prevention of hepatic vein outflow obstructions.[6-19] Sugawara et al.,[18,36] Hwang et al.,[19] and Goralczyk et al.[6] introduced V- or diamond-shaped patch plasty, quilt venoplasty, and posterior cavoplasty for RHV reconstruction, respectively. Suehiro et al.[9] and Takemura et al.[10] reported venoplasty with cavoplasty and patch plasty in left liver grafts, respectively. Each method

was designed to enlarge the hepatic vein anastomosis and make adjustments for the changes caused by liver regeneration.

For the same reason, we perform patch plasty on the anterior wall of the hepatic vein with the recipient's PV. Our method is much simpler and is applicable to every type of liver graft, including left lobe grafts, right lobe grafts with the MHV, right lobe grafts without the MHV, and right lateral sector grafts. Each procedure is easy to perform on the bench, and there is no need to cross-clamp the recipient's IVC. Mizuno et al.[8] reported that this method improved hemodynamics and liver function. We have confirmed the advantages of this method by a retrospective study of many patients over a long follow-up period.

For years, we have made an effort to prevent outflow obstructions after hepatic vein reconstruction.[3,20,30,31,37] Although cadaveric vein grafts are useful for the complicated arrangements of reconstructions,[36] they are difficult to prepare because of the low supply and high costs. The harvesting of the vein wall as a patch from the PV of the extirpated native liver is applicable in almost all cases. For the prevention of outflow obstructions, it is necessary (but not sufficient) to make a large anastomosis for the hepatic vein. Although the calibers of the anastomoses with patch plasty were statistically larger than the calibers of the anastomoses without patch plasty (31.3 ± 6.3 and 29.3 ± 4.8 mm, $P = 0.01$) in this study, the clinical significance of this slight difference (2 mm) is unclear. The calibers of the hepatic vein anastomoses at the time of LDLT in the 3 patients who suffered from posttransplant outflow obstructions were 22, 30, and 35 mm; indeed, except for 1 case, these vessels were not small. We observed no outflow obstructions in the 159 patients who underwent LDLT with patch plasty on the anterior wall of the hepatic vein, regardless of the liver graft type. Some slack in the anterior wall of the anastomosis can help to relieve tension in the hepatic vein and IVC as well as torsion and kinking caused by liver regeneration. The procedure is very simple and is available for every type of LDLT, and it results in excellent outcomes. We propose hepatic vein plasty with a patch from the native PV as a standard procedure for hepatic vein reconstruction in adult LDLT.

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ORIGINAL ARTICLE

Left-sided grafts for living-donor liver transplantation and split grafts for deceased-donor liver transplantation: Their impact on long-term survival

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Summary
Background: A small-for-size graft is important in living-donor liver transplantation (LDLT) and deceased-donor liver transplantation (DDLT).
Subjects and methods: First, we confirmed the effect of initial graft volume on survival using a rat model of liver transplantation (LT). We then evaluated the actual long-term survival based on graft type in 1421 LTs (including 1364 LDLTs) at Kyoto University and 2000 DDLTs at the Mayo Clinic, to evaluate donor safety in LDLT and the possibility of shifting to split orthotopic liver transplantation (SOLT) in DDLT.
Results: In the rat model, SOLTs with 40%- and 20%-grafts had a poor survival. A total of 697 pediatric LTs showed good long-term outcomes (survival rate was 0.764 at 21.2 years). The survival rate of 724 adult LTs was 0.664 at 17.8 years. The survival rates of auxiliary partial orthotopic liver transplantation with a left-sided graft (0.421 at 15.0 years) and SOLT with a left-sided graft (0.000 at 0.8 years) need to be improved. Although the survival rate of 1965 adult DDLTs with a whole-liver graft in the Mayo Clinic was 0.727 at 12.8 years, that of adult SOLT was 0.595 at 11.0 years.
Conclusion: From the viewpoint of greater donor safety and expanded donor candidates in LDLT, the choice of a left-sided graft still remains controversial. A shift to SOLT to achieve excellent results should be established to resolve a donor shortage in DDLT.

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Background

Use of a small-for-size graft is still controversial in the liver transplantation (LT) field, i.e., living-donor liver transplantation (LDLT) and deceased-donor liver transplantation (DDLT). A small-for-size graft is defined as a graft to recipient weight ratio (GRWR) less than 0.8 or a ratio of graft weight against standard liver volume (SLV) less than 40% [1,2], and these grafts result in a high mortality and morbidity.

Anatomically, in normal liver, the right and left lobes have hepatic volumes of approximately 60% and 40% against the whole-liver, respectively. Although a right lobectomy is currently a safe procedure because of surgical development, a left lobectomy is safer from the viewpoint of hepatic remnant for the living donor. Moreover, the choice of a left-sided graft for recipients is preferred from the viewpoint of greater donor safety and expanded donor candidates. Additionally, successful split orthotopic liver transplantation (SOLT) [3] for recipients could resolve a donor shortage in DDLT. Although the GRWR and percentage SLV are affected by the recipient's weight or size, the selection of the graft type itself is also crucial for LT to increase donor safety in LDLT and to resolve a donor shortage in DDLT.

In the current study, first, we confirmed the effect of initial graft volume on survival by using an animal model, because many factors may affect the clinical survival after LT. We then retrospectively evaluated the actual long-term survival based on graft type (not GRWR or percentage SLV) in LDLT and DDLT, to evaluate donor safety in LDLT and the possibility of a shift to SOLT in DDLT.

Subjects and methods

Animals

Male Lewis rats (haplotype in major histocompatibility complex: RT-1^l) at eight to 10 weeks of age (body weight of 230–250 g) were used as donors and recipients. The grafts were syngeneic. The study protocol was approved by the institutional ethics review committee (IACUC A19609).

Animal models for orthotopic liver transplantation

An institutional model of rat transplantation has been developed during the last two decades. Operative procedures are described in detail elsewhere for orthotopic liver transplantation (OLT) with a whole-liver graft (100%-OLT) [4] and SOLT [5]. Anatomical findings, surgical materials, graft type and postoperative care are described in detail elsewhere [4,5]. For the SOLT models, we performed SOLTs with graft volumes of 20%, 40% and 60% against the SLV value [5]. Cold ischemic time was two hours in 4 °C of normal Ringer's solution. Each group comprised 10 cases. Previously, we reported that the most important factor for successful OLT was an anhepatic phase less than 15 minutes and that inappropriate samples should be omitted by autopsy findings and histopathological assessment because surgical complications due to technical difficulty will affect the data [4,5]. All recipients in this study fulfilled the criterion of an anhepatic phase less than 15 minutes and there were no surgical complications. This study focused on survival curves, and therefore, we closely monitored survival after surgery (every four hours in 100%-OLT and every one hour in each SOLT).

Overall long-term survival in a large number of living-donor liver transplantations

Although Kyoto University started an LT program from 1990, LDLT is still mainly used. Institutional graft selection and surgical procedures in LDLT are described in detail elsewhere [6]. A total of 1421 recipients who underwent LT from 1990 to 2009 (1364 LDLTs, 31 auxiliary partial orthotopic liver transplantations [APOLTs], 18 OLTs with a whole-liver graft in DDLT or domino liver transplantation [DLT] and eight SOLTs in DDLT or DLT) were evaluated. The follow-up period was 7.76 ± 5.61 years. Overall survivals were separately evaluated in pediatric and adult recipients. Moreover, survivals were separately assessed according to LT type and graft type. The study protocol was approved by institutional ethics review committees (C-279).

A total of 697 LTs at Kyoto University were pediatric recipients. Pediatric recipients were divided into DDLT (OLT) with a whole-liver graft ($n = 1$), LDLT with a right-lobe graft without the middle hepatic vein (MHV) ($n = 13$), LDLT with a left-lobe graft ($n = 83$), LDLT with an extended lateral-segment, lateral-segment, mono-segment or reduced mono-segment graft ($n = 587$), APOLT with an extended lateral-segment or lateral-segment graft ($n = 9$) and DDLT or DLT (SOLT) with an extended lateral-segment, lateral-segment or left-lobe graft ($n = 4$).

A total of 724 LTs at Kyoto University were adult recipients. Adult recipients were divided into DDLT or DLT (OLT) with a whole-liver graft ($n = 17$), LDLT with a right-lobe graft (with or without MHV) ($n = 555$), LDLT with an extended lateral-segment, posterior segment or left-lobe graft ($n = 126$), APOLT with a right-lobe graft ($n = 3$), APOLT with an extended lateral-segment or left-lobe graft ($n = 19$), DDLT (SOLT) with a right-lobe graft ($n = 2$) and DDLT or DLT (SOLT) with a left-lobe graft ($n = 2$).

Overall long-term survival in a large number of deceased-donor liver transplantations

DDLT is the main LT used in the USA, and a total of 2000 recipients who underwent LT in the Mayo Clinic from 1998 to 2011 were evaluated. All recipients were adults, and recipients were divided into DDLT (OLT) with a whole-liver graft ($n = 1965$), DDLT (SOLT) with a right-lobe graft ($n = 18$) and DDLT (SOLT) with a left-lobe graft ($n = 17$). The follow-up period was 4.82 ± 3.21 years. Institutional graft selection and surgical procedures in DDLT are described in detail elsewhere [7–9]. Survivals were separately evaluated according to graft type. The study protocol was approved by institutional ethics review committees (IRB 09-003057).

Statistical analysis

Data are presented as mean ± standard deviation. The Kaplan-Meier method (the log-rank test) was used for

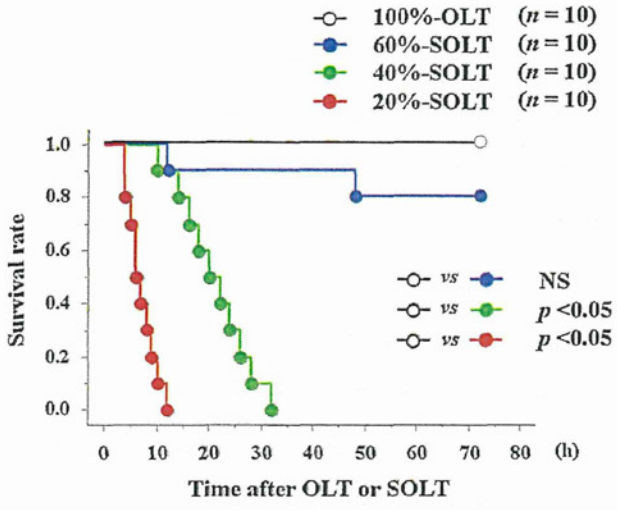

Figure 1 Survival curves of each graft volume in rats. Syngeneic grafts were used in this study. NS: not significant ($P \geq 0.05$).

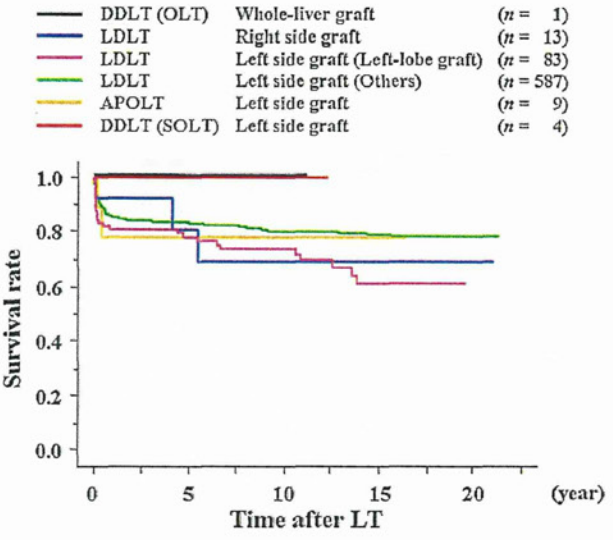

Figure 2 Survival curves of pediatric living-donor liver transplantation.

survival curves and survival rate analysis. Statistical calculations were performed by SPSS Version 16.0 (SPSS Software Version 16.0; SPSS Inc., Chicago, IL, USA). A *P* value less than 0.05 was considered statistically significant, and a *P* value greater or equal to 0.05 was considered as not significant.

Results

Survival curves in the animal model

Actual survival curves are shown in Fig. 1. Both 40%-SOLT and 20%-SOLT were significantly worse compared with 100%-OLT ($P < 0.0001$), but 60%-SOLT did not reach statistical difference ($P = 0.5006$).

Survival curves of pediatric living-donor liver transplantations

Survival curves for each graft type are shown in Fig. 2. Although the survival rate at 21 years after LDLT was 0.692 in LDLT with a right-lobe graft, the survival rate at 19.5 years after LDLT was 0.0609, even in LDLT with a left-lobe graft, which appeared to have the worst long-term survival. Overall, pediatric LT showed good long-term outcomes (survival rate in all 697 cases at 21.2 years after LT was 0.764).

Survival curves of adult living-donor liver transplantations

Survival curves for each graft type are shown in Fig. 3. The survival rate in all 724 cases at 17.8 years after LT was 0.664. Overall, APOLT with a left-sided graft (survival rate at 15.0 years after LDLT was 0.421) and SOLT with a left-sided graft (survival rate at 0.8 years after LDLT was 0.000) need to have improved long-term outcomes, even if LDLT with left-sided grafts is considered acceptable (survival rate at 17.8 years after LDLT was 0.629). Overall, survival needs to be improved in LTs with left-sided grafts.

Survival curves of adult deceased-donor liver transplantations

Survival curves for each graft type are shown in Fig. 4. Survival rates were 0.727 at 12.8 years after OLT, 0.637 at 10.8 years after SOLT with a left-lobe graft and 0.556 at 11.0 years after SOLT with a right-lobe graft. Overall, unexpectedly, it appeared that DDLT (SOLT) with a left-lobe graft showed a better survival curve than that with a right-lobe graft, but this was not significantly different ($P = 0.6599$). The SOLT survivals appeared to be poor compared with those for OLT with a whole-liver graft, but there were no significant differences with SOLT ($P = 0.8161$ in a left-lobe graft

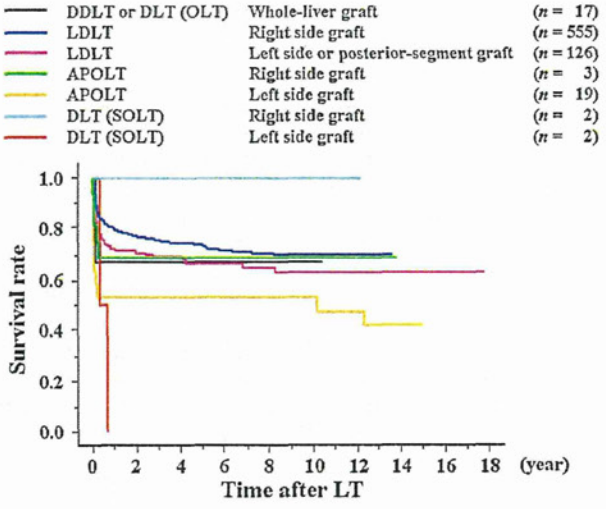

Figure 3 Survival curves of adult living-donor liver transplantation.

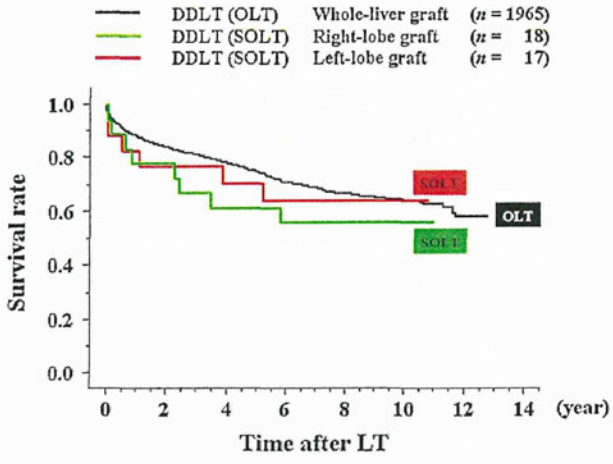

Figure 4 Survival curves of adult deceased-donor liver transplantation.

and $P = 0.3007$ in a right-lobe graft). The SOLT survival rate needs to be improved (survival rate was 0.595 at 11.0 years after SOLT).

Discussion

After LT, liver regeneration occurs even if the initial graft volume is insufficient, and there is still immunological tolerance with implantation of allogeneic antigens. Organically and geometrically, many factors have mutual effects on the postoperative course and outcome of LT. Many clinical studies have already documented important risk factors or reliable predictors of postoperative course or outcome after LT, such as recipient age, donor age, original disease, Model for End-Stage Liver Disease or Pediatric End-Stage Liver Disease score, cold ischemic time, GRWR, percentage SLV, operative time, blood loss, ABO compatibility and lymphocyte cross-match [10—16]. It is difficult to determine how graft type affects outcome. Therefore, at first, we confirmed the effect of initial graft volume on survivals using an animal model using syngeneic grafts. According to the definition of a small-for-size graft, SOLTs with a graft volume less than 40% showed poor outcomes.

In pediatric LT, even smaller sized grafts can provide sufficient GRWR or percentage SLV, because the recipient body is also small. Paradoxically, a large-for-size graft is problematic in the pediatric LT field. Mono-segment or reduced mono-segment grafts have already been introduced [17], and then this issue was resolved from the viewpoint of graft volume. Similar to previous studies, we showed that pediatric LT usually showed good outcomes, although a poor outcome in LT for newborns or infants still remains a problem [18].

On the other hand, insufficient graft volume is predestinate in adult LDLT. The minimum graft size required for LDLT to provide adequate hepatic function has been reported to be a SLV of 40% or GRWR of 0.8 [2]. For insufficient graft volume, APOLT was established to increase liver volume after LT [19], although there are some limitations in the choice of recipients. From the viewpoint of graft size, a right-lobe graft with or without the MHV has been introduced in adult LDLT [20,21]. From the viewpoint of the donor safety, the major concern in adult LDLT is the selection of right-lobe graft, with or without the MHV. In our institution, an algorithm of graft selection based on the congestion volume in each segment (i.e., the segmental drainage of MHV) is well worked in adult LDLT [22—24]. Preoperative careful evaluation of the donor anatomy is crucial for the donor safety, especially in the adult LSLT using a right-lobe graft with the MHV. The right-lobe graft has become the standard graft type for adult LDLT, although the harvest of a larger graft has a high risk in some donors. Therefore, donor safety and graft volume conflict with each other. This is an ironic dilemma. A smaller sized graft is safer for living donors, but satisfactory results still need to be achieved for these grafts.

Donor shortage is problematic in DDLT. Although DDLT is still not widespread in Japan according to the concept of death (e.g., being brain-dead is not always considered as being dead), donor shortage is severe even in the USA and Europe. If whole-liver allografts from cadaveric donors can always be split, a cadaver donor can provide liver allografts to more DDLT recipients. It is also preferred that OLT with a whole-liver graft eventually shifts to SOLT with a guarantee of excellent results in DDLT recipients who receive smaller sized grafts. Even though it unexpectedly appeared that DDLT (SOLT) with a left-lobe graft showed a better survival curve than that with a right-lobe graft in our study, the survival rate of SOLT is still not acceptable.

Problems in the LT field such as ABO incompatibility may be resolved on a daily basis [14]. Since we recognized that intentional modulation of portal pressure during LDLT prevents small-for-size syndrome [1,25,26], the acceptable minimum graft size at Kyoto University is currently a GRWR greater than 0.7 at graft selection [1]. The GRWR value already became to never reflect clinical course and outcome [27], and the smallest GRWR with a successful LDLT is 0.49 [1]. Graft types clearly shifted from left-sided grafts to right-lobe grafts after this surgical strategy was reported [27]. However, it appears that more advanced strategies using the approach of developments in pretransplant evaluations, immunological tolerance, treatments for original diseases, postoperative infectious controls and methodologies for excellent liver regeneration are also crucial in the LT field.

Many basic researchers focus on severe small-for-size grafts such as the 20%-graft, because the results are more drastic, and differences are obvious if their hypotheses are correct. In adult recipients of LDLT or DDLT (SOLT), we often experience the fulfilment of small-for-size grafts (GRWR < 0.8 or SLV < 40%), especially in the choice of a left-sided graft rather than a right-lobe graft, although graft selection of SLV less than 20% is impossible. Although GRWR and percentage SLV are affected by factors of the recipient, a stable graft selection of a left-sided graft has an advantage in LDLT and DDLT (SOLT). Based on the current status of long-term survivals, to overcome a smaller sized graft, use of an approximately 40%-graft appeared to have a reasonable effect and an actual advantage for LT, even though in our study, it unexpectedly appeared that DDLT (SOLT) with a left-lobe graft showed a better survival curve than that with a right-lobe graft. Establishment of excellent results with a 40%-graft will ultimately provide the