TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Clinical significance of gastrointestinal bleeding after living donor liver transplantation

Koichi Kimura, Toru Ikegami, Yuki Bekki, Mizuki Ninomiya, Yo-ichi Yamashita, Tomoharu Yoshizumi, Shohei Yoshiya, Yuji Soejima, Noboru Harada, Ken Shirabe and Yoshihiko Maehara

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

Keywords
gastrointestinal bleeding, graft dysfunction, living donor liver transplantation.

Correspondence
Koichi Kimura MD, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan.
Tel.: +81 92 642 5466;
fax: +81 92 642 5482;
e-mail: cubicseal@gmail.com

Conflicts of interest
The authors have no conflicts of interest to disclose.

Received: 7 January 2014
Revision requested: 17 February 2014
Accepted: 24 March 2014
Published online: 10 May 2014

doi:10.1111/tri.12325

Summary

The clinical presentations of gastrointestinal bleeding (GIB) occurring after living donor liver transplantation (LDLT) have not been fully described. We performed a retrospective analysis of 297 LDLT cases. Nineteen patients (6.4%) experienced GIB after LDLT. The etiology of GIB included bleeding at the jejunojejunostomy following hepaticojejunostomy ($n = 13$), peptic ulcer disease ($n = 2$), portal hypertensive gastropathy ($n = 2$), and other causes ($n = 2$). Hemostasis was achieved in 13 patients (68.4%) by endoscopic ($n = 3$), surgical ($n = 1$), or supportive treatments ($n = 15$), but not in the other six patients. Graft dysfunction ($P < 0.001$), hepaticojejunostomy ($P = 0.01$), portal vein pressure at the end of surgery >20 mmHg ($P = 0.002$), and operative blood loss >10 L ($P = 0.004$) were risk factors. One-year graft survival rate was significantly lower in patients with GIB than in patients without GIB ($P < 0.001$). The inhospital mortality rate was 52.6% for patients with GIB, 75.0% for patients with graft dysfunction, and 14.3% for patients without graft dysfunction ($P = 0.028$). Despite its infrequency after LDLT, GIB has strong correlation with graft dysfunction and inhospital mortality.

Introduction

Although liver transplantation is the treatment of choice for patients with end-stage liver disease, several matters still need to be addressed, especially early postsurgical complications such as gastrointestinal bleeding (GIB) [1]. In prior reports, the prevalence of GIB after deceased donor liver transplantation (DDLT) using whole liver grafts was around 10%, with peptic ulcer disease being the most common cause of GIB [2,3]. It was also reported that the risk of graft and patient mortality attributable to GIB increased significantly after LDLT [2].

In Japan, the predominant mode of liver transplantation is living donor liver transplantation (LDLT), even though the procurement of deceased donor organs was legalized in 1997, with revisions in eligibility criteria in 2009 [4]. Therefore, for the last two decades, strategies to improve the success of LDLT in adults have been the focus of research by identifying unique but significant factors that affect the outcomes of LDLT [5–7]. Although some factors, including graft size mismatch or recipient disease severity, could influence the outcomes of LDLT, continuous and significant portal hypertension caused by excessive graft inflow was proposed as the major factor responsible for poor outcomes [8–11]. For this reason, we hypothesized that such factors could also contribute to the development of GIB after LDLT in adults. To date, however, very few reports have investigated the etiology of GIB in LDLT. Therefore, in this study, we reviewed the cases of GIB after LDLT in adults treated at a single center. We sought to characterize the possible risk factors, pathophysiology, and outcomes of GIB, and hopefully to guide preventive strategies.

Materials and methods

Patients

A total of 297 adults (>20 years old) who underwent LDLT at Kyushu University Hospital from January 2003 to

December 2012 were included in this study. The graft types included left lobe grafts ($n = 166$), right lobe grafts ($n = 118$), and posterior segment grafts ($n = 5$). All LDLT procedures were performed after obtaining full informed consent from the patients. The liver transplantation committee and the institutional review board at Kyushu University approved this study in compliance with the Declaration of Helsinki. Medical charts were retrospectively reviewed to obtain the patients' data.

Graft selection process

Grafts were selected as previously described [12]. Left lobe grafts were considered the primary graft type if the desired GV/SLV was >35%. Right lobe grafts were considered if the simulated GV/SLV of the left lobe graft was <35% and the donor's remnant liver volume was >35%. Major middle hepatic vein tributaries >5 mm in diameter were maximally reconstructed to maintain uncongested GV/SLV >40% in right lobe grafts [12]. The surgical procedures involved in graft procurement are described in our previous report [13].

Recipient surgical procedures

Risky gastroesophageal varices were treated before LDLT by endoscopic approaches. The surgical procedures in the recipients are described in our previous report [14]. PVP was continuously measured during surgery using a cannula (Medicut LCV-UK catheter 14G™; Nippon Sherwood Inc., Tokyo, Japan) placed in the superior mesenteric vein. After total hepatectomy with or without venovenous bypass, the grafts were transplanted in a piggyback fashion. The orifice of the recipient's hepatic vein was enlarged with an incision on the vena cava for the venous anastomosis to provide sufficient outflow. After venous anastomoses, the portal vein was reconstructed, followed by reperfusion. Arterial anastomosis was performed under a microscope.

Biliary reconstruction was performed after reperfusion using a method chosen according to the number and size of graft duct openings and the anatomic variation of the biliary system. Duct-to-duct anastomosis was performed if possible [15]. If duct-to-duct anastomosis was not possible because of poor biliary blood supply, inflamed/sclerosed bile ducts, primary sclerosing cholangitis as the primary disease or if the bile duct was injured, hepaticojejunostomy with jejunojejunostomy was performed instead. Interrupted 6-0 PDS-II (Ethicon Inc., Somerville, NJ, USA) sutures were used for duct-to-duct biliary anastomosis and hepaticojejunostomy. For jejunojejunostomy, the conventional Albert–Lembert method was performed with continuous 4-0 PDS-II (Ethicon Inc.) sutures for the full intestinal layer followed by interrupted 4-0 PDS-II sutures for seromuscular reinforcement.

Splenectomy was indicated and performed in patients with hypersplenism or elevated PVP, and in patients with hepatitis C treated with interferon after LDLT [16]. The bloodless procedures used in splenectomy are described in our prior report [17]. We also ligated major (≥10 mm) portosystemic shunt vessels to prevent portal steal phenomena [18]. The shunts are controlled and left open during the anhepatic phase to minimize portal venous congestion and are ligated after reperfusion [18]. For gastroesophageal shunts, we applied endostapling devices to the base of the left gastric ligament, including the left gastric artery, coronary vein, and collateral vessels, which was followed by *en bloc* division using endostapling devices (Echelon Flex Endopath™ Staplers 60-2.5; Ethicon Endo-Surgery Inc., Cincinnati, OH, USA) [18]. Our concept for inflow modulation involves normalizing portal hemodynamics by removing enlarged spleen and obstructing the draining major shunts.

Diagnosis of GIB

In this study, GIB was defined as gross melena or hematemesis. Positive fecal occult blood without gross melena or hematemesis was not referred to as GIB. GIB was diagnosed by operative and/or endoscopic procedures. Bleeding episodes were defined as the presence of hematemesis and/or melena. For patients with hematemesis and/or melena, upper esophago-gastro-duodenoscopy was performed, followed by colonoscopy and double-balloon enteroscopy if indicated. For patients with fresh melena, total colonoscopy was performed first.

PGD

PGD was defined as graft dysfunction without apparent technical, anatomic, immunologic, or hepatitis-related issues after LDLT and was characterized by hyperbilirubinemia (total bilirubin ≥20 mg/dl) [7].

Statistical analysis

All values are expressed as means and standard deviations. Categorical variables were compared using chi-squared tests, and receiver operating characteristic curves were used to determine the best cutoff points for continuous variables. Cumulative graft survival was analyzed using the Kaplan–Meier method and the log-rank test. Values of $P < 0.05$ were considered statistically significant. All statistical analyses were performed using JMP software (SAS Institute Japan, Tokyo, Japan).

Results

Characteristics of the recipients, donors, and grafts

We performed 297 adult-to-adult LDLTs between January 2003 and December 2012. The mean age of the recipients was 53.1 ± 10.9 years. The mean Model for End-Stage Liver Disease (MELD) score was 16.8 ± 6.7. The indications for LDLT included acute liver failure in 25 patients (12.7%), cholestatic cirrhosis in 56 patients (18.9%), viral cirrhosis in 176 patients (59.3%), and another indication in 40 patients (13.5%). The majority of the patients were Child class C (n = 179 [60.3%]).

The mean age of the donors was 36.1 ± 11.0 years. The graft types included left lobe grafts for 166 cases (55.9%), right lobe grafts in 124 cases (41.8%), and posterior segment grafts in seven cases (2.4%). The mean graft volume (GV)/standard liver volume (SLV) ratio was 41.5 ± 8.2%. Sixteen donors (5.4%) provided blood-type incompatible grafts.

Hepaticojejunostomy was performed in 41 patients (13.8%), and splenectomy was performed in 177 patients (59.6%). The mean blood loss was 6.4 ± 15.0 L.

The one-year cumulative graft survival rate was 84.2%.

Characteristics of patients with GIB

Overall, 19/297 patients developed GIB within 3 months after LDLT. The bleeding source was the esophagus in one patient (ruptured varix: n = 1), the stomach in four patients (portal hypertensive gastropathy: n = 2; peptic ulcer disease: n = 2), the jejunojejunostomy following hepaticojejunostomy in 13 patients (anastomotic bleeding: n = 13), and the large intestine in one patient (ulceration: n = 1) (Table 1). One of the patients with bleeding from the jejunojejunostomy required surgery and hemostasis was achieved. Three patients underwent endoscopic procedures (clipping was performed for one patient with hepaticojejunostomy bleeding, ethanol injection was performed in one patient with peptic ulcer disease, and variceal ligation was performed in one patient with a ruptured varix). Although 15 patients received supportive treatments, hemostasis was not achieved in six (Fig. 1). Endoscopic examinations were performed for all the patients with GIB, and the origin was defined in 14/19 (73.7%). Five unidentified patients were not performed jejunoscopy due to the era before the introduction of jejunoscopy as a common procedure (n = 4) or severely deteriorated patient condition (n = 2). The patients with supportive treatment with available hemostasis included diffuse portal hypertensive gastropathy (n = 2), multiple acute gastric mucosal lesions with ulceration (n = 2), diffuse oozing from jejunal mucosa (n = 1), and almost hemostat jejunojejunostomy with clots (n = 2). The treatments included no oral intake, proton pump inhibitors, gastrointestinal mucosa protective agents including sodium alginate and sucralfate, and blood rodents including fresh frozen plasma and platelets. On the other hand, the patients with unsuccessful supportive treatments had GIB on severely deteriorated conditions. Five of them had graft failure before the onset of GIB and one of had graft versus host disease, resulting in mortality in all. Same supportive treatments as those with successful hemostasis were performed. Thus, the patients with successful supportive treatment included diffuse or already hemostat lesions, and those with unsuccessful supportive treatment had pre-existent graft failure or very severe general condition. For patients with identified specific bleeding lesion, surgical or endoscopic treatments were performed if condition of a patient affords.

Table 1. Region and etiology of gastrointestinal bleeding.

Region	No. of cases	Etiology	*n*
All cases	19		
Esophagus	1	Ruptured varix	1
Stomach	4	Portal hypertensive gastropathy	2
		Peptic ulcer disease	2
Bowel			
Small intestine	13	Anastomotic bleeding at jejunojejunostomy	13
Large intestine	1	Ulceration	1

Risk factors for GIB

Univariate analyses (Table 2) showed that intra-operative blood loss >10 L (yes vs. no: 36.8% vs. 10.4%; P = 0.004), hepaticojejunostomy (yes vs. no: 68.4% vs. 12.3%; P < 0.001), portal vein pressure (PVP) >20 mmHg at the end of the surgery (yes vs. no: 38.9% vs. 9.8%; P = 0.002)

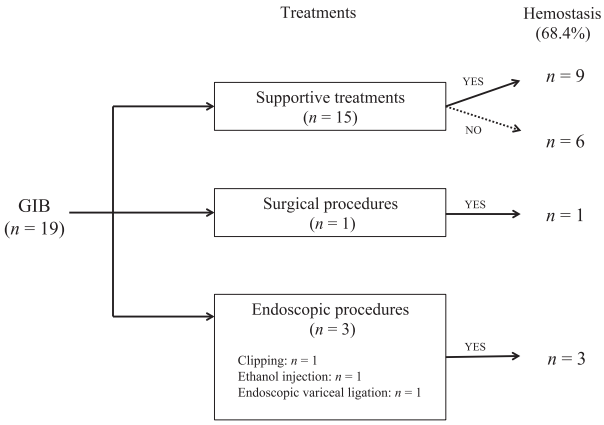

Figure 1 Treatments applied and outcomes of patients with gastrointestinal bleeding after living donor liver transplantation. GIB, gastrointestinal bleeding.

Table 2. Univariate analysis of factors in relation to the occurrence of GIB.

Factors	GIB		*P*-value
	Yes (n = 19)	No (n = 278)	
Recipient factors			
Age >55 years	5 (26.3)	129 (46.4)	0.081
Gender, male	9 (47.4)	132 (47.5)	0.992
Acute liver failure	1 (5.2)	27 (9.7)	0.489
MELD score >20	4 (21.1)	73 (26.3)	0.609
Donor factors			
Age >45 years	5 (26.3)	62 (22.3)	0.691
Left lobe graft	11 (57.9)	155 (55.8)	0.146
GV/SLV ratio >40%	8 (42.1)	147 (53.3)	0.346
Incompatible blood type	1 (5.3)	15 (5.4)	0.980
Operative factors			
Operative blood loss >10 L	7 (36.8)	29 (10.4)	0.004
Hepaticojejunostomy	13 (68.4)	34 (12.3)	<0.001
Splenectomy	12 (63.2)	165 (59.6)	0.756
PVP at the end of surgery >20 mmHg	7 (38.9)	16 (9.8)	0.002
Postoperative factors			
Acute rejection	4 (21.1)	24 (8.6)	0.113
Bile duct complication	2 (10.5)	44 (15.8)	0.517
Postoperative portal vein thrombus	2 (10.5)	9 (3.2)	0.173
Postoperative hepatic artery thrombus	0 (0.0)	2 (0.7)	0.603
PGD	13 (68.4)	23 (8.3)	<0.001

GIB, gastrointestinal bleeding; MELD, Model for End-stage Liver Disease; GV, graft volume, SLV, standard liver volume; PVP, portal venous pressure; PGD, primary graft dysfunction.

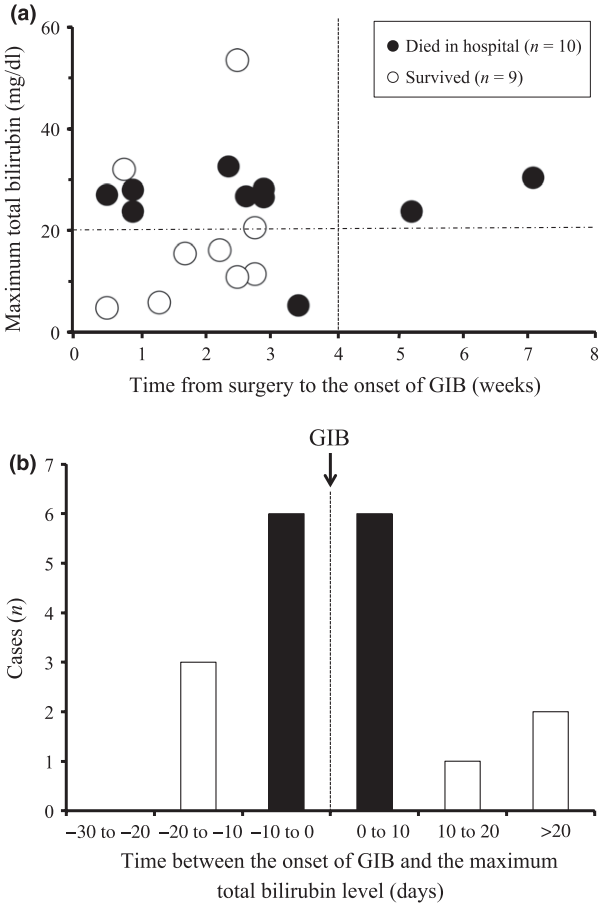

Figure 2 (a) Association between the time from living donor liver transplantation (LDLT) to the onset of gastrointestinal bleeding (GIB) with the maximum bilirubin level after LDLT. (b) Association between the time between the onset of GIB and the day on which the maximum total bilirubin level was reached after LDLT. GIB, gastrointestinal bleeding.

and postoperative maximum bilirubin >20 mg/dl (defined as PDG: primary graft dysfunction) (yes vs. no: 68.4% vs. 8.3%; $P < 0.001$) were risk factors for GIB. Graft type, GV/SLV, splenectomy, and postoperative portal vein thrombus were not significant risk factors for GIB (Table 2). Among the 23 patients with PVP > 20 mmHg at the end of surgery, two patients had hepaticojejunostomy and one of the two had GIB at 17 days after LDLT with mortality due to graft dysfunction. The risk factors for PGD included donor age > 40 years old (73.9% vs. 29.1%, $P < 0.001$), operative blood loss > 10 L (30.6% vs. 9.6%, $P = 0.001$), transfusion of packed red blood cell > 20 units (41.7% vs. 13.8%, $P = 0.001$), and portal venous pressure at the end of surgery > 20 mmHg (38.1% vs. 9.6%, $P = 0.001$). The incidence of GIB was significantly more frequent in those with PGD than those without (13/36 = 36.1% vs. 6/297 = 2.3%, $P < 0.001$).

Relationship between the onset of GIB and inhospital mortality

We investigated the relationship between the onset of GIB and inhospital mortality. GIB occurred within 4 weeks after LDLT in 17/19 patients (94.7%). Overall, 10 patients (52.6%) with GIB died while in hospital. In total, 9/12 patients (75.0%) with PGD died while in hospital versus 1/7 patient (14.3%) without PGD ($P = 0.028$) (Fig. 2a). In 12/19 patients (63.2%), GIB occurred within 10 days before or after the peak total bilirubin level (Fig. 2b). Therefore, GIB occurred either shortly before or after the onset of PGD in most patients.

Graft survival

The effects of GIB on cumulative graft survival are shown in Fig. 3a. The one-year graft survival rate was 47.4% (9/19 patients) in grafts with GIB ($n = 19$) versus 93.2% (259/278 patients) in grafts without GIB ($P < 0.001$). The inhospital mortality rate was significantly higher in patients with PGD than in those without PGD (75.0% vs. 14.3%, $P = 0.028$) (Fig. 3b).

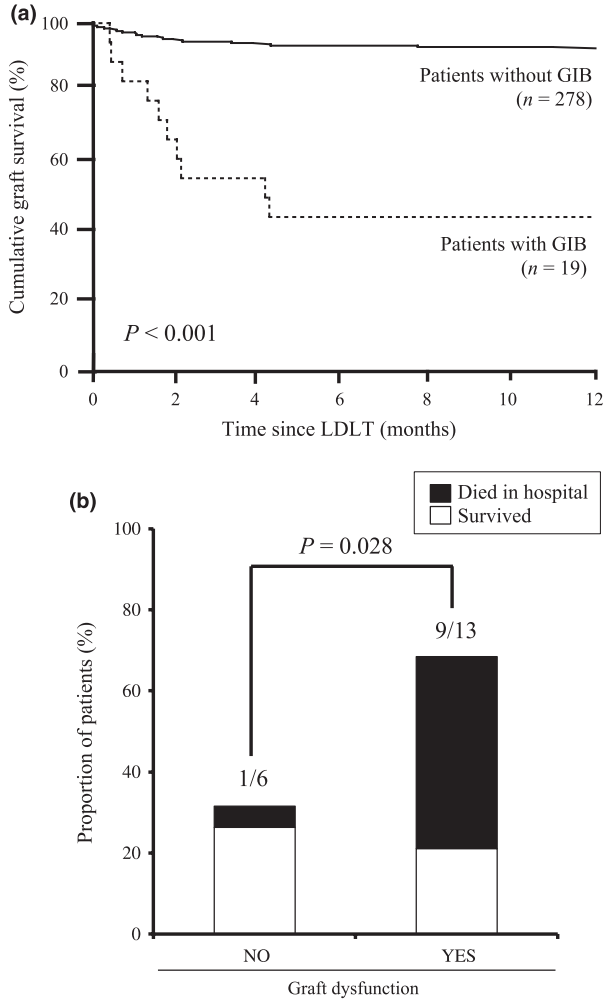

Figure 3 (a) Cumulative graft survival in patients with or without gastrointestinal bleeding. (b) Inhospital mortality rate in patients with or without graft dysfunction.

Discussion

This study revealed that in the majority of cases of GIB, it occurred within 4 weeks of LDLT, usually within 1–3 weeks after graft implantation, and the jejunojejunostomy was the most common site of bleeding. GIB occurring after LDLT was also associated with elevated PVP after graft implantation and massive operative blood loss. Furthermore, GIB frequently occurred within 10 days of the maximum bilirubin level, which indicates that GIB after LDLT is linked to graft dysfunction and impaired portal runoff. Thus, short-term graft survival was significantly worse in patients with GIB than in those without after LDLT.

In DDLT using whole liver grafts, Tabasco-Minguillan *et al.* [2] reported that GIB was caused by ulcers in 22.9% of patients, gastroenteritis in 21.1% of patients, portal hypertensive gastroenteropathy or varices in 13.8% of patients, and Roux-en-Y jejunojejunostomy in 5.5% of patients. Therefore, the causes of GIB differed between patients who underwent LDLT in our study and patients who underwent DDLT in the study by Tabasco-Minguillan *et al.*, especially in terms of early portal hypertension. However, they also mentioned that the patients with bleeding from portal hypertensive lesions had episodes within 2 weeks of DDLT or later than 9 months after transplantation, and the rate of graft failure was 50%, suggesting portal hypertensive bleeding may also occur in cases of DDLT with dysfunctional grafts [2].

LDLT frequently involves the use of partial small grafts, especially in adults, and such grafts could be classified as marginal grafts [5–7]. However, healthy LDLT grafts regenerate and are capable of supporting the recipient's body and display portal over-inflow, which persists for 1–3 months and is most notable for the first 2 weeks after reperfusion [19–22]. Numerous studies have shown that implantation of a partial graft is characterized by increased inflow into the graft and secondary liver regeneration, but excessive inflow results in a swollen dysfunctional graft with secondary portal hypertension and portal steal phenomena [11,23–25]. In 2002, Hirata *et al.* [8] reported that in adult recipients of left lobe grafts with a mean GV/SLV of 41%, varices ruptured in 86% of cases. By contrast, in pediatric recipients of left lobe or left lateral segment grafts with a mean GV/SLV of 86%, the varices ruptured in 24% (left lobe) and 4% (left lateral segment grafts). They also reported that GIB was caused by portal hypertensive variceal rupture in 44% of cases. Therefore, portal hypertension occurring soon after LDLT could be a major cause of GIB. In our study, the mean GV/SLV was also 41%, but the incidence of variceal rupture was much lower. A likely explanation is that we perform pretransplant endoscopic treatment of risky varices and divide shunt vessels, including gastroesophageal shunts, during surgery [18].

The causes of graft dysfunction and early post-transplant portal hypertension could involve a combination of multiple factors, including graft size, donor age, steatosis, pretransplant, or postreperfusion portal pressure [26–31]. We now refer to poor functional grafts with a high mortality risk as PGD characterized by persistent hyperbilirubinemia instead of small-for-size graft syndrome [7]. Emond *et al.* [32] reported that these dysfunctional LDLT grafts were characterized by systemic and local cholestasis. We reported that the pathological features in these patients included centrizonal ballooned cholestatic necrosis, indicating poor graft perfusion due to increased tissue, increased portal pressure, poor graft compliance, and an inability to metabolize bilirubin [7]. Our results, including the finding that increased PVP at the end of surgery is a risk factor for GIB after LDLT, are understandable considering

the link between portal hypertension, GIB, graft dysfunction, and poor graft outcomes. The short time between the maximum bilirubin level and the onset of GIB also supports the close link between poor graft compliance and portal hypertension.

Uniquely, jejunojejunostomy was the major site of GIB after LDLT in the present study. By contrast, Hirata *et al.* reported that only 5.5% of cases of post-transplant GIB were attributed to jejunojejunostomy in DDLT and there were no such cases of GIB in LDLT [2,8]. This difference might be explained by our policy to eradicate or obstruct shunt vessels, especially coronary or mesocaval shunts, to prevent portal steal during graft regeneration under splenectomy for portal decompression. Thus, the only gastrointestinal region that may develop bleeding during graft regeneration and portal hypertension could be at the jejunojejunostomy. Jejunojejunostomy as the frequent bleeding origin around several days after LDLT could be attributed to increased portal and mesenteric venous pressure due to graft regeneration and tissue healing process with vascular remodeling after intestinal anastomosis, both several days after LDLT [18,24,33]. Intestinal edema for difficult make healthy anastomotic condition could also be among the causes. Duct-to-duct biliary anastomosis might be preferable in LDLT to jejunojejunostomy in terms of preventing the chances of GIB.

However, the use of Roux-en-Y for hepaticojejunostomy decreased significantly following the introduction of duct-to-duct biliary reconstruction in 2000 [15]. Now, we only perform hepaticojejunostomy in patients with primary sclerosing cholangitis as a primary liver disease or if a dissected hepatic artery with poor blood flow precludes biliary tract reconstruction in the recipient. Thus, duct-to-duct biliary reconstruction is not only superior in terms of bile physiology and easier endoscopic access for treating biliary stenosis, but also avoids the creation of an enteric anastomosis that may result in GIB following LDLT [15,34–36]. However, it is clear that jejunojejunostomy is not a source of GIB in pediatric patients with biliary atresia because of the larger graft size, huge vascular beds, and complete healing of the anastomosis long after surgery [37,38].

Finally, an important finding of the present study was that GIB occurring after LDLT without graft dysfunction could be treated by conventional, endoscopic, or surgical procedures. Therefore, GIB is unlikely to result in death in patients with well-functioning LDLT grafts. However, GIB carries a high mortality risk in patients with graft dysfunction, and re-transplantation might be an option. Overall, we think that knowledge of the clinical features of GIB could help with the management of patients in actual clinical settings.

Some limitations of this analysis should be mentioned. First, we selected patients from one center. A multicenter study with a larger number of patients and greater variation in surgical techniques would help us to reach more definitive conclusions. Second, this was a retrospective study and might be subject to investigative bias.

In conclusion, GIB occurring shortly after LDLT in adults was associated with jejunojejunostomy and physiologic or nonphysiologic portal hypertension. Although GIB could be treated successfully in patients without graft dysfunction, GIB has strong correlation with graft dysfunction and inhospital mortality.

Authorship

KK: drafting of the manuscript. TI: study design and concept. YB, MN, Y-iY, SY, YS, NH: data collection. TY: critical revision of the manuscript. KS: approval of the manuscript. YM: final approval of the manuscript.

Funding

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare of Japan (H23-kanen-ippan-003).

Acknowledgement

The authors thank Megumi Yoshida for her technical assistance.

References

1. Nyckowski P, Pawlak J, Zieniewicz K, *et al.* Liver transplantation in patients with hepatic failure. *Transplant Proc* 2002; **34**: 631.
2. Tabasco-Minguillán J, Jain A, Naik M, *et al.* Gastrointestinal bleeding after liver transplantation. *Transplantation* 1997; **63**: 60.
3. Wood RP, Shaw BW Jr, Starzl TE. Extrahepatic complications of liver transplantation. *Semin Liver Dis* 1985; **5**: 377.
4. Sakamoto S, Uchida H, Hamano I, *et al.* Impact of the current organ allocation system for deceased donor liver transplantation on the outcomes of pediatric recipients: a single center experience in Japan. *Pediatr Surg Int* 2013; **29**: 1109.
5. Freise CE, Gillespie BW, Koffron AJ, *et al.* Recipient morbidity after living and deceased donor liver transplantation: findings from the A2ALL Retrospective Cohort Study. *Am J Transplant* 2008; **8**: 2569.
6. Bourdeaux C, Darwish A, Jamart J, *et al.* Living-related versus de- ceased donor pediatric liver transplantation: a multivariate analysis of technical and immunological complications in 235 recipients. *Am J Transplant* 2007; **7**: 440.
7. Ikegami T, Shirabe K, Yoshizumi T, *et al.* Primary graft dysfunction after living donor liver transplantation is

characterized by delayed functional hyperbilirubinemia. *Am J Transplant* 2012; **12**: 1886.
8. Hirata M, Kita Y, Harihara Y, *et al.* Gastrointestinal bleeding after living-related liver transplantation. *Dig Dis Sci* 2002; **47**: 2386.
9. Morioka D, Egawa H, Kasahara M, *et al.* Outcomes of adult-to-adult living donor liver transplantation: a single institution's experience with 335 consecutive cases. *Ann Surg* 2007; **245**: 315.
10. Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. *Am J Transplant* 2005; **5**: 2605.
11. Kiuchi T, Tanaka K, Ito T, *et al.* Small-for-size graft in living donor liver transplantation: How far should we go? *Liver Transpl* 2003; **9**: S29.
12. Yonemura Y, Taketomi A, Soejima Y, *et al.* Validity of preoperative volumetric analysis of congestion volume in living donor liver trans- plantation using three-dimensional computed tomography. *Liver Transpl* 2005; **11**: 1556.
13. Taketomi A, Morita K, Toshima T, *et al.* Living donor hepatectomies with procedures to prevent biliary complications. *J Am Coll Surg* 2010; **211**: 456.
14. Ikegami T, Soejima Y, Taketomi A, *et al.* Explanted portal vein grafts for middle hepatic vein tributaries in living-donor liver transplantation. *Transplantation* 2007; **84**: 836.
15. Soejima Y, Shimada M, Suehiro T, *et al.* Feasibility of duct-to-duct biliary reconstruction in left-lobe adult-living-donor liver transplantation. *Transplantation* 2003; **75**: 557.
16. Ikegami T, Toshima T, Takeishi K, *et al.* Bloodless splenectomy during liver transplantation for terminal liver diseases with portal hypertension. *J Am Coll Surg* 2009; **208**: e1.
17. Yoshizumi T, Taketomi A, Soejima Y, *et al.* The beneficial role of simultaneous splenectomy in living donor liver transplantation in patients with small-for-size graft. *Transpl Int* 2008; **21**: 833.
18. Ikegami T, Shirabe K, Nakagawara H, *et al.* Obstructing spontaneous major shunt vessels is mandatory to keep adequate portal inflow in living-donor liver transplantation. *Transplantation* 2013; **95**: 1270.
19. Yagi S, Iida T, Taniguchi K, *et al.* Impact of portal venous pressure on regeneration and graft damage after living-donor liver transplantation. *Liver Transpl* 2005; **11**: 68.
20. Ninomiya M, Harada N, Shiotani S, *et al.* Hepatocyte growth factor and transforming growth factor beta1 contribute to regeneration of small-for-size liver graft immediately after transplantation. *Transpl Int* 2003; **16**: 814.
21. Eguchi S, Yanaga K, Sugiyama N, *et al.* Relationship between portal venous flow and liver regeneration in patients after living donor right-lobe liver transplantation. *Liver Transpl* 2003; **9**: 547.
22. Kawasaki S, Makuuchi M, Ishizone S, *et al.* Liver regeneration in recipients and donors after transplantation. *Lancet* 1992; **339**: 580.
23. Yagi S, Uemoto S. Small-for-size syndrome in living donor liver transplantation. *Hepatobiliary Pancreat Dis Int* 2012; **11**: 570.
24. Ninomiya M, Shirabe K, Terashi T, *et al.* Deceleration of regenerative response improves the outcome of rat with massive hepatectomy. *Am J Transplant* 2010; **10**: 1580.
25. Shimamura T, Taniguchi M, Jin MB, *et al.* Excessive portal venous inflow as a cause of allograft dysfunction in small-for-size living donor liver transplantation. *Transplant Proc* 2001; **33**: 1331.
26. Moon JI, Kwon CH, Joh JW, *et al.* Safety of small-for-size grafts in adult-to-adult living donor liver transplantation using the right lobe. *Liver Transpl* 2010; **16**: 864.
27. Yi NJ, Suh KS, Lee HW, *et al.* Improved outcome of adult recipients with a high model for end-stage liver disease score and a small- for-size graft. *Liver Transpl* 2009; **15**: 496.
28. Chan SC, Lo CM, Ng KK, *et al.* Alleviating the burden of small-for-size graft in right liver living donor liver transplantation through accumulation of experience. *Am J Transplant* 2010; **10**: 859.
29. Hill MJ, Hughes M, Jie T, *et al.* Graft weight/recipient weight ratio: how well does it predict outcome after partial liver transplants? *Liver Transpl* 2009; **15**: 1056.
30. Kiuchi T, Onishi Y, Nakamura T. Small-for-size graft: not defined solely by being small for size. *Liver Transpl* 2010; **16**: 815.
31. Yoshizumi T, Taketomi A, Uchiyama H, *et al.* Graft size, donor age, and patient status are the indicators of early graft function after living donor liver transplantation. *Liver Transpl* 2008; **14**: 1007.
32. Emond JC, Renz JF, Ferrell LD, *et al.* Functional analysis of grafts from living donors. Implications for the treatment of older recipients. *Ann Surg* 1996; **224**: 544.
33. Houdart R, Lavergne A, Valleur P, *et al.* Vascular evolution of single-layer end-on colonic anastomosis. A microangiographic study of 180 anastomoses in the rat from two to 180 days. *Dis Colon Rectum* 1985; **28**: 475.
34. Ikegami T, Shirabe K, Morita K, *et al.* Minimal hilar dissection prevents biliary anastomotic stricture after living donor liver transplantation. *Transplantation* 2011; **92**: 1147.
35. Icoz G, Kilic M, Zeytunlu M, *et al.* Roux-en-Y bleeding after living donor liver transplantation: a novel technique for surgical treatment. *Transplant Proc* 2003; **35**: 1463.
36. Lebeau G, Yanaga K, Marsh JW, *et al.* Analysis of surgical complications after 397 hepatic transplantations. *Surg Gynecol Obstet* 1990; **170**: 317.
37. Kitajima T, Sakamoto S, Uchida H, *et al.* Living donor liver transplantation with alternative porto-left gastric vein anastomosis in patients with post-Kasai extrahepatic portal vein obstruction. *Pediatr Transplant* 2013; **17**: E100.
38. Ling SC, Pfeiffer A, Avitzur Y, *et al.* Long-term follow-up of portal hypertension after liver transplantation in children. *Pediatr Transplant* 2009; **13**: 206.