kidney, spleen, and pancreas (11, 12). Recently, several studies have shown that ARFI is a useful modality for noninvasive evaluation of liver diseases (13, 14). Moreover, our data have also shown that liver stiffness evaluated by ARFI is significantly correlated with the elevation of serum total bilirubin levels after donor hepatectomy (15).

SFS syndrome is characterized by impairments of graft function such as prolonged cholestasis and increased ascites output (2). Although there are several noninvasive methods for the evaluation of graft function after LDLT, the value of ARFI in the assessment of graft stiffness has not been reported so far. The purpose of this study was to investigate the clinical utility of measuring graft stiffness using ARFI after LDLT.

Patients and methods

Patients

Between April 2010 and March 2011, a total of 27 cases of adult LDLT were performed at Kyushu University Hospital. Among these, seven recipients were excluded because of the difficulty in obtaining their consent, and consequently, 20 recipients were enrolled in the study. LDLTs were performed as a result of liver cirrhosis resulting from hepatitis C (n = 11), alcoholic cirrhosis (n = 4), primary biliary cirrhosis (n = 1), primary sclerosing cholangitis (n = 1), and others (n = 3). Graft types included left lobes (LL) with the middle hepatic vein (MHV) and caudate lobes (n = 11), right lobes (RL) without the MHV (n = 7), and right posterior segments (n = 2). All the LDLTs were performed after obtaining full informed consent from the patients and approval by the Liver Transplantation Committee of Kyushu University Hospital. The study protocol was conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Donor and graft selection

Donors were selected from among the candidates who offered to be living donors (16, 17). They were limited to within the third degree of consanguinity with recipients or spouses and were aged between 20 and 65 yr. For a donor beyond the third degree of consanguinity with the recipient, individual approval was obtained from the Ethics Committee of Kyushu University Hospital. Three-dimensional computed tomography was used for volumetric analysis and delineation of vascular anatomy. Our decision on the type of liver graft was based on the preoperatively predicted GV/SLV ratio. LL grafts were selected when the predicted GV/SLV ratio was >35%. We decided to use RL grafts for recipients whose GV/SLV ratio was going to be <35% if LL grafts were selected, or for recipients with a high model for end-stage liver disease (MELD) score. Moreover, our selection criteria for RL grafts included the requirement that the estimated remnant liver volume was >35% in the donor. However, graft selection is still carried out on a case-by-case basis, considering various factors such as anatomical variations and recipient and donor conditions.

Operative procedure

The surgical procedures for both donors and recipients have been described elsewhere (17, 18). Briefly, parenchymal transection of the donor liver was performed using the Cavitron Ultrasonic Surgical Aspirator (Valleylab Inc, Boulder, CO, USA) and electrocautery. The recipient total hepatectomy was usually performed while preserving the vena cava. After venous and portal anastomoses, hepatic arteries were reconstructed under the operative microscope. MHV tributaries in the anterior segment of RL graft were reconstructed according to a previously described algorithm (19). Biliary reconstruction was performed using duct-to-duct anastomosis (n = 19) or hepatico-jejunostomy (n = 1). Simultaneous splenectomy (n = 14) was performed to decrease the portal pressure or alleviate persistent thrombocytopenia (20), and three cases had undergone splenectomy prior to LDLT.

Assessment of portal hemodynamics and postoperative graft function

Intra-operative portal venous pressure (PVP) was monitored via a branch of the mesenteric vein. PVF was measured by an electromagnetic blood flowmeter (MVF-3100; Nihon Koden Corp., Tokyo, Japan) during surgery. The serum levels of alanine aminotransferase (ALT), total bilirubin, and the amount of daily production of ascites were recorded daily for seven d after surgery to assess postoperative graft function. Ascites production was defined as the loss of the fluid through indwelling drains and surgical wounds.

Assessment of tissue stiffness by VTTQ

The stiffness of the graft was measured by ARFI, using the ACUSON S2000 ultrasound system (Mochida Siemens Medical Systems, Tokyo, Japan) with the VTTQ software package. Measurements were performed daily for seven d after surgery. B-mode images were obtained throughout

the liver graft, after which ARFI was performed in all patients. Each measurement was triggered at the end of an expiratory phase, and its timing was intended to avoid the effect of the heartbeat to reduce the motion artifacts (21). The region of interest was placed at a depth between 2 and 5 cm below the liver capsule and kept away from the large blood vessels (11). To ensure the quality of the data, a total of 10 valid measurements per liver segment (S2, 3, 4, 5, 6 and 8) were performed, and their mean values were recorded (i.e., the VTTQ value of the right liver graft was the mean of S5, 6, and 8, and that of the left liver graft was the mean of S2, 3, and 4). The VTTQ value of the donor liver before surgery was also measured (S2, 3, 4, 5, 6, and 8). The results of the VTTQ measurement were expressed as meters per second (m/s).

Statistical analysis

All values were expressed as mean ± standard error of the mean. All statistical analyses were performed using the StatView® 5.0 software package (Abacus Concepts, Berkeley, CA, USA). Statistical significance was determined by the Student's *t*-test or the Mann–Whitney *U*-test. Correlation between VTTQ value and variable parameters was determined by linear regression analysis. The differences were considered to be significant if $p < 0.05$.

Results

Patients characteristics

The clinical parameters of patients are summarized in Table 1. The mean age of the recipients was 56.2 ± 2.0 yr (range, 40–72), and the sex ratio (M:F) was 8:12. The mean Child–Pugh score and MELD score were 9.8 ± 0.5 and 16.3 ± 1.3. The mean GV/SLV ratio and GRWR were 40.4 ± 2.0% and 0.76 ± 0.04%, respectively. Post-LDLT PVP measured at the end of the operation was 15.0 ± 0.8 mmHg, which was significantly lower than that of pre-LDLT (24.4 ± 1.2 mmHg, $p < 0.0001$). The mean PVF measured at the end of the operation was 1744.5 ± 133.1 mL/min, and portal venous flow to graft volume (PVF/GV) ratio was 3.8 ± 0.3 mL/min/g. The mean age of the donors was 35.0 ± 2.3 yr (range, 20–55), and the sex ratio (M:F) was 14:6.

Table 1. Clinical features of patients

Variables	Number of patients
Age (yr)	
Mean (range)	56.2 (40–72)
Gender	
Male:female	8:12
Indications	
Liver cirrhosis	
Hepatitis C (HCC)	11 (11)
Alcohol (HCC)	4 (2)
Primary biliary cirrhosis	1
Primary sclerosing cholangitis	1
Others	3
Child–Pugh score	9.8 ± 0.5
MELD score	16.3 ± 1.3
Donor age (yr)	
Mean (range)	35.0 (20–55)
Donor gender	
Male:female	14:6
Blood combination	
Identical: compatible: imcompatible	13:4:3
GV (g)	473.8 ± 28.8
GV/SLV (%)	40.4 ± 2.0
GRWR (%)	0.76 ± 0.04
Operative time (min)	757.5 ± 28.0
Cold ischemic time (min)	83.5 ± 9.8
Warm ischemic time (min)	36.5 ± 1.9
Blood loss (g)	2348.8 ± 480.5
Pre-LDLT PVP (mmHg)	24.4 ± 1.2
Post-LDLT PVP (mmHg)	15.0 ± 0.8
PVF (mL/min)	1744.5 ± 133.1
PVF/GV (mL/min/g)	3.8 ± 0.3
Peak ALT (U/L)	489.9 ± 162.2
Peak T-Bil (mg/dL)	7.8 ± 0.9
Peak ascites production (mL/d)	1226.5 ± 249.3

HOC, hepatocellular carcinoma; MELD, model for end-stage liver disease; GV, graft volume; SLV, standard liver volume; GV/SLV, graft volume-to-recipient standard liver volume; GRWR, graft-to-recipient weight ratio; LDLT, living donor liver transplantation; PVP, portal venous pressure; PVF, portal venous flow; PVF/GV, portal venous flow to graft volume; ALT, alanine aminotransferase; T-Bil, total bilirubin.

Changes in the stiffness of the graft

Figure 1A shows the serial changes in the VTTQ values in all patients after LDLT. The baseline value before the operation in the donor liver was 1.21 ± 0.03 m/s. The VTTQ value level rose after LDLT, reaching a maximum level on postoperative day (POD) 4, and the level declined thereafter. The patients were divided into three groups according to graft type: LL graft (n = 11), RL graft (n = 7), and right posterior segment graft (n = 2). There were no significant differences in the VTTQ values between the LL graft and RL graft after LDLT (Fig. 1B).

Correlation between the value of VTTQ and clinical parameters

Correlations between VTTQ and clinical parameters were analyzed. Significant correlations were observed between the postoperative maximum value of VTTQ and GV/SLV ratio ($R^2 = 0.233$,

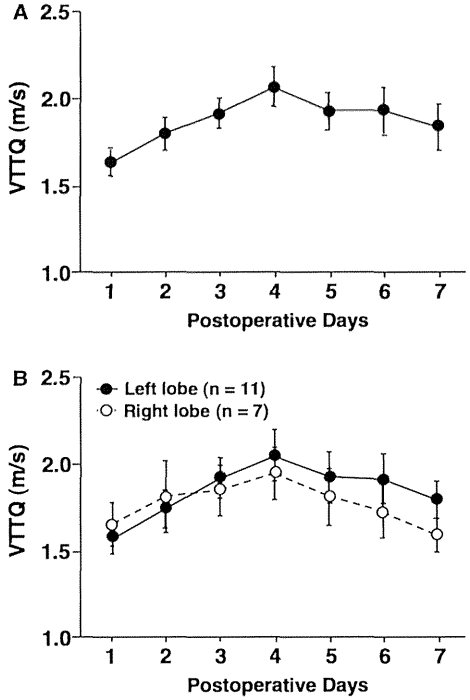

Fig. 1. Serial changes in the virtual touch tissue quantification (VTTQ) of the graft after LDLT. (A) The VTTQ values in all patients increased after LDLT until postoperative day (POD) 4 and then tended to decrease. (B) There were no significant differences in the VTTQ values between the left lobe (LL) graft and right lobe (RL) graft types.

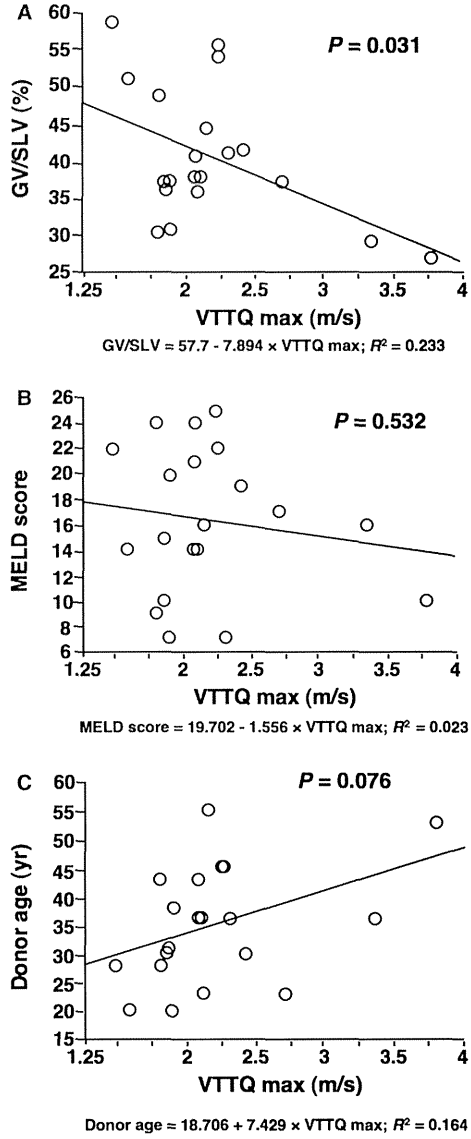

Fig. 2. Correlation between the values of virtual touch tissue quantification (VTTQ) and graft volume-to-recipient standard liver volume (GV/SLV) ratio, model for end-stage liver disease (MELD) score, and donor age. Although a significant correlation was observed between the postoperative maximum value of VTTQ and GV/SLV ratio (R^2 = 0.233, $p < 0.05$) (A), MELD score (B), and donor age (C) were not correlated with VTTQ.

$p < 0.05$) (Fig. 2A), and GRWR (R^2 = 0.248, $p < 0.05$). However, MELD score and donor age were not correlated with VTTQ (Fig. 2B,C). Although PVF was not correlated with VTTQ, there were significant correlations between VTTQ and PVF/GV (R^2 = 0.401, $p < 0.005$), and post-LDLT PVP (R^2 = 0.403, $p < 0.005$) (Fig. 3A,B). The postoperative maximum serum ALT level was significantly correlated with VTTQ (R^2 = 0.349, $p < 0.01$) (Fig. 4A); in contrast, serum total bilirubin level was not correlated. There was a very strong correlation between VTTQ and the maximum ascites fluid production (R^2 = 0.705, $p < 0.001$) (Fig. 4B).

Impact of the value of VTTQ on clinical course

The patients were divided into two groups based on the median postoperative maximum value of VTTQ (2.08 m/s): group L (low VTTQ value ≤2.08, n = 10) and group H (high VTTQ value >2.08, n = 10). The mean VTTQ values were 1.83 ± 0.06 in group L and 2.54 ± 0.18 in group H. There were no significant differences in post-transplant hospital stay and graft survival between both groups. However, the patients in group L had a significantly shorter time to extubation (1.2 ± 0.2 vs. 3.8 ± 1.0 d, $p < 0.05$) and intensive care unit (ICU) length of stay (4.7 ± 1.3 vs. 6.6 ± 1.0 d, $p < 0.05$) compared with those in group H after LDLT.

Discussion

In the present study, the graft stiffness measured by ARFI increased after LDLT until POD 4, and tended to decrease thereafter. The highest degree of graft stiffness during the early post-LDLT period was significantly correlated with perioperative

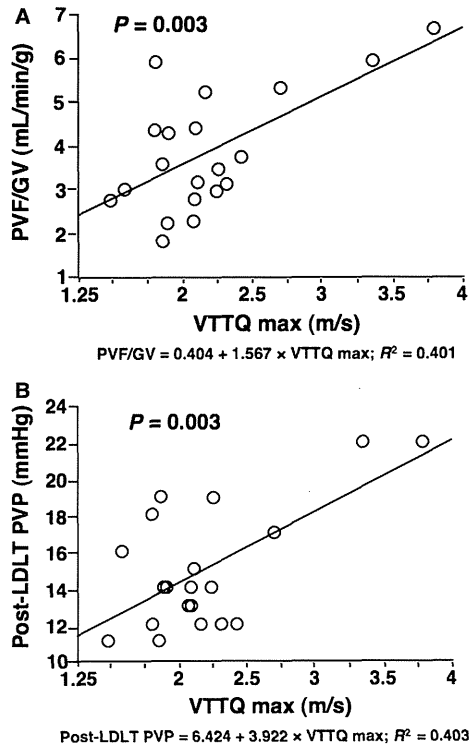

Fig. 3. Correlation between the values of virtual touch tissue quantification (VTTQ) and portal venous flow to graft volume (PVF/GV) ratio, and post-LDLT portal venous pressure (PVP). The postoperative maximum value of VTTQ had strong correlations with both PVF/GV ratio (R^2 = 0.401, p < 0.005) (A) and post-LDLT PVP (R^2 = 0.403, p < 0.005) (B).

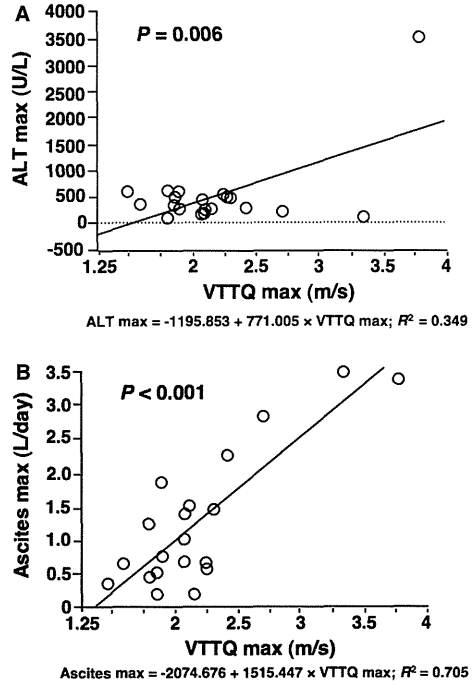

Fig. 4. Correlation between the values of virtual touch tissue quantification (VTTQ) and the postoperative maximum serum alanine aminotransferase (ALT) level, and ascites fluid production. The postoperative maximum serum ALT level was significantly correlated with VTTQ (R^2 = 0.349, p < 0.01) (A), and there was a very strong correlation between VTTQ and the maximum ascites fluid production (R^2 = 0.705, p < 0.001) (B).

variables, including graft size, portal hypertension, graft injury, and graft dysfunction. However, there were no significant differences in stiffness between LL graft and RL graft types.

SFS syndrome, which is characterized clinically by prolonged cholestasis, ascites, and coagulopathy, is one of the major causes of graft failure after LDLT (3, 4). Previous reports have suggested that multiple risk factors affect the development of SFS syndrome (6). These factors can be divided into graft-related factors such as graft size and donor age and recipient-related factors such as severity of cirrhosis and portal hypertension (6, 22, 23). In the setting of adult-to-adult LDLT, small grafts are exposed to relatively excessive portal perfusion and pressure, as cirrhotic recipients demonstrate higher portal flow than non-cirrhotic patients (24). It is thought that shear stress resulting from portal hypertension might lead to sinusoidal endothelial cell injury and the release of deleterious mediators, which is ultimately a cause of serious graft injury (9). Our data show that graft stiffness was negatively correlated with GV/SLV ratio and GRWR and had a strong positive correlation with PVF/GV and post-LDLT PVP. Moreover, graft stiffness was positively correlated with the postoperative maximum level of serum ALT. These data suggest that graft injury induced by the excessive shear stress might play an important role in the elevation of graft stiffness during the early post-LDLT period.

Ascites production also had a strong positive correlation with graft stiffness. Shirouzu et al. (25) suggest that sinusoidal endothelial injury caused by relative portal hyperperfusion into the graft may be a mechanism of ascites production. From the data presented, we assume that increased graft stiffness may also be an important factor involved in the pathogenesis of ascites production after LDLT. During the early post-LDLT period, excessive portal perfusion and pressure can increase graft stiffness, which generates an altered physiological state, including additional portal hypertension, which may contribute to an increase in ascites production. Notably, Cirera et al. (26) have reported that post-sinusoidal portal hypertension due to difficulty in hepatic venous outflow is one of the major causes of massive ascites production after liver transplantation. Although we have no data regarding hepatic venous pressure after LDLT, we have speculated that there are no hepatic outflow complications in our patients, because

the hepatic venous flow evaluated by daily Doppler ultrasound examination demonstrates no significant abnormalities.

In contrast, graft stiffness was not significantly correlated with MELD score and donor age. Moreover, the choice of graft type (LL or RL) had no significant influence on graft stiffness during the early post-LDLT period. Previously, we have reported a predictive model, which has indicated that graft size, donor age, and patient status (MELD score and presence of shunts) are important factors relating to early graft function after LDLT (6). In the present study, the choice of graft type was also made in consideration of this predictive model. Although LL grafts were mainly selected in cases of younger donors and low MELD score recipients, RL grafts were used in cases of high MELD score recipients to maximize the safety of both donors and recipients. Therefore, it seems that our patients would have almost the same level of graft function regardless of graft type, donor age, and MELD score during the early post-LDLT period. Consequently, we could also find no significant correlation between graft stiffness and these factors, because our data suggested that graft stiffness might reflect the graft function.

In the present study, the elevation of graft stiffness during the early post-LDLT period was significantly associated with a longer time to extubation and ICU stay. Based on these results, we also assume that graft stiffness reliably reflects the graft function. Although our data did not show that the elevation of graft stiffness could predict post-transplant survival, further evaluation during the post-LDLT period might reveal the relationship between graft stiffness and survival. Therefore, it is possible that the serial assessment of graft stiffness can play an important role in the management of patients after LDLT.

Although several studies have shown that the measurement of liver stiffness is useful for the assessment of liver diseases, including liver fibrosis and non-alcoholic fatty liver disease (13, 14, 27), there are few reports concerning changes in liver stiffness evaluated by ARFI during the early post-operative period. Recently, we have demonstrated that ARFI can be an efficient modality for the assessment of the remnant liver after a living donor hepatectomy (15). Distinct from the recipient data presented in this study, the type of donor remnant liver had a significant influence on the elevation of the stiffness. It is possible that the patient status may be the cause of the difference. Exposure of the graft-to-portal hyperperfusion in cirrhotic recipients can result in the elevation of graft stiffness. In contrast, the remnant liver volume seems to have a great influence on the change of stiffness in healthy donors with normal PVF, because our data have shown that PVF/GV has a strong positive correlation with the graft stiffness.

The question of whether liver regeneration influences the changes of graft stiffness after LDLT is not resolved by our data. After donor hepatectomy, the hepatocyte proliferation and subsequent formation of hepatic islands may reflect the increases in the stiffness of the remnant liver. However, it is not clear whether the transplanted liver, which is damaged by the portal hyperperfusion and ischemia-reperfusion injury, can go through the normal regeneration process. The evaluation of graft stiffness for longer during the post-LDLT period may be necessary to provide clues to the answers to these questions.

In summary, our studies demonstrate that the elevation of graft stiffness measured by ARFI is associated with the factors that influence the development of graft dysfunction, especially in SFS grafts, during the early post-LDLT period. Further studies may reveal the usefulness of the measurement of graft stiffness for assessment of other forms of graft injury, including acute cellular rejection and the recurrence of hepatitis C. Therefore, ARFI seems to be an effective diagnostic tool for the noninvasive and quantitative evaluation of severity of graft dysfunction after LDLT.

References

1. Florman S, Miller CM. Live donor liver transplantation. Liver Transpl 2006: 12: 499.
2. 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.
3. Kiuchi T, Kasahara M, Uryuhara K et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation 1999: 67: 321.
4. Ikegami T, Shimada M, Imura S et al. Current concept of small-for-size grafts in living donor liver transplantation. Surg Today 2008: 38: 971.
5. 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.
6. Yoshizumi T, Taketomi A, Uchiyama H et al. Graft size, donor age, and patients status are the indicators of early graft function after living donor liver transplantation. Liver Transpl 2008: 14: 1007.
7. Man K, Fan ST, Lo CM et al. Graft injury in relation to graft size in right lobe live donor liver transplantation: a study of hepatic sinusoidal injury in correlation with portal hemodynamics and intragraft gene expression. Ann Surg 2003: 237: 256.
8. Masetti M, Siniscalchi A, De Pietri L et al. Living donor liver transplantation with left liver graft. Am J Transplant 2004: 4: 1713.

9. Xu X, Man K, Zheng SS et al. Attenuation of acute phase shear stress by somatostatin improves small-for-size liver graft survival. Liver Transpl 2006: 12: 621.
10. Nightingale K, Soo MS, Nightingale R, Trahey G. Acoustic radiation force impulse imaging: in vivo demonstration of clinical feasibility. Ultrasound Med Biol 2002: 28: 227.
11. Gallotti A, D'Onofrio M, Pozzi Mucelli R. Acoustic radiation force impulse (ARFI) technique in ultrasound with virtual touch tissue quantification of the upper abdomen. Radiol Med 2010: 115: 889.
12. Palmeri ML, Frinkley KD, Zhai L et al. Acoustic radiation force impulse (ARFI) imaging of the gastrointestinal tract. Ultrason Imaging 2005: 27: 75.
13. Carrion JA, Torres F, Crespo G et al. Liver stiffness identifies two different patterns of fibrosis progression in patients with hepatitis C virus recurrence after liver transplantation. Hepatology 2010: 51: 23.
14. Toshima T, Shirabe K, Takeishi K et al. New method for assessing liver fibrosis based on acoustic radiation force impulse: a special reference to the difference between right and left liver. J Gastroenterol 2011: 46: 705.
15. Ninomiya M, Shirabe K, Ijichi H et al. Temporal changes in the stiffness of the remnant liver and spleen after donor hepatectomy as assessed by acoustic radiation force impulse: a preliminary study. Hepatol Res 2011: 41: 579.
16. Shimada M, Shiotani S, Ninomiya M et al. Characteristics of liver grafts in living-donor adult liver transplantation: comparison between right- and left-lobe grafts. Arch Surg 2002: 137: 1174.
17. Yoshizumi T, Shirabe K, Soejima Y et al. Living donor liver transplantation in patients older than 60 years. Transplantation 2010: 90: 433.
18. Soejima Y, Taketomi A, Yoshizumi T et al. Feasibility of left lobe living donor liver transplantation between adults: an 8-year, single center experience of 107 cases. Am J Transpl 2006: 6: 1004.
19. Toshima T, Taketomi A, Ikegami T et al. V5-drainage-preserved right lobe grafts improve graft congestion for living donor liver transplantation. Transplantation 2012: 93: 929.
20. 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 2008b: 21: 833.
21. Fahey BJ, Palmeri ML, Trahey GE. The impact of physiological motion on tissue tracking during acoustic force imaging. Ultrasound Med Biol 2007: 33: 1149.
22. Sanefuji K, Iguchi T, Ueda S et al. New prediction factors of small-for-size syndrome in living donor adult liver transplantation for chronic liver disease. Transpl Int 2010: 23: 350.
23. Ben-Haim M, Emre S, Fishbein TM et al. Critical graft size in adult-to-adult living donor liver transplantation: impact of the recipient's disease. Liver Transpl 2001: 7: 948.
24. Eguchi S, Yanaga K, Sugiyama N, Okudaira S, Furui J, Kanematsu T. Relationship between portal venous flow and liver regeneration in patients after living donor right-lobe liver transplantation. Liver Transpl 2003: 9: 547.
25. Shirouzu Y, Ohya Y, Suda H, Asonuma K, Inomata Y. Massive ascites after living donor liver transplantation with a right lobe graft larger than 0.8% of the recipient's body weight. Clin Transplant 2010: 24: 520.
26. Cirera I, Navasa M, Rimola A et al. Ascites after liver transplantation. Liver Transpl 2000: 6: 157.
27. Palmeri ML, Wang MH, Rouze NC et al. Noninvasive evaluation of hepatic fibrosis using acoustic radiation force-based shear stiffness in patients with nonalcoholic fatty liver disease. J Hepatol 2011: 55: 666.

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Effect of Body Composition on Outcomes after Hepatic Resection for Hepatocellular Carcinoma

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ABSTRACT

Purpose. To evaluate the effect of body composition on outcomes after hepatic resection for patients with hepatocellular carcinoma (HCC).

Methods. We performed 190 hepatic resections for HCC and divided the patients into 2 groups on the basis of visceral fat area (VFA), assessed by computed tomographic measurement at the level of the umbilicus, into high VFA (H-VFA) ($n = 106$) and low VFA (L-VFA) ($n = 84$) groups. We compared the surgical outcomes between the two groups.

Results. L-VFA was significantly correlated with a lower body mass index, sarcopenia, lower serum albumin, and liver cirrhosis. There was no difference in the incidence of postoperative complications and mortality between the 2 groups. Patients in the L-VFA group had a significantly poorer prognosis than those in the H-VFA group in terms of both overall ($P = 0.043$) and recurrence-free ($P = 0.001$) survival. The results of multivariate analysis showed that sarcopenia rather than L-VFA was an independent and prognostic indicator after hepatic resection with HCC.

Conclusions. Body composition is an important factor affecting cancer outcomes after hepatic resection for HCC in Japan.

Hepatocellular carcinoma (HCC) is the most frequent epithelial cancer of the liver, one of the most common cancers worldwide, and a major cause of death in many countries, especially Japan.[1,2] Hepatic resection remains one of the most common effective treatments for HCC.[3–5] However, a considerable number of patients develop intrahepatic recurrence, and although surgical techniques have recently been improved, postoperative morbidity in patients with HCC remains high.[5–10]

Body mass index (BMI) has been widely used as an indicator of obesity and is easily calculated using a patient's height and weight. The effects of BMI on surgical outcome are controversial in patients who undergo abdominal surgery.[11–13] Evidence has emerged that BMI is not the most sensitive predictor of outcomes after abdominal surgery and that measures of visceral fat area (VFA) better identify high-risk patients.[14,15] However, this issue is also contentious. Recently, several body composition features have been associated with cancer outcomes, and we previously reported that sarcopenia, or severe muscle depletion, was a marker of poor prognosis after hepatic resection in patients with HCC.[16]

To our knowledge, no previous data have been published on VFA for patients undergoing hepatic resection for HCC. Therefore, we retrospectively investigated the relationship between VFA and surgical outcomes after hepatic resection in patients with HCC.

MATERIALS AND METHODS

Patients

We included 190 patients who underwent hepatic resection for initial HCC without simultaneous procedures such as biliary reconstruction, gastrointestinal resection, or colorectal resection, at the Department of Surgery and Science, Kyushu University Hospital, between 2004 and

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2009. Patients' clinical, surgical, and pathological data were collected retrospectively from the institute's database, as well as from each patient's medical chart. All patients underwent preoperative computed tomography (CT). The degree of proportional visceral adiposity and skeletal muscle mass was measured from the patients' preoperative CT images. VFA was measured from a single axial slice at the level of the umbilicus.[17,18] VFA was calculated by measuring pixels with densities of −190 to −30 HU (Hounsfield units). A transverse CT image at the third lumbar vertebra (L3) in the inferior direction was assessed from each scan, and skeletal muscle was identified and quantified by HU thresholds of −29 to +150 (water is defined as 0 HU and air as 1000 HU).[16] Multiple muscles were quantified, including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique abdominal muscles, and rectus abdominis muscle. CT measurements were calibrated with water and air at fixed intervals, and VFA and skeletal muscle mass were measured by manual outlining on the CT images and checked by the radiologist.

The details of the surgical techniques and patient selection criteria have been previously reported.[10] Selection criteria for hepatic resection were as follows: ascites not detected or controllable by diuretics; serum total bilirubin level <2.0 mg/ml; and indocyanine green dye retention test at 15 min of <40 %. Parenchymal transection was performed by the Cavitron Ultrasonic Surgical Aspirator (CUSA system; Valleylab, Boulder, CO, USA) and a monopolar dissecting sealer (TissueLink; TissueLink Medical, Dover, NH, USA). Inflow vascular control was performed with intermittent hemi- or total Glisson sheath occlusion.[19]

Postoperative morbidity was graded according to the Dindo-Clavien classification, and we analyzed postoperative complications of Clavien grade IIIa or higher.[20] Patients were strictly followed after the hepatic resection, with monthly measurement of the levels of α-fetoprotein and des-gamma carboxy prothrombin, as well as monthly ultrasonography. Dynamic CT was performed every 6 months by radiologists, and an angiographic examination was performed after admission when there was a strong suspicion of disease recurrence.

Statistical Analysis

Continuous variables without normal distribution were compared by the Mann–Whitney *U*-test. Categorical variables were compared by the χ^2 test or Fisher's exact test. The Cox proportional hazard model was used for univariate analysis of survival data including covariates that were significant at $P < 0.05$ in the model. The overall survival and disease-free survival rates were calculated by the Kaplan–Meier (product limit) estimator and compared by the log rank test. Differences were considered significant at $P < 0.05$. All statistical analyses were performed by StatView 5.0 (Abacus Concepts, Berkeley, CA, USA).

RESULTS

The BMI groupings were as follows: BMI <18.5 kg/m^2 (underweight), 15 patients; BMI ≥18.5 kg/m^2 to <25 kg/m^2 (normal weight), 130 patients; BMI 25 to <30 kg/m^2 (overweight), 41 patients; and BMI ≥30 kg/m^2 (obese), 4 patients, categorized according to World Health Organization criteria.[21] We observed a significant positive correlation between BMI and VFA ($P < 0.0001$; $R^2 = 0.562$), although a wide range of VFA results existed within each BMI class (Fig. 1).

The median VFA of all patients was 98.4 cm^2 (range 17.9–410.5 cm^2) and in male patients was 108.0 cm^2 (range 17.9–410.5 cm^2), which was more than that in female patients (median 76.0; range 32.2–220.5 cm^2; $P = 0.010$). Cutoff values for VFA associated with overall survival were defined as 103 cm^2 for men and 69 cm^2 for women, which is recognized as a measure of metabolic abnormalities in

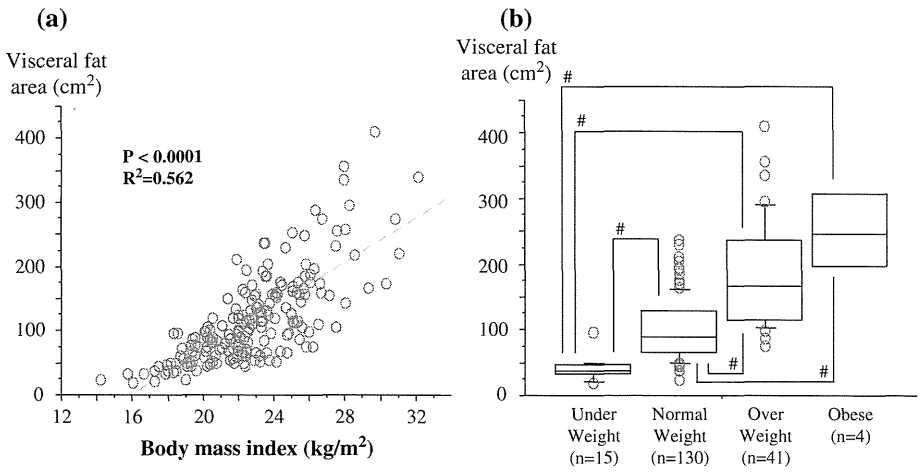

FIG. 1 VFA distribution according to body mass index as a continuous variable (**a**) or as a categorical variable (**b**). #$P < 0.01$

TABLE 1 Characteristics of patients with HCC who underwent hepatic resection

Characteristic	Low VFA ($n = 84$)	High VFA ($n = 106$)	P
Age, year	68 (34–87)	69 (31–83)	0.918
Sex, M/F	67/17	79/27	0.395
BMI, kg/m^2	20.5 (14.2–26.1)	24.0 (18.7–32.1)	<0.001
Sarcopenia	52 (61.9 %)	25 (23.5 %)	<0.001
Diabetes mellitus	25 (39.7 %)	36 (34.6 %)	0.538
Albumin, g/dl	3.9 (2.1–4.6)	4.1 (2.8–5.0)	0.007
Total bilirubin, mg/dl	0.7 (0.4–2.0)	0.7 (0.1–2.6)	0.527
Platelets, $\times 10^4$/mm^3	14.3 (5.2–41.3)	15.6 (4.1–36.3)	0.141
$ICGR_{15}$, %	13.4 (3.3–39.0)	13.4 (1.6–34.6)	0.883
Total cholesterol, mg/dl	169 (105–254)	165 (107–305)	0.326
Liver cirrhosis	33 (39.2 %)	27 (25.4 %)	0.041
Tumor size, cm	3.2 (1.0–15.0)	3.3 (1.0–16.5)	0.794
Solitary/multiple	44/40	70/36	0.073
Poorly differentiation	28 (33.3 %)	28 (26.4 %)	0.298
Microvascular invasion	29 (34.5 %)	36 (33.9 %)	0.935
AFP, ng/ml	16.2 (0.8–170668)	9.1 (0–577660)	0.171
DCP, mAU/ml	44.0 (2.4–75000)	77.0 (2.0–75000)	0.194
Anatomical resection	55 (65.4 %)	66 (62.2 %)	0.674
Operation time, min	325 (117–613)	370 (147–770)	0.142
Blood loss, g	454 (1–4800)	500 (15–3152)	0.280
Blood transfusion	8 (9.5 %)	13 (12.2 %)	0.549
Any complication	17 (20.2 %)	19 (17.9 %)	0.686
Wound infection	11 (13.0 %)	9 (8.4 %)	0.304
Intra-abdominal infection	5 (5.9 %)	3 (2.8 %)	0.469
Bile leakage	3 (3.5 %)	5 (4.7 %)	>0.999
Ascites	3 (3.5 %)	1 (0.9 %)	0.323
30 days mortality	0 (0 %)	0 (0 %)	>0.999
90 days mortality	0 (0 %)	0 (0 %)	>0.999

VFA visceral fat area, *BMI* body mass index, *$ICGR_{15}$* indocyanine green dye retention test at 15 min, *AFP* α-fetoprotein, *DCP* des-gamma carboxy prothrombin

Japan.[22] We divided the study population into two groups according to high VFA (H-VFA) or low VFA (L-VFA). Cutoff values for skeletal muscle were defined as 43.75 cm^2/m^2 for men and 41.10 cm^2/m^2 for women.[16] On the basis of this cutoff, patients were assigned to one of two groups, depending on the presence or absence of sarcopenia.

The clinicopathological characteristics for patients in the L-VFA group ($n = 84$) and the H-VFA group ($n = 106$) are shown in Table 1. Serum albumin levels in the L-VFA group were significantly lower than in the H-VFA group ($P = 0.007$). The percentages of patients with liver cirrhosis ($P = 0.041$) and sarcopenia ($P < 0.001$) in the L-VFA group were significantly higher than in the H-VFA group, and no differences were noted between the two groups in terms of other liver function data, tumor factors, and surgical factors. There was no difference in the incidence of postoperative complications and mortality between the two groups.

Figure 2 shows the overall and recurrence-free survival curves after hepatic resection between the two groups. The 3-, 5-, and 7-year overall survival rates were 86.5, 78.2, and 74.3 % in the H-VFA group and 79.0, 65.3, and 45.2 % in the L-VFA group, respectively. The 3-, 5-, and 7-year recurrence-free survival rates were 54.7, 46.4, and 36.5 % in the H-VFA group and 37.3, 23.7, and 14.4 % in the L-VFA group, respectively. Patients with L-VFA had a significantly worse prognosis than those with H-VFA with respect to both overall ($P = 0.043$) and recurrence-free ($P = 0.001$) survival.

Table 2 shows the results of the univariate analysis used to identify the significant factors closely related to the long-term survival rate after hepatic resection in patients with HCC. Poor prognostic factors included L-VFA, sarcopenia, multiple tumors, microvascular invasion, and intraoperative blood transfusion. The Cox proportional hazard model was used to assess the effect of different variables on overall survival. Poor prognostic factors identified by multivariate analysis included sarcopenia, multiple tumors, microvascular invasion, and intraoperative blood transfusion; these were factors that influenced the overall survival rate in patients with HCC.

Significant prognostic factors for recurrence-free survival were L-VFA, BMI <25 kg/m^2, sarcopenia, liver cirrhosis, multiple tumors, poor differentiation, and microvascular invasion (Table 3). Multivariate analysis identified two prognostic factors (multiple tumors and microvascular invasion) that influenced recurrence-free survival.

DISCUSSION

We found that L-VFA was highly correlated with lower BMI, sarcopenia, lower serum albumin level, and liver cirrhosis. Short-term outcomes including mortality and postoperative complications were not correlated with VFA. Indicators of host factors such as sarcopenia and neutrophil-to-lymphocyte ratio, tumor factors such as tumor size, des-gamma carboxy prothrombin, expression of focal adhesion kinase, and expression of diacylglycerol kinase have previously been reported to be predictors of poor prognosis in patients with HCC.[16,23–26] Our results showed that L-VFA was not an independent predictor of poor survival after hepatic resection in patients with HCC. To our knowledge, this is the first clinical study to assess the relationships between VFA and surgical outcomes after hepatic resection in patients with HCC.

In this study, VFA was not related to tumor factors but was significantly correlated with host factors including BMI, skeletal muscle mass (sarcopenia), serum level of

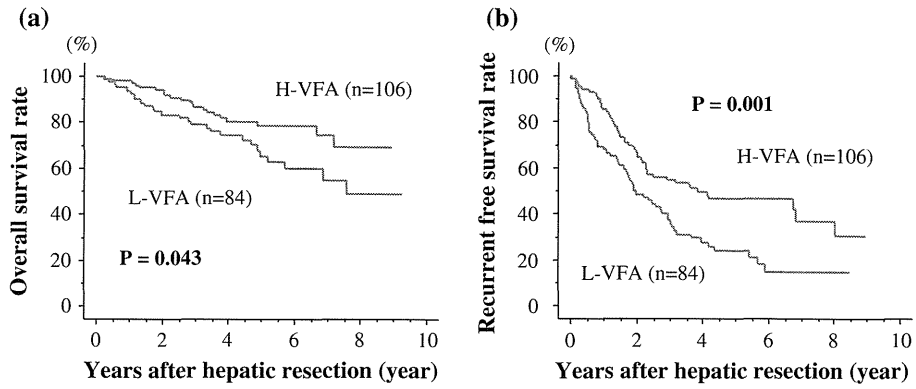

FIG. 2 **a** Overall and **b** recurrence-free survival curves after hepatic resection in patients with HCC comparing high visceral fat area (H-VFA) and low visceral fat area (L-VFA). **a** $P = 0.043$, **b** $P = 0.001$ (log rank test)

TABLE 2 Univariate and multivariate Cox proportional hazard analysis of factors related to overall survival in patients with HCC who underwent hepatic resection

Variable	Univariate			Multivariate		
	Hazard ratio	95 % CI	*P*	Hazard ratio	95 % CI	*P*
Age ≥65 year	1.58	0.84–3.03	0.158			
Male	0.99	0.50–1.95	0.993			
L-VFA	1.78	1.00–3.15	0.046	1.51	0.80–2.83	0.194
BMI <25 kg/m^2	1.93	0.86–4.31	0.106			
Sarcopenia	2.08	1.18–3.69	0.012	1.96	1.06–3.74	0.031
Albumin <3.6 g/dl	1.06	0.47–2.37	0.884			
Platelet <10.0 × 10^4/mm^3	1.75	0.90–3.44	0.097			
Liver cirrhosis	1.21	0.67–2.17	0.523			
Tumor size ≥5.0 cm	1.62	0.90–2.91	0.105			
Multiple tumors	2.17	1.23–3.84	0.007	2.34	1.31–4.18	0.003
Poorly differentiation	1.72	0.97–3.05	0.064			
Microvascular invasion	2.18	1.23–3.87	0.007	2.50	1.38–4.52	0.002
Blood loss >1,000 g	1.27	0.62–2.56	0.503			
Intraoperative blood transfusion	2.35	1.17–4.73	0.016	2.80	1.35–5.78	0.005
Postoperative complication	1.36	0.69–2.66	0.370			

CI confidence interval, *L-VFA* low visceral fat area, *BMI* body mass index

albumin, and liver cirrhosis. Likewise, we previously reported that BMI and skeletal muscle mass were not related to tumor factors.[13,16] Taken together, this suggests that body composition would not correlate with tumor factors but would be related to host factors.

Several recent reports have suggested that VFA is more strongly associated with postoperative intra-abdominal infectious complications in patients with gastric cancer and colon cancer.[14,15] However, Gaujoux et al.[27] found that BMI and VFA were not correlated with postoperative complications after pancreaticoduodenectomy for pancreatic adenocarcinoma. We previously reported that overweight status was not a risk factor for postoperative complications or mortality in patients with HCC after hepatic resection, and Saunders et al. reported that there were no differences across BMI groups in overall and specific morbidity after liver resection.[13,28] We found that VFA was significantly correlated with BMI but was not correlated with diabetes mellitus or serum total cholesterol level, which are known metabolic disorders.[29] These data indicate that there is no effect of VFA on short-term surgical outcomes after hepatic resection in patients with HCC.

Few investigators have studied the effect of VFA on long-term outcomes after surgery. Gaujoux et al.[27] found that BMI and VFA were not correlated with prognosis after pancreaticoduodenectomy in terms of both overall and recurrence-free survival for 328 patients with pancreatic adenocarcinoma. Van Vledder et al.[30] reported that VFA did not predict overall survival after hepatic resection in patients with colorectal liver metastases. In our study, we found that L-VFA was a significantly worse long-term prognostic factor for survival in patients with HCC after hepatic resection in univariate analysis. However, the results of the multivariate analysis showed sarcopenia

TABLE 3 Univariate and multivariate Cox proportional hazard analysis of factors related to recurrence-free survival in patients with HCC who underwent hepatic resection

Variable	Univariate			Multivariate		
	Hazard ratio	95 % CI	*P*	Hazard ratio	95 % CI	*P*
Age ≥65 year	1.16	0.75–1.79	0.483			
Male sex	1.17	0.73–1.86	0.511			
L-VFA	1.85	1.27–2.68	0.001	1.44	0.94–2.21	0.086
BMI <25 kg/m^2	2.08	1.25–3.45	0.004	1.19	0.66–2.13	0.557
Sarcopenia	1.62	1.11–2.36	0.012	1.30	0.85–2.00	0.215
Albumin <3.6 g/dl	1.01	0.61–1.69	0.941			
Platelet <10.0 × 10^4/mm^3	1.30	0.79–2.13	0.300			
Liver cirrhosis	1.52	1.03–2.24	0.031	1.27	0.85–1.90	0.240
Tumor size ≥5.0 cm	1.47	0.99–2.19	0.053			
Multiple tumors	2.57	1.76–3.75	<0.001	2.40	1.63–3.53	<0.001
Poor differentiation	1.48	1.00–2.20	0.046	1.19	0.79–1.79	0.392
Microvascular invasion	1.54	1.05–2.27	0.026	1.69	1.12–2.56	0.019
Blood loss >1,000 g	1.02	0.61–1.70	0.918			
Intraoperative blood transfusion	1.35	0.75–2.42	0.303			
Postoperative complication	1.08	0.67–1.75	0.725			

CI confidence interval, *L-VFA* low visceral fat area, *BMI* body mass index

rather than L-VFA to be an independent and prognostic indicator after hepatic resection with HCC. Patients with relatively H-VFA may have more sufficient nutritional and physiologic reserves than L-BMI patients.

An abundance of experimental and epidemiologic evidence has demonstrated that metabolic regulation and the immune response are highly integrated and that the proper functioning of each is dependent on the other.[31] Serum albumin level is a marker for nutritional status, and we found that the serum albumin level in the H-VFA group was significantly higher than that in the L-VFA group.[32] However, the percentage of patients with liver cirrhosis in the L-VFA group was significantly higher than in the H-VFA group. The relationship between the serum level of albumin and VFA is complicated in the presence of underlying liver disease. Recent studies have measured body fat distribution including abdominal wall fat, hip girdle fat, visceral fat, and abdominal depth measuring intra-abdominal fat using a simple radiologic analysis and found that increased body fat was advantageous for long-term survival after pancreaticoduodenectomy in 408 patients with pancreatic adenocarcinoma.[33] Additional studies are required to clarify the relationship between VFA and nutritional status in patients with liver disease.

It was interesting that sarcopenia was a stronger prognostic factor than L-VFA for overall survival after hepatic resection of HCC. Sarcopenia is defined as a low level of skeletal muscle mass—a level below the healthy young adult mean.[34] Although sarcopenia is associated with aging, it can also be present as a result of chronic diseases and malignancy.[30,35] We previously found that sarcopenia was significantly correlated with lower albumin levels and BMI, and that it was an independent predictor of poor survival after hepatic resection in patients with HCC.[16] In our data including VFA and sarcopenia, L-VFA and sarcopenia were not independent predictors for recurrence-free survival, but sarcopenia rather than L-VFA was an independent predictor for overall survival after hepatic resection in patients with HCC. This cutoff value of VFA is recognized as a measure of metabolic abnormalities in Japan.[22] Patients with H-VFA might be assumed to have good nutritional status, but all patients with L-VFA might not have poor nutritional status. This multivariate data may suggest that skeletal muscle is a better parameter than visceral fat to describe malnutrition.

Our study has several limitations. It is a single institutional and retrospective review; we included a relatively small number of patients, especially those with BMI ≥30 kg/m^2 and BMI <18.5 kg/m^2; and the cutoff value in this study is an indication for Japanese patients, and the cutoff value of VFA might differ in patients with liver disease. These limitations will need to be addressed in multi-institutional reviews and possible clinical studies.

In conclusion, our study found that VFA did not have an effect on short-term outcomes including postoperative mortality and complications after hepatic resection in patients with HCC. Better nutritional status, including H-VFA, might be advantageous for long-term survival after hepatic resection for HCC in Japan.

REFERENCES

1. Bruix J, Lovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology*. 2002;35:519–24.
2. Bosch FX, Ribes J, Díaz M, et al. Primary liver cancer: worldwide incidence and trends (review). *Gastroenterology*. 2004;127: S5–16.
3. Takenaka K, Kawahara N, Yamamoto K, et al. Results of 280 liver resections for hepatocellular carcinoma. *Arch Surg*. 1996;131:71–6.
4. Shirabe K, Takeishi K, Taketomi A, et al. Improvement of long-term outcomes in hepatitis C virus antibody-positive patients with hepatocellular carcinoma after hepatectomy in the modern era. *World J Surg*. 2011;35:1072–84.
5. Itoh S, Morita K, Ueda S, et al. Long-term results of hepatic resection combined with intraoperative local ablation therapy for patients with multinodular hepatocellular carcinomas. *Ann Surg Oncol*. 2009;16:3299–307.
6. Yamashita Y-i, Taketomi A, Itoh S, et al. Longterm favorable results of limited hepatic resections for patients with hepatocellular carcinoma. *J Am Coll Surg*. 2007;205:19–26.
7. Itoh S, Fukuzawa K, Shitomi Y, et al. Impact of the VIO system in hepatic resection for patients with hepatocellular carcinoma. *Surg Today*. 2012;42:1176–82.
8. Uchiyama H, Itoh S, Higashi T, et al. A two-step hanging maneuver for a complete resection of Couinaud's segment I. *Dig Surg*. 2012;29:202–5.
9. Taketomi A, Kitagawa D, Itoh S, et al. Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. *J Am Coll Surg*. 2007; 204:580–7.
10. Itoh S, Shirabe K, Taketomi A, et al. Zero mortality in more than 300 hepatic resections: validity of preoperative volumetric analysis. *Surg Today*. 2012;42:435–40.
11. Merkow RP, Bilimoria KY, McCarter MD, et al. Effect of body mass index on short-term outcomes after colectomy for cancer. *J Am Coll Surg*. 2009;208:53–61.
12. Mullen JT, Davenport DL, Hutter MM, et al. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. *Ann Surg Oncol*. 2007;15: 2164–72.
13. Itoh S, Ikeda Y, Kawanaka H, et al. The effect of overweight status on the short-term and 20-y outcomes after hepatic resection in patients with hepatocellular carcinoma. *J Surg Res*. 2012;178:640–5.
14. Sugisawa N, Tokunaga M, Tanizawa Y, et al. Intra-abdominal infectious complications following gastrectomy in patients with excessive visceral fat. *Gastric Cancer*. 2012;15:206–12.
15. Cecchini S, Cavazzini E, Marchesi F, et al. Computed tomography volumetric fat parameters versus body mass index for predicting short-term outcomes of colon surgery. *World J Surg*. 2011;35:415–23.
16. Harimoto N, Shirabe K, Yamashita YI, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg*. 2013;100:1523–30.
17. Kvist H, Chowdhury B, Sjöström L, et al. Adipose tissue volume determination in males by computed tomography and 40 K. *Int J Obes*. 1988;12:249–66.
18. Yoshizumi T, Nakamura T, Yamane M, et al. Abdominal fat: standardized technique for measurement at CT. *Radiology*. 1999; 211:283–6.
19. Pringle JH. Notes on the arrest of hepatic hemorrhage due to trauma. *Ann Surg*. 1908;48:58–62.
20. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complication: five-year experience. *Ann Surg*. 2009;250:187–96.
21. World Health Organization. Obesity: preventing and managing the global epidemic. Geneva, Switzerland: World Health Organization; 2000.
22. Kashihara H, Lee JS, Kawakubo K, et al. Criteria of waist circumference according to computed tomography-measured visceral fat area and the clustering of cardiovascular risk factors. *Circ J*. 2009;73:1881–6.
23. Mano Y, Shirabe K, Yamashita Y, et al. Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival after hepatectomy for hepatocellular carcinoma: a retrospective analysis. *Ann Surg*. 2013;258:301–5.
24. Shirabe K, Itoh S, Yoshizumi T, et al. The predictors of microvascular invasion in candidates for liver transplantation with hepatocellular carcinoma—with special reference to the serum levels of des-gamma-carboxy prothrombin. *J Surg Oncol*. 2007; 95:235–40.
25. Itoh S, Maeda T, Shimada M, et al. Role of expression of focal adhesion kinase in progression of hepatocellular carcinoma. *Clin Cancer Res*. 2004;10:2812–7.
26. Takeishi K, Taketomi A, Shirabe K, et al. Diacylglycerol kinase alpha enhances hepatocellular carcinoma progression by activation of Ras-Raf-MEK-ERK pathway. *J Hepatol*. 2012;57:77–83.
27. Gaujoux S, Torres J, Olson S, et al. Impact of obesity and body fat distribution on survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg Oncol*. 2012;19:2908–16.
28. Saunders JK, Rosman AS, Neihaus D, et al. Safety of hepatic resections in obese veterans. *Arch Surg*. 2012;147:331–7.
29. Dindo D, Muller MK, Weber M, et al. Obesity in generalelective surgery. *Lancet*. 2003;361:2032–5.
30. van Vledder MG, Levolger S, Ayez N, et al. Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg*. 2012;99:550–7.
31. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444:860–7.
32. Sacks GS, Dearman K, Replogle WH, et al. Use of subjective global assessment to identify nutrition-associated complications and death in geriatric long-term care facility residents. *J Am Coll Nutr*. 2000;19:570–577.
33. Pausch T, Hartwig W, Hinz U, et al. Cachexia but not obesity worsens the postoperative outcome after pancreatoduodenectomy in pancreatic cancer. *Surgery*. 2012;152(3 Suppl 1):S81–8.
34. Rolland Y, Czerwinski S, Abellan Van Kan G, et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. *J Nutr Health Aging*. 2008;12:433–450.
35. Lang T, Streeper T, Cawthon P, et al. Sarcopenia: etiology, clinical consequences, intervention, and assessment. *Osteoporos Int*. 2010;21:543–59.

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ORIGINAL ARTICLE

Clinical significance of gastrointestinal bleeding after living donor liver transplantation

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

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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)

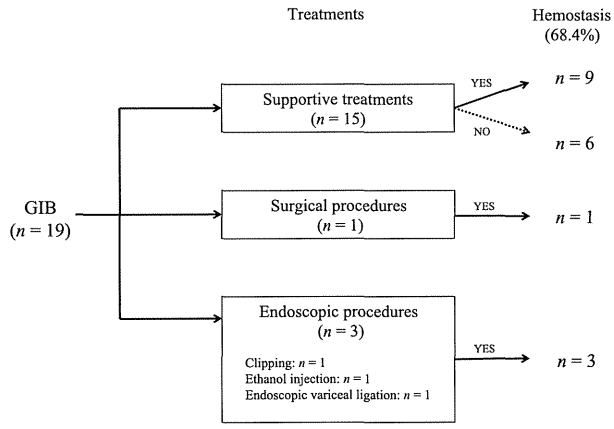

Figure 1 Treatments applied and outcomes of patients with gastrointestinal bleeding after living donor liver transplantation. GIB, gastrointestinal bleeding.

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.

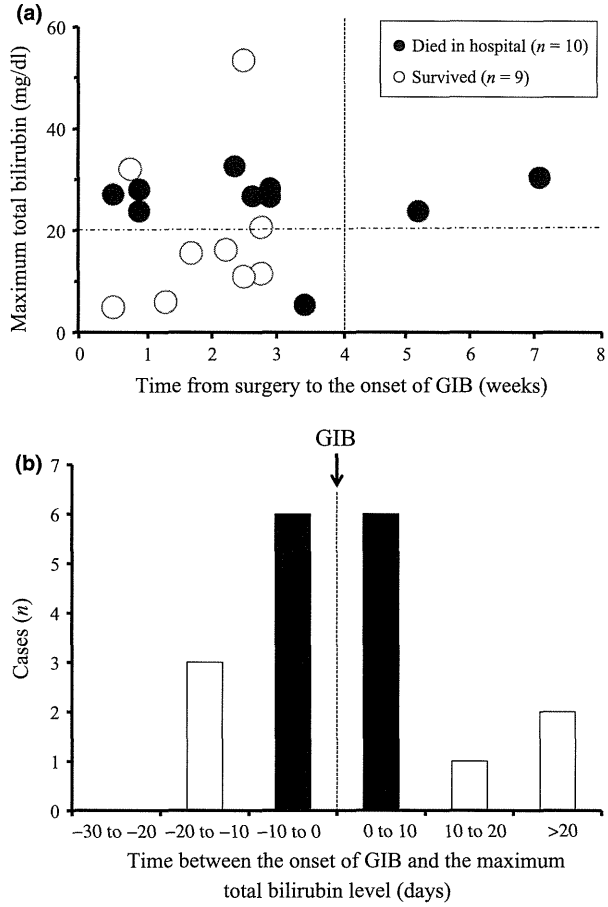

Figure 2 (a) Association between the time from living donor liver transplantation (LDLT) to the onset of gastrointestinal bleeding (GIB) with the maximum bilirubin level after LDLT. (b) Association between the time between the onset of GIB and the day on which the maximum total bilirubin level was reached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

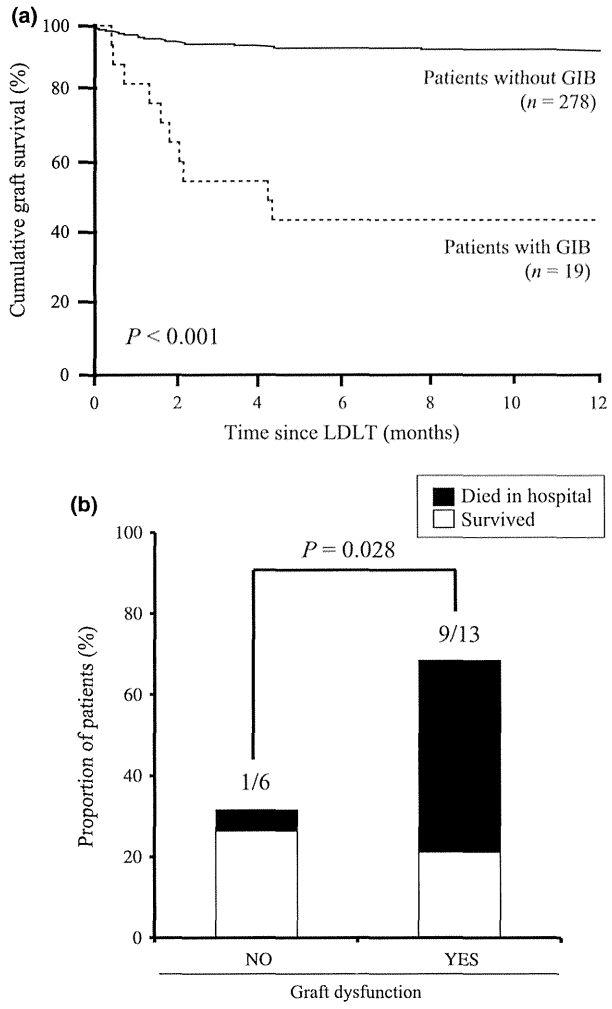

Figure 3 (a) Cumulative graft survival in patients with or without gastrointestinal bleeding. (b) Inhospital mortality rate in patients with or without graft dysfunction.

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.

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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.

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LETTER FROM THE FRONTLINE

Fairly Rare De Novo Inflammatory Pseudotumor in a Graft After Living Donor Liver Transplantation

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TO THE EDITORS:

De novo solid tumors rarely occur in a graft after liver transplantation, although some de novo hepatocellular carcinomas have been reported.[1] To the best of our knowledge, there have been no reports of de novo inflammatory pseudotumors (IPTs) in a liver graft. Here we report the first case of a de novo IPT in a liver graft after living donor liver transplantation (LDLT).

The patient was a 54-year-old female with end-stage liver disease secondary to cryptogenic liver cirrhosis. She underwent LDLT with a left lobe graft donated by her 57-year-old husband. Her postoperative immunosuppression consisted of cyclosporine, mycophenolate mofetil, and steroids. This patient did not experience acute cellular rejection or biliary complications (eg, cholangitis, biliary leakage, or biliary strictures) after LDLT. One year after LDLT, routine abdominal ultrasound screening revealed an asymptomatic solid liver tumor in the transplanted graft that was adjacent to the umbilical portion. Enhanced computed tomography (CT) revealed a solid tumor in segment 3 and 4 of the graft with B2 (biliary duct in segment 2) dilatation (Fig. 1A,B). The levels of tumor markers were as follows: α-fetoprotein, 1.8 ng/mL (normal range < 6.2 ng/mL); des-γ-carboxyprothrombin, 49 mAU/mL (normal range < 40 mAU/mL); carcinoembryonic antigen, 1.2 ng/mL (normal range < 3.2 ng/mL); and carbohydrate antigen 19-9, 82 U/mL (normal range < 37 U/mL). Enhanced magnetic resonance imaging and CT angiography showed a hypovascular tumor consistent with cholangiocellular carcinoma. Endoscopic retrograde cholangiography revealed a B2 (biliary duct in segment 2) stricture that was caused by the tumor and distal dilation (Fig. 1C). ^{18}F-fluorodeoxy glucose positron emission tomography demonstrated abnormal ^{18}F-fluorodeoxy glucose uptake by the tumor (maximum standardized uptake value = 23.3; Fig. 1D). Therefore, we diagnosed de novo cholangiocellular carcinoma in the graft just above the umbilical portion.

Because the tumor location was very delicate, we planned to perform surgical tumor biopsy followed by partial hepatectomy. However, the biopsy sample indicated that the tumor was an IPT (Fig. 2). Therefore, we immediately suspended the procedure and treated the patient conservatively with antibiotics.

IPTs of the liver are rare benign tumors. Although the etiology and pathogenesis of IPTs are unclear, they were initially histologically characterized by dense hyalinized fibrosis and/or infiltrating inflammatory cells, including large numbers of foamy histiocytes, lymphocytes, and plasma cells.[2] Typical radiological findings from enhanced CT include hypoattenuation of the mass with respect to the hepatic parenchyma with a variable degree of enhancement in the internal septa or periphery in the portal or equilibrium phase. Therefore, it is difficult to distinguish IPTs from malignant tumors and especially cholangiocellular carcinomas.[3] Ahn et al.[3] reported that 78.2% of their patients with IPTs had symptoms, including abdominal pain (54.5%), febrile sensation (22.7%), and malaise (4.5%), although some patients were asymptomatic. Interestingly, they also found that carbohydrate antigen 19-9 and α-fetoprotein levels were elevated in 22.7% and 4.5% of their patients, respectively.

IPTs can be treated conservatively with antibiotics with or without nonsteroidal anti-inflammatory drugs or with surgical resection. Surgical resection should be recommended for patients with poor responses to conservative therapy, tumor growth, increasing tumor marker levels, or an uncertain diagnosis.

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The authors declare no conflicts of interest.

This study obtained institutional review board acceptance.

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