selection of smaller sized grafts with greater donor safety and a good result for the recipient in LDLT. Establishment of excellent results with a split liver graft will also provide the resolution of a donor shortage with good SOLT results in DDLT.

From the viewpoint of greater donor safety and expanded donor candidates in LDLT, a stable choice of a left-sided graft still remains controversial. A shift to SOLT with excellent results should be established to resolve a donor shortage in DDLT. Although splitting a liver maximizes the number of transplanted recipients, it may increase the morbidity and mortality for the individual recipient. Also, specific regulations for splitting liver graft and ethical policies for SOLT were still not established in some countries. Advanced technological developments in the SOLT have resulted in these ethical dilemmas. The SOLT must be improved all around the world. The transplant surgeons all around the world should explore these difficult issues and propose a general ethical policy for SOLT. The question can be asked: ''Where should liver transplant surgeons head in the next decade?'' We consider that it is important to focus on improving split liver grafts including approximately 40%-grafts.

Disclosure of interest

The authors declare that they have no financial conflict of interest concerning this article.

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Antibody-mediated rejection after adult living-donor liver transplantation triggered by positive lymphocyte cross-match combination

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Abstract

A 46-year-old female suffering from liver cirrhosis was referred to us for living-donor liver transplantation (LDLT). Pre-transplant lymphocyte cross-match tests were positive. The recipient showed immunoreactivity against donor human leukocyte antigen (HLA) Class I antigens, a finding confirmed by flow cytometry. Additional tests confirmed donor-specific lymphocyte immunoreactivity against HLA B 55. As no other suitable donor was available, we performed LDLT coupled with splenectomy, despite the positive cross-match. Tacrolimus, methylprednisolone and mycophenolate mofetil were used postoperatively for immunosuppression. The postoperative course was uneventful until Day 3 when blood tests showed disorders in liver function and the patient's condition suddenly worsened. Although intensive care (including plasma exchange) was given, her condition continued to deteriorate. Flow cytometry initially showed that immunoreactivity against Class I antigens was down-regulated immediately after LDLT, but further testing showed that it had increased again. We diagnosed humoral rejection based on clinical, immunological and histopathological findings and suggest that this was mediated by an immune response to donor-specific antigens. The patient experienced multi-organ failure and died on post-operative Day 9.

Keywords antibody-mediated rejection, cross-match, human leukocyte antigen, humoral rejection, liver transplantation

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Introduction

Classically, allograft rejection in organ transplantation is considered to be mediated by alloantigen recognition by T cells. Immunosuppressants such as cyclosporine and tacrolimus have shown good results in controlling the rejection process, and therapies for acute cellular rejection mediated by T cells (such as steroid pulse) are also well-established. However, though positive lymphocyte cross-match combinations of donor and recipient are rare, humoral rejection (HR) or antibody-mediated rejection (AMR) is still a serious problem after organ transplantation because treatment is difficult and in some cases, grafts are lost.

The importance of lymphocyte cross-matching and human leukocyte antigen (HLA) histocompatibility have been reported for kidney transplantation and combined kidney-liver transplantation [1-4]. The role of anti-donor HLA antibodies in graft loss is also well-known [5,6]. However, the impact of lymphocyte cross-matching and HLA compatibility upon HR or AMR after liver transplantation (LT) is still unclear.

We report the case of a patient referred to us for a living-donor liver transplantation (LDLT) with a positive cross-match that had a poor post-operative outcome, and discuss strategies to further improve the prognosis in such cases.

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Conflict of Interest: None

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Case report

A 46-year-old female was admitted suffering from well-developed liver cirrhosis. Hepatitis C virus infection was diagnosed at 39 years of age and she had been treated at an-

other hospital for the last seven years. Although the number of different medications used to treat the condition (furosemide, spironolactone, ursodeoxycholic acid, lactulose, and branched-chain amino acids) and their dosages had slowly increased over the last year, her condition was not well-controlled. She had frequent episodes of esophageal variceal rupture over the last year and had suffered from intractable ascites and a right pleural effusion. Because of her deteriorating condition, she was referred to our division for LDLT. On admission, she had a low-grade fever and cell counts in the ascites and pleural effusion were 2270 /mm^3 and 2580 /mm^3, respectively. We diagnosed spontaneous bacterial peritonitis and pleuritis which were managed pre-operatively by drainage, hydration and cefotaxime i.v. The low-grade fever disappeared after treatment. Her status according to the United Network for Organ Sharing was IIB. Her scores for Child-Pugh and the model for end-stage liver disease were 14 and 25, respectively.

Pre-transplant lymphocyte cross-match tests were performed using direct complement-dependent cytotoxicity (CDC) and anti-human globulin assays (anti-human immunoglobulin lymphocytotoxicity test, AHG-LCT) [7,8]. The results of these tests were positive. Moreover, the patient showed strong reactions against donor HLA Class I antigens (Fig. 1). Also, flow cytometry (FCM) showed that the lymphocytes of the recipient were reactive against HLA Class I antigens (Fig. 2). The HLA typing of both the recipient and the donor is shown (Fig. 3). We also performed additional tests to assess the patient's immunoreactivity to specific HLA Class I antigens. The lymphocytes of the recipient showed strong immunoreactivity against HLA Class I loci including HLA B 55. Tests showed that the donor had this HLA B locus (Fig. 3), which meant that the patient could potentially mount a donor-specific anti-HLA antibody response after transplantation.

Although the results of the cross-matching tests were positive for this particular donor and recipient, the ABO blood group was compatible and the patient had no history of receiving blood transfusions from the donor. As we were unable to find a more suitable donor, the ethics committee of our institution granted approval for the procedure and written informed consent was obtained from both the recipient and the donor. During surgery we found that the patient had splenomegaly and developed collateral vessels (umbilical vein and coronary vein) and so we performed a splenectomy and ligation of collateral vessels to obtain improved intra-operative control of portal venous pressure. We reported that portal venous pressure <15 mmHg is a key for successful LDLT [9,10], and the final pressure was 13 mmHg in this case. The surgery lasted 822 minutes and intra-operative blood loss was 7700 mL. The graft was a left-lobe graft and the graft weight was 450 g. The graft:recipient weight ratio was 0.91. The patient received 24 units of red cells, 16 units of plasma and 30 units of platelets during the procedure. We used tacrolimus, methylprednisolone and mycophenolate mofetil as immunosuppressants and the trough level of tacrolimus was kept at 8–10 ng/mL during the early post-operative period. Methylprednisolone was given intravenously (1 mg/kg) once daily from post-operative Day (POD) 1 to POD 3 followed by 0.5 mg/kg once daily for the next 3 days. The dosage of mycophenolate mofetil was 10 mg/kg/d from POD 1.

Post-operative splanchnic in-flow and out-flow were excellent as assessed by Doppler ultrasound studies. The

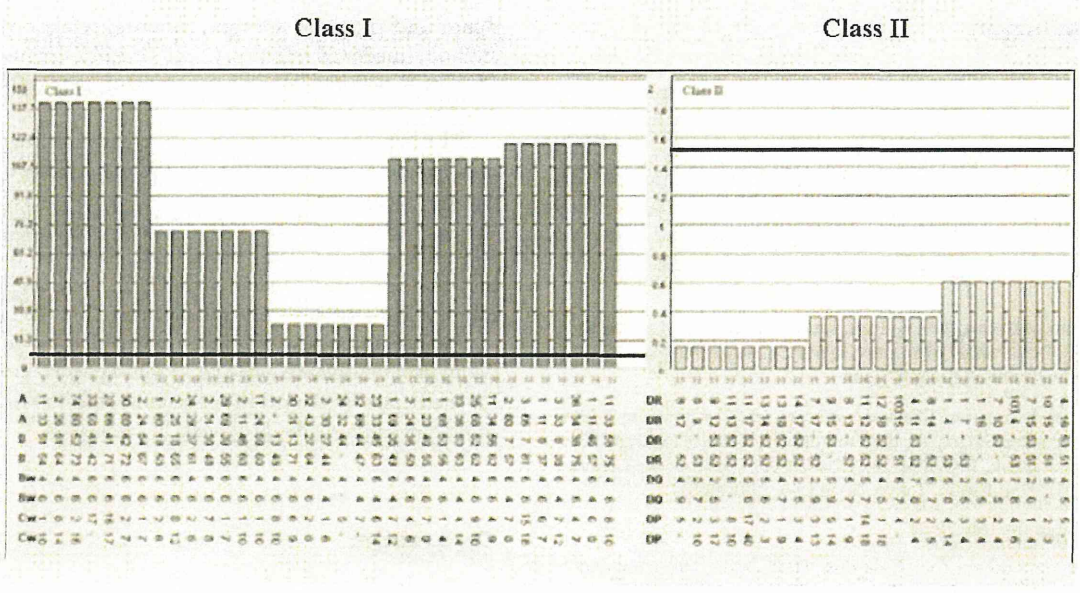

Figure 1 Recipient's lymphocyte reactivity against HLA class I and II antigens. Recipient lymphocytes had obvious immunoreactivity against donor HLA class I antigens, though reactivity against donor HLA class II antigens was below the threshold level. The threshold level was 1.53 (horizontal lines)

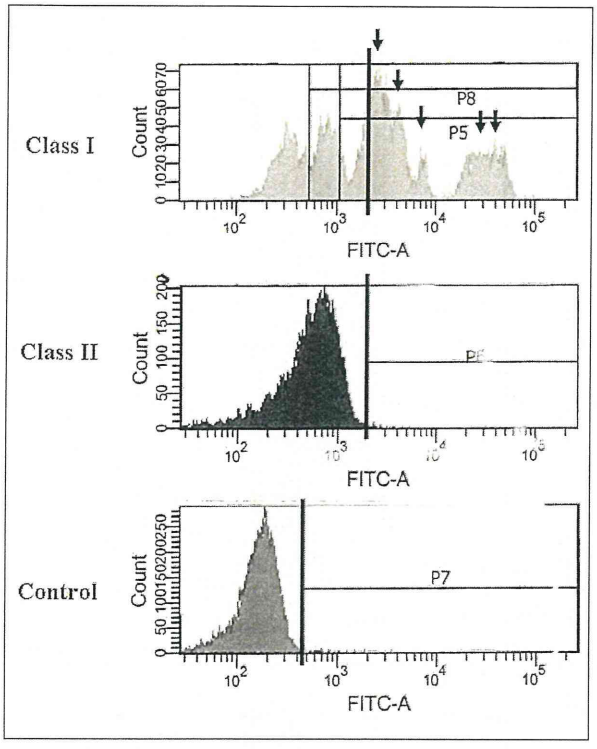

Figure 2 Recipient pre-transplant immunoreactivity against donor antigens, as assessed by FCM. The recipient's lymphocytes clearly show reactivity against donor HLA class I antigens (arrows). The vertical lines represent reactivity against the same antigen in a third party (other recipients).

post-operative course was uneventful until POD 3 when the patient experienced a sudden elevation of serum lactate dehydrogenase (LDH) levels, a decrease in the platelet count and severe fragmentation of red blood cells. Serum total bilirubin (T-Bil) levels were increased after POD 3 leading to a prolonged case of jaundice. On POD 4 a chest X-ray was taken and showed an acute respiratory distress syndrome-like condition. Blood gas analysis revealed significant respiratory insufficiency. The patient's respiratory function worsened to a point where she required mechanical ventilation. Plasma exchange (PE) (80 mL/kg/d) was performed daily after POD 4 (Fig. 4) and she received steroid pulse therapy (methylprednisolone at 10 mg/kg, i.v.) from POD 5. The gated area represented immunoreactivity against Class I antigens, and the percentages were calculated as the counts in the gated area/the whole counts. The percentages at pre-LDLT, PODs 2, 5, 6, 8 and 9 were 71.7, 1.7, 1.9, 11.2, 7.3 and 25.8 %, respectively. Although immunoreactivity against HLA Class I antigen was down-regulated during the early period after LDLT it increased again from POD 6. Note that this immunoreactivity was down-regulated on POD 5 even though graft dysfunction began on POD 3 and that this immunoreactivity remained from POD 6 even after repeated PE. On POD 8, peripheral blood examination showed evidence of hemolysis and that haptoglobin levels had fallen (<5.0 mg/dL). Percutaneous microecchymosis was noted and coagulation profiles were consistent with disseminated intravascular coagulation (DIC). The patient's condition worsened and she did not respond to further treatment, including daily PE. On POD 9 we performed a liver needle biopsy under US guidance. Histopathological examination clearly showed severe graft damage

	A	B	BW	C	DR	DQ
Recipient	**24, 26**	**48, 60**	**6**	**8, 14**	**9, 16**	**3(9), 5**
Donor	**2. 11**	**51, 55**	**4, 6**	**1, 14**	**4, 9**	**3(9), 4**

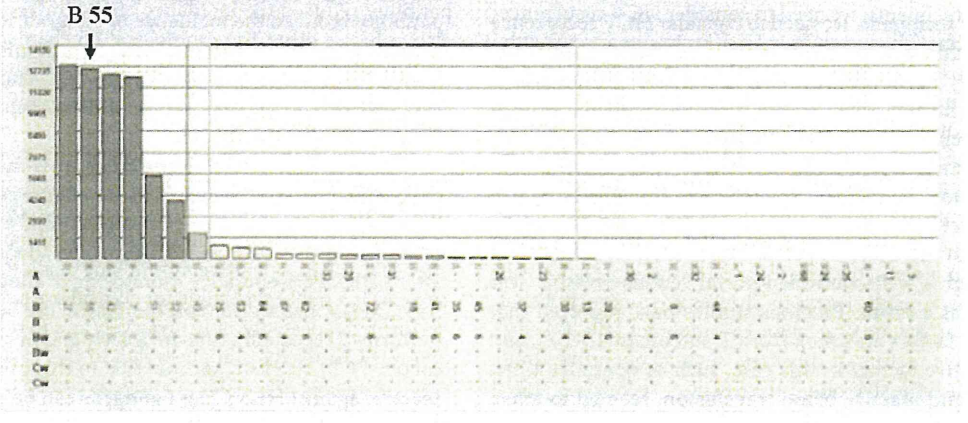

Figure 3 Serological HLA typing of both the recipient and donor and the recipient's lymphocyte immunoreactivity against specific HLA class I antigens. The recipient was not homozygous for HLA loci. The donor has the HLA-B 55 locus (underlined).The recipient's lymphocytes show specific activity against HLA-B locus 55 (black arrow).

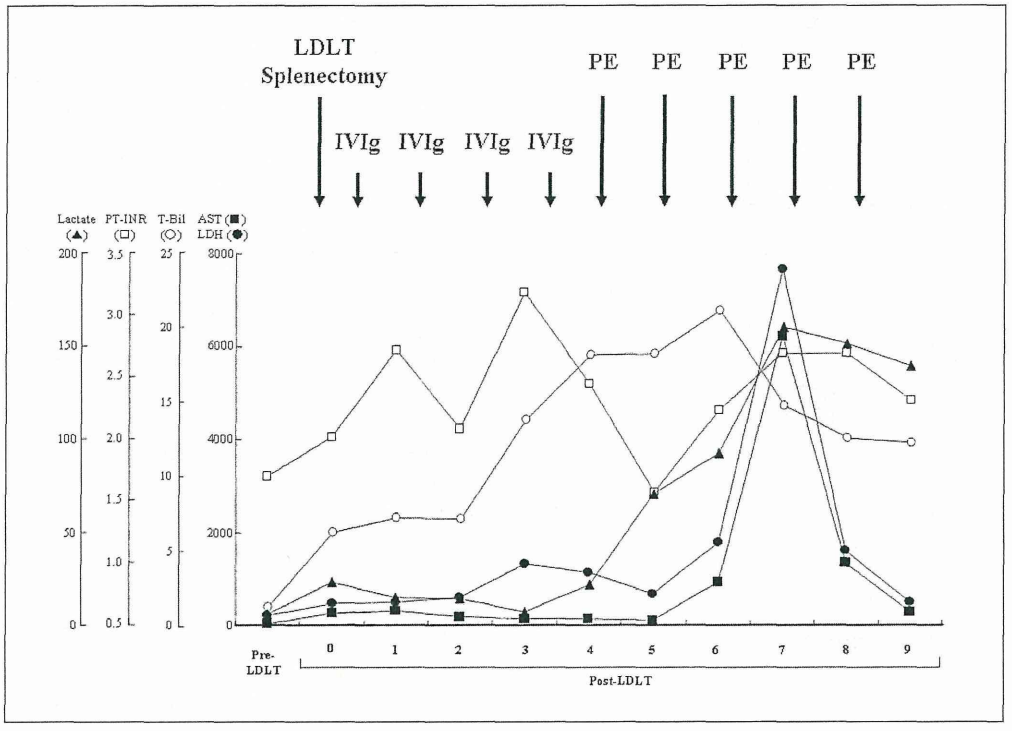

Figure 4 Changes in the patient's blood biochemistry after LDLT. Temporal changes in each of the variables are represented as follows: closed square, AST; closed circle, LDH; open circle, T-Bil; open square, PT-INR; closed triangle, lactate.

(Fig. 5). We diagnosed HR mediated by an antigen-specific immune response to the donor tissue based on the clinical, immunological and histopathological findings. The patient experienced multi-organ failure accompanied by DIC and died at POD 9 despite intensive treatment.

Discussion

In HCV recipients, we need to consider HCV recurrence after LDLT, although our results in HCV recipients are currently excellent [11]. Previously, post-operative recovery of the platelet counts was limited when severe thrombocytopenia existed [12]. Recipients with HCV may require combination therapy with ribavirin and interferon after LDLT [11]. Therefore, in our institution, concurrent splenectomy was performed in HCV recipients to treat thrombocytopenia regardless of the PVP level. In this case, we performed splenectomy based on HCV, though a well-controlled portal venous pressure was confirmed as a result. Previous studies have reported that many other factors are crucial for LT outcomes [13-20], and intra-operative factors in this case, such as operative time, blood loss and massive blood transfusion, seemed to affect the post-operative course and outcome.

There have been many contradictory reports regarding the importance of cross-matching and HLA compatibility in LT [26-29]. Some studies have reported the importance of appropriate cross-matching while others have concluded that a positive cross-match has no bearing on the outcome of LT [21-29]. Therefore, the significance of a positive cross-match combination between donor and recipient still remains a matter of debate within the field. Some investigators have suggested that HLA histocompatibility for Class I is crucial for graft survival after LT while others have indicated there may be a dualistic effect of HLA histocompatibility in liver allogeneic grafts. They suggest that although HLA histocompatibility reduced the incidence of allograft rejection it may also enhance other immunological mechanisms which can lead to allograft dysfunction [23,25-29]. Thus, there is still no consensus on the importance of cross-matching and HLA compatibility in the LT field.

Previous reports have shown that a cross-match can change from a positive one to a negative one after organ transplantation [2-4]. Strict real-time evaluation based on the results of immunological assays is important for adequate treatment after LDLT. Peri-operative monitoring of allogeneic antigens by FCM is a method suitable for clinical use because it can be performed repeatedly, non-invasively and in real-time. Based on our FCM results it appears that in this case lymphocytes reactive against HLA Class I antigens can be controlled during the early post-operative period but proliferate again after this initial period of down-regulation. It is worth noting that immunoreactivity against HLA Class I antigens was down-

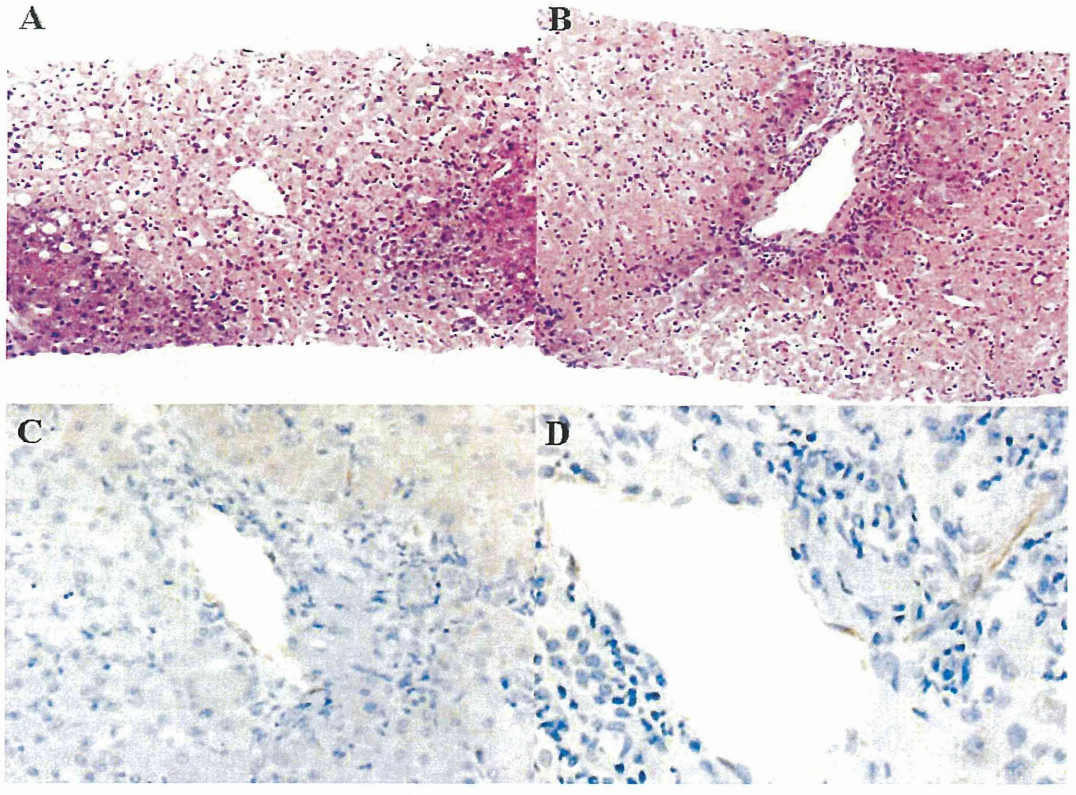

Figure 5 Histopathological findings from liver needle biopsy. The hematoxylin-eosin stained specimens show massive necrosis of hepatocytes and disappearance of bile ducts (**A** and **B**). C4d immunostaining shows endothelial-positive (**C**) and stromal-positive (**D**) staining in portal areas. These findings indicate humoral rejection.

regulated on POD 5 even though graft dysfunction was evident from POD 3, and that this immunoreactivity remained from POD 6 even after repeated PE. A possible explanation for the phenomenon seen on POD 5 is the immunoabsorption of anti-graft antibodies by PE [30]. This case suggests that PE can have positive effects on the anti-graft immune response in the initial period after LDLT, but repeated PE has limited use as a treatment for HR or AMR. Some investigators have suggested that more aggressive immunosuppression is probably needed in immunologically high-risk patients, including those with a positive cross-match [31,32]. In our case, the target trough level of tacrolimus was slightly low due to the consideration of the patient's pre-operative infectious condition, and the intravenous administration of immunoglobulins (IVIg) was also low-dose just as a complement. This case suggests that strong immunosuppression may be needed in positive cross-match cases in order to maintain a negative cross-match after LDLT.

PE and high-dose IVIg are considered to be the standard therapies for HR or AMR after organ transplantation [33-35]. However, splenectomy is considered as a suitable intra-operative strategy to prevent post-operative AMR [36]. In our case, splenectomy and intensive post-operative treatment were not successful. Therefore, we hypothesize that pre-operative induction therapy to prevent HR or AMR after LDLT is crucial in positive cross-match LDLT recipients. The usefulness of the anti-CD20 antibody (rituximab) is well reported in this respect. Rituximab is key in order to prevent HR or AMR after organ transplantation, including LDLT [33,34,37]. The use of a living related donor may leave more time for immunological testing and the induction of suitable preconditions for LT than is the case for a cadaver donor LT. Therefore, having studied the literature around pre-operative conditioning for positive cross-match LDLT recipients, rituximab treatment alongside PE prior to LDLT is now under consideration in our institution.

Although the use of living related donors maybe leave more time to select a suitable donor, donor compatibility is still a serious problem and this will continue to be the case. There is an obvious limitation of suitable donors in the case of LDLT. There were no ideal candidates in the case we present here and so we performed LDLT regardless of the positive cross-match. Because of the shortage of compatible donors and the difficulties in treating HR or AMR successfully, peri-operative strategies for cross-match positive LDLT recipients are sorely needed.

Currently, by using an advantage of flexible timing in LDLT, a pretransplant preconditioning already overcame

the ABO incompatibility in LDLT [37]. As described above, LDLT has an advantage for preoperative immunological testing and the induction of suitable preconditions for LT than is the case for a cadaver donor LT. Because the influence of lymphocyte cross-matching is considered to be debatable in LT, including deceased donor LT, many transplant centers in the United States and Europe do not perform cross-mach tests before LDLT or only investigate lymphocyte cross-matching retrospectively for cost-saving reasons. We have demonstrated convincingly that a positive lymphocyte cross-matching has a negative impact on LDLT. Because not all of our lymphocyte cross-matching positive cases died, we suggest that positive lymphocyte cross-matching itself does not contraindicate LDLT, but advanced immunologic strategies should be established for lymphocyte cross-matching-positive LDLT as well as for ABO-incompatible LDLT.

In conclusion, we suggest that our case will be thought-provoking for organ transplant surgeons and may provide important information about the use of novel immunological strategies for the management of positive cross-match LDLT recipients. Further improvements in peri-operative immunological strategies and further case studies will be indispensable in achieving improved results for positive cross-match combinations in LDLT.

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Clinical Transplantation

How transplant surgeons can overcome the inevitable insufficiency of allograft size during adult living-donor liver transplantation: strategy for donor safety with a smaller-size graft and excellent recipient results

Hori T, Ogura Y, Ogawa K, Kaido T, Segawa H, Okajima H, Kogure T, Uemoto S. How transplant surgeons can overcome the inevitable insufficiency of allograft size during adult living-donor liver transplantation: strategy for donor safety with a smaller-size graft and excellent recipient results.

Abstract: Small-for-size grafts are an issue in liver transplantation. Portal venous pressure (PVP) was monitored and intentionally controlled during living-donor liver transplantation (LDLT) in 155 adult recipients. The indocyanine green elimination rate (*k*ICG) was simultaneously measured in 16 recipients and divided by the graft weight (g) to reflect portal venous flow (PVF). The target PVP was <20 mmHg. Patients were divided by the final PVP (mmHg): Group A, PVP < 12; Group B, 12 ≤ PVP < 15; Group C, 15 ≤ PVP < 20; and Group D, PVP ≥ 20. With intentional PVP control, we performed splenectomy and collateral ligation in 80 cases, splenectomy in 39 cases, and splenectomy, collateral ligation, and additional creation in five cases. Thirty-one cases received no modulation. Groups A and B showed good LDLT results, while Groups C and D did not. Final PVP was the most important factor for the LDLT results, and the PVP cutoffs for good outcomes and clinical courses were both 15.5 mmHg. The respective *k*ICG/graft weight cutoffs were 3.5580×10^{-4}/g and 4.0015×10^{-4}/g. Intentional PVP modulation at <15 mmHg is a sure surgical strategy for small-for-size grafts, to establish greater donor safety with good LDLT results. The *k*ICG/graft weight value may have potential as a parameter for optimal PVF and a predictor for LDLT results.

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Key words: graft/recipient weight ratio – liver transplantation – portal hypertension – portal pressure – shear stress – small-for-size

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In living-donor liver transplantation (LDLT), a partial graft is inevitable. A small-for-size graft is defined as a graft/recipient weight ratio (GRWR) of <0.8 or a graft weight/standard liver volume of <40%, and these grafts result in high mortality and morbidity. From the viewpoint of graft size, a right-lobe graft with or without the middle hepatic vein was introduced into adult LDLT (1, 2). Since then, a right-lobe graft has become the standard graft type for adult LDLT, although the harvesting of a larger graft may involve high risk in some donors. Donor safety and graft volume fiercely collide with one another, which is an ironic dilemma. A smaller-size graft is safer for the living donor, and our institution introduced intentional modulation of the portal venous pressure (PVP) during LDLT from April 2006, as a strategy for the selection of relatively small-for-size grafts with

certain recipient outcomes. Here, we retrospectively evaluated the effects of PVP control during LDLT on the clinical courses and outcomes. In addition, we discuss an intraoperative strategy for small-for-size grafts, to establish greater donor safety with good recipient results.

Patients and methods

Patients

A total of 155 adult recipients who underwent LDLT from 2006 to 2009 were enrolled in this study. The follow-up period was 3.06 ± 1.38 yr. The patients comprised 84 men and 71 women, with a mean age of 61.5 ± 12.0 yr. The primary diseases resulting in LDLT included 85 cases of liver cirrhosis caused by hepatitis B virus and/or hepatitis C virus (HCV), 17 cases of primary biliary cirrhosis, 11 cases of graft loss after LDLT, 10 cases of alcoholic liver cirrhosis, eight cases of fulminant hepatic failure, six cases of autoimmune hepatitis, five cases each of biliary atresia (post-Kasai portoenterostomy) and liver cirrhosis (secondary and etiology unknown), three cases of primary sclerosing cholangitis, two cases of Budd–Chiari syndrome, and one case each of glycogen-storage disease type 3a, Wilson disease and primary hyperoxaluria type 1. A total of 58 cases were accompanied by hepatocellular carcinoma, and 31 cases fulfilled the Milan criteria. The United Network for Organ Sharing statuses were estimated to be IIB in 90 cases, III in 32 cases, IIA in 25 cases, and I in 8 cases. The protocol used in this study was approved by the Ethics Review Committee for Clinical Studies of Kyoto University Graduate School of Medicine (Approval No. C-279).

Selection of graft type

The institutional graft selection procedure was described in detail elsewhere (3). Graft selection of the right lobe, right lobe with middle hepatic vein, or left lobe was decided based on volumetric analyses. The acquired data including the drainage territory of each segmental hepatic vein were further analyzed with the software HepaVision (MeVis, Bremen, Germany). In a right-lobe graft, the drainage veins from the anterior segment were preserved for hepatic venous reconstruction. A left lobe graft always included the middle hepatic vein. In our institution, histidine-tryptophan-ketoglutarate solution was used for LDLT. The harvested graft was perfused with cold histidine-tryptophan-ketoglutarate solution, and the graft weight was measured after the perfusion. This actual weight was used as the graft weight in the present study.

Surgical procedures

Our institutional surgical procedures were also described in detail elsewhere (3). Briefly, the recipient hepatectomy was performed without temporary veno-venous bypass for the preservation of the inferior vena cava. To maximize the hepatic venous orifice, venoplasty was generally added at the back table. Anastomosis of the hepatic vein and the portal vein between the recipient and the graft was performed in an end-to-end fashion. The hepatic artery was anastomosed under surgical loupe magnification. Immediately after all vessel reconstructions, intraoperative Doppler ultrasound was performed to confirm triphasic hepatic venous outflow, sufficient portal flow, and excellent intrahepatic arterial flow. Vascular complications that will lead to high PVP, such as outflow blockade and anastomosis stricture of the portal vein, were excluded by this survey.

Intentional PVP control is mainly achieved by splenectomy and by additional creation of a portosystemic shunt if indicated. Portosystemic collaterals, such as a splenorenal shunt and an esophageal/gastric varix, usually developed around the coronary, splenic, mesenteric, and umbilical veins. These collaterals were ligated if a PVP of <20 mmHg was maintained in the test clamp. In brief, splenectomy and shunt creation were made to decrease PVP, and collateral ligation was made to increase portal PVP.

In HCV recipients, we need to consider HCV recurrence after LDLT, although our results in HCV recipients are currently excellent (4). Previously, postoperative recovery of the platelet counts was limited when severe thrombocytopenia existed (5). Recipients with HCV may require combination therapy with ribavirin and interferon after LDLT (4). Therefore, in our institution, concurrent splenectomy was performed in HCV recipients to treat thrombocytopenia regardless of the PVP level.

Real-time PVP monitoring during LDLT and the PVP control procedure

An 18-gauge antithrombotic catheter was inserted via the branch of the inferior mesenteric vein before the native liver was removed. The tip of the catheter was positioned in the portal vein or the splenic vein and fixed by ligation and a rubber band after confirmation of display of a reasonable flat wave. A flowchart for the intentional PVP control during LDLT is shown in Fig. 1.

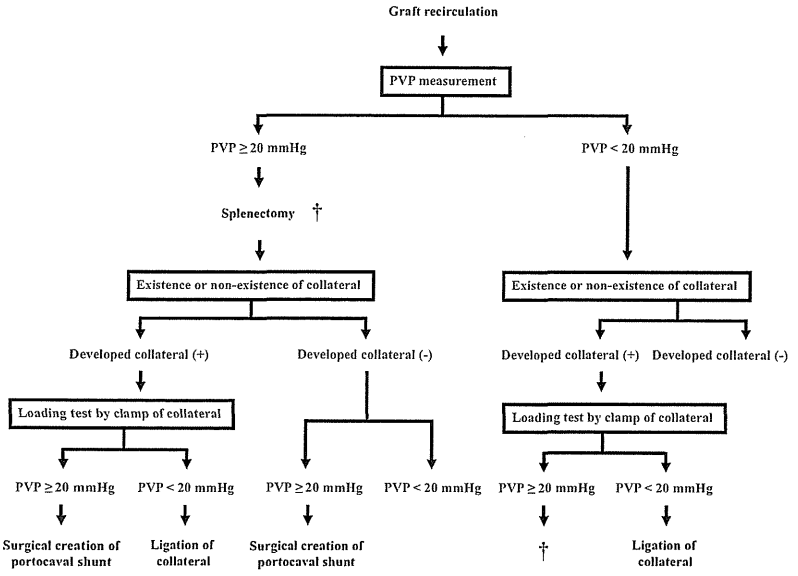

Fig. 1. Flowchart for intentional portal venous pressure modulation.

Immunosuppression

Immunosuppression after LDLT comprised tacrolimus and methylprednisolone. The trough level of tacrolimus was maintained at 8–15 ng/mL during the early postoperative period, based on the clinical findings in each case. Methylprednisolone was given intravenously (1 mg/kg) once daily from postoperative days (PODs) 1–3 followed by 0.5 mg/kg once daily for the next three d. On POD 7, 0.3 mg/kg of methylprednisolone was given intravenously. Steroids were switched to oral prednisolone 0.3 mg/kg once daily on POD 8, and this dose was reduced to 0.1 mg/kg at four wk after LDLT. Thereafter, the immunosuppression was controlled according to each clinical course. Our regimens for ABO incompatibility, including heparin usage, were described previously (6).

Histopathological analysis of native livers and liver needle biopsy (LNB) results

Native livers and LNB samples were assessed macroscopically and microscopically by at least two experienced histopathologists. An LNB was performed after LDLT, if necessary. Liver fibrosis of the native liver was scored according to the METAVIR scoring system (7). The graft damage score after LDLT was documented elsewhere (8, 9).

Indocyanine green (ICG) elimination rate (*k*ICG)

ICG is a non-toxic dye that has no known side effects other than a rare iodine allergy (10). Therefore, we consider that only patients with no history of any allergic responses should be registered. Patients who agreed to a perioperative ICG study after informed consent according to an approved protocol joined this pilot study. The *k*ICG value was noninvasively measured by pulse dye densitometry (PDD) at a stable systemic hemodynamic state. A sensor was placed on the finger of each patient before the ICG injection. Twenty milligrams of ICG was injected through a central venous catheter and immediately flushed with 20 mL of normal saline. The basic principles of PDD have been detailed elsewhere (10). A PDD apparatus (DDG-2001; Nihon Kohden, Tokyo, Japan) was used to measure the blood ICG concentrations and analyze the dye densitography.

Patient classification

Previous researchers conventionally categorized patients with portal hypertension by a PVP of 12 or 15 mmHg (approximately 16 or 20 cmH_2O, because 1 mmHg $\approx$ 1.316 cmH_2O). In this study, the recipients were divided into four groups based on the final PVP (mmHg): Group A, PVP < 12; Group B, $12 \leq$ PVP < 15; Group C, $15 \leq$ PVP < 20; and Group D, PVP $\geq$ 20. Thus, recipients were classified based on the final PVP, and then important factors in each group were shown in Table 1.

Statistical analysis

Data are presented as the mean ± SD. The Mann–Whitney *U*-test and chi-square test were used for

Table 1. Group classification

Group	Group A (n = 29)	Group B (n = 49)	Group C (n = 73)	Group D (n = 4)
Final PVP for classification (mmHg)	PVP < 12	12 < PVP < 15	15 < PVP < 20	20 < PVP
Parameters				
HCV	14/29 (48.3%)	18/49 (36.7%)	31/73 (42.5%)	2/4 (50.0%)
UNOS status				
I	5/29 (17.2%)	0/49 (0.0%)	3/73 (4.1%)	0/4 (0.0%)
IIA	4/29 (13.8%)	6/49 (12.3%)	14/73 (19.2%)	1/4 (25.0%)
IIB	14/29 (48.3%)	30/49 (61.2%)	43/73 (58.9%)	3/4 (75.0%)
III	6/29 (20.7%)	13/49 (26.5%)	13/73 (17.8%)	0/4 (0.0%)
MELD score (point)	25.9 ± 12.7	22.1 ± 9.8	22.4 ± 9.6	21.8 ± 15.8
GRWR	0.973 ± 0.194	0.955 ± 0.191	0.965 ± 0.278	0.841 ± 0.145
Initial PVP (mmHg)	21.8 ± 6.7	23.3 ± 6.2	22.6 ± 4.7	29.5 ± 7.9
PVP immediately after graft recirculation (mmHg)	14.8 ± 4.4	18.0 ± 3.8	18.8 ± 4.0	24.5 ± 2.6
Final PVP (mmHg)	9.9 ± 1.2	13.3 ± 0.7	16.6 ± 1.4	24.5 ± 1.7
Developed collateral	19/29 (65.5%)	42/49 (85.7%)	67/73 (91.8%)	4/4 (100%)
Intentional modulation	18/29 (62.0%)	43/49 (87.8%)	59/73 (80.8%)	4/4 (100%)
Surgical procedures				
None	11/29 (38.0%)	6/49 (12.2%)	14/73 (19.2%)	0/4 (0.0%)
Splenectomy	9/29 (31.0%)	19/49 (38.8%)	11/73 (15.1%)	0/4 (0.0%)
Collateral ligation	0/29 (0.0%)	5/49 (10.2%)	11/73 (15.1%)	0/4 (0.0%)
Splenectomy and collateral ligation	9/29 (31.0%)	19/49 (38.8%)	35/73 (47.9%)	1/4 (25.0%)
Splenectomy and shunt creation	0/29 (0.0%)	0/49 (0.0%)	0/73 (0.0%)	1/4 (25.0%)
Splenectomy, collateral ligation and shunt creation	0/29 (0.0%)	0/49 (0.0%)	2/73 (2.7%)	2/4 (50.0%)

PVP, portal venous pressure; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; GRWR graft/recipient weight ratio; UNOS, United Network for Organ Sharing.

unpaired continuous or discontinuous variables between two groups. The Kaplan–Meier method (log-rank test) was used for survival curves. Logistic regression analysis was used to analyze the important predictive factors for good outcomes and clinical courses. Correlations between continuous data were analyzed by Pearson correlation coefficient. A receiver-operating characteristic (ROC) curve was used for the area under the curve (AUC), and the cutoff value was determined by the highest Youden's index. Statistical calculations were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered to indicate statistical significance, and values of $p > 0.05$ were described as not significant (NS).

Results

Actual surgical procedures

The rate of intentional PVP modulation was 80.0% (124/155), and the actual procedures are summarized in Table 2. Splenectomy and collateral ligation were performed in 64 cases. Splenectomy alone was performed in 39 cases. Collateral ligation alone was performed in 16 cases. Splenectomy, collateral ligation, and additional shunt creation were required in four cases. Splenectomy and additional shunt creation were performed in one case. No modulations were required in 31 cases.

Confirmation of effects of intraoperative PVP modulation

Initially, we examined the survival curves based on the GRWR. There was no difference between recipients with a GRWR of <0.8 and those with a GRWR of ≥ 0.8 (Fig. 2). In addition, the correlation between GRWR and PVP immediately after graft recirculation was investigated, and the *r* value was 0.431 ($p = 0.2272$).

Next, we checked the correlation between the GRWR and the final PVP. There was no

Table 2. Surgical procedures for intentional modulation of PVP during LDLT

Surgical procedure	Cases (%)
None	31/155 (20.0)
Splenectomy only	39/155 (25.2)
Collateral ligation only	16/155 (10.3)
Splenectomy and collateral ligation	64/155 (41.3)
Splenectomy and shunt creation	1/155 (0.6)
Splenectomy, collateral ligation and shunt creation	4/155 (2.6)

PVP, portal venous pressure; LDLT, living-donor liver transplantation.

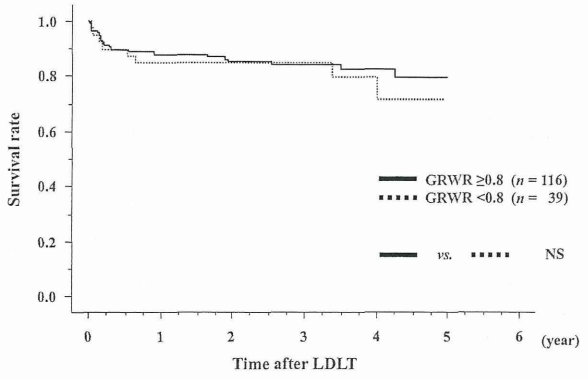

Fig. 2. Survival curves based on the graft/recipient weight ratio.

correlation between the GRWR and the final PVP (Fig. 3). In addition, we considered that the ascites volume (mL/d) after LDLT was a factor that reflected the portal pressure. The postoperative ascites volume was well correlated with the final PVP (Fig. 4).

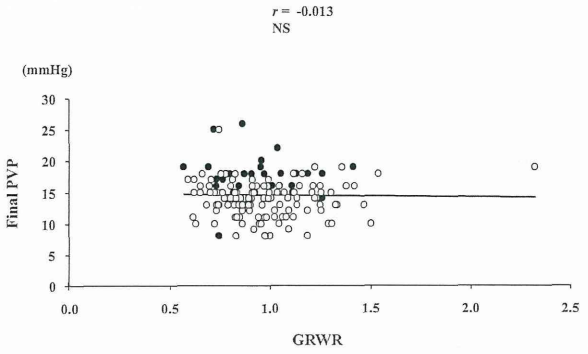

Fig. 3. Correlation between the graft/recipient weight ratio and the final portal venous pressure.

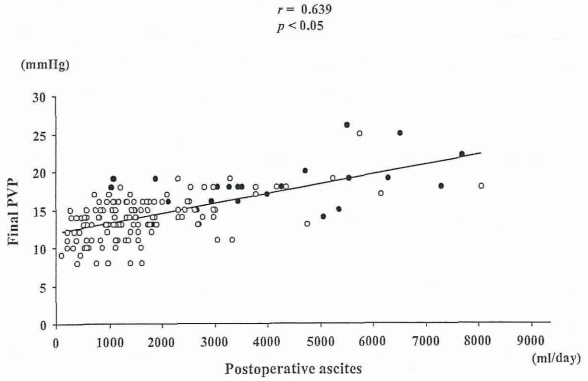

Fig. 4. Correlation between the postoperative ascites volume and the final portal venous pressure.

Overall survival rates

The survival curves are shown in Fig. 5. The differences between two groups were significant, except for the difference between Groups A and B.

Complications

The complications in each group are shown in Table 3. The surgical complications included ileus and torsion of enterostomy. The recipients in Group D and some of those in Group C suffered complications according to portal hypertension, such as intractable ascites, intestinal bleeding owing to congestion and coagulopathy caused by poor graft function. Organ failure, respiratory complications, severe rejection, severe infection (bacterial or mycotic) including sepsis, thrombosis, neurological complications, coagulopathy, and subsequent bleeding tendency were considered to be severe and/or fatal complications, and their rates were increased according to the final PVP.

Pretransplant and intraoperative factors

Previously, many researchers have documented risk factors for outcomes and complications of liver transplant recipients, such as recipient age, original disease, Model for End-stage Liver Disease (MELD) score, ABO blood group, operative time, blood loss, cold ischemic time (CIT), and GRWR (11–14). These factors are shown in Table 4, and the statistical differences between two groups for each factor are summarized in Table 5. The PVP was continuously monitored during LDLT, and the PVP values were evaluated at three time points: initial PVP (native liver), PVP immediately after graft recirculation, and final PVP after intentional modulation (Fig. 6).

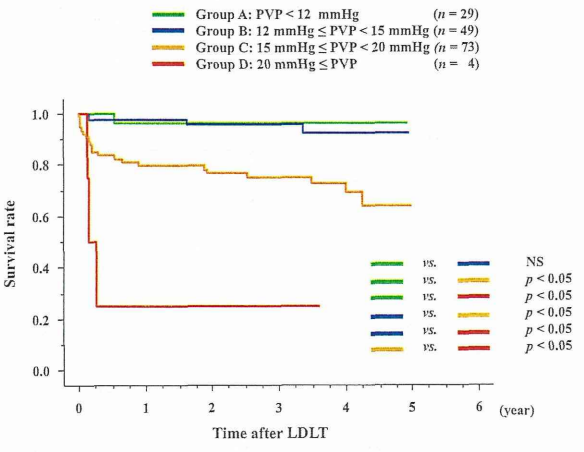

Fig. 5. Survival curves of the four groups.

Table 3. Postoperative complications

PVP (mmHg)	Group A, % (n = 29)	Group B, % (n = 49)	Group C, % (n = 73)	Group D, % (n = 4)
Cases with complications	55.2 (16/29)	67.3 (33/49)	83.6 (61/73)	100.0 (4/4)
Cases with severe and/or fatal complications	13.8 (4/29)	18.4 (9/49)	57.5 (42/73)	100.0 (4/4)
Organ disorder				
Drug-mediated liver/kidney disorder	10.3 (3/29)	12.2 (6/49)	11.0 (8/73)	25.0 (1/4)
Respiratory complications	3.4 (1/29)	2.0 (1/49)	12.3 (9/73)	75.0 (3/4)
Renal failure	0.0 (0/29)	0.0 (0/49)	1.4 (1/73)	75.0 (3/4)
Immunological complications				
Acute cellular rejection	20.7 (6/29)	22.4 (11/49)	17.8 (13/73)	25.0 (1/4)
Chronic rejection	0.0 (0/29)	4.1 (2/49)	5.5 (4/73)	25.0 (1/4)
Humoral rejection	0.0 (0/29)	0.0 (0/49)	1.4 (1/73)	0.0 (0/4)
PTLD	0.0 (0/29)	0.0 (0/49)	1.4 (1/73)	0.0 (0/4)
De novo autoimmune hepatitis	0.0 (0/29)	0.0 (0/49)	1.4 (1/73)	0.0 (0/4)
Infections				
Viral infection (EBV and CMV)	20.7 (6/29)	22.4 (11/49)	19.2 (14/73)	25.0 (1/4)
Mycotic infection (*Candida* and *Aspergillus*)	0.0 (0/29)	6.9 (3/49)	2.7 (2/73)	75.0 (3/4)
Peritonitis (bacterial or viral)	0.0 (0/29)	2.0 (1/49)	5.5 (4/73)	75.0 (3/4)
Pneumocystis carinii pneumonia	0.0 (0/29)	0.0 (0/49)	1.4 (1/73)	0.0 (0/4)
Sepsis	3.4 (1/29)	10.2 (5/49)	19.2 (14/73)	100.0 (4/4)
Thrombosis or coagulopathy				
Intraperitoneal bleeding	3.4 (1/29)	0.0 (0/49)	24.7 (17/73)	75.0 (3/4)
Intrapleural hemorrhage	0.0 (0/29)	2.0 (1/49)	1.4 (1/73)	0.0 (0/4)
Digestive tract hemorrhage	3.4 (1/29)	2.0 (1/49)	2.7 (2/73)	25.0 (1/4)
PVT	0.0 (0/29)	0.0 (0/49)	2.7 (2/73)	0.0 (0/4)
HAT	0.0 (0/29)	4.1 (2/49)	1.4 (1/73)	0.0 (0/4)
Thrombotic microangiopathy	0.0 (0/29)	0.0 (0/49)	2.7 (2/73)	0.0 (0/4)
Neurological complications				
Brain bleeding or infarction (cerebral, cerebellar or brainstem)	0.0 (0/29)	0.0 (0/49)	4.1 (3/73)	0.0 (0/4)
Myelopathy or encephalopathy	0.0 (0/29)	0.0 (0/49)	1.4 (1/73)	0.0 (0/4)
Surgical or technical issues				
Surgical complications	3.4 (1/29)	4.1 (2/49)	9.6 (7/73)	50.0 (2/4)
Biliary complications	3.4 (1/29)	18.4 (9/49)	9.6 (7/73)	0.0 (0/4)
Pancreatic leak	0.0 (0/29)	0.0 (0/49)	1.4 (1/73)	0.0 (0/4)
Oncological or original diseases				
HCV hepatitis recurrence	3.4 (1/29)	6.1 (3/49)	2.7 (2/73)	0.0 (0/4)
HCC recurrence	0.0 (0/29)	0.0 (0/49)	1.4 (1/73)	0.0 (0/4)
Primary lung cancer	3.4 (1/29)	0.0 (0/49)	0.0 (0/73)	0.0 (0/4)

Results were shown as the percentage and the case number.
PTLD, posttransplant lymphoproliferative disease; EBV, Epstein-Barr virus; CMV, cytomegalovirus; PVT, portal vein thrombosis; HAT, hepatic artery thrombosis; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

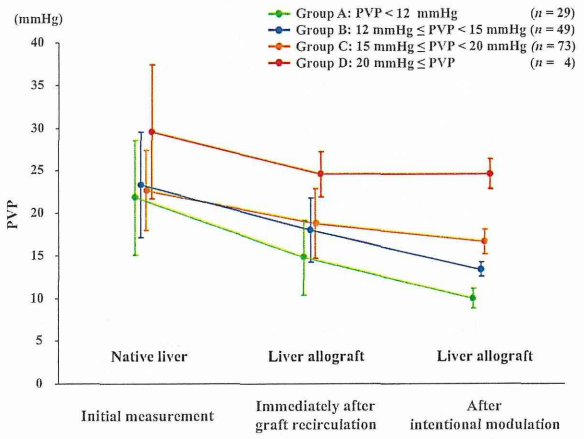

Fig. 6. Changes in the portal venous pressure during living-donor liver transplantation in the four groups.

Postoperative profiles

The postoperative profiles are shown in Table 3, and the statistical differences between two groups for each factor are summarized in Table 5. Except for the comparisons between Groups A and B, the other comparisons showed significant differences because Groups C and D had poor clinical courses. It should be noted that ascites and drain placement were significantly affected by the final PVP.

Most important factor for outcomes

In the univariate analyses, a total of seven factors showed significant differences in at least one comparison between two groups. Therefore, the most important factor for the outcomes was subse-

Table 4. Perioperative profiles

Parameters	Group A (n = 49)	Group B (n = 29)	Group C (n = 73)	Group D (n = 4)
Pre-transplant factors				
Recipient age (yr)	52.7 ± 10.7	50.7 ± 12.1	53.0 ± 10.7	53.6 ± 5.4
Original disease (benign vs. malignant)	17:12	18:31	22:51	2:2
Liver cirrhosis (cirrhotic vs. non-cirrhotic)[a]	24:5	48:1	71:2	4:0
Child-Pugh score (point)	10.2 ± 2.9	10.3 ± 2.1	10.5 ± 2.2	10.0 ± 2.7
MELD score (point)	25.9 ± 12.7	22.1 ± 9.8	22.4 ± 9.6	21.8 ± 15.8
ABO blood group (identical or compatible vs. incompatible)	26:3	39:10	58:15	1:3
Lymphocyte cross-match (negative vs. positive)	29:0	47:2	67:6	4:0
Intra-operative factors				
Collateral development (%)	65.5% (19/29)	85.7% (42/49)	91.8% (67/73)	100.0% (4/4)
Operative time (min)	740.3 ± 128.1	771.5 ± 126.7	807.0 ± 168.9	842.3 ± 100.6
Blood loss (mL)	6314.4 ± 5483.9	8423.6 ± 6385.9	10268.0 ± 11251.8	13144.0 ± 6748.5
CIT (min)	109.3 ± 104.2	101.9 ± 70.4	130.8 ± 107.2	236.3 ± 219.9
GRWR	0.973 ± 0.194	0.955 ± 0.191	0.965 ± 0.278	0.841 ± 0.145
Initial PVP (mmHg)	21.8 ± 6.7	23.3 ± 6.2	22.6 ± 4.7	29.5 ± 7.9
PVP immediately after graft recirculation (mmHg)	14.8 ± 4.4	18.0 ± 3.8	18.8 ± 4.0	24.5 ± 2.6
Final PVP (mmHg)	9.9 ± 1.2	13.3 ± 0.7	16.6 ± 1.4	24.5 ± 1.7
Postoperative profiles				
ICU stay (d)	5.0 ± 2.7	4.6 ± 1.6	6.7 ± 7.2	29.8 ± 21.3
Ascites (mL/d)	986.6 ± 757.8	1438.6 ± 1001.7	2539.2 ± 1645.5	6362.3 ± 784.0
Drain placement (d)	12.9 ± 6.9	18.4 ± 12.3	23.8 ± 16.6	38.0 ± 14.7
The peak of GOT until POD 14 (IU/L)	413.2 ± 256.7	407.5 ± 272.5	616.4 ± 819.9	1646.3 ± 2187.7
The peak of GPT until POD 14 (IU/L)	437.5 ± 408.2	364.7 ± 240.5	579.9 ± 549.7	743.0 ± 646.9
The peak of LDH until POD 14 (IU/L)	540.7 ± 246.6	506.9 ± 251.8	762.4 ± 1090.5	1171.5 ± 1365.8
The peak of T-Bil until POD 14 (mg/dL)	6.8 ± 4.3	8.9 ± 6.1	12.5 ± 8.5	23.9 ± 15.7
Prolonged jaundice after POD 14 (%)[b]	6.9 (2/29)	14.3 (7/49)	35.6 (26/73)	75.0 (3/4)
Lactate at 24 h after surgery (mM)	25.9 ± 12.6	18.8 ± 10.5	22.8 ± 12.3	63.8 ± 53.5
Lactate at 48 h after surgery (mM)	16.3 ± 9.2	13.6 ± 4.2	17.4 ± 15.8	65.8 ± 72.9
Interval of normalization of PT-INR (d)	3.3 ± 1.2	5.3 ± 5.1	9.7 ± 19.0	24.5 ± 21.6
Postoperative LNB (%)	72.4 (21/29)	65.3 (32/49)	63.0 (46/73)	75.0 (3/4)
Graft damage score (point)[c]	2.8 ± 1.5	3.6 ± 1.7	4.8 ± 2.9	6.7 ± 1.5

PVP, portal venous pressure; MELD, Model for End-stage Liver Disease; CIT, cold ischemic time; GRWR, graft/recipient weight ratio; ICU, intensive care unit; GOT, glutamic oxaloacetic transaminase; POD, postoperative day; GPT, glutamic pyruvic transaminase; LDH, lactate dehydrogenase; T-Bil, total bilirubin; PT-INR, prothrombin time-international normalized ratio; LNB, liver needle biopsy.
[a]Histological assessment in the native liver.
[b]Prolonged jaundice was defined as T-Bil >5.0 mg/dL after POD 14.
[c]LNB within one month after LDLT.

quently analyzed. In multivariate analyses, only the final PVP showed statistical significance ($p = 0.0001$) (Table 6).

Most important factor for severe and/or fatal complications

The most important factor for severe and/or fatal complications was also analyzed. In multivariate analyses, only the final PVP showed statistical significance ($p < 0.0001$) (Table 6).

Cutoffs of the final PVP for a good outcome and clinical course

The cutoff of the final PVP for a good outcome was 15.5 mmHg (sensitivity = 0.7857, specificity = 0.7323, AUC = 0.817, and Youden's index = 0.5180), and the cutoff for a good clinical course (without severe and/or fatal complications) was also 15.5 mmHg (sensitivity = 0.6500, specificity = 0.8211, AUC = 0.786, and Youden's index = 0.4711) (Fig. 7).

*k*ICG/graft weight cutoffs for a good outcome and clinical course

This pilot study was started in April 2008 in our institution. The number of patients was still only 16 during the present study period. The *k*ICG/graft weight values were calculated in each case. The cutoff for a good outcome was 3.5580×10^{-4}/g, and the cutoff for a good clinical course (without severe and/or fatal complications) was

Table 5. Univariate analysis of perioperative profiles

Parameters	Group A vs. Group B	Group A vs. Group C	Group A vs. Group D	Group B vs. Group C	Group B vs. Group D	Group C vs. Group D
Pretransplant factors						
Recipient age (yr)	NS	NS	NS	NS	NS	NS
Original disease (benign vs. malignant)	NS	NS	NS	NS	NS	NS
Liver cirrhosis (cirrhotic vs. non-cirrhotic)	$p < 0.05$	$p < 0.05$	NS	NS	NS	NS
Child-Pugh score (point)	NS	NS	NS	NS	NS	NS
MELD score (point)	NS	NS	NS	NS	NS	NS
ABO blood group (identical or compatible vs. incompatible)	NS	NS	$p < 0.05$	NS	$p < 0.05$	$p < 0.05$
Lymphocyte cross-match (negative vs. positive)	NS	NS	N/A	NS	NS	NS
Intraoperative factors						
Collateral development (yes vs. no)	$p < 0.05$	$p < 0.05$	NS	NS	NS	NS
Operative time (min)	NS	$p < 0.05$	NS	NS	NS	NS
Blood loss (mL)	NS	$p < 0.05$	$p < 0.05$	NS	NS	NS
CIT (min)	NS	NS	NS	NS	NS	NS
GRWR	NS	NS	NS	NS	NS	NS
Initial PVP (mmHg)	NS	NS	NS	NS	NS	NS
PVP immediately after graft recirculation (mmHg)	$p < 0.05$	$p < 0.05$	$p < 0.05$	NS	NS	$p < 0.05$
Final PVP (mmHg)	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$
Postoperative profiles						
ICU stay (d)	NS	NS	$p < 0.05$	<0.05	$p < 0.05$	$p < 0.05$
Ascites (mL/d)	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$
Drain placement (d)	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$
The peak of GOT until POD 14 (IU/L)	NS	NS	$p < 0.05$	NS	$p < 0.05$	NS
The peak of GPT until POD 14 (IU/L)	NS	NS	NS	$p < 0.05$	NS	NS
The peak of LDH until POD 14 (IU/L)	NS	NS	NS	NS	NS	NS
The peak of T-Bil until POD 14 (mg/dL)	NS	$p < 0.05$	$p < 0.05$	$p < 0.05$	NS	NS
Prolonged jaundice after POD 14 (yes vs. no)[a]	NS	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	NS
Lactate at 24 h after surgery (mM)	$p < 0.05$	NS	NS	$p < 0.05$	$p < 0.05$	$p < 0.05$
Lactate at 48 h after surgery (mM)	NS	NS	NS	NS	$p < 0.05$	NS
Interval of normalization of PT-INR (d)	NS	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$
Graft damage score (point)[b]	$p < 0.05$	$p < 0.05$	$p < 0.05$	NS	$p < 0.05$	NS

NS, not significant; N/A, not available; MELD, Model for End-stage Liver Disease; PVP, portal venous pressure; CIT, cold ischemic time; GRWR, graft/recipient weight ratio; ICU, intensive care unit; GOT, glutamic oxaloacetic transaminase; T-Bil, total bilirubin, POD, postoperative day; GPT, glutamic pyruvic transaminase; LDH, lactate dehydrogenase; PT-INR, prothrombin time-international normalized ratio; LNB, liver needle biopsy.
[a]Prolonged jaundice was defined as T-Bil >5.0 mg/dL after POD 14.
[b]LNB within one month after LDLT.

4.0015×10^{-4}/g (Fig. 8). Because the number of patients was still not sufficient, the sensitivity, specificity, AUC, and Youden's index were all 1.0000 for both cutoffs.

Discussion

We understand that it is difficult to clarify how only the final PVP directly affected the clinical course and outcome. Many factors will have mutual effects on the postoperative course. In the LDLT field, more advanced developments in approaches in the immunological, infectious control, and liver regeneration fields are also crucial. Although ABO incompatibility is currently resolved (6), infectious complications still remained as a cause of fatal conditions. However, at least, excellent liver regeneration after LDLT is indispensable for a good clinical course and outcome (9, 15). The portal venous flow (PVF) has a large influence on liver regeneration after LDLT (9, 15–17). We focused on intraoperative modulation of the PVF with real-time PVP monitoring, and previously reported that recipients with a high final PVP showed very poor outcomes (18, 19). Because transplanted grafts with smaller GRWR will show higher PVP after graft recirculation, we initially expected that GRWR and PVP immediately after graft recirculation will show well correlation. However, this correlation was statistically not significant in this study, even if the r values which changed 0.431 to −0.013 before and after intentional PVP modulation may suggest that our PVP modulation worked. We eventually failed to control the final PVP of patients in Group D at <20 mmHg, and all cases in Group D and some cases in Group C showed severe complications related to portal hypertension from the early postoperative period, and the symptoms triggered poor outcomes in these patients. Although the actual

Table 6. Multivariate analysis of pretransplant and intraoperative factors

Pretransplant and intraoperative factors	The p value
Survivals	
Liver cirrhosis (cirrhotic vs. non-cirrhotic)	0.1820
ABO blood group (identical or compatible vs. incompatible)	0.2529
Collateral development (yes vs. no)	0.9455
Operative time (min)	0.4337
Blood loss (mL)	0.1404
PVP immediately after graft recirculation (mmHg)	0.9758
Final PVP (mmHg)	0.0001*
Severe complications	
Liver cirrhosis (cirrhotic vs. non-cirrhotic)	0.1097
ABO blood group (identical or compatible vs. incompatible)	0.3359
Collateral development (yes vs. no)	0.6899
Operative time (min)	0.1358
Blood loss (mL)	0.3727
PVP immediately after graft recirculation (mmHg)	0.6209
Final PVP (mmHg)	<0.0001*

PVP, portal venous pressure.
*p < 0.05.

surgical procedures have not changed from the protocol shown in Fig. 1, the target PVP level has been changed to <15 mmHg in our institution (20). Portal hypertension is a clinical syndrome defined by a pathological increase in a high PVP, and the most common parameter that reflects PVP is currently the hepatic venous pressure gradient (21). Surgery has an advantage for direct measurement of PVP, but the paradoxically normal range of PVP in healthy individuals remains controversial. Previous researchers conventionally used a PVP or a hepatic venous pressure gradient of 12 or 15 mmHg for group classification (21–23), and we followed these two values in the group classification. We know that many researchers set their goals as pressure values of 12 mmHg or less, and the question arises as to whether surgeons need to decrease the final PVP to less than 12 mmHg. We will not necessarily do this. In the present study, Groups A and B showed good results compared with Groups C and D, and seemed to show no differences. Therefore, we should not set the target final PVP as <12 mmHg, even though the patients in Group A showed more stable postoperative courses and the cause of a death in Group A had no relationship with the liver allograft (primary lung cancer). In addition, the cutoffs of PVP for a good clinical course and outcome were both 15.5 mmHg. Although this may appear to increase the recipient's risk from the viewpoint of the normal range of PVP, we should never forget that a partial liver graft is inevitable in LDLT, and we consider that a PVP of 15 mmHg during LDLT is

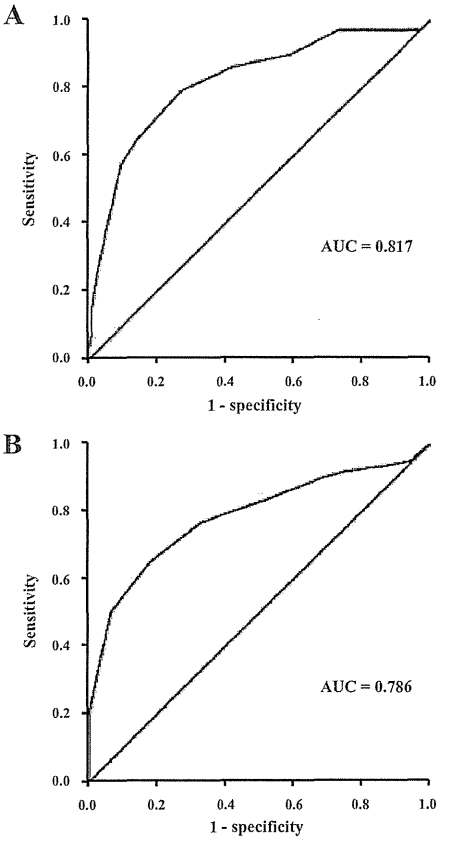

Fig. 7. Cutoffs of the final portal venous pressure (PVP) for a good outcome and clinical course. (A) The final PVP cutoff for a good outcome was 15.5 mmHg (sensitivity = 0.7857, specificity = 0.7323, area under the curve (AUC) = 0.817, and Youden's index = 0.5180). (B) The final PVP cutoff for a good clinical course (without severe and/or fatal complications) was 15.5 mmHg (sensitivity = 0.6500, specificity = 0.8211, AUC = 0.786, and Youden's index = 0.4711).

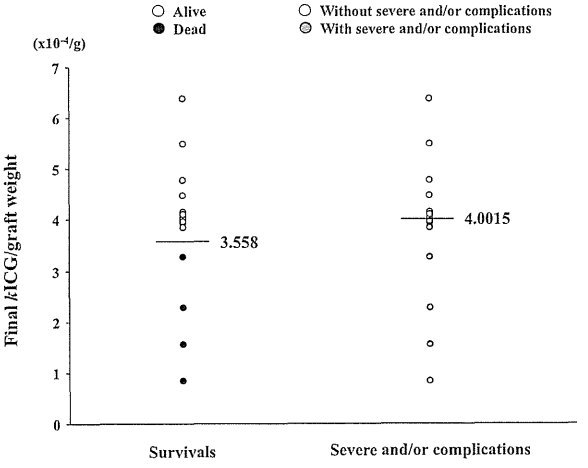

Fig. 8. Cutoffs of the *k*ICG/graft weight value for a good outcome and clinical course.

a reasonable and permissive target level not only for the intraoperative strategy but also for the selection of a smaller-size graft with greater donor safety and good recipient results.

As described above, splenectomy and shunt creation were made to decrease PVP, and collateral ligation was made to increase portal PVP, because we expected that higher PVF caused increased PVP and lower PVF results in decreased PVP. In our institution, splenectomy comes first to decrease PVP. On the other hand, we consider that collaterals should be ligated to prevent steal phenomenon at some situations, which increase PVP after LDLT (such as rejection). Roughly speaking, we decreased PVP by splenectomy, and thereafter collaterals were ligated as possible, under real-time monitoring. However, we have experienced some peculiar cases who showed subtle decreases or no changes of PVP after collateral ligations. Hemodynamics in end-stage liver disease is complicate, and then collateral flow sometimes gave us a mystery. We suggest that the careful consideration during LDLT is a key for successful PVP control, based on the real-time monitoring and loading test, because final PVP is an important factor to overcome small-for-size graft.

The peculiar systemic hemodynamic state in advanced liver cirrhosis is called a hyperdynamic state (9, 16, 17). Developed portosystemic collaterals do not disappear even after LDLT (9, 16, 17) and can easily cause a steal phenomenon of the PVF with the postoperative increase in graft resistance (20). Even subtle complications that increase graft resistance may cause unpredictable hemodynamic behavior, because cirrhotic recipients persist in a hyperdynamic state even after LDLT (9, 16, 17). These collaterals should be ligated as much as possible, although such ligations may increase the PVP to a range that is less than the target PVP. As a result, the actual surgical procedures for intentional PVP modulation controlled the PVF. Paradoxically, our initial hypothesis raises one simple question. Even if a surgical modulation under monitoring of PVP makes sense, pressure, and flow are distinct. Therefore, how accurately can the PVP inform the surgeon of the archive of the optimal PVF during LDLT? Even if an intentional surgical modulation under PVP monitoring during LDLT works well, we currently suggest that the employment of an additional parameter that directly reflects the PVF during LDLT is useful. Some researchers have reported the usefulness of the ICG elimination rate as a graft function test after LDLT (9,24–26) and as a predictive factor of LDLT outcomes at the early postoperative period (9,24,25). From the viewpoint of transplant surgeons, indicators before and during LDLT have advantages as predictive factors for improving the LDLT results. In addition, the establishment of a reliable indicator before or during LDLT may enhance donor safety by the choice of a smaller-size graft with good LDLT results. Currently, to set an optimal PVF during LDLT, we hypothesized that the ICG kinetics is a reliable intraoperative parameter for an optimal PVF archive. ICG clearly reflects two factors, namely the functional hepatocyte volume and the effective PVF (9, 16, 17). In LDLT, the CIT is short and the hepatocytes are well preserved. Therefore, division by the graft weight is one simple method that allows the *k*ICG to reflect only the PVF, by taking advantage of the shorter CIT in LDLT. The sensitivity, specificity, AUC, and Youden's index were 1.0 for both *k*ICG/graft weight cutoffs because the case number was still too small to detect statistically reliable cutoffs for the optimal PVF. However, in some cases, we clearly experienced that *k*ICG/graft weight value showed no changes even after decreases or increases in the PVP, and that the *k*ICG increased even after an increase in the PVP by ligation of developed portosystemic collaterals. We have the impression that the *k*ICG may reflect the optimal PVF and plan to continue this pilot study to emphasize the objectivity. Based on our experience, if the *k*ICG is measured once, an interval of at least 30 min is required before the next measurement. The disadvantages of the *k*ICG are that the timing should be carefully considered and real-time monitoring like that of the PVP is impossible, even though the measurement methodology is noninvasive. Although the case number is still small, we speculate that simultaneous fulfillment of a final PVP of <15 mmHg and a final *k*ICG of $> 4 \times 10^{-4}/g \times$ the graft weight (g) is a sure strategy for archiving the optimal PVF during LDLT. We understand that it is so difficult to detect the "optimum" of PVF during LDLT. In a word, intentional PVP modulation based on real-time monitoring and the confirmation of optimal *k*ICG/graft weight value reflecting PVF are actual and useful procedures for liver transplant surgeons during LDLT.

Intentional modulation of the PVP to <15 mmHg is a simple and sure strategy during LDLT for transplant surgeons. Because intentional PVP modulation during LDLT will prevent small-for-size syndrome, the acceptable minimum graft size in our institution is currently a GRWR of ≥ 0.7 at graft selection (20). Although intentional PVP control seemed to overcome GRWR < 0.7, these grafts still caused critical problems retrospectively (20). In a current status, we guarantee the results of LDLT with GRWR $\geq$ 0.7, based on the

results during two decades (20). We hope that our intentional PVP control will ensure the excellent results in more drastic small-for-size grafts in the future. Also, we hope that the confirmation of *k*ICG/graft weight value during LDLT will predict the optimal PVF. Preoperative imaging studies have progressed and become very powerful tools for detailed preoperative assessment of the donor liver (27), and smaller-size grafts have become acceptable with increased donor safety and good LDLT results in our institution. Some parameters that directly reflect the PVF will be informative for an optimal PVF archive, and the final *k*ICG/graft weight value during LDLT may have potential as an accurate parameter for the optimal PVF and as a reliable predictor for the postoperative course and outcome. Accurate evaluation and an optimal archive of the PVF during LDLT will overcome the problems of small-for-size grafts and provide greater donor safety with excellent recipient results. This theory can also apply in the deceased-donor liver transplantation field, especially for split liver allografts and pediatric allografts.

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