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SECTION 12. LIVING DONOR LIVER TRANSPLANTATION FOR PATIENTS WITH HIGH MODEL FOR END-STAGE LIVER DISEASE SCORES AND ACUTE LIVER FAILURE

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Abstract. Living donor liver transplantation (LDLT) for patients with high model for end-stage liver disease score and acute liver failure patients have little or not gained any substantial following among Western centers because of the "donor high risk-low recipient benefit scenario" that puts the donor at a significant risk against the survival odds for a recipient who is receiving a partial graft and considered marginal by Western standards. In most Asian countries, there is sometimes no other source of live graft but a willing live liver donor. There are individual Asian center reports that conclude that LDLT has comparable outcome to deceased donor liver transplant. However, the outcomes of a large number of patients after undergoing adult LDLT for high model for end-stage liver disease scores and acute liver failure at a single center have not been investigated. Here in, we present our experience with such subgroup of patients undergoing LDLT.

Keywords: Liver transplantation, Model for end-stage liver disease score, Acute liver failure.

Living donor liver transplantation (LDLT) for patients with high model for end-stage liver disease (MELD) scores remains debatable. Some reports describe decreased overall patient and graft survival rates for patients with high MELD scores after LDLT (*1, 2*). Others report that LDLT could provide excellent graft function and survival rates in such patients (*3, 4*). Liver transplantation is also an effective modality for treating acute liver failure (ALF) when patients are refractory to medical treatment. Acute liver failure has been predominantly treated using LDLT in Asian countries such as Japan and Korea (*5–7*). However, the outcomes of a large number of patients after undergoing adult LDLT for ALF at a single center have not been investigated.

We therefore assessed the impact of MELD scores on the outcomes of 223 patients who underwent adult-to-adult LDLT between January 2006 and April 2011 at Kyoto University. We also reviewed 72 adult patients who underwent LT for ALF at a single center over a period of 15 years.

LDLT FOR PATIENTS WITH HIGH MELD SCORES

This study enrolled 223 patients who underwent adult-to-adult LDLT between January 2006 and April 2011 at Kyoto University. Patients who underwent a repeated LT or LT for ALF were excluded. The ethics committee at Kyoto University approved the study, which proceeded in accordance with the Declaration of Helsinki of 1996.

The median MELD score was 17 (range, 6–47; Fig. 1). The graft-to-recipient weight ratio and incidence of ABO-incompatible LT did not differ among patients with MELD scores of <10, ≥10–15, ≥15–20, ≥20–25, ≥25–30, ≥30–35, and >35. Overall patient survival rates did not differ among the patients assigned to these groups. Overall patient survival rates also did not significantly differ between patients with low (<25) and high (≥25) MELD scores (Fig. 2). In conclusion, LDLT can facilitate acceptable outcomes for patients with high MELD scores.

LDLT FOR ACUTE LIVER FAILURE

We reviewed data from 72 adult ALF patients (male, n=33; median age, 42 years, range 19–68 years) with a median MELD score of 19 (range, 7–41) who underwent LDLT at a single center over a period of 15 years. Six patients were ABO incompatible, and 66 were identical or compatible. Total scores for predictive variables affecting the mortality of each patient with ALF were calculated based on the proposal of the Study Group of Intractable Hepatobiliary Diseases in Japan (*8*).

Among the 72 patients, 17 and 55 had acute and subacute ALF, respectively. The etiologies of ALF were hepatitis B virus (n=29), drug exposure (n=11), autoimmune hepatitis (n=2), and unknown (n=30). The total scores for predictive variables varied from 2 to 10 with a median of 7. The average score was significantly higher in patients with subacute than acute ALF (7.2 vs. 4.4; $P<0.001$).

Patient survival rates were 65%, 65%, and 61% at 1, 3, and 5 years, respectively. The overall survival rates did not differ among patients according to the etiology of ALF ($P=0.693$), type of ALF ($P=0.745$), ABO compatibility ($P=0.912$), total scores for predictive variables ($P=0.975$), or having a graft-to-recipient weight ratio above or below 0.8% ($P=0.063$). Among the 72 patients, 27 died at a median of 1 (range, 0–60) month after LT. The most frequent cause of death after LT was infection (n=14) followed by multiple

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

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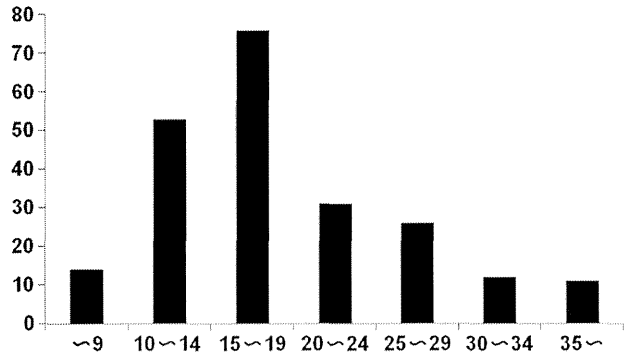

FIGURE 1. Distribution of MELD scores.

organ failure (n=3), cerebral bleeding (n=2) and graft failure (n=2). Moreover, overall patient survival rates did not significantly differ between patients with (n=20) and without (n=223) ALF among those who underwent LDLT between January 2006 and April 2011 (Fig. 3).

DISCUSSION

The overall survival rates in the present study were worse than those previously reported. One possible reason is that our tertiary care center might have included patients that had generally worse overall clinical status than those investigated in other studies. More than half of the patients in the present study died of infection, which is in line with our previous report that analyzed the mortality of all patients after LDLT (*9*). We recently reported that early posttransplant enteral nutrition with a new immune-modulating diet enriched with hydrolyzed whey peptide significantly prevented posttransplant bacteremia (*10*). This finding indicates that posttransplant intervention such as this type of nutritional therapy could effectively prevent lethal bacteremia arising even in patients with ALF who have little time to receive any preoperative intervention.

In conclusion, LDLT facilitates favorable outcomes in adult patients with ALF irrespective of the etiology, type of ALF, or pretransplant liver condition. The findings of these two short studies indicate that LDLT could afford acceptable

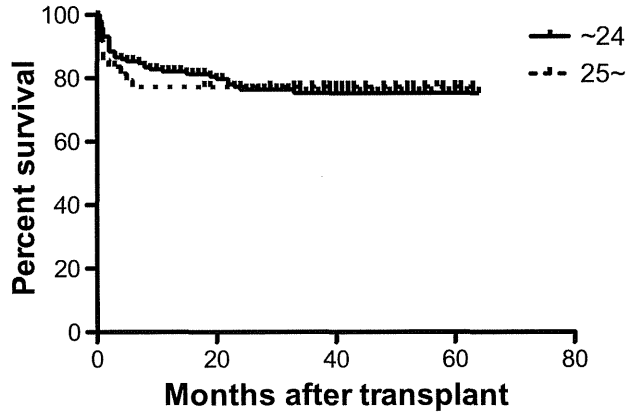

FIGURE 2. Overall survival rates in patients with low (<25) and high (≥25) MELD scores.

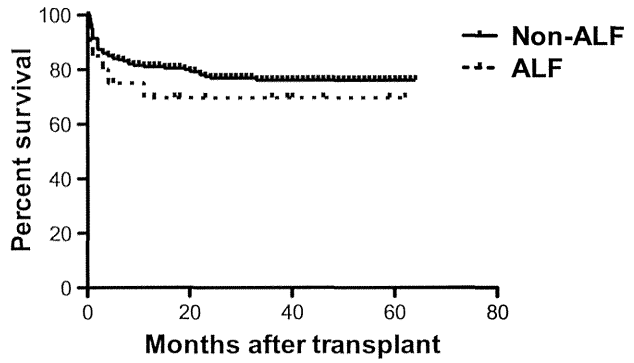

FIGURE 3. Overall survival rates in patients with ALF (n=20) and those with non-ALF (n=223) among those who underwent LDLT between January 2006 and April 2011.

outcomes for patients with high MELD scores or ALF in high volume centers.

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SECTION 13. SHORT-COURSE PRETRANSPLANT ANTIVIRAL THERAPY IS A FEASIBLE AND EFFECTIVE STRATEGY TO PREVENT HEPATITIS C RECURRENCE AFTER LIVER TRANSPLANTATION IN GENOTYPE 2 PATIENTS

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Perioperative changes of procalcitonin levels in patients undergoing liver transplantation

T. Kaido, K. Ogawa, Y. Fujimoto, A. Mori, E. Hatano, H. Okajima, S. Uemoto. Perioperative changes of procalcitonin levels in patients undergoing liver transplantation.
Transpl Infect Dis 2014: **16**: 790–796. All rights reserved

Abstract: *Background.* Severe sepsis is a life-threatening complication after liver transplantation (LT) that can be difficult to diagnose and appropriately treat after LT because of patients being treated with immunosuppressants. The present study examines perioperative changes in serum procalcitonin (PCT), a specific marker of systemic bacterial infection, and determines the value of PCT as a diagnostic tool for bacteremia or rejection.
Methods. Perioperative serum PCT levels were prospectively assessed in 104 consecutive adult patients undergoing LT (living-donor LT, n = 90; deceased-donor LT, n = 14) between May 2010 and August 2012.
Results. Serum PCT levels remarkably increased soon after LT and gradually decreased thereafter, but were not increased in patients diagnosed with cytomegalovirus infection or acute cellular rejection. Serum PCT levels in patients who underwent deceased-donor LT were significantly higher than in those who underwent living-donor LT until postoperative day (POD) 7. Serum PCT levels were significantly higher in patients with bacteremia than in those without bacteremia after POD 14. In patients with post-transplant bacteremia, PCT levels increased again after POD 7 in patients who died within 3 months of LT, while levels remained low after POD 7 in patients who were alive. A positive predictive value of 83.3% for bacteremia and a negative predictive value of 97.4% were obtained at PCT cutoffs of 2.0 and 0.5 ng/mL, respectively.
Conclusion. Serum PCT measurement, using appropriate cutoff values, could help diagnose severe infection, and might be able to differentiate bacteremia from acute cellular rejection.

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Key words: liver transplantation; procalcitonin; bacteremia

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Significant infections are the most frequent causes of morbidity and in-hospital death after liver transplantation (LT) (1). Post-transplant immunosuppressants, preoperatively impaired nutritional status, and multiple catheter insertions all act to generate vulnerability to postoperative infection. Therefore, early diagnosis and the prompt initiation of appropriate treatment are crucial to prevent post-transplant sepsis and death. However, in clinical practice it is not always easy to diagnose infection in a timely manner and discriminate infection from rejection, as both complications usually are accompanied by increases in white blood cells (WBC) and C-reactive protein (CRP). Moreover, treatment for infection and rejection are antagonistic. Inappropriate immunosuppression augmentation causes infection to deteriorate, whereas inadequate immunosuppressant dose reduction leads to rejection. Therefore, a new biological marker is needed that could differentiate between these 2 major complications and play an important role in the perioperative management of LT.

Procalcitonin (PCT) is the prohormone for calcitonin and is comprised of 116 amino acids (2). It does not normally circulate in the bloodstream of healthy individuals. Circulating levels of PCT under conditions such as bacterial infection can reach levels that are

several thousand-fold above normal. The approximate half-life of PCT is 24–30 h in the circulation (3). Therefore, PCT can accurately discriminate systemic bacterial infection from non-infectious acute inflammatory states in the setting of the intensive care unit, whereas WBC and serum CRP cannot (4–6). However, the prognostic value and diagnostic accuracy of PCT in patients undergoing LT with immunosuppressive treatment remain to be determined.

The aim of this study was to determine the value of PCT as a diagnostic tool for bacteremia or acute cellular rejection (ACR). Moreover, we compared serum PCT levels in patients who underwent living-donor LT (LDLT) and deceased-donor LT (DDLT).

Patients and methods

Patients

We prospectively analyzed data derived from 104 consecutive adult (age ≥18 years) patients (49 men, 55 women) who underwent LT (LDLT, n = 90; DDLT, n = 14) at Kyoto University Hospital between May 2010 and August 2012. We measured perioperative serum PCT levels (on the day before LDLT or immediately before DDLT, as well as at postoperative day [POD] 2 or 3, 5, 7, 14, 21, and 28). The Ethics Committee of Kyoto University approved the study, which proceeded in accordance with the Declaration of Helsinki (2000).

The median patient age was 52 (range, 19–69) years. Median Model for End-stage Liver Disease (MELD) score was 19 (range, 4–44). Twenty-five patients were ABO blood type incompatible, and 79 were identical or compatible. The Child–Pugh classifications were C, B, and A for 77, 24, and 3 patients, respectively. The indications for LT were hepatocellular diseases, such as hepatitis B or C virus-associated liver cirrhosis (n = 25), followed by progressive intrahepatic cholestatic diseases, including primary biliary cirrhosis and primary sclerosing cholangitis (n = 23), hepatocellular carcinoma (n = 20), biliary atresia (n = 7), acute liver failure (n = 8), alcoholic liver cirrhosis (n = 3), metabolic liver diseases (n = 4), Budd–Chiari syndrome (n = 3), and other causes (n = 11).

Surgical procedures and immunosuppressive treatments

The selection criteria for the recipients as well as surgical techniques for the donors and recipients have been described in detail elsewhere (7–9). Orthotopic LDLT proceeded using left lobe, right lobe, and posterior segment grafts for 48, 40, and 2 patients, respectively. DDLT proceeded using a whole liver graft for 8 patients, and left and right lobe grafts obtained by splitting a whole liver graft for 3 patients each. The median graft-to-recipient body weight ratio was 0.92 (range, 0.53–3.40). At the time of surgery, in all except those recipients who received a whole liver graft, a tube jejunostomy for enteral nutrition was placed in the proximal jejunum using a 9-French enteral tube.

Immunosuppressive therapy usually consisted of tacrolimus or cyclosporine and low-dose steroids, as described elsewhere (10–12). All patients received intravenous prophylaxis with ampicillin (0.5 g) and cefotaxime (0.5 g) twice daily for 3 days starting 30 min before surgery. We started antibiotics as soon as possible in patients with the diagnosis of bacteremia on the basis of culture results from specimens obtained at infection onset. Perioperative nutritional therapy is described elsewhere (12).

Liver allograft biopsy was performed to determine the cause of allograft dysfunction. ACR was diagnosed by the pathologist according to the Banff criteria (13).

Bacteremia and cytomegalovirus (CMV) antigenemia

Infections were defined using the criteria proposed by the Centers for Disease Control and based on reports regarding liver transplant patients (14). The isolation of bacteria other than common skin contaminants from a single blood culture in the presence of clinical symptoms or signs of infection was considered bacteremia. When caused by common skin contaminants, bacteremia was considered significant only if an organism was isolated from 2 blood cultures and clinical signs of infection were evident. We looked for CMV antigenemia regularly twice a week after LT until POD 30. Postoperative CMV infection was defined as the presence of postoperative CMV antigenemia, regardless of preoperative CMV antibody-positive donors and recipients. Routine prophylactic antiviral therapy was not performed.

Analyzed parameters

Serum PCT levels were measured using electrochemical luminescence immunoassays (ECLusys Brahms PCY; Roche Diagnostics, Berlin, Germany) with an upper normal limit of 0.05 ng/mL. Levels of PCT >2.0 ng/mL were supposed to indicate severe sepsis (15).

The primary endpoint of this study was to investigate whether the value of PCT could be used as a diagnostic

tool for bacteremia or rejection. The secondary endpoint of this study was to examine the difference of PCT levels between LDLT and DDLT patients. We initially compared serum PCT levels in patients with bacteremia or CMV infection, from immediately before or at the time when these infections were diagnosed until POD 30. For patients with simultaneous infection of bacteremia and CMV, the PCT levels were classified as those in the bacteremia group. We then assessed perioperative changes in PCT in all patients and compared those between patients who underwent LDLT (n = 90) and DDLT (n = 14). We next compared perioperative changes in PCT between patients with (n = 39) or without (n = 65) post-transplant bacteremia by POD 30. Furthermore, we compared PCT levels in patients with bacteremia that occurred between POD 8 and 30, and between those who remained alive (n = 20) or died (n = 19) within 3 months of LT. We analyzed correlations between PCT levels and WBC counts or CRP levels at POD 14. Next, we investigated PCT levels in patients histologically diagnosed with ACR between POD 8 and 30. Finally, we investigated the possibility of PCT serving as a biomarker of severe infection after LT and calculated sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV) using 2 cutoffs, 2.0 and 0.5 ng/mL. We compared PCT levels in patients diagnosed with bacteremia between POD 8 and 30, with maximum PCT levels determined in patients without bacteremia within the same time frame.

Statistical analysis

Data are presented as means ± standard deviation for continuous variables except patient age, MELD score, and graft-to-recipient body weight ratio. Continuous variables and significant differences between groups on each POD were non-parametrically analyzed using the Mann–Whitney U-test. As for perioperative changes in serum PCT levels, significant differences between groups were tested using 1-way analysis of variance followed by Bonferroni post test. Correlations between 2 variables were analyzed using Spearman's rank correlation coefficient. A P-value of <0.05 was considered significant. All statistical data were generated using Prism 5 (GraphPad Software Inc., La Jolla, California, USA).

Results

Serum PCT levels in bacteremia and CMV infection

Among 45 (43.3%) of 104 patients who developed postoperative bacteremia, the first episode of bacteremia occurred in 39 of them before POD 30 (Fig. 1).

Serum PCT levels in patients at the time bacteremia was diagnosed (5.71 ± 1.27 ng/mL) were significantly higher than those in patients diagnosed with CMV infection (0.53 ± 0.08 ng/mL) (P < 0.001) (Fig. 2).

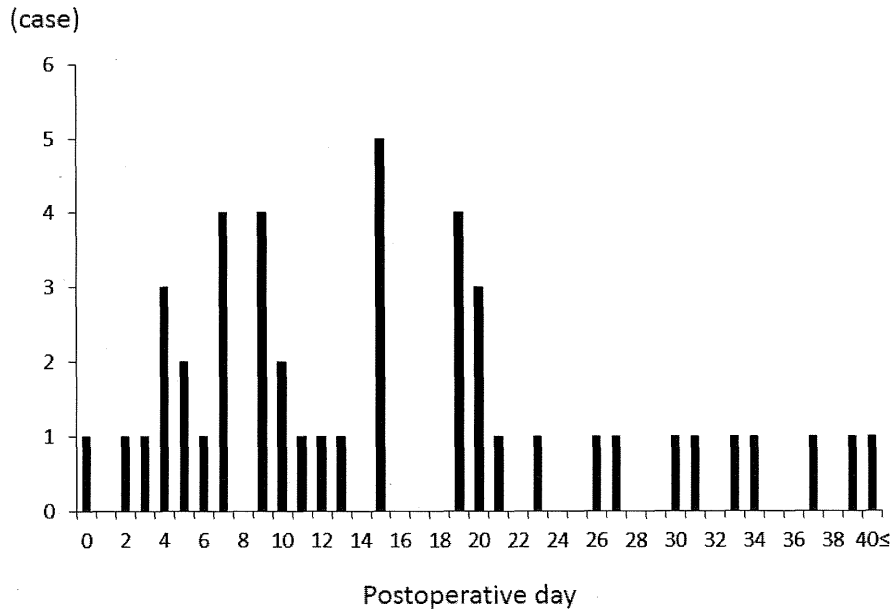

Fig. 1. Number of patients with the first episode of bacteremia.

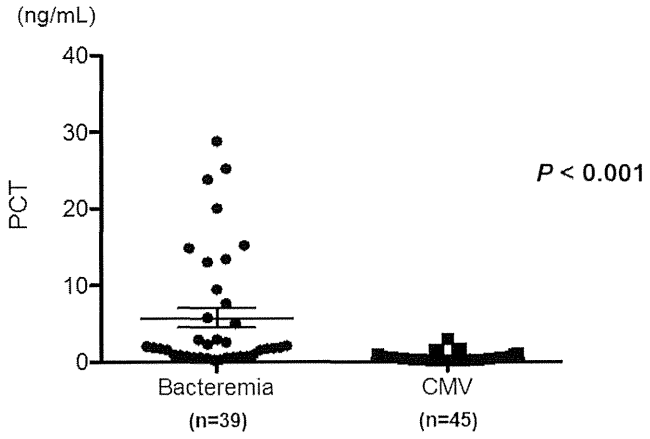

Fig. 2. Serum procalcitonin (PCT) levels in patients when bacteremia and cytomegalovirus (CMV) infection were diagnosed.

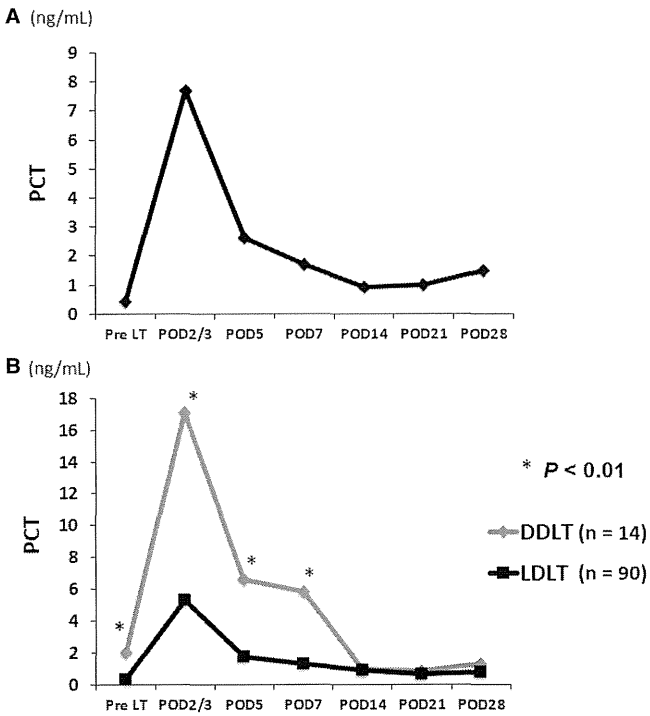

Fig. 3. Perioperative changes in serum procalcitonin (PCT) levels in all patients (A) and in patients who underwent living-donor liver transplantation (LDLT) or deceased-donor liver transplantation (DDLT) (B). *P*-value means significant difference between the 2 groups on each postoperative day (POD). Pre LT, before liver transplant.

Perioperative changes in serum PCT levels

Serum PCT levels in all patients remarkably increased after LT, with a peak at POD 2/3, and gradually decreased thereafter (Fig. 3A). Serum PCT levels in patients who underwent DDLT were significantly higher than in those who underwent LDLT until POD 7 (Fig. 3B). However, no differences were found between these 2 groups after POD 14. No significant difference was seen in the incidence of bacteremia within 30 days after LT (DDLT 35.7% vs. LDLT 37.8%). Moreover, we compared PCT levels between ABO-incompatible patients and identical/compatible patients until POD 28. PCT levels did not differ significantly between the 2 groups.

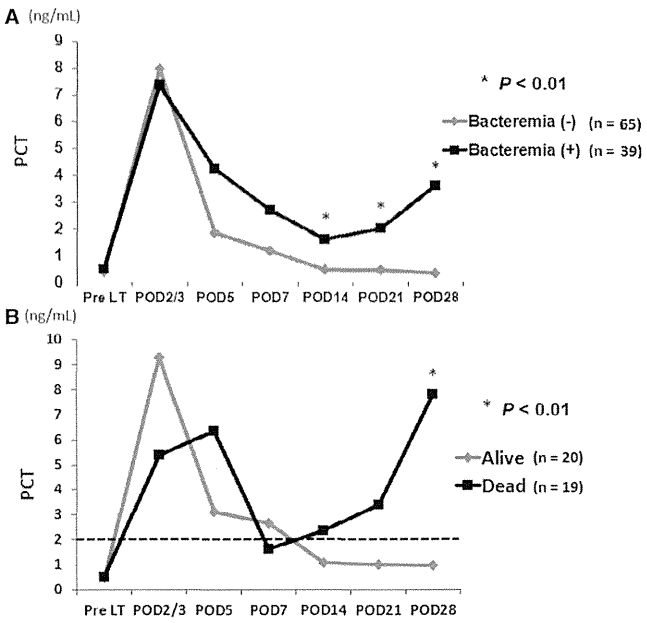

Fig. 4. Perioperative changes in serum procalcitonin (PCT) levels in patients stratified according to occurrence of bacteremia (A), and in patients with post-transplant bacteremia who were dead or alive at 3 months after liver transplantation (LT) (B). *P*-value means significant differences between the 2 groups on each postoperative day (POD).

According to the occurrence of bacteremia, serum PCT levels were significantly higher after POD 5 in patients with bacteremia (n = 39) than in those without bacteremia (n = 65) (Fig. 4A). Moreover, PCT levels increased again after POD 14 in patients with bacteremia.

We next examined perioperative changes only in patients with post-transplant bacteremia (n = 39). Levels of PCT increased again after POD 7 in patients who died within 3 months of LT (n = 19), while those levels remained low after POD 7 in patients who were alive (n = 20) (Fig. 4B). Seventeen of 19 patients who died within 3 months of LT died of bacteremia. The other 2 patients died of cerebral bleeding and antibody-mediated rejection, respectively. Both curves crossed between POD 7 and 14 at a PCT value of about 2 ng/mL.

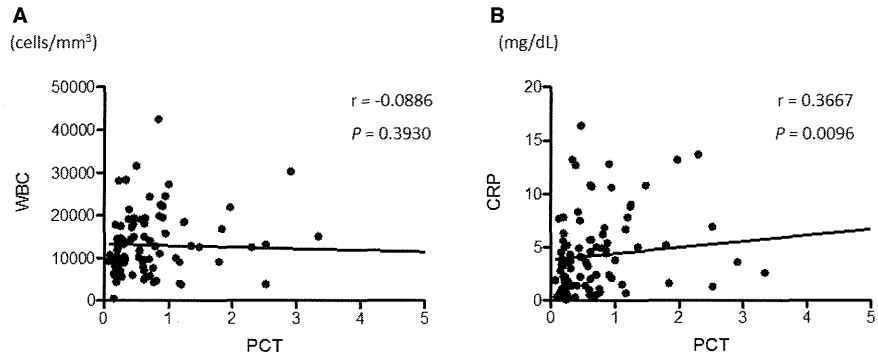

Fig. 5. Correlation between serum procalcitonin (PCT) levels and white blood cell (WBC) counts (A) or C-reactive protein (CRP) (B) at postoperative day 14.

Correlations between PCT levels and WBC or CRP

We therefore focused on PCT levels after POD 8 and examined correlations between PCT levels and WBC counts or CRP levels at POD 14 in all patients. Levels of PCT did not significantly correlate with WBC counts at POD 14 ($r = -0.0886$, $P = 0.3930$) (Fig. 5A), but closely correlated with levels of CRP ($r = 0.3667$, $P = 0.0096$) (Fig. 5B).

Possibility of PCT as a diagnostic tool of rejection or bacteremia

Twenty-six patients had histologically proven ACR between POD 8 and 30. Mean PCT levels at around the time of diagnosis of ACR were 0.42 ± 0.18 ng/mL, significantly lower than those in patients diagnosed with bacteremia (5.71 ± 1.27 ng/mL) ($P < 0.001$).

We investigated whether PCT could serve as a post-transplant marker of bacteremia after POD 8 in all patients. We selected 2.0 and 0.5 ng/mL as cutoffs (Table 1). Sensitivity, specificity, and the PPVs at PCT ≥2.0 ng/mL were 38.5%, 96.9%, and 83.3%, respectively. At PCT ≥0.5 ng/mL, sensitivity, specificity, and the NPVs were 96.2%, 56.9%, and 97.4%, respectively.

Distribution of patients according to bacteremia and procalcitonin (PCT) cutoff level of 2 ng/mL (A) or 0.5 ng/mL (B)

PCT (ng/mL)	Bacteremia (+) *N*	Bacteremia (−) *N*	Total *N*
(A)			
≥2	10	2	12
<2	16	63	79
Total	26	65	91
(B)			
≥0.5	25	28	53
<0.5	1	37	38
Total	26	65	91

Table 1

Discussion

In the present study, we show the characteristics of perioperative change of PCT levels in LT. As far as we are aware, this study is the longest and largest study of perioperative serial changes in PCT levels in patients undergoing LT, along with a report by van den Broek et al. (16). Others have examined the postoperative course of PCT in the early postoperative period in 22–40 patients after LT (17–20), whereas our study included 104 patients who underwent LT. Most PCT levels were measured until POD 7, whereas we continued measurements from the perioperative period until POD 28. We also investigated whether or not PCT could serve as a marker with which to monitor post-transplant bacteremia or to differentiate severe infection from rejection. Furthermore, to our knowledge, no reports have compared postoperative PCT levels between DDLT and LDLT. van den Broek et al. (16) studied clinical courses of 135 LT recipients, and reported that the peak PCT levels in patients with clinically significant infections were significantly higher than in patients without clinically significant infections. However, they did not compare PCT levels in patients with or without CMV infection nor ACR.

The present study showed that 43.3% of LT recipients developed postoperative bacteremia, higher than the

rate reported by other investigators. Saner et al. (14) reported that bloodstream infection occurred in 24% (13/55) of LDLT recipients. Kim et al. (21) reported that 24% (34/144) of LDLT recipients developed bacteremia. The high incidence of bacteremia in the present study can be partly explained by differences in the general preoperative conditions of the recipients, because our center is the tertiary LT center in Japan. The median MELD score in our study was 19, while that in the reports by Saner et al. (14) and Kim et al. (21) were 13.5 and 16.6, respectively. These findings show that our report included more patients with greater impairment of general conditions, such as liver dysfunction, than other studies.

The PCT levels remarkably increased immediately after LT and gradually decreased, in line with previous reports, to low levels around POD 7 (16–19). The mechanism of the transient increase in PCT immediately after LT remains unclear. Some investigators have suggested that PCT synthesis in the graft liver transiently increases just after LT, direct endotoxin influx into the systemic circulation from the small intestine and colon increases during the anhepatic phase, and that transient impairment of endotoxin clearance in the graft liver would be involved (19, 22, 23). In the present study, serum PCT levels until POD 7 in patients who underwent DDLT were significantly higher than in those who underwent LDLT, although the number of DDLT was small (n = 14). The reason may be the difference of the graft liver condition including longer cold ischemic time and inferior liver function in DDLT compared with LDLT; the finding of no significant difference in the incidence of bacteremia between the 2 groups supports this hypothesis. We, therefore, focused on changes in PCT levels between POD 8 and 30, as the increase in PCT levels was non-specific until POD 7.

Infection and rejection are the 2 major adverse events that can arise after organ transplantation and they are not always easy to discriminate in clinical practice, because rejection as well as infection is often accompanied by leukocytosis and fever. However, the adjustment of immunosuppressants to counter rejection is quite antagonistic to that needed to combat infection. In such circumstances, inappropriate augmentation of immunosuppressants could worsen infection, whereas inadequate dose reduction could lead to rejection. Therefore, a new biological marker is required to differentiate these 2 major complications and play an important role in the perioperative management of LT. In the present study, PCT levels in patients with the diagnosis of ACR were low. Furthermore, PCT 0.5 and 2.0 ng/mL had a high NPV of 96.2% that could exclude, and a moderate PPV of 83.3% that could diagnose bacteremia, respectively. That is, PCT levels of >2.0 and <0.5 ng/mL could diagnose or rule out bacteremia, respectively. Decisions based on these 2 cutoff values would thus be useful to start prompt and appropriate treatment for these contrary complications. We are presently undertaking a prospective study to validate these PCT-based strategies.

Limitations of this study must be considered. First, we measured perioperative serum PCT levels on the day before LDLT or immediately before DDLT, on POD 2 or 3, 5, 7, 14, 21, and 28 according to the study protocol. Therefore, PCT levels at the time when bacteremia and ACR were diagnosed were not necessarily measured in a timely fashion. Maximal PCT levels might have been somewhat higher when bacteremia was diagnosed. However, this difference would have little impact on the major findings of this study. Second, individual values of PCT levels in bacteremia and CMV cases had a wide overlap. Therefore, it is impossible to distinguish bacterial infection from CMV infection with low PCT level. Postoperative CMV infection was diagnosed with the presence of CMV antigenemia in the present study. CMV infection usually is associated with fever, like bacteremia, and measurement of CMV antigenemia takes 2 days at our institute. If PCT level was low, we could at least avoid unnecessary use of antibiotics. To more clearly understand the impact of PCT levels, we are now investigating the possibility of whether PCT can be used as a predictive factor not only for severe infection but also for ACR. Third, we diagnosed CMV infection as being CMV-antigenemia positive in this study. Recently, viremia is a more useful indication. We would like to use viremia as the diagnosis of CMV in our next study. Finally, we could not compare PCT levels with other inflammatory markers, including interleukin (IL)-6 and IL-8. Harbarth et al. (5) assessed the diagnostic value of PCT, IL-6, and IL-8 in critically ill patients with suspected infection, and reported that PCT yielded the highest discriminative value, with an area under the receiver operating characteristic curve of 0.92, followed by IL-6 (0.75) and IL-8 (0.71). However, the diagnostic value of those parameters in patients who underwent LT is unclear. Steroid administration usually suppresses IL-6 production and reduces serum IL-6 level. Therefore, PCT could be a better marker for severe infection than IL-6. As for WBC and CRP, WBC and PCT levels at POD 14 did not significantly correlate in the present study. In contrast, PCT levels closely correlated with CRP levels. Although the reason for this difference is unclear, the immunosuppressive state after LT might be involved.

In conclusion, serum PCT measurement, using appropriate cutoff values, could help diagnose severe infection, and might be able to differentiate bacteremia from ACR. Further prospective studies are required to confirm our findings.

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Author contributions: T.K.: design of the study, execution of the study, data collection and analysis, and writing of the article. K.O.: design and execution of the study. Y.F., A.M., E.H., and H.O.: execution of the study. S.U.: design of the study, execution of the study, and critical revision of the article.

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

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

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

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

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

GRAFT SELECTION

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

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

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

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

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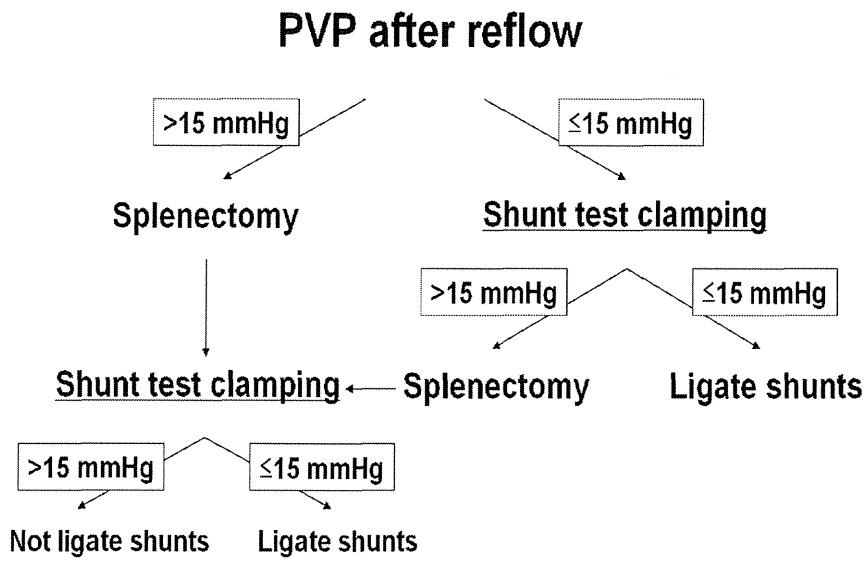

FIGURE 1. Current strategy for intentional portal pressure control.

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

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

PORTAL FLOW MODULATION

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

RECIPIENT OUTCOME OF NEW STRATEGY

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

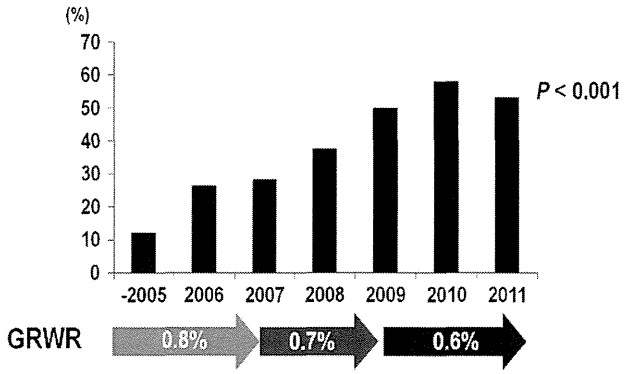

FIGURE 2. The ratio of left lobe graft.

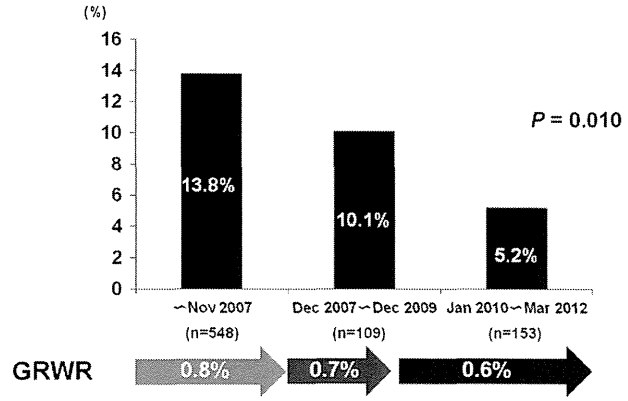

FIGURE 3. Donor complication rates.

CONCLUSION

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

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

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

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

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

Risk Factors

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

Clinical Signs and Symptoms

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

Imaging Diagnosis

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

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ORIGINAL ARTICLE

Donor morbidity in right and left hemiliver living donor liver transplantation: the impact of graft selection and surgical innovation on donor safety

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Summary

This study investigated adequate liver graft selection for donor safety by comparing postoperative donor liver function and morbidity between the right and left hemilivers (RL and LL, respectively) of living donors. Between April 2006 and March 2012, RL (n = 168) and LL (n = 140) donor operations were performed for liver transplantation at Kyoto University Hospital. Postoperative hyperbilirubinemia and coagulopathy persisted in RL donors, whereas the liver function of LL donors normalized more rapidly. The overall complication rate of the RL donors was significantly higher than that of the LL donors (59.5% vs. 30.7%; $P < 0.001$). There were no significant differences in severe complications worse than Clavien grade IIIa or in biliary complication rates between the two donor groups. In April 2006, we introduced an innovative surgical procedure: hilar dissection preserving the blood supply to the bile duct during donor hepatectomy. Compared with our previous outcomes (1990–2006), the biliary complication rate of the RL donors decreased from 12.2% to 7.2%, and the severity of these complications was significantly lower. In conclusion, LL donors demonstrated good recovery in postoperative liver function and lower morbidity, and our surgical innovations reduced the severity of biliary complications in living donors.

Introduction

The first living donor liver transplantation (LDLT) using the left lateral segment was performed for a paediatric recipient in 1988 [1]. After the first successful case was reported in 1990 [2], LDLT in children became accepted worldwide within a few years. LDLT has emerged as an alternative method for reducing the waiting period and the mortality of patients on the waiting list [3,4]. Given the success of paediatric liver transplantation (LT) and the unavailability of deceased donor organs, Japanese LT surgeons extended the indications for LDLT to adult patients, and the first successful LDLT using a left hemiliver (LL) graft in an adult patient was performed [5]. LL grafts subsequently became common for use in adult patients.

The first LDLT using a right hemiliver (RL) graft in a child was performed at our institution [6], and because an inferior graft survival rate with smaller grafts [less than a graft-to-recipient weight ratio (GRWR) of 0.8%] was reported [7], the transplantation of RL grafts in adult patients has rapidly expanded as a standard procedure worldwide.

Donor safety is the first priority in LDLT, and among the most important complications of donor surgery are biliary complications, including bile leakage and biliary stricture. Our previous study reported that biliary complications occurred more frequently in RL donations than in LL donations and that the severity was also greater in RL donations [8]. Hence, in April 2006, we introduced a surgical procedure to avoid biliary complications in donor surgery. We also modified our graft selection criteria. We

introduced minimum dissection of the bile duct at the hilus to preserve the blood supply to the bile duct. The GRWR was reduced from 0.8% to 0.6% as a new graft selection criterion; LDLT using an LL graft subsequently increased in our institution.

This study aimed to evaluate the usefulness of this new surgical procedure and to report on the donor morbidity with RL and LL liver transplantation by comparing the postoperative liver function and complication details between the two groups.

Patients and methods

Donors and grafts

Between April 2006 and March 2012, 429 consecutive LTs [411 LDLT, 16 deceased donor liver transplantations (DDLTs) and two domino LTs] were performed at Kyoto University Hospital. Of the 411 living donors, 168 underwent a donor operation for an RL graft with (n = 11) or without (n = 157) the middle hepatic vein (MHV), and 140 underwent a donor operation for an LL graft with (n = 76) or without (n = 64) the caudate lobe. In this study, donors of the lateral segment, extended lateral segment, mono segment and posterior segment were excluded from the analysis. The donor and graft demographic data, duration of surgery, intraoperative blood loss, postoperative hospital stay, liver function test and complications/morbidity were evaluated. As a postoperative liver function test, serial changes in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil) and prothrombin time–international normalized ratio (PT-INR) were measured in the peripheral blood on postoperative days (PODs) 1, 2, 3, 5, 7, 10, 14, 21 and 28.

This study was approved by the Ethics Committee of Kyoto University and was conducted in accordance with the Declaration of Helsinki of 2000.

Donor and graft selection

Potential donors underwent blood tests, including blood counts, blood chemistry, infection analyses, tumour markers, blood type determination, human leucocyte antigen typing and mixed lymphocyte reaction assays. Nonalcoholic steatohepatitis (NASH) was evaluated using the homoeostatic model assessment index. For all potential donors, multidetector-row computed tomography (CT) imaging was performed to detect hepatic anatomical variations and to evaluate the donor's whole liver volume, graft volume and remaining donor liver volume. Instead of a needle biopsy of the donor liver, the liver-to-spleen CT attenuation value ratio (L/S ratio) was used in our institution to assess steatosis of the liver. The L/S ratio indicates the grade of hepatic steatosis. The optimal L/S ratio to predict more than 30% hepatic steatosis is 1.1 [9]. Since November 2002, HepaVision2 (MeVis, Bremen, Germany), which is software specifically developed for image analysis and risk analysis of the liver, was used to estimate the graft volume and congestive volume in the graft [10]. Using raw data obtained from multislice CT, various anatomic sites can be visualized, and volumetry of the portal and venous regions can be performed. Conventional volumetry, including whole liver volume, RL volume with or without MHV, LL volume and remnant liver volume, was calculated. To assess the biliary tree, routine magnetic resonance cholangiopancreatography (MRCP) was performed.

Our graft selection criteria were modified in April 2006; the GRWR minimum was reduced from 0.8% to 0.6%, and LL became the first choice for the graft whenever feasible. The RL was considered when the GRWR of the LL was <0.6%. However, if the remnant liver volume was <30% of the total liver volume, the person was excluded as a donor candidate.

Surgical procedure for the donor operation

The donor operation was performed as described previously [11,12]. Briefly, under general anaesthesia, a thorough laparotomy was performed. After a retrograde cholecystectomy, a catheter was inserted into the cystic duct for intraoperative cholangiography. Depending on the type of liver graft donation, the right or left portal vein and the right or left hepatic artery were isolated, and the demarcation line was noted by temporally clamping the graft's side vessels. Liver parenchymal transection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA system, Valleylab Inc., Boulder, CO, USA) and bipolar electrocautery without inflow occlusion prior to cutting the hepatic duct. The cutting line of the hepatic duct was carefully determined based on intraoperative cholangiography using a static X-ray film unit. After parenchymal transection was initiated, hilar dissection was performed without dissection of the pericholedochal tissue to preserve the blood supply around the hepatic duct. The hepatic duct within the hilar plate was separated with fine scissors, and the stumps of the remnant hepatic duct were meticulously closed with 6–0 polydioxanone absorbable monofilament sutures. To ensure the absence of bile leakage and stricture, a cholangiogram was performed again. Systemic administration of heparin was performed following complete parenchymal transection. Thereafter, the hepatic artery, portal vein and hepatic vein were cut sharply. All the grafts were perfused ex situ via the portal vein with a histidine-tryptophan-ketoglutarate solution (Custodiol; Chemie GmbH, Alsbach-Hahnlein, Germany).

Modifications of the surgical procedure in the donor operation

We modified the surgical procedure in the donor surgery as follows. Since April 2002, a biliary decompression tube has been placed through the cystic duct into the residual bile duct to prevent bile leakage from the bile duct stump in donors with difficulty in hepatic duct end closure. Since June 2004, abdominal drainage has been reduced to bile duct drainage only, except in donors at high risk for biliary complications based on the intraoperative findings. Since April 2006, parenchymal transection has been started before cutting the hepatic duct, and we have introduced the method of hilar dissection during parenchymal transection. This procedure minimizes the dissection of the bile duct, thus preserving the blood supply to the bile duct of both the graft and the remnant liver.

Definition of the grade of postoperative donor complications

Postoperative donor complications were graded according to the Clavien classification [13]. Complications worse than Grade IIIa were recognized as major complications. Hyperbilirubinemia was defined as serum total bilirubin levels >3 mg/dl at POD 7 without coagulopathy.

Statistical analysis

All the values are presented as the means and standard deviations for each group. Categorical variables were compared with the chi-square test or Fisher's exact test. The statistical analyses of the groups at each time point were tested with 2-way analysis of variance and Bonferroni's *post hoc* test. For the patient survival analysis, the Kaplan–Meier method with the log-rank test was used. P values <0.05 were considered statistically significant. The analysis was performed using GRAPHPAD PRISM software version 5 (GraphPad Software, La Jolla, CA, USA).

Results

Changes in graft types

Figure 1 demonstrates the changes in the numbers of LDLT graft types since April 2006. After the introduction of the new modified graft selection criteria, LDLT using LL grafts gradually increased. Since 2009, the frequency of LL grafts has become nearly equal to that of RL grafts.

Donor demographics

The demographic data of the RL and LL donors are summarized in Table 1a. Regarding the donor and graft characteristics, there was no significant difference in the gender distribution or donor age between the RL and LL donors. The mean body weight and body mass index of the LL donors were significantly higher than those of the RL donors. Regarding the donor operative outcomes, the duration of surgery and blood loss were comparable between the RL and LL donors. We administered no homologous blood transfusions to donors of either graft type. No significant difference was found in the postoperative hospital stay between the RL and LL donors.

Postoperative liver function test

There were no significant differences in the peak serum AST or ALT levels between the RL (324 ± 193 IU/l and 325 ± 161 IU/l, respectively) and LL (289 ± 136 IU/l and 339 ± 150 IU/l, respectively) donors. However, the peak serum T-Bil level was significantly higher in the RL donors (4.3 ± 1.8 mg/dl) than in the LL donors (2.6 ± 2.1 mg/dl) ($P < 0.05$).

Figure 2a and b show the postoperative serial changes in the serum T-Bil and PT-INR levels, respectively. The RL donors presented a significant increase in serum T-Bil during the week after donor surgery ($P < 0.05$) (Fig. 2a). Moreover, the PT-INR was significantly higher in the RL donors at PODs 1, 2, 3 and 5 than that in the LL donors ($P < 0.05$) (Fig. 2b). Essentially, liver damage persisted longer in the RL donors than in the LL donors.

Donor complications

No donor mortality or life-threatening complications were observed in the 308 living donor hepatectomies during this study period. The donor complications are shown in Table 2. The overall complication rate of the RL donors (59.5%) was significantly higher than that of the LL donors (30.7%) ($P < 0.001$). The rates of biliary complications in the RL and LL donors were 7.1% and 5.0%, respectively (P = NS). Regarding the complications in the RL donors, there were 12 biliary complications, including 11 instances of bile leakage (6.5%) and one biliary stricture (0.6%). The number of bile leakage and biliary stricture occurrences in the LL donors was 5 (3.6%) and 2 (1.4%), respectively. Regarding the rate of each biliary complication, there were no significant differences between the donors. The mean time to the occurrence of bile leakage in the 11 RL and 5 LL donors was 10.7 and 12.0 days, respectively. One biliary stricture in an RL donor occurred 33 days after donor surgery. Two LL donors were diagnosed as having biliary strictures 47 and 118 days after surgery.

Regarding nonbiliary complications, intra-abdominal fluid collection had the highest incidence in the RL donors, occurring in 26 (15.5%) donors and significantly more often than in the LL donors (2.1%) ($P < 0.001$). Moreover,

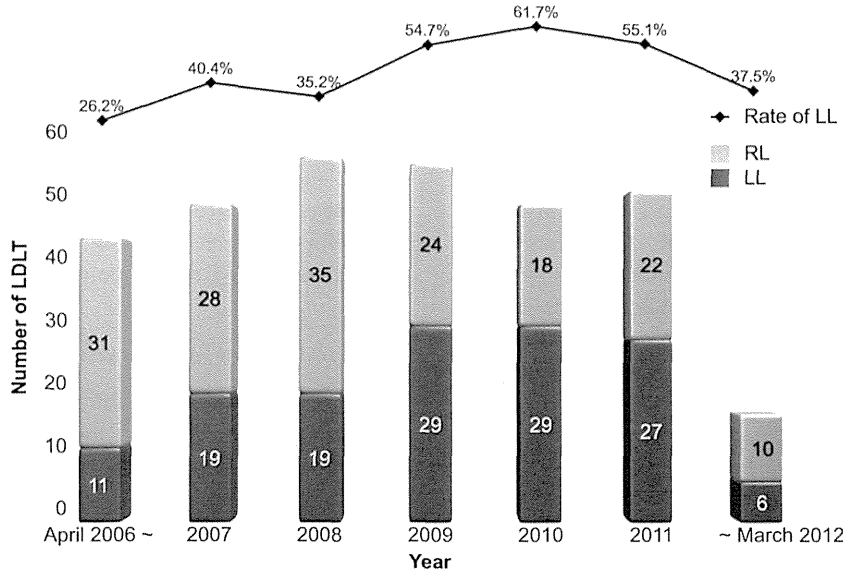

Figure 1 Changes in the numbers of graft types. Modified graft selection criteria were introduced in 2006; the use of LL grafts for LDLT has increased compared with RL grafts.

Table 1. (a) Donor and graft demographic data. (b) Comparison of recipients by graft type.

Variables	RL (n = 168)	LL (n = 140)	P value
(a)			
Gender (M/F)	75/93	50/90	0.130
Age (year)	43.9 ± 12.6	42.8 ± 11.4	0.452
Body weight (kg)	58.7 ± 10.5	63.7 ± 11.2	<0.001*
BMI (%)	21.9 ± 2.8	22.8 ± 2.9	0.009*
Actual graft volume (g)	667 ± 106	417 ± 85	<0.001*
GRWR (%)	1.02 ± 0.21	0.87 ± 0.25	<0.001*
Duration of operation (min)	406 ± 82	420 ± 77	0.135
Blood loss (g)	345 ± 224	338 ± 257	0.799
Hospital stay (day)	17.7 ± 29.4	14.6 ± 7.0	0.196
(b)			
Gender (M/F)	155/53	40/100	<0.0001*
Recipient age (year)	50.8 ± 12.9	44.1 ± 18.5	0.0003*
Recipient body weight (kg)	67.2 ± 11.5	50.2 ± 11.4	<0.0001*
Recipient MELD score	17.6 ± 7.5	19.0 ± 8.9	0.2524

*P < 0.05.

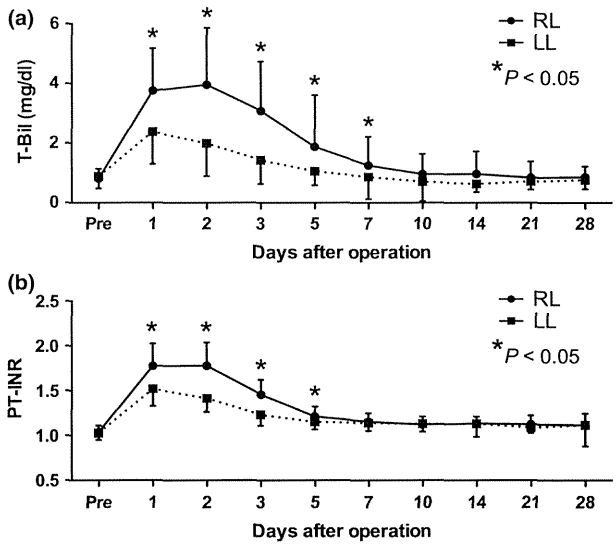

Figure 2 Postoperative serial changes in serum T-Bil and PT-INR levels. (a) The serum T-Bil levels of the RL graft donors were significantly higher than those of the LL graft donors 1 week after donor surgery (P < 0.05). (b) PT-INR levels were significantly higher in the RL graft donors at PODs 1, 2, 3 and 5 than in the LL graft donors (P < 0.05).

the rate of hyperbilirubinemia was notably higher in the RL donors (2.4%) than in the LL donors (0.7%); however, this difference was not significant. The highest incidence of complications in the LL donors involved skin wound problems, which occurred more frequently in the LL donors (11.4%) than in the RL donors (6.0%); however, this difference was not significant. No significant differences were found in other abdominal complications. Two venous thromboses, including one hepatic venous thrombosis and one portal venous thrombosis, occurred in the RL donors. These two donors with venous thromboses were diagnosed via postoperative CT scan, and the thrombi were detected in the MHV and the stump of the right portal vein, respectively. These thrombi disappeared after anticoagulant therapy, and these two donors were discharged without any further complications.

Regarding extra-abdominal complications, pleural effusion occurred significantly more frequently in the RL donors (5.4%) than in the LL donors (0.7%) (P < 0.05).

Table 2. Comparison of donor complications.

	RL (n = 168)	LL (n = 140)	P value
All complications	100 (59.5%)	43 (30.7%)	<0.001*
Biliary complications	12 (7.1)	7 (5.0)	0.484
Bile leakage	11 (6.5)	5 (3.6)	0.307
Biliary stricture	1 (0.6)	2 (1.4)	0.593
Other abdominal complications			
Fluid collection	26 (15.5)	3 (2.1)	<0.001*
Skin wound problem	10 (6.0)	16 (11.4)	0.101
Small bowel obstruction	1 (0.6)	2 (1.4)	0.593
Intra-abdominal abscess	2 (1.2)	–	0.503
Drug-induced hepatotoxicity	4 (2.4)	7 (5.0)	0.360
Massive ascites	3 (1.8)	–	0.254
Hyperamylasemia	3 (1.8)	1 (0.7)	0.629
Hyperbilirubinemia	7 (4.2)	1 (0.7)	0.076
Gastritis/intractable ulcer	1 (0.6)	–	1.000
Venous thrombosis	2 (1.2)	–	0.503
Extra-abdominal complications			
Pleural effusion	9 (5.4)	1 (0.7)	0.025*
Atelectasis	1 (0.6)	1 (0.7)	1.000
Pneumothorax	1 (0.6)	–	1.000
Pulmonary embolism	–	1 (0.7)	0.455
Fever of unknown origin	5 (3.0)	1 (0.7)	0.226
Others	13 (7.7)	2 (1.4)	0.014*

*P < 0.05.

There were no significant differences in other extra-abdominal complications.

Postoperative complication grade

The postoperative complication grades of the RL and LL donors are shown in Table 3. In the RL donors, the complication rates of Grades I and II were 22.0% and 23.2%, respectively. Regarding major complications, the incidence of Grade IIIa complications was 14.3%; no complications worse than Grade IIIb occurred during this study period. The 24 Grade IIIa complications included nine biliary complications, six cases of intra-abdominal fluid collection, two skin wound problems, two intra-abdominal abscesses, four pleural effusions and one pneumothorax. Of the 11 RL donors with bile leakage, endoscopic nasobiliary drainage was necessary in 3 (1.8%) donors (Grade II), and percutaneous drainage of the bile was performed in 8 (4.8%) donors (Grade IIIa). Moreover, endoscopic retrograde biliary drainage was necessary for 1 (0.6%) biliary stricture (Grade IIIa).

The complication rates of Grades I, II and IIIa were 13.6%, 8.6% and 7.9%, respectively, in the LL donors. Regarding major complications, 11 Grade IIIa complications (six biliary complications, three skin wound problems, one small bowel obstruction and one pulmonary embolism) occurred. A Grade IIIb complication occurred in only 1 (0.7%) LL donor. In this donor, reoperation (hepaticojejunostomy) was necessary for delayed biliary stricture 7 months after donor surgery.

Table 3. Complication grades of RL and LL donors.

	I	II	IIIa	IIIb
All complications				
RL	37 (22.0%)	39 (23.2%)	24 (14.3%)	–
LL	19 (13.6%)	12 (8.6%)	11 (7.9%)	1 (0.7%)
Biliary complications				
RL	–	3 (1.8%)	9 (5.4%)	–
LL	–	–	6 (4.3%)	1 (0.7%)

	Complication rate	P
Severe complications above grade III		
RL	14.3% (24/168 cases)	0.15
LL	8.6% (12/140 cases)	

The complication rate of RL donors was Grade IIIa and was comparable with that of LL donors (P = 0.15). During this study period, no Grade IV or V complications were experienced.

Comparison of biliary complications in RL donors during different periods

Table 4 shows the biliary complication rate and major complication rate in the RL donors according to different periods. The biliary complication rate in the RL donors decreased from 14.2% (Period 1: June 1990 to March 2002) to 12.9% (Period 2: April 2002 to March 2006). During this study period (Period 3: April 2006 to March 2012), the overall biliary complication rate of RL donors was 7.1%, which was significantly lower than that during Period 1. The major complication rate showed a tendency to decrease over time, but there were no significant differences among the three periods.

Comparison of recipients by graft type

The recipients' characteristics and the model for end-stage liver disease (MELD) score are summarized in Table 1b. Significant differences were found in recipient gender distribution, age and body weight. The MELD scores of the

Table 4. Biliary complications in RL donors according to period.

Period	Biliary complication rate (%)	P	Major complication rate (%)
June 1990 to March 2002	14.2		16.6
April 2002 to March 2006	12.9	0.03	17.8
April 2006 to March 2012	7.1		14.3

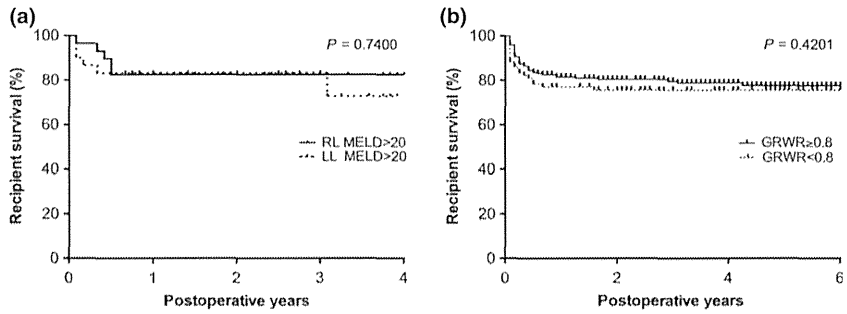

Figure 3 Comparison of recipient survival according to MELD score and GRWR. (a) Survival rate of recipients with MELD scores >20 was comparable between RL and LL graft recipients. (b) The log-rank test found no statistically significant differences in survival rate of recipients with GRWR ≥0.8 and those with GRWR <0.8.

RL and LL recipients were 17.6 ± 7.5 and 19.0 ± 8.9, respectively. Figure 3a shows that the survival rate of the LL recipients with MELD scores >20 was comparable with that of the RL recipients ($P = 0.7400$). Moreover, as shown in Fig. 3b, there was no significant difference in the survival rate between recipients with a GRWR <0.8% and those with a GRWR ≥0.8% ($P = 0.4201$).

Discussion

In LDLT, the safety of the donor is the ultimate priority. However, we experienced the first instance of donor death in Japan in 2003, which resulted from liver failure caused by RL graft donation and NASH. Trotter reported 13 living liver donor deaths that were 'definitely' related to donor surgery [14]. Similarly, Ringe identified 33 living liver donor deaths, including 21 deaths related to the surgical procedure. Of these 21 deaths, at least 14 cases involved RL graft donation. They concluded that the incidence of donor death was 0.1–0.3% and likely reached 0.5% when using an RL graft for adult-to-adult LDLT [15]. Therefore, the selection of graft type is very important for donor safety.

We previously reported on the surgery-related morbidity in LDLT, in which multivariate analysis demonstrated that RL donation was an independent risk factor for complications in these donors [8]. Recently, the feasibility and usefulness of LL grafts for adult-to-adult LDLT have been reported [16,17]. The safety of LL grafts for adult-to-adult LDLT was compared with that of RL grafts. Moreover, the outcomes of LL grafts in LDLT were not inferior to those of RL grafts in LDLT. However, small-for-size syndrome (SFSS) occurred more often in LL graft LDLT than in RL graft LDLT.

There are still many debates regarding the relationship between the MELD score and post-transplant outcomes. Theoretically, a high MELD score is associated with poor patient and graft survival following LT. Hayashi reported that there was no correlation between the 1-year survival rate and the MELD score [18]. Although Li reported that MELD score emerged as an independent risk factor for SFSS, they also reported that the 1- and 3-year survival and postoperative complication rates were similar between recipients with high MELD scores and those with low MELD scores [19,20]. RL grafts are recommended for recipients with MELD scores >20 [21], yet the present study showed that LL grafts were feasible for recipients with MELD scores >20, with a survival rate comparable with that of RL grafts (Fig. 3a). In addition, our recent study indicated that pretransplant sarcopenia and the absence of perioperative nutritional therapy were independent risk factors for post-transplant mortality in patients undergoing LDLT, whereas the MELD score is not [22]. However, the recipient's pretransplant general condition (MELD, portal hypertension, renal dysfunction, pretransplant diabetes mellitus, etc.) is a risk factor affecting recipient and graft survival [21,23,24]. Thus, we may modify our graft selection criteria in the future.

We modified our graft selection criteria and introduced new recipient portal pressure control in 2006. The lower limit for GRWR was reduced to 0.6%. Regarding the recipient's portal pressure, our previous study showed that a final portal pressure <15 mmHg was an important factor for better outcomes in adult-to-adult LDLT using smaller grafts [25]. The present study demonstrated that the recipient survival rate was comparable between patients with a GRWR <0.8% and those with a GRWR ≥0.8% (Fig. 3b). Therefore, we believe that small grafts can be safely available via portal pressure control without SFSS, and LDLT using an LL graft has been increasingly used in our institution since 2006 (Fig. 1).

Our study showed that the overall complication rate of RL donors was significantly higher than that of LL donors and that Clavien grade II and IIIa complications occurred significantly more frequently in RL donors than in LL donors. Additionally, LL donors showed significantly better improvement in serum T-Bil and PT-INR levels. Our study demonstrated that LL donors could achieve earlier liver function recovery after donor hepatectomy than RL

donors. This result was due to a sufficient remnant liver volume. Hyperbilirubinemia and coagulopathy persisted in RL donors. Because the early recovery of postoperative liver function can contribute to donor safety, LL grafts offer significant advantages in donor safety compared with RL grafts. Essentially, LL grafts offer significant advantages in postoperative liver regeneration. Previously, we had primarily performed RL graft donor surgeries in LDLT, and we reported several studies on donor morbidity in RL and LL grafts [8,26,27]. Based on our experience in donor surgery, our donor surgery procedure and postoperative management have been continuously modified and improved in the effort to reduce severe donor morbidity. The team experience of each organ transplant centre is believed to be the most critical factor in reducing donor morbidity; living donor morbidity after liver donation has been strongly correlated with the experience of the centre [28,29].

Biliary complications remain among the most common problems associated with LDLT, and the rate of these complications has been reported to range from 0% to 38.6% [30]. Table 5 shows the biliary complications and compares the RL donors with the LL donors; our previous reports are included [8,16,26,31–35]. Nearly all centres have reported that the overall biliary complication rate was higher in the RL donors than in the LL donors. Anatomic variations in the biliary tract might significantly contribute to the higher biliary complication rate in the RL donors. The anterior and posterior segmental branches of the right hepatic duct (RHD) often diverge immediately proximal to the bifurcation of the RHD and left hepatic duct (LHD). Therefore, the RHD must be cut within a few millimetres of the bifurcation. Furthermore, RL grafts often have multiple biliary orifices, whereas LL grafts usually have a single orifice. RL grafts also have larger biliary stamps than LL grafts, which result in a higher incidence of biliary leakage among RL donors.

The hilar plexus is a set of communicating arcade vessels that bridge the right and left hepatic arterial systems, and it is located within the hilar plate. The blood supply to the RHD arises from both the right hepatic artery and the hilar plexus. The LHD is supplied by a plexus that is continuous with the plexus at the confluence of the RHD and the common bile duct. Therefore, dissection of the hilar plate and hepatic artery can easily destroy the communicating arcade of the hilar bile duct. Minimizing the dissection of the hepatic artery and portal vein is important to avoid damage to the arterial plexus and to ensure that the surrounding tissues remain attached to the common and branched hepatic ducts. The high hilar dissection technique during recipient hepatectomy might contribute to reducing the biliary complications by preserving adequate blood supply to the bile duct [36]. We have applied this hilar dissection technique in donor hepatectomy since April 2006.

According to a previous study from our institution, the biliary complication rate in RL donors decreased from 18.6% [26] to 14.5% [27]. In 2010, Iida updated our published experiences and reported that the incidence of biliary complications in RL donors from April 2002 to March 2006 decreased to 12.9% [8]. During this study period (April 2006 to March 2012), the overall biliary complication rate of RL donors was 7.1%, and we did not experience complications worse than Clavien grade IIIb in the RL donors. We believe that surgical refinements and innovations, especially in the dissection of the bile duct, have assisted in reducing the incidence of biliary complications.

Although the biliary complication rate of the LL donors was lower than that of the RL donors, the Clavien grade IIIb complication of biliary stricture occurred in only one LL donor. This previously reported donor had a trifurcated portal vein and a rare biliary anomaly [37]. When rare biliary anatomy is observed in the LL, precise preoperative identification of the biliary anomalies is essential.

Table 5. World reports of biliary complications in living donors for liver transplantation.

First author (reference)	Year	Institute	Number of donor (RL:LL)	Number of biliary complication		Biliary complication rate (%) (RL:LL)
				Bile leakage (RL:LL)	Biliary stricture (RL:LL)	
Fujita [23]	2000	Kyoto, Japan	43:99	8:3	N/A	18.6:3.0
Lo [28]	2003	Multicenter, Asia	561:334	34:8	6:0	7.1:2.4
Hwang [29]	2006	Seoul, Korea	591:571 (*89)	3:2	5:0	1.4:0.4†
Shio [30]	2008	Kyoto, Japan	434:297 (*237)	43:5	9:3	11.1:2.4†
Taketomi [16]	2009	Fukuoka, Japan	69:137	3:2	4:2	10.1:2.9
Iida [8]	2010	Kyoto, Japan	500:762 (*493)	53:36	8:2	12.2:4.9†
Kousoulas [31]	2010	Hanover, Germany	36:51 (*47)	1:3	N/A	2.8:5.9†
Shin [32]	2012	Seoul, Korea	698:129 (*108)	N/A	N/A	2.0:0.9†
Present study	2014	Kyoto, Japan	168:140	11:5	1:2	7.1:5.0

N/A, not applicable.
*The number of lateral segment.
†The number of lateral segment graft.