Disclosure Statement

The authors have no conflict of interest.

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Table 1. Posttransplant course

POD	Renal replacement/ water removal, ml	Ascites, ml	Body weight, kg
1	CHDF/420	385	54.1
2	CHDF/1,290	122	54.5
3	CHDF/1,010	278	54.1
4	HD/2,000	191	53.1
5	none	65	52.5
6	none	none	53.6
7	HD/1,800	none	52.8

POD = Postoperative day; HD = hemodialysis.

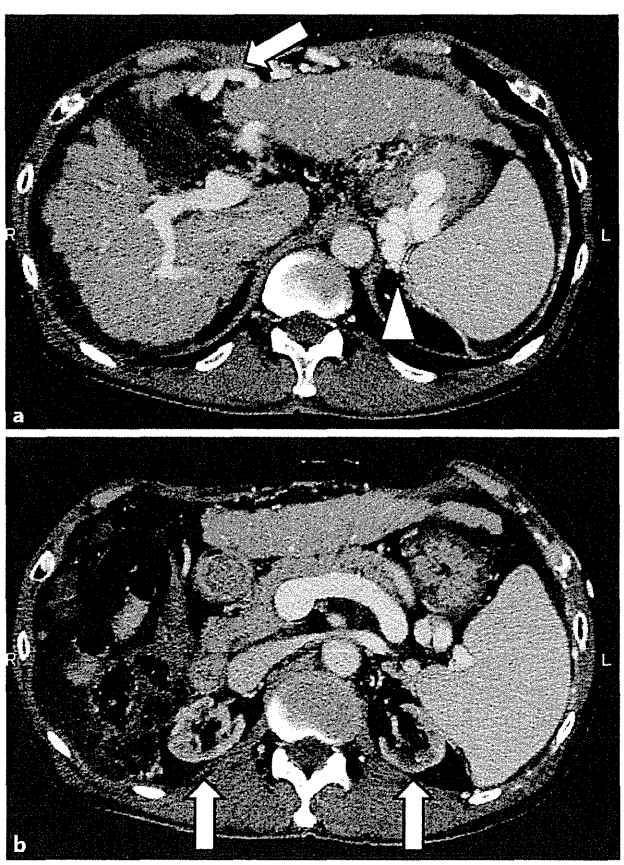

Fig. 1. Pretransplant computed tomography scan. **a** The liver was cirrhotic and had no definite hepatocellular carcinomas. Moderate ascites, recanalized paraumbilical vein (arrow), gastric varices (arrowhead) and splenomegaly were identified. **b** The bilateral kidneys were very atrophic (arrows).

LETTER FROM THE FRONTLINE

Fairly Rare Spontaneous Disappearance of a Hepatic Artery Aneurysm Following Living Donor Liver Transplantation

Received April 8, 2013; accepted May 3, 2013.

TO THE EDITORS

The patient was a 54-year-old female with end-stage liver disease secondary to primary biliary cirrhosis without a hepatic artery aneurysm. She underwent ABO-incompatible living donor liver transplantation (LT) with a left lobe graft donated by her 58-year-old husband. Preoperatively, the patient underwent plasma exchange several times and rituximab administration for the removal of anti–blood type antibodies. The hepatic artery of the graft (A2/3) was anastomosed end to end to the recipient's left hepatic artery, and A4 was anastomosed to the middle hepatic artery. The cold and warm ischemia times were 67 and 39 minutes, respectively. Postoperative immunosuppression was induced with cyclosporine with mycophenolate mofetil and steroids. Routine follow-up dynamic computed tomography 1 week after LT revealed no hepatic artery aneurysm (Fig. 1A). However, a tiny globular pseudoaneurysm at the distal side of the anastomosis with the thrombus at the main trunk of the portal vein was revealed 2 weeks after LT (Fig. 1B). Coumadin administration at 2 mg/day was initiated, and good control was achieved with an international normalized ratio of 1.5 to 2.0; this prevented the development of the portal thrombus. The pseudoaneurysm developed with a spindle-shaped form 1 month after LT (Fig. 1C), and 2 months after LT, it had a diameter of 7 mm (Fig. 1D). Open surgery for resecting and reconstructing the pseudoaneurysm was planned. However, a computed tomography examination revealed the spontaneous disappearance of the hepatic artery pseudoaneurysm 10 days after a pause in the anticoagulant administration (Fig. 1E). There was no new development of the pseudoaneurysm 1 month after its disappearance.

DISCUSSION

A hepatic artery pseudoaneurysm is an unusual and potentially serious complication that can occur after LT, and it is characterized by a high mortality rate.[1] Early diagnosis and treatment (eg, surgical reconstruction and catheter-based endovascular treatment of stent or coil embolization) are essential for preventing life-threatening hemorrhaging.[2] However, these therapies involve considerable associated risks.[3] The mechanism of hepatic artery pseudoaneurysm development after LT is usually a technical problem involving a bacterial infection and inflammation around the hepatic artery, which cause weakening of the vessel wall.[1-3] In the case reported here, there was excessive local anticoagulant around the hepatic artery anastomosis site, which may have been unable to adapt to any qualitative or quantitative changes because of decreased elasticity and strength. The minute intimal hemorrhage consequently may have induced the development of the hepatic artery pseudoaneurysm.[3,4] In this case, the sequence of anticoagulant treatment, treatment of the portal thrombus, and no surgical resection of the pseudoaneurysm allowed the development of the hepatic pseudoaneurysm and its later disappearance to be observed for the first time. The pseudoaneurysm developed first as a tiny, spindle-shaped form before it became a larger globular body and vanished without a trace. If the anticoagulation had been discontinued earlier as the pseudoaneurysm was developing from the spindle-shaped form, the risk of rupture would have been very low.

Fistouris et al.[4] extensively reviewed their cases and showed that an infectious etiology (particularly bile leakage) may be closely related to the occurrence of pseudoaneurysms.[4] They also showed the major

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The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by our institutional review board.

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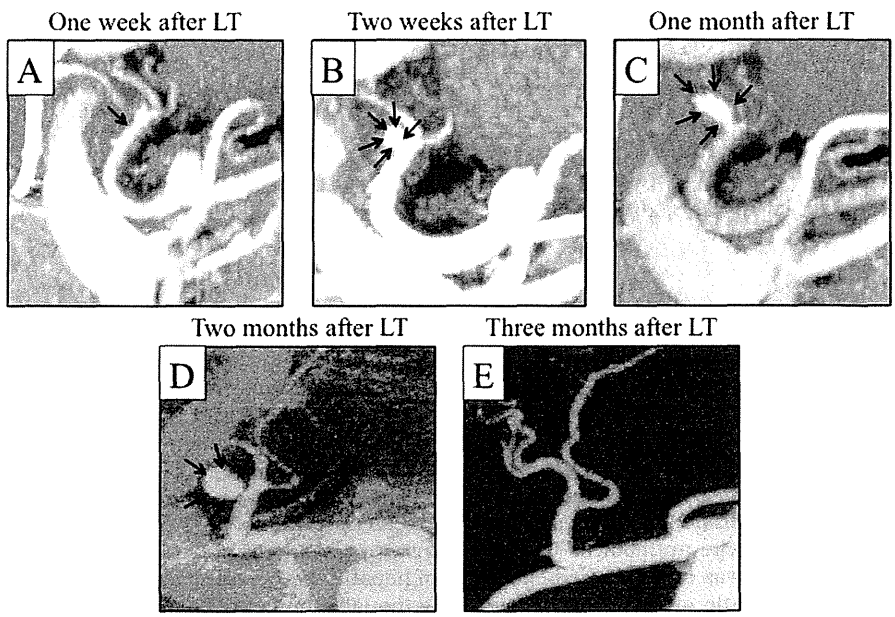

Figure. 1. Development of a hepatic artery pseudoaneurysm as observed with dynamic computed tomography after LT. (A) One week after LT, there was no hepatic artery aneurysm. (B) Two weeks after LT, a tiny globular pseudoaneurysm was evident at the distal side of the anastomosis. (C) One month after LT, the pseudoaneurysm was developing as a spindle-shaped form. (D) Two months after LT, the pseudoaneurysm had grown to 7 mm in diameter. (E) Three months after LT, the hepatic artery pseudoaneurysm spontaneously disappeared (10 days after a pause in the anticoagulant administration).

responsible bacterium to be *Candida albicans* and identified hepaticojejunostomy as one of the risk factors. Molecular biological analysis has shown that tumor necrosis factor α production from endothelial cells, which are often highly expressed in infectious insults, may prevent the fibrotic organization of the internal elastic lamina and aggravate hepatic artery pseudoaneurysms.[5] In light of such evidence, only the manipulation of the anticoagulant series could have clinically caused the pseudoaneurysm in this case because there were no intraoperative and postoperative infectious insults.

Here we report a rare case of a hepatic artery pseudoaneurysm that disappeared after living donor LT. This case suggests that a wait-and-see strategy may be appropriate with careful case-by-case consideration when an anticoagulant treatment is being used.

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D-MELD as a Predictor of Early Graft Mortality in Adult-to-Adult Living-Donor Liver Transplantation

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Background. Ensuring a good match between donor and recipient is critically important to achieve acceptable graft outcomes after living-donor liver transplantation (LDLT). Our objective was to evaluate the product of donor age and Model for End-stage Liver Disease score (D-MELD) as a predictor of graft survival after LDLT.

Methods. We retrospectively evaluated the records of 355 adults who underwent LDLT for chronic liver disease and explored the relationship between D-MELD and graft outcome.

Results. High MELD score and advanced donor age were significantly associated with graft survival; D-MELD had the strongest association with in-hospital mortality. Receiver operating characteristic curve analysis showed that a D-MELD score of 462 had the highest sensitivity for predicting in-hospital mortality. Patients were allocated to three groups based on D-MELD (Class A [≤449; n=142], Class B [450–899; n=163], and Class C [≥900; n=50]) and were found to have stratified cumulative 2-year graft survivals of 94.1%, 85.3%, and 63.1%, respectively ($P<0.01$). Although D-MELD Class C patients had larger graft volume-to-standard liver volume ratio ($P<0.01$) and received right lobe grafts more often ($P<0.01$), they still exhibited significantly higher rates of primary graft dysfunction ($P<0.01$) and in-hospital mortality ($P<0.01$). Outcomes in D-MELD Class C were significantly worse in hepatitis C–positive patients ($P<0.05$).

Conclusions. The D-MELD score is a simple and reliable predictor of early graft survival that assists the matching of donors and recipients in LDLT in adults.

Keywords: Living-donor liver transplantation, Donor age, MELD, Primary graft dysfunction.

(*Transplantation* 2013;00: 00–00)

There are a number of factors that influence graft outcome after liver transplantation (*1–3*). In living-donor liver transplantation (LDLT), these include poor recipient condition, smaller graft volume (GV), and advanced donor age (*4–7*). When planning a procedure, however, these factors need to be considered together rather than individually (*4*). The decision to undertake LDLT can be difficult when the living-donor graft is marginal and the recipient is judged to be at high risk of complications.

In the United States, the Model for End-stage Liver Disease (MELD) score has been used to quantify the severity of recipient disease objectively and to prioritize organ allocation in patients awaiting deceased-donor liver transplantation (DDLT) (*8*). In recognition that donor factors also affect outcome after liver transplantation, Halldorson et al. used the product of MELD score and donor age (D-MELD) to predict outcome after DDLT and reported that a D-MELD score in excess of 1600 was associated with poor graft outcome (*3*). In LDLT, there is, as yet, no simple means of predicting graft survival during donor–recipient matching, although this is a critical step in achieving the most favorable graft outcomes.

We hypothesized that the D-MELD score could also be used to quantify an incremental gradient of risk of graft dysfunction and mortality after LDLT.

RESULTS

Factors Associated with Short-term Graft Survival

Factors that could be evaluated preoperatively to predict short-term outcome after LDLT are shown in SDC 1

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T.I. participated in the study concept and design and drafting of the article. D.I., T.Y., and K.S. participated in the critical revision of the article. H.W. participated in the statistical analyses. Y.Y., M.N., T.I., and Y.B. participated in the data collection. Y.M. participated in the final approval of the article.

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(http://links.lww.com/TP/A890). Univariate analyses showed that MELD score ≥20 (72.1% vs. 89.7% for 2-year graft survival; $P<0.01$) and donor age ≥45 years (77.8% vs. 89.0%; $P<0.01$) were significantly associated with poor graft outcome. The cutoff values for MELD, donor age, and ischemic time were obtained using receiver operating characteristic curve analysis. GV/standard liver volume (SLV) did not have significant impact on graft survival. Multivariate analyses also showed that MELD score ≥20 (hazard ratio, 2.9; 95% confidence interval, 1.6–5.2; $P<0.01$) and donor age ≥45 years (hazard ratio, 4.8; 95% confidence interval, 2.2–5.3; $P<0.01$) were independently associated with reduced graft survival.

Significance of D-MELD for Predicting In-Hospital Mortality

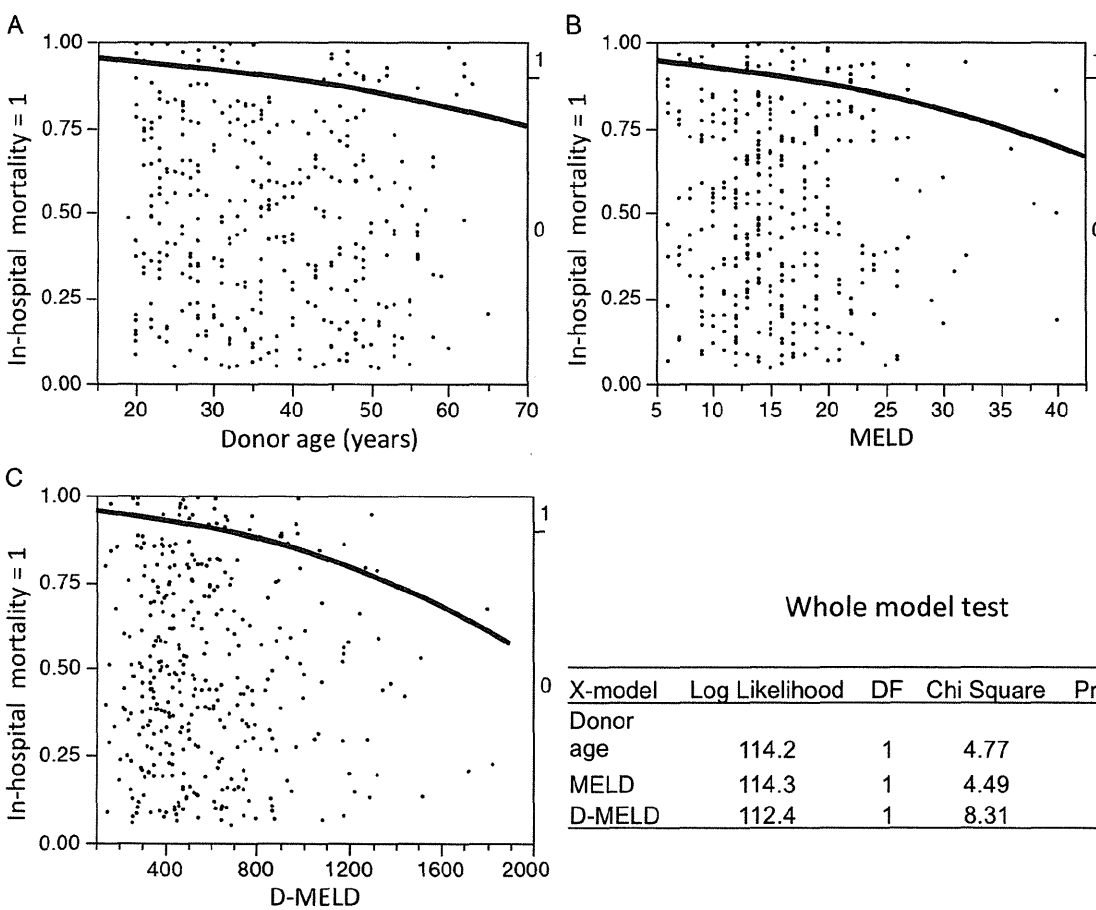
Cumulative logistic probability plots showed that there were significant relationships between graft survival and donor age, MELD score, and D-MELD score, with downward sloping fit lines (Fig. 1A–C). D-MELD (χ^2=8.31; Prob>χ^2= 0.004) demonstrated the strongest association: there was a progressively diminishing probability of graft survival as D-MELD increased. Receiver operating characteristic curve analysis showed that a D-MELD score of 462 was the optimal cutoff for discriminating in-hospital mortality after LDLT. The area under the receiver operating characteristic curve for this value was 0.65 (see **SDC 2,** http://links.lww.com/TP/A890).

Classifying D-MELD

The mean D-MELD score was 583±299 (median, 506; range, 138–1824; Fig. 2A). Guided by the receiver operating characteristic curve analysis and Kaplan–Meier method (*3*), we chose cutoff values of 450 and 900 to best differentiate survival and therefore define D-MELD classes: Class A (≤449; n=142; 40.0%), Class B (450–899; n=163; 45.9%), and Class C (≥900; n=50; 14.1%). The mean D-MELD score was 334±79 in Class A, 623±123 in Class B, and 1160±231 in Class C, respectively. Kaplan–Meier survival curves were used to evaluate graft survival for each D-MELD class. The cumulative 2-year graft survival rate was 94.1% in Class A, 85.3% in Class B, and 63.1% in Class C. The differences between the classes were all statistically significant ($P<0.01$; Fig. 2B).

Comparison between D-MELD Classes

Clinical parameters, including recipient and donor operative and postoperative, were compared for each D-MELD class. D-MELD Class C was characterized by more advanced



Whole model test

X-model	Log Likelihood	DF	Chi Square	Prob>ChiSq
Donor age	114.2	1	4.77	0.029
MELD	114.3	1	4.49	0.034
D-MELD	112.4	1	8.31	0.004

FIGURE 1. Logistic regression analysis of (A) MELD score, (B) donor age, and (C) D-MELD score plotted against graft survival. Although all curves demonstrated a significant relationship, a steeper curve was seen with D-MELD, indicating a stronger relationship.

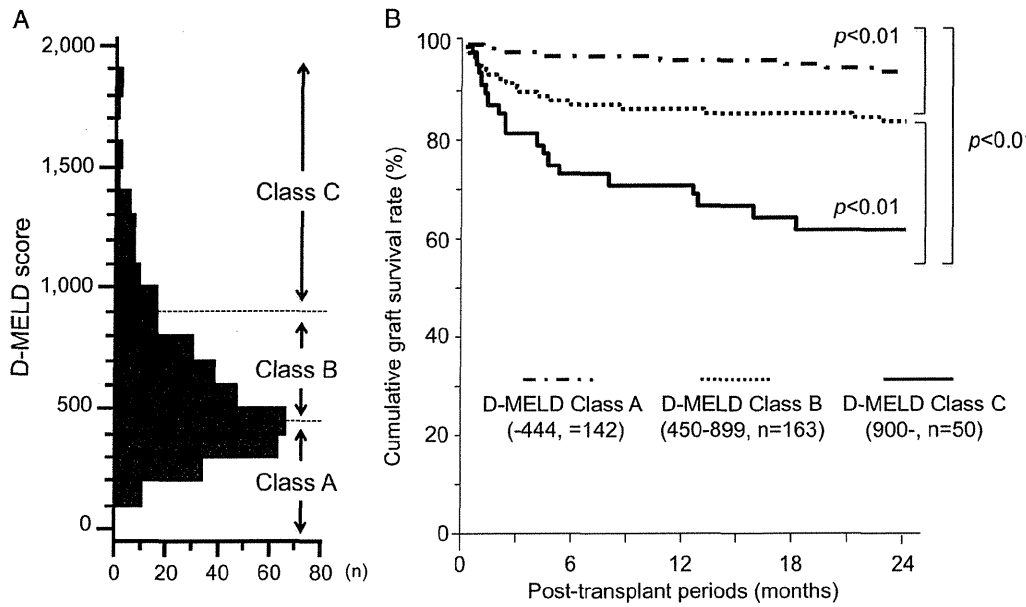


FIGURE 2. A, distribution of LDLT by D-MELD scoring. B, cumulative graft survival rate by D-MELD Classes A, B, and C.

liver disease, comprising a larger proportion of Child–Pugh Class C patients ($P<0.01$), significantly higher MELD scores ($P<0.01$), younger age of recipients ($P<0.01$), and increased use of right lobe grafts ($P<0.01$) procured from significantly older donors ($P<0.01$) with larger GV ($P=0.03$) and larger GV/SLV ($P<0.01$) compared with the other classes (Table 1). As a consequence of the increased use of right lobe grafts in D-MELD Class C patients ($P<0.01$), cold and warm ischemic times were significantly prolonged ($P<0.01$ for both). Intraoperative blood loss was also significantly greater in D-MELD Class C patients. Postoperatively, there were no significant differences in the rates of acute rejection or vascular and biliary complications; however, advanced D-MELD class was characterized by an increased incidence of primary graft dysfunction with bacterial sepsis and in-hospital mortality.

Hepatitis C Subpopulation

Patients were also subdivided based on their hepatitis C status: 168 (47.3%) were hepatitis C virus (HCV) positive. In HCV-positive subgroups, the cumulative 2-year graft survival rate was 93.5% in D-MELD Class A (n=80), 84.9% in Class B (n=6), and 44.2% in Class C (n=19), respectively. Six of the 19 HCV-positive D-MELD Class C patients (31.5%) had primary graft dysfunction and 3 (15.7%) had aggressive hepatitis C recurrence. The graft survival rate in D-MELD Class C was significantly lower compared with the other classes ($P<0.01$ for both; Fig. 3A).

In HCV-negative subgroups, the cumulative 2-year graft survival rate was 94.3% in D-MELD Class A (n=57), 86.7% in Class B (n=93), and 73.5% in Class C (n=31). The primary disease without HCV included primary biliary cirrhosis (n=57), hepatitis B (n=37), nonalcoholic steatohepatitis (n=22), primary sclerosing cholangitis (n=15), alcoholic cirrhosis (n=13), biliary atresia (n=12), autoimmune hepatitis (n=7), giant hemangioma (n=2), hemangioendothelioma (n=2), Wilson disease (n=2), secondary biliary cirrhosis (n=2), and others (n=16). The graft survival rate in D-MELD Class C was significantly lower compared with the other classes ($P<0.01$ for both). The cumulative graft survival rate was significantly inferior in hepatitis C–positive D-MELD Class C patients than those who were HCV negative ($P=0.04$; Fig. 3B).

DISCUSSION

The principal utility of the D-MELD score is to improve the clinical decision-making process when considering high-risk donor–recipient combinations for DDLT (*3*). Although the graft properties and selection processes were quite different, our study shows that D-MELD can also be used to evaluate the risk of in-hospital mortality after LDLT in certain donor–recipient combinations. The rationale for evaluating the risk of in-hospital mortality after LDLT is to inform the decision about whether the risks of major hepatectomy in a healthy donor outweigh the potential benefits to the recipient (*9, 10*); it is essential to ensure the optimal outcome for donors and recipients.

Our findings show that D-MELD can be used as a tool to inform risk-benefit decisions when planning LDLT in various donor–recipient combinations. For example, if the MELD score of a recipient with decompensated cirrhosis is 15 and the donor is 52 years old, the D-MELD score is 780, indicating an acceptable expected 24-month graft survival rate of 85%. If the MELD score of a recipient is 28 and the donor is 52 years old, the D-MELD score is 1456 and expected 24-month graft survival is 63%. If the same recipient had cirrhosis due to hepatitis C, the expected 24-month graft survival would be less than 50%. In the last scenario, we think LDLT is not justified or would need to be performed after very extensive discussion with the donor and recipient.

GV of the grafts, selected under institutional guideline and bias, did not appear to have a significant influence on

TABLE 1. D-MELD classes and operative and postoperative characteristics of donors and recipients

D-MELD	Class A (≤449; n=142)	Class B (450–899; n=163)	Class C (≥900; n=50)	*P*
D-MELD score	334±79	623±123	1,160±231	<0.01
Recipient age (years)	53.5±10.7	53.1±11.7	45.3±11.4	<0.01
Child–Pugh Class C (%)	64 (45.1)	118 (72.4)	45 (90.0)	<0.01
MELD score	11.7±3.5	16.7±4.0	24.3±6.5	<0.01
Total bilirubin (mg/dL)	3.0±3.1	6.8±7.2	16.4±13.2	<0.01
Prothrombin time INR	1.4±0.2	1.5±0.3	1.9±0.5	<0.01
Creatinine (mg/dL)	0.7±0.3	0.7±0.3	1.3±1.6	<0.01
Hepatitis C	80 (56.4)	69 (42.3)	19 (38.0)	0.02
Hepatocellular carcinoma	93 (53.5)	68 (39.1)	13 (7.5)	<0.01
Donor age (years)	30.3±9.7	38.9±9.9	48.7±6.9	<0.01
Left lobe graft (%)	101 (71.1)	94 (57.6)	17 (34.0)	<0.01
GV (g)	466±103	485±106	511±108	0.03
GV/SLV (%)	40.3±8.4	42.3±8.1	44.4±8.5	<0.01
Blood type incompatibility (%)	8 (5.6)	8 (4.9)	2 (4.0)	0.89
Splenectomy (%)	70 (49.3)	95 (58.3)	29 (58.0)	0.25
Cold ischemic time (min)	84±56	94±52	123±77	<0.01
Warm ischemic time (min)	39±10	43±15	44±12	<0.01
PVP at laparotomy (mmHg)	23.2±5.9	25.3±5.4	25.1±26.2	<0.01
PVP at closure (mmHg)	17.0±4.0	17.1±4.8	17.1±3.5	0.94
HA flow (mL/min)	112±78	122±122	117±55	0.10
PV flow (L/min)	1.6±0.6	1.7±0.7	1.7±0.6	0.09
Operative time (min)	789±178	810±117	843±216	0.17
Blood loss (L)	4.2±3.6	9.3±20.1	11.8±16.7	<0.01
Acute rejection (%)	22 (15.5)	19 (11.7)	7 (14.0)	0.61
Biliary stenosis (%)	31 (21.8)	30 (18.4)	11 (22.0)	0.72
HA thrombosis (%)	0 (0.0)	2 (1.2)	1 (2.0)	0.32
PV thrombosis (%)	3 (2.1)	4 (2.5)	1 (2.0)	0.97
CMV antigenemia (%)	22 (15.5)	34 (20.9)	15 (30.0)	0.08
Bacterial sepsis (%)	10 (7.1)	18 (11.0)	12 (24.0)	<0.01
Total bilirubin on day 14 (mg/dL)	4.9±5.9	7.1±8.4	14.0±10.6	<0.01
Primary graft dysfunction (%)	5 (3.5)	20 (12.3)	18 (36.0)	<0.01
Early graft mortality (%)	5 (3.5)	18 (11.0)	13 (26.0)	<0.01
Mean hospital stay (days)	35.9±20.1	42.9±32.1	56.1±41.2	<0.01

CMV, cytomegalovirus; HA, hepatic artery; INR, international normalized ratio; PV, portal vein.

short-term graft survival in our cohort, although this association has been reported before (*4*). It just does not mean a graft with GV/SLV<20% works. Therefore, we only used the product of donor age and MELD score to calculate D-MELD, in accordance with the method described for DDLT (*3*). To the best of our knowledge, all institutions at which LDLT is performed have lower limits for donated GV and remnant donor liver volume that include a safety margin: GV/SLV >30% to 40% or graft recipient weight ratio >0.6 to 0.8 for transplanted GV and remnant donor liver volume >30% to 35% of total liver volume (*4–7, 11–13*). Our finding that GV was not among the risk factors for in-hospital mortality indicates that these lower limits are effective (*4–7*). We have previously shown that use of a larger GV as a partial LDLT graft did not confer a survival advantage if GV exceeded 35% (*14*). Therefore, with careful donor and recipient selection for LDLT, in which an appropriately sized graft under selection bias with institutional cutoff for lower limit without steatosis is transplanted without a prolonged ischemic time, it is logical that donor age should be the most important contributing factor to graft outcome (*4*). Nevertheless, regarding the impact of graft size on graft survivals especially for sick patients, larger multicenter studies, with different institutional cutoffs for LDLT donors, should confirm or disprove the role of graft size in prognostic tools.

In the previous studies of D-MELD in DDLT, the cutoff for donor–recipient combinations with the highest risk for graft loss was 1600 to 1700 compared with 900 in our analysis (*3, 15, 16*). The balance of ethical issues that need to be considered in LDLT, which apply differently to DDLT, could explain this difference. For example, DDLT may be indicated for recipients in very poor condition and there are no concerns about risk to the donor. In LDLT, donation should be performed only if the risk to the donor is justified by the expectation of an acceptable outcome for the recipient, as stated by the Vancouver Forum in 2005 (*17*). A limit to the age of donors may also be a contributing factor: although donations for LDLT are not usually accepted from

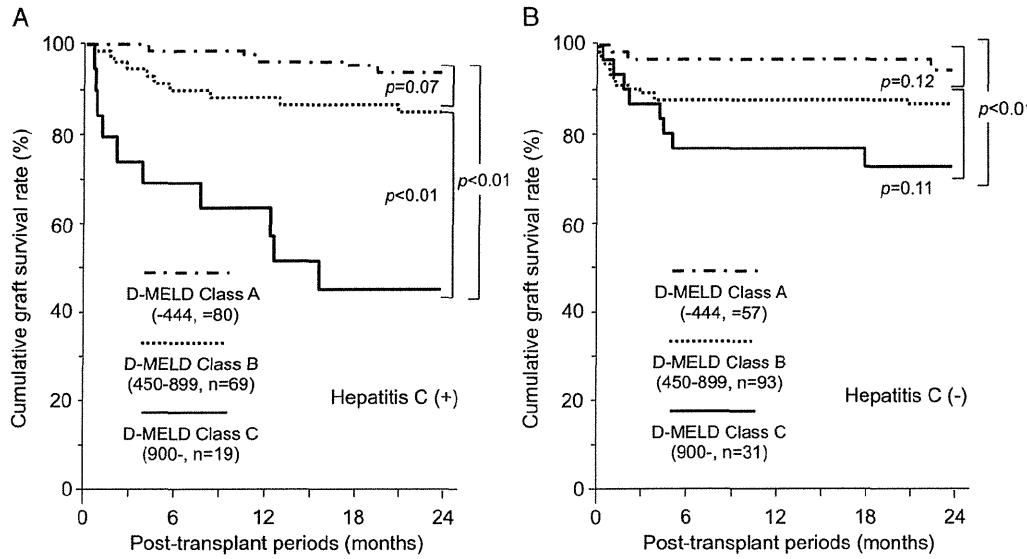


FIGURE 3. Cumulative graft survival rate by D-MELD classes in (A) hepatitis C patients and (B) non–hepatitis C patients.

those aged over 65 years due to increased risks to donor and recipient, this does not necessarily apply in DDLT (*18*).

Regarding recipient factors, it is well recognized that disease severity is the most significant factor that determines graft outcomes (*6, 7*). Although MELD score, Child–Pugh score or grade, or clinical symptoms and signs such as intractable ascites or encephalopathy have been used to reflect the manifestation of severe hepatic disease in these reports, only MELD score has the precision to accurately predict outcome. Another advantage is that D-MELD can also be calculated before surgery, whereas some risk stratification systems rely on perioperative or postoperative data (*3*). Thus, we think D-MELD is made from donor age and MELD score, both of which are continuous variables known before LDLT and significant factors for graft outcomes.

Comparison of patients allocated to the three D-MELD Classes was also illuminating. We found that recipients in D-MELD Class C were more likely to have portal venous hypertension at laparotomy than the other classes. As a consequence of this observation, and the advanced age of donors and poorer condition of the recipients, more right lobe grafts were used. Although postoperative portal venous pressures (PVP) were comparable with the other groups, the incidences of primary graft dysfunction, bacterial sepsis, and graft loss were still greater. Patients with primary graft dysfunction, characterized by hyperbilirubinemia, tend to have bacterial sepsis, and the finding is consistent with a previous report (*5, 19*). This finding should guide clinical practice, as the influences of advanced donor age and poor recipient condition could not be overcome by selecting larger GVs or by intentional decompression of portal hypertension (*5*). Thus, to achieve acceptable outcomes in adult-to-adult LDLT for chronic liver disease, a reasonable approach would be to undertake surgery in patients with D-MELD scores<900. Given our findings, it can be argued that LDLT is only indicated for patients with a D-MELD score in excess of 900 if they are HCV negative.

The negative impact of HCV infection on graft outcomes in D-MELD Class C patients is a particularly important finding and concurs with previous reports (*21, 24*). Onaca et al. found that HCV-positive patients with a MELD score in excess of 25 had significantly worse graft survival (*20*). The negative influence of advanced donor age in HCV-positive recipients has also been reported (*21, 22*). In LDLT, Yoshida et al. found that both positive HCV status and advanced donor age were significant risk factors for graft loss in patients with high MELD scores (*22*). As D-MELD score includes donor age, it follows that it effectively predicts outcome after LDLT in HCV-positive patients. Unless results can be improved, high-risk combinations with D-MELD >900 especially in HCV patients should probably not undergo LDLT.

The main limitation of this study is that data were collected and analyses were performed retrospectively. Reports from other centers are also necessary to help generalize our findings. Further studies with larger numbers of patients are required to characterize the very high-risk subgroup of patients in D-MELD Class C.

In conclusion, D-MELD score is a useful predictor of in-hospital mortality, enabling simple and reliable evaluation of donor–recipient matching for LDLT in adults.

MATERIALS AND METHODS

Patients

We reviewed the records of 358 adults with chronic liver disease who underwent LDLT at Kyushu University Hospital, Japan, between July 1998 and May 2013. We did not include patients with acute liver failure in this study, as their clinical features may have introduced confounding variables into our analysis (*23*). Two patients who underwent auxiliary LDLT and one patient who underwent dual graft LDLT were excluded; therefore, 355 patients were included in the analysis.

MELD score was calculated without exception points, and D-MELD score was calculated as the product of donor age and laboratory-based MELD score (capped at 40 years) as described previously by Halldorson et al. (*3*).

The primary outcome was graft survival measured in terms of in-hospital mortality and 2-year cumulative graft survival.

Graft Selection and Surgical Procedures

Grafts were selected as described previously (*24*). Left lobe grafts were used as the primary graft type if the desired GV/SLV was ≥35%. Right lobe grafts were used if the simulated GV/SLV of the left lobe graft was <35% and the donor's remnant liver volume was ≥35%. Other factors, such as anatomical variations and recipient condition, were also taken into account to achieve the optimal outcome for each patient.

The surgical procedures used in donors and recipients have been described previously (*25–27*). Briefly, procured living-donor grafts were preserved in University of Wisconsin solution (Viaspan; DuPont, Wilmington, DE). After recipient hepatectomy, the grafts were transplanted in a piggyback fashion. Arterial reconstruction was performed under a microscope. Splenectomy was usually performed to address high PVP as described previously (*27*). Major spontaneous portosystemic shunt ligation was also performed (*28*). The reasons for aggressive inflow control with favorable outcomes were described before (*14*). Biliary reconstruction was performed by duct-to-duct biliary anastomosis whenever possible.

Posttransplantation Medical Care

The basic immunosuppression protocol consisted of tacrolimus or cyclosporine with mycophenolate mofetil and steroids, gradually tapered to calcineurin monotherapy within 1 year of LDLT (*14*).

Primary graft dysfunction was defined as graft insufficiency with possible in-hospital mortality, without technical, anatomical, immunologic, or hepatitis-related issues (*5*). Graft insufficiency was defined as hyperbilirubinemia (total serum bilirubin ≥20 mg/dL), occurring at least 7 days after surgery and persisting for ≥7 consecutive days (*5*). Bacterial sepsis was defined as the isolation of bacteria other than common skin contaminants from a single blood culture within 3 months of transplantation, along with clinical symptoms, including pyrexia, shivering, dyspnea, altered mental status, tachycardia, or hypotension. In-hospital mortality was defined as graft loss during the hospitalization for LDLT surgery, and the mean period from LDLT to in-hospital mortality (n=36) was 0.17±0.11 months.

Statistical Analysis

Variables were analyzed using the chi-square test for categorical values or the Mann–Whitney test for continuous variables. Cumulative survival analyses were determined using the Kaplan–Meier method with the log-rank test and Cox proportional hazards multivariate model. Values are expressed as mean±SD. Only statistically significant variables were used in multivariate analyses. $P<0.05$ was considered statistically significant.

Cumulative probability plots for logistic regression were performed by plotting in-hospital mortality of LDLT (y-axis) as the categorical response against the continuous variables (x-axis) including MELD score, donor age, and D-MELD score. Receiver operating characteristic curve analysis was also performed to identify the optimal cutoff of D-MELD score for discriminating in-hospital mortality. All statistical analyses were performed using JMP version 7.0.1 (SAS Institute, Cary, NC).

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CASE REPORT

Renoportal anastomosis in right lobe living donor liver transplantation: report of a case

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Abstract End-stage liver disease is often accompanied by thrombosis of the portal vein and the formation of splanchnic collateral vessels. Successful liver transplantation in such situations is more likely if the surgeon uses a strategy to establish a graft inflow. A 59-year-old male with a decompensated liver secondary to idiopathic portal hypertension underwent living donor liver transplantation (LDLT) using a right lobe liver graft donated from his son. His portal venous trunk was atrophied and a splenorenal shunt drained the mesenteric venous flow into the systemic circulation. LDLT was performed with renoportal anastomosis (RPA) using his right internal jugular vein as an interposed venous graft, without dissecting the collateral vessels. Although he developed temporary functional hyperbilirubinemia, he was discharged from the hospital 23 days after LDLT. This case suggests that RPA is a useful technique to manage patients with an obstructed portal vein and a splenorenal shunt.

Keywords Living donor liver transplantation · Portal vein thrombosis · Splenorenal shunt

Abbreviations

LDLT	Living donor liver transplantation
LRV	Left renal vein
PV	Portal vein
RPA	Renoportal anastomosis
SRS	Splenorenal shunt

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Introduction

End-stage liver disease is often accompanied by thrombosis or atrophy of the portal vein (PV) or inferior vena cava, thus resulting in the formation of splanchnic collateral vessels [1, 2]. Although such complications are considered to be difficult to overcome, recent improvements in surgical techniques have allowed these conditions to be operable [2, 3]. Recent innovations in the surgical techniques for thrombosis or atrophy of the PV include portal venous thrombectomy, resection and reconstruction of the atrophied PV, or placement of a graft to bridge the mesenteric vein and the graft PV [4]. Renoportal anastomosis (RPA) is a strategy to establish a portal inflow in patients with an occluded portal inflow in patients undergoing liver transplantation and was first described by Kato et al. [3]. Despite the rationale for this technique, anastomosis has been reported in very few cases. This report presents a case in which RPA was performed using the patient's internal jugular vein during right lobe living donor liver transplantation (LDLT). The report also discusses the relevance of this technique to LDLT and examines the feature of each vein graft used in RPA.

A case report

A 59-year-old male was referred to our hospital for possible LDLT because of a decompensated liver. He was negative for viral hepatitis markers, including hepatitis B

and hepatitis C, or immune-mediated hepatic disorders, and was thought to have cryptogenic cirrhosis of an unknown origin. He had a history of ruptured esophageal varices that were treated by endoscopic sclerotherapy and subsequent partial splenic embolization. His hepatic profiles was: total bilirubin 2.9 mg/dl, albumin 2.0 g/dl, aspirate aminotransferase 44 IU/l, alanine aminotransferase 22 IU/l, creatinine 0.9 mg/dl, international normalized ratio 1.71, ammonia 100 μg/dl, white blood cell count 5,500 cells/μl, hemoglobin 13.4 g/dl, and platelet count 6.8 × 10^4 cells/μl. His Child-Pugh score was 11 (Grade C), and his model for end-stage liver disease score was 16. Abdominal computed tomography (CT) showed atrophy of the PV, an active splenorenal shunt (SRS) draining from the splenic vein into the left renal vein (LRV) via the left adrenal vein, and a deformed spleen because of the prior partial splenic embolization (Fig. 1). The donor was the 31-year-old son of the patient and had the identical blood type. He had no prior medical problems and his liver function tests were normal.

LDLT was started with the patient placed in a supine position with neck extension. A longitudinal incision was created on the right side of the neck and was deepened at the medial border of the sternocleidomastoid muscle. The right internal jugular vein was identified, taped, isolated from the surrounding tissue, and then removed. The length of the obtained internal jugular vein was 8 cm. The abdomen was opened via a bilateral subcostal incision with a midline extension. Total hepatectomy was performed as described elsewhere [5].

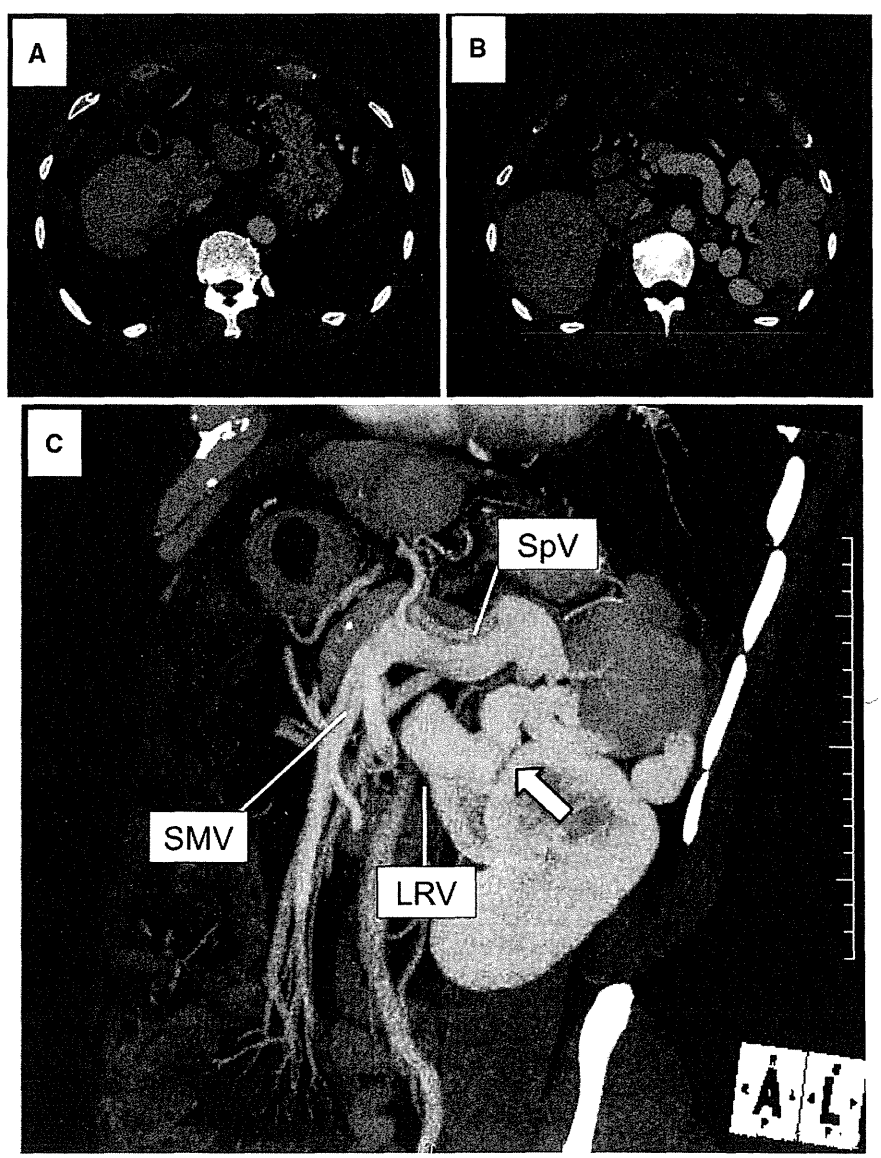

Fig. 1 Abdominal CT scans showing (**a**) atrophy of the liver with minimum portal flow and (**b**) a highly active splenorenal shunt with a deformed spleen. **c** Maximum intensity projection image. The *white arrow* indicates the junction of the splenorenal shunt into the LRV. *SMV* Superior mesenteric vein, *LRV* left renal vein, *SpV* splenic vein

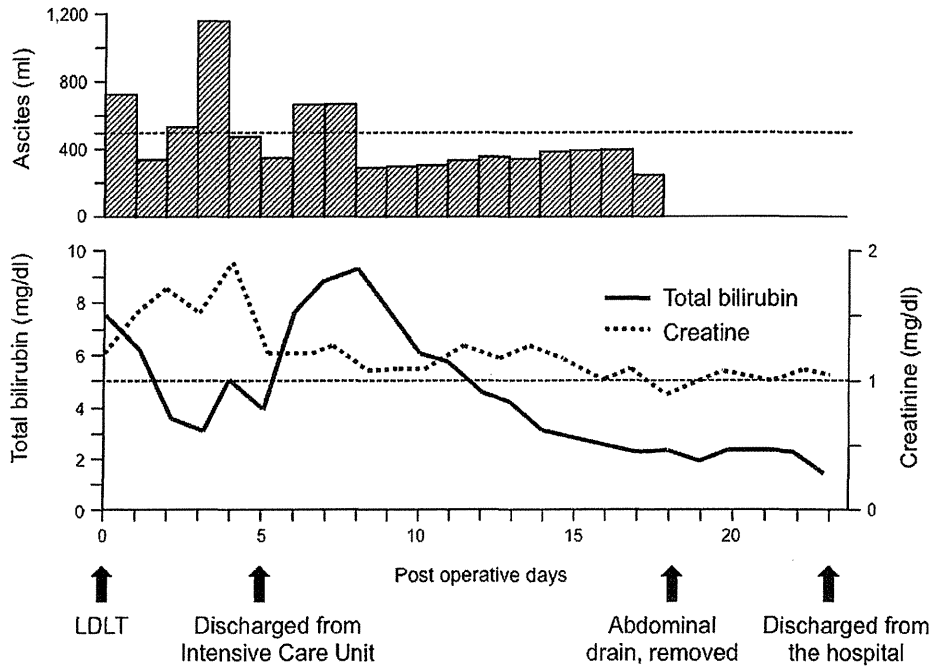

Fig. 2 Postoperative course. The patient showed a temporary increase in the output of ascites and hyperbilirubinemia

The right lobe LDLT graft donated from his son weighed 580 g, representing 44.1 % of the calculated standard liver volume. The graft had a right hepatic vein and a V5 vein for venous drainage. The opening of the V5 was anastomosed to the manually dilated explanted PV, which was connected to the right hepatic vein in a side-to-side fashion, to enable one-step venous anastomosis. A venovenous bypass was used for circulatory stabilization during the anhepatic phase.

The second portion of the duodenum was mobilized from the retroperitoneum and the LRV was identified and controlled with a tape, clamped, and divided. The supra- and infra-hepatic vena cava was clamped and total hepatectomy was performed. The right lobe graft was placed in the body and venous anastomosis between the conduit of the graft venous system and the vena cava was performed using continuous 5-0 PDS sutures. The right internal jugular vein was anastomosed to the LRV using continuous 6-0 PDS sutures coated with growth factor. The interposed jugular vein was then connected to the grafted PV. Reperfusion was initiated and the circulatory system remained stable. The cold, warm and anhepatic times were 150 min, 44 min and 284 min, respectively. Portal venous pressure at the end of surgery was 24 mmHg. The total surgical time and operative blood loss were 819 min and 6.3 L, respectively.

The patient's post-transplant course is shown in Fig. 2. Although the patient temporarily showed an increased output of ascites and hyperbilirubinemia, he was discharged from the hospital on postoperative day 23 with normal liver function tests. CT showed a patent smooth portal venous flow from the persistent large SRS scans at 4 months after surgery (Fig. 3).

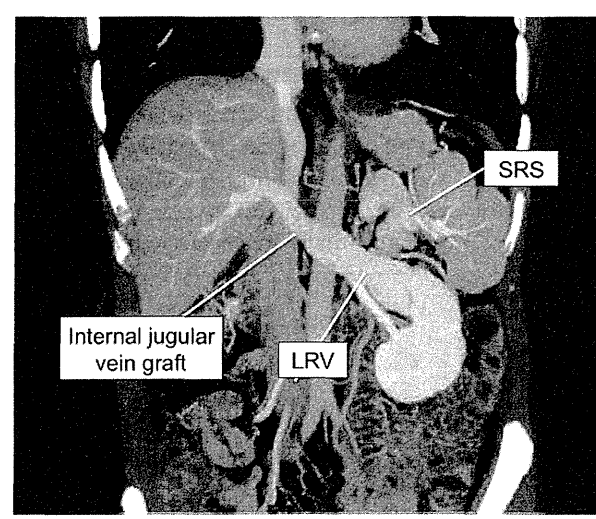

Fig. 3 Maximum intensity projection image taken 4 months after transplantation. *LRV* Left renal vein, *SRS* splenorenal shunt

Discussion

Thrombectomy or patch plasty of the PV followed by direct anastomosis between the graft and recipient PV may be possible for most patients with thrombosis or atrophy of the PV [4]. However, establishing an appropriate portal flow capacity is essential to prevent re-thrombosis of the

anastomosed PV or graft dysfunction because of the decreased portal inflow [5]. The obstruction of these vessels is necessary to prevent the occurrence of steal phenomenon in patients with major porto-systemic shunt vessels. However, the ligation of such large and fragile shunt vessels in a deep surgical field is technically difficult and may cause significant bleeding, morbidity or mortality [6].

RPA offers one solution to establish graft inflow in patients with a large SRS and either an occluded or markedly reduced portal inflow, using an anomalous shunt [7]. Marubashi et al. [8] first reported three patients who underwent this technique during LDLT. Moon et al. [9] used a prosthetic graft in an end-to-side fashion to establish a renoportal connection, and thus achieved an excellent graft function. However, a prosthetic graft has the disadvantage of its thickness and rigidity, and the patients must receive aspirin daily to prevent prosthetic graft thrombosis. Furthermore, they have the risk of developing prosthetic infection caused by immunosuppressant. Table 1 is the respective data of the variations in vein grafts. The internal jugular vein is used in this department. The removal of the internal jugular vein does not have any harmful effects on the central nervous system. An external iliac vein is usually 7–8 cm and shorter than the internal jugular vein. The main advantage of creating a RPA is that manipulation or dissection around the large and fragile shunt vessels is unnecessary. Moreover, an adequate blood flow into the graft is guaranteed, which drains from the mesenteric and left renal system. The PV flow/graft volume ratio in this case was 2.90 ml/min, which is considered to be an acceptable score.

However, this technique does have some disadvantages in comparison to direct portal anastomosis. First, an excessive inflow caused by the addition of a left venous return into a graft is possible after LDLT, in which a smaller graft is implanted. Graft dysfunction caused by an excessive portal inflow has been called small-for-size syndrome, and it is characterized by the production of persistent ascites and prolonged hyperbilirubinemia [10]. The present patient's maximum output of ascites was 1 L on postoperative day 4 and his maximum total bilirubin concentration was 9.4 mg/dl on postoperative day 8. Although these values do not necessarily indicate small-for-seize graft syndrome, the post-operative clinical characteristics of the present recipient, including a model for end-stage liver disease score of 16 and a sufficient graft volume/standard liver volume ratio of 44.1 %, are consistent with graft over-perfusion syndrome.

Possible congestion of the left kidney may be another disadvantage of RPA. The serum creatinine levels were elevated for 1 week, in the present patient with levels reaching 2.0 mg/dl. However, Lee et al. [11] reported that manipulation of the outflow of the LRV after the ligation of the proximal LRV in patients with a large SRS causes only a temporary renal impairment. These surgical procedures caused a temporary renal impairment in the present case, and the creatinine levels returned to the normal range within 1 month after LDLT.

Finally, the indications for RPA in patients with hepatitis C are considered to be another topic for debate. In our institute, splenectomy is suggested for patients undergoing LDLT for hepatitis C to treat hypersplenism and facilitate

Table 1 Primary disease, graft type, venous graft, and prognosis of patients that underwent RPA during LTx renoportal anastomosis in adult-to-adult living donor liver transplantation

Reference	Primary disease	Liver graft	GV/SLV (%)	GRWR	Vascular graft	Technique	Complications
Marubashi et al. [8]	PSC	Right	56	N/A	Jugular vein	End-to-end	Ascites
	Cryptogenic	Right	49	N/A	Jugular vein	End-to-end	–
	Wilson	Right	38	N/A	Jugular vein	End-to-end	Ascites, pneumonia
Moon et al. [15]	Hepatitis B	Right	46	N/A	Iliac vein	Side-to-end	Ascites
	Hepatitis B, HCC	Right	73	N/A	Iliac vein	End-to-end	–
	Hepatitis B, HCC	Dual graft (2 left lobe)	79	N/A	Iliac vein with IVC	Side-to-end	Cerebral hemorrhage, ascites, decrease of PV flow
	Hepatitis B, HCC	Right	45	N/A	Aorta	Side-to-end	–
	Alcoholic	Right	52	N/A	Aorta + GSV	Side-to-end	–
Moon et al. [9]	Hepatitis B	Right	N/A	1.14	ES-PTFE	Side-to-end	–
Present case	IPH	Right	44.1	0.81	Jugular vein	End-to-end	Ascites, hyperbilirubinemia

ES-PTFE Externally stented polytetrafluoroethylene, *GV* graft volume, *IPH* idiopathic portal hypertension, *N/A* not available, *PSC* primary sclerosing cholangitis, *SLV* standard liver volume, *GRWR* graft-recipient body weight ratio, *IVC* inferior vena cava, *GSV* great saphenous vein

post-transplant interferon treatment for the almost inevitable recurrence of hepatitis C [12]. Persistent hypersplenism in LDLT is a major cause of discounting interferon treatment discontinuation in patients with hepatitis C [12, 13]. Cirrhosis occurs in almost 10–30 % of patients with untreated hepatitis C within 5 years of liver transplantation [14]. Therefore, RPA, in which the spleen stays in place, should not be indicated for patients with hepatitis C. However, RPA may be considered in patients with hepatitis C with severe portal vein stenosis or thrombosis.

In summary, RPA is therefore thought to be a useful option for patients with portal occlusion and large SRS undergoing LDLT, particularly in cases selected based on appropriate indications by carefully considering the limitations of RPA.

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ELSEVIER

Two-step Selection Criteria for Living Donor Liver Transplantation in Patients With Hepatocellular Carcinoma

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ABSTRACT

We have proposed risk factors for tumor recurrence, such as tumor nodule ≥5 cm and des-gamma-carboxy prothrombin ≥300 mAU/mL after living donor liver transplantation (LDLT) for hepatocellular carcinoma (HCC). The aim of this study was to clarify the risk factors for HCC recurrence and mortality within our criteria. We enrolled 152 adult recipients who had undergone LDLT for end-stage liver disease with HCC who met our criteria. The recurrence-free survival rates after LDLT were calculated. Risk factors for tumor recurrence were identified. On univariate analysis, factors affecting recurrence-free survival were pretransplant treatment for HCC, neutrophil-to-lumphocyte ratio (NLR) >4, alpha-fetoprotein ≥400 ng/mL, ≥5 nodules, and bilobar tumor distribution. Multivariate analysis identified that NLR >4 and ≥5 nodules were independent risk factors for tumor recurrence after LDLT ($P = .003$ and $P = .002$, respectively). Two-step selection criteria enable selection of patients who have high-risk of tumor recurrence.

HEPATOCELLULAR CARCINOMA (HCC) is the fifth most common neoplasm worldwide and the third most common cause of cancer-related death. Its incidence is increasing because of the dissemination of hepatitis B and C virus infection.[1] Liver transplantation (OLT), which offers the theoretical advantage of removing both the tumor and the organ that are at risk of developing future malignancy, is an established therapy for HCC in patients with liver cirrhosis.[2] In Asian countries, religious, living donor OLT (LDLT) is a choice for treating such HCC patients after various treatments, such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and/or hepatic resection.[3] We have reported the outcome of LDLT for otherwise unresectable and/or untreatable HCC patients and have proposed 2 risk factors for recurrence-free survival: tumor size >5 cm and des-gamma-carboxy prothrombin (DCP) levels >300 mAU/mL [Kyushu University (KU) criteria].[4,5] More LDLTs for HCC patients have been performed under the KU criteria, thus generating a larger cohort.

The neutrophil-to-lymphocyte ratio (NLR) has recently emerged as a useful prognostic factor for recurrence of several gastroenterologic malignancies. NLR ≥5 has been reported to be a marker of survival in colorectal cancer patients.[6] Recently, it has been demonstrated that a preoperative NLR ≥5 is an adverse predictor of recurrence-free survival for patients undergoing hepatic resection for HCC.[7] Furthermore, an elevated NLR significantly increases the risk of HCC recurrence after OLT.[8,9]

These data have encouraged us to investigate whether NLR could be a risk factor for HCC recurrence, to create new selection criteria for HCC patients undergoing LDLT. The aim of the present study was to clarify the risk factors for HCC recurrence and mortality after LDLT in patients who met the KU criteria and to create new selection criteria.

PATIENTS AND METHODS

Patients

One hundred fifty-eight adult recipients underwent LDLT for end-stage liver disease with HCC at KU Hospital between April 1999 and December 2011. Six recipients did not meet the KU criteria.

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Therefore, 152 recipients were enrolled in the study. In 12 of 152 cases, LDLT was performed for indications other than HCC, and the 12 cases were included in this study as HCC was found on explant pathology. One hundred five recipients underwent pretransplant treatment for HCC, such as RFA, TACE, microwave coagulation therapy, and/or hepatic resection, depending on the recipient's liver function and tumor status. Graft types included left lobe with caudate lobe (LL+C) graft ($n = 95$), right lobe graft without the middle hepatic vein ($n = 52$), posterior segment graft ($n = 4$), and dual graft ($n = 1$). The etiology of liver cirrhosis was hepatitis C ($n = 109$), hepatitis B ($n = 27$), cryptogenic ($n = 6$), and alcohol abuse ($n = 5$), autoimmune hepatitis ($n = 3$), and primary biliary cirrhosis ($n = 2$). Our selection criteria to perform LDLT for HCC patients were as follows: (1) no modality except LDLT available to cure the patients with HCC; (2) no extrahepatic metastasis; and (3) no major vascular infiltration.[4,5] There were no restrictions on tumor size, number of nodules, or pretransplant treatment. Since we proposed the KU criteria, we have not performed LDLT for HCC patients who have both tumor size >5 cm and DCP level >300 mAU/mL.

Pretransplant imaging was used to estimate number of nodules, up-to-seven criteria, and Milan criteria. Alpha-fetoprotein (AFP) and NLR were measured just prior to LDLT.

Donor and Graft Selection

Donors were selected from candidates who hoped to be living donors.[10] Donors were required to be within the third degree of consanguinity with recipients or spouses and to be between 20 and 65 years of age. Eligible donors proceeded to the imaging studies, including chest and abdominal X-rays and 3-mm-slice computed tomography (CT) scans for graft volumetric analysis. Three-dimensional CT was introduced for volumetric analysis and delineation of vascular anatomy. The standard liver weight (SLW) of recipients was calculated according to the formula of Urata.[10] Graft weight (GW) was predicted by CT volumetric analysis. Our decision about graft type for recipients was based on the preoperatively predicted GW-to-SLW ratio. LL+C graft was used when the preoperatively predicted GW-to-SLW ratio was >35%. When GW-to-SLW ratio with LL+C graft was <35% and remnant donor liver volume after right lobectomy was >35%, right lobe graft was used. Posterior segment graft was considered when the donor's vascular anatomy was suitable to take a posterior segment.

Postoperative Management

Immunosuppression was initiated using a protocol based on either tacrolimus (Prograf; Astellas Pharma Inc, Tokyo, Japan) or cyclosporine (Neoral; Novartis Pharma K.K., Tokyo, Japan) with steroid and/or mycophenolate mofetil (MMF; Chugai Pharmaceutical Co Ltd, Tokyo, Japan). A target trough level of tacrolimus was set at 10 ng/mL for 3 months after LDLT, followed by 5 to 10 ng/mL thereafter. A target trough level of cyclosporine was set at 250 ng/mL for 3 months after LDLT, followed by 150 to 200 ng/mL thereafter. Methylprednisolone was initiated on the day of LDLT, then tapered and converted to prednisolone 7 days after LDLT. Prednisolone treatment was tapered and discontinued 6 months after LDLT. MMF was used in 134 recipients and was started at 1 g/d on the day after LDLT, then tapered and discontinued until 6 months after LDLT. A trough level was not measured for MMF.

All patients were followed monthly, and the median follow-up period was 1660 days, with 791 days and 2617 days as the 25th and 75th percentiles, respectively.

Table 1. Risk Factors for Tumor Recurrence: Univariate Analysis

Variables	*n*	Recurrence-free survival (%) 1 y	3 y	5 y	*P* value
Recipient variables					
Gender					
Male	85	91.2	89.8	87.5	.75
Female	67	98.4	88.3	88.3	
Age (y)					
>60	63	91.5	89.2	89.2	.88
≤60	89	96.4	89.9	87.7	
Etiology					
HCV	110	94.3	89.9	88.0	.90
Others	42	94.4	88.1	88.1	
Pretransplant MELD					
<15	119	94.6	88.5	86.9	.44
≥15	33	93.6	93.6	93.6	
Diabetes mellitus					
Yes	37	91.1	86.7	81.3	.43
No	115	95.4	90.2	90.2	
NLR					
>4	22	84.7	72.8	54.6	.0012
≤4	130	95.9	92.0	92.0	
Splenectomy					
Yes	94	93.1	88.5	88.5	.94
No	58	96.4	90.7	88.5	
Calcineurin inhibitor					
TAC	71	95.5	90.4	90.4	.82
CyA	78	93.3	88.6	86.5	
Donor variables					
Gender[a]					
Male	109	96.0	91.3	89.5	.13
Female	42	90.2	84.5	84.5	
Donor age (y)[a]					
>40	37	100	96.4	96.4	.10
≤40	114	92.6	87.2	85.6	
GW-SLW ratio					
<35	32	89.6	81.6	81.6	.19
≥35	120	95.6	91.4	89.8	
Tumor variables					
Pretransplant treatment for HCC					
Yes	105	91.7	84.4	82.6	.01
No	47	100	100	100	
AFP (ng/mL)					
≥400	25	82.9	71.9	62.9	<.0001
<400	127	96.6	92.8	92.8	
Bilobar tumor distribution					
Yes	69	89.0	81.8	79.4	.003
No	83	98.7	95.8	95.8	
Number of nodules					
≥5	38	77.5	63.4	63.4	<.0001
<5	114	100	97.8	96.0	

MELD, Model for End-stage Liver Disease; NLR, neutrophil-to-lymphocyte ratio; TAC, tacrotimus; CyA, cyclosporine; GW, graft weight; SLW, standard liver weight; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; LDLT, living donor liver transplantation; HCV, hepatitis C virus.
[a]A case that used dual graft was excluded.

Post-LDLT Tumor Recurrence and Risk Factors

All patients had abdominal CT scan every 3 months and had chest CT scan and bone scintigraphy every 6 months for 5 years after

Table 2. Risk Factors for Tumor Recurrence: Multivariate Analysis

Variables	Odds ratio	95% CI	*P* value
Number of nodules ≥5	10.3	2.04–77.7	.002
NLR >4	7.73	2.04–26.4	.003
Pretransplant treatment for HCC[a]	4.81	0.63–∞	.14
AFP ≥400 ng/mL	2.13	0.46–8.56	.39
Bilobar distribution	0.92	0.12–8.87	>.999

NLR, neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; HCC, hepatocellular carcinoma.
[a]Median unbiased estimates.

LDLT. Tumor recurrence was defined when any imaging studies, such as chest or abdominal CT scan or bone scintigraphy, revealed recurrence of HCC. Recurrence-free survival was defined as the time between LDLT and tumor recurrence. Univariate and multivariate analyses were performed to identify the factors associated with the recurrence-free survival after the LDLT.

Statistical Analysis

Recurrence-free survival rates were calculated by the Kaplan–Meier product-limited method. Cox regression analysis was applied to the multivariate analyses. Variables that were used for the analysis included recipient age, donor age, Model for End-stage Liver Disease score, presence of hepatitis C virus, presence of diabetes mellitus, recipient sex, donor sex, GW-to-SLW ratio, pretransplant treatment for HCC, number of nodules obtained by imaging study, pretransplant NLR, pretransplant AFP, tumor distribution, splenectomy, and a type of calcineurin inhibitor. All statistical analyses were performed using JMP 9.0 software (SAS, Inc, Cary, NC, USA). A P value of <.05 was considered significant.

RESULTS

Fifty-seven of 152 recipients (38%) did not meet the Milan criteria. The 1-, 3-, and 5-year recurrence-free survival rates in the recipients were 94.4%, 89.4%, and 88.1%, respectively. Sixteen of the 152 recipients had HCC recurrence after LDLT. Fifteen of those recurrent recipients did not meet the Milan criteria but were within KU criteria. Univariate analysis revealed that pretransplant treatment for HCC, NLR >4, AFP ≥400 ng/mL, ≥5 nodules, and bilobar tumor distribution were risk factors for HCC recurrence after LDLT ($P = .01$, $P = .001$, $P < .0001$, $P < .0001$, and $P = .003$, respectively; Table 1). Multivariate analysis revealed that NLR >4 and ≥5 nodules were independent risk factors for tumor recurrence after LDLT ($P = .003$ and $P = .002$, respectively; Table 2). The enrolled 152 recipients were divided into 3 groups according to score for risk factors for HCC recurrence. The recipients in group 1 had no risk factor ($n = 97$). The recipients in group 2 had a sum of risk factors equal to 1 ($n = 50$). The recipients in group 3 had a sum of risk factors equal to 2 ($n = 5$). The 1-, 3-, and 5-year recurrence-free survival rates of recipients in group 1 were all 100%. The 1-, 3-, and 5-year recurrence-free survival rates in group 2 were 89.1%, 74.0%, and 69.4%, respectively. The 1-year recurrence-free survival rate in group 3 was 30.0%. The 3- and 5-year recurrence-free survival rates were not available. Duration of LDLT and recurrence was 74 days, 89 days, and 219 days, respectively. Twelve recipients in group 2 had HCC recurrences after LDLT. The mean duration of LDLT and recurrence was 571 days. The recurrence-free survival rates of recipients in group 3 were significantly worse than those of recipients in group 1 and group 2 ($P < .0001$; Fig 1).

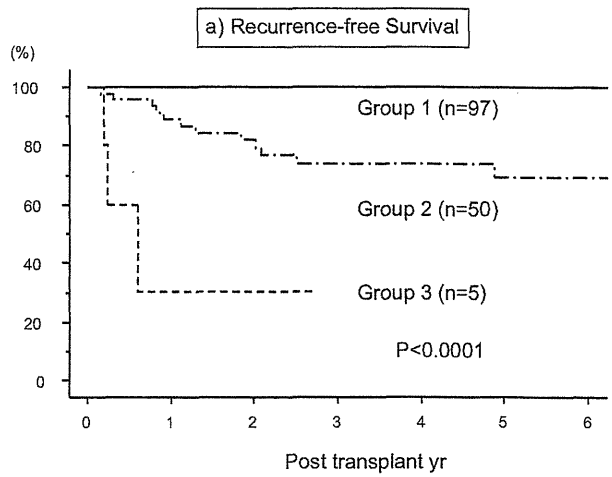

Fig 1. Recurrence-free recipient survival after living donor liver transplantation for hepatocellular corcinoma (HCC). The 152 recipients were divided into 3 groups according to score for risk factors for HCC recurrence. The 1-, 3-, and 5-year recurrence-free survival rates of recipients in group 1 ($n = 97$) were all 100%. The 1-, 3-, and 5-year recurrence-free survival rates in group 2 ($n = 50$) were 89.1%, 74.0%, and 69.4%, respectively. The 1-year recurrence-free survival rate in group 3 ($n = 5$) was 30.0%. The recurrence-free survival rates of recipients in group 3 were significantly worse than those of recipients in groups 1 and 2 ($P < .0001$).

DISCUSSION

It is crucial to exclude HCC patients with high risks of tumor recurrence. We should focus on how we can predict the

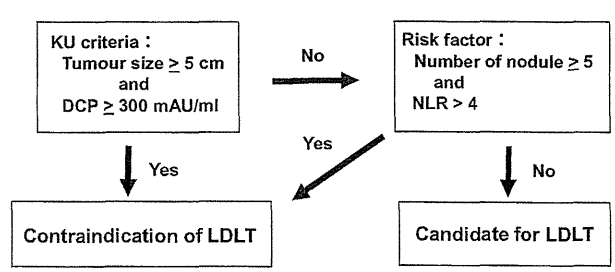

Fig 2. Two-step selection criteria to prevent hepatocellular corcinoma (HCC) recurrence after living donor liver transplantation (LDLT). When HCC patients have a maximum tumor size ≥5 cm and des-gamma carboxy prothrombin ≥300 mAU/mL (beyond the Kyushu University [KU] criteria), they are contraindicated for LDLT. Even when HCC patients meet the KU criteria, those with ≥5 nodules and neutrophil-to-lymphocyte ratio >4 are contraindicated for LDLT. The other HCC patients are good candidates for LDLT.

high-risk patients before LDLT. Therefore, for univariate and multivariate analysis, we chose variables that were obtained before transplantation. We observed that NLR >4 and ≥5 nodules were independent risk factors of HCC recurrence after LDLT for patients with HCC who met the KU criteria. The recipients were well stratified according to the number of risk factor.

By using receiver operating characteristics (ROC) analysis for tumor recurrence after LDLT, the area under the ROC curve of NLR was 0.695. A cutoff value of NLR was set as 4 using the analysis (data not shown). There are several possible mechanisms to explain the predictive role of preoperative elevated NLR.[11] Infiltration of proinflammatory macrophages, cytokines, and chemokines in the tumor microenvironment can boost tumor growth, invasion, and metastases.[12,13] Furthermore, high expressions of granulocyte colony-stimulating factor in tumor tissue and macrophage colony-stimulating factor in peritumoral tissue are associated with the elevated circulating neutrophils and poor prognosis.[14] However, reduced lymphocyte infiltration is a predictor of HCC recurrence after OLT.[15] The interpretation of NLR in patients with end-stage liver disease, often complicated with hypersplenism and pancytopenia, requires to need caution. Therefore, there may be limitation for the evaluation in such patients. Mean white blood cell (WBC) count of the patients was 3466/mm^3 in the present study (range 1060–8700). It was interesting that WBC count of patients with NLR >4 were higher than that of patients with NLR ≤4 ($P = .003$).

We will continue to use the KU criteria as the first exclusion criteria for LDLT. According to our results, we can use 2-step selection criteria for HCC patients as shown in Fig 2. In the first step, which is actually the same as the KU criteria that we used, patients are selected by tumor size and level of DCP. For patients who meet the KU criteria, patients are selected by NLR level and number of nodules.

In conclusion, our 2-step selection criteria enable selection of patients who have high risk of tumor recurrence. LDLT should not be performed in patients with HCC with NLR >4 and ≥5 nodules to achieve better outcome.

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Prognostic Factors Affecting Survival at Recurrence of Hepatocellular Carcinoma After Living-Donor Liver Transplantation: With Special Reference to Neutrophil/Lymphocyte Ratio

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Background. In living-donor liver transplantation (LDLT) for hepatocellular carcinoma (HCC), it is important to predict not only who may be susceptible to recurrence but also who may survive longer. The neutrophil/lymphocyte ratio (NLR) is useful to properly assess the patient without decreasing the long-term survival after LDLT. In this study, we investigated the relationship between NLR and prognosis of patients with recurrent HCC after LDLT.
Methods. In total, 167 LDLTs for HCC were enrolled in this study. Clinicopathologic factors for HCC recurrence after LDLT were investigated and prognostic factors were examined with respect to survival.
Results. The following factors were found to be significant in patients with HCC recurrence compared with the controls: α-fetoprotein ≧300 ng/mL, des-γ-carboxyprothrombin ≧300 mAU/mL, NLR ≧4, tumor number >3, tumor size ≧5 cm, duration of last treatment of HCC to LDLT <3 months, Milan criteria exceeded, histologic tumor number ≧10, histologic tumor size >5 cm, poor differentiation, presence of histologic vascular invasion, adjuvant chemotherapy, and interferon therapy against patients with hepatitis C virus. Male sex, interferon therapy against patients with hepatitis C virus, α-fetoprotein ≧300 ng/mL at recurrence, NLR ≧4 at recurrence, and nonsurgical resection for recurrent HCC were significantly related to poor prognosis. The 3-year survival rate after recurrence was 0% in patients with NLR ≧4 and 43.6% in patients with NLR <4. NLR was reelevated after LDLT in patients who later died; however, NLR gradually decreased in surviving patients.
Conclusion. NLR at recurrence is a prognostic factor affecting survival after recurrence in LDLT for HCC.

Keywords: Hepatocellular carcinoma, Living-donor liver transplantation, Recurrence, Neutrophil/lymphocyte ratio, Biomarker.

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Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world (*1, 2*). Because of advances in the diagnosis and management of HCC, significant improvements in the overall survival rate for HCC after hepatectomy have been achieved. However, even when curative resection is performed, the high postoperative recurrence rate remains an issue. Liver transplantation (LT) is currently the treatment of choice for early unresectable HCC owing to poor liver function and with candidate selection according to the Milan criteria (one nodule of 5 cm or two to three nodules all of 3 cm) (*3, 4*). Some LT centers have expanded the criteria, such as the up-to-seven criteria (*5*), because of the concern that the Milan criteria are too stringent. In Japan, some biomarkers, such as α-fetoprotein (AFP), des-γ-carboxyprothrombin (DCP), or neutrophil/lymphocyte ratio (NLR), in addition to the tumor size and the number of tumors, have been reported to be useful to properly assess the candidate without decreasing the long-term survival after living-donor LT (LDLT) (*6–8*).

A high NLR has been reported to be a predictor of poor survival after hepatic resection, radiofrequency ablation, transarterial chemoembolization, and LT for HCC. We recently showed that NLR was an important prognostic factor in patients with HCC after hepatic resection (*9*) and patients who underwent LDLT (*10*).

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N.H. participated in the research design, data analysis, and writing of the article. K.S., T.I., and Y.M. contributed to the discussion and reviewed the article. H.N., T.T., and Y.Y. participated in the data collection. T.I., T.Y., and Y.S. participated in the research design.
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