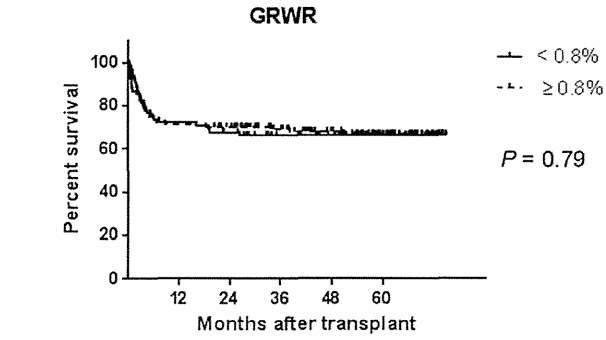
67.3%, and 66.4%, respectively. Overall survival rates and graft survival, defined as the time from LT to death or retransplantation, did not significantly differ between recipients with GRWR $\geq$ 0.8% and those with GRWR < 0.8% [P = 0.79 (Fig. 1) and P = 0.87, respectively].



No. at risk

< 0.8%	67	50	44	33	27	12
≥ 0.8%	141	100	92	70	51	31

Figure 1. Overall survival rates according to GRWR.

Baseline Assessments of the Whole Cohort

Marked decreases in zinc (45.4 ± 12.1 μg/dL), prealbumin (7.0 ± 2.4 mg/dL), and TLC (863.3 ± 207.3/μL) and marked increases in ammonia (98.1 ± 17.8 μg/dL) and tyrosine (138.8 ± 12.0 μmol/L) were seen before LDLT. The pretransplant BCAA level (395.2 ± 51.0 μmol/L) was low but still within the reference range. Consequently, the BTR (3.0 ± 0.5) was subnormal.

Peritransplant Changes in the Parameters

The low pretransplant zinc level steeply dropped for 2 to 3 days after LDLT and subsequently increased to reach the pretransplant level at about POD 5, continued to increase until it was normalized during w2, and gradually improved thereafter (Fig. 2A). The low pretransplant prealbumin level increased gradually after LDLT and took up to 1 year to normalize (Fig. 2B). The high pretransplant ammonia level notably declined immediately after LDLT to normalize within

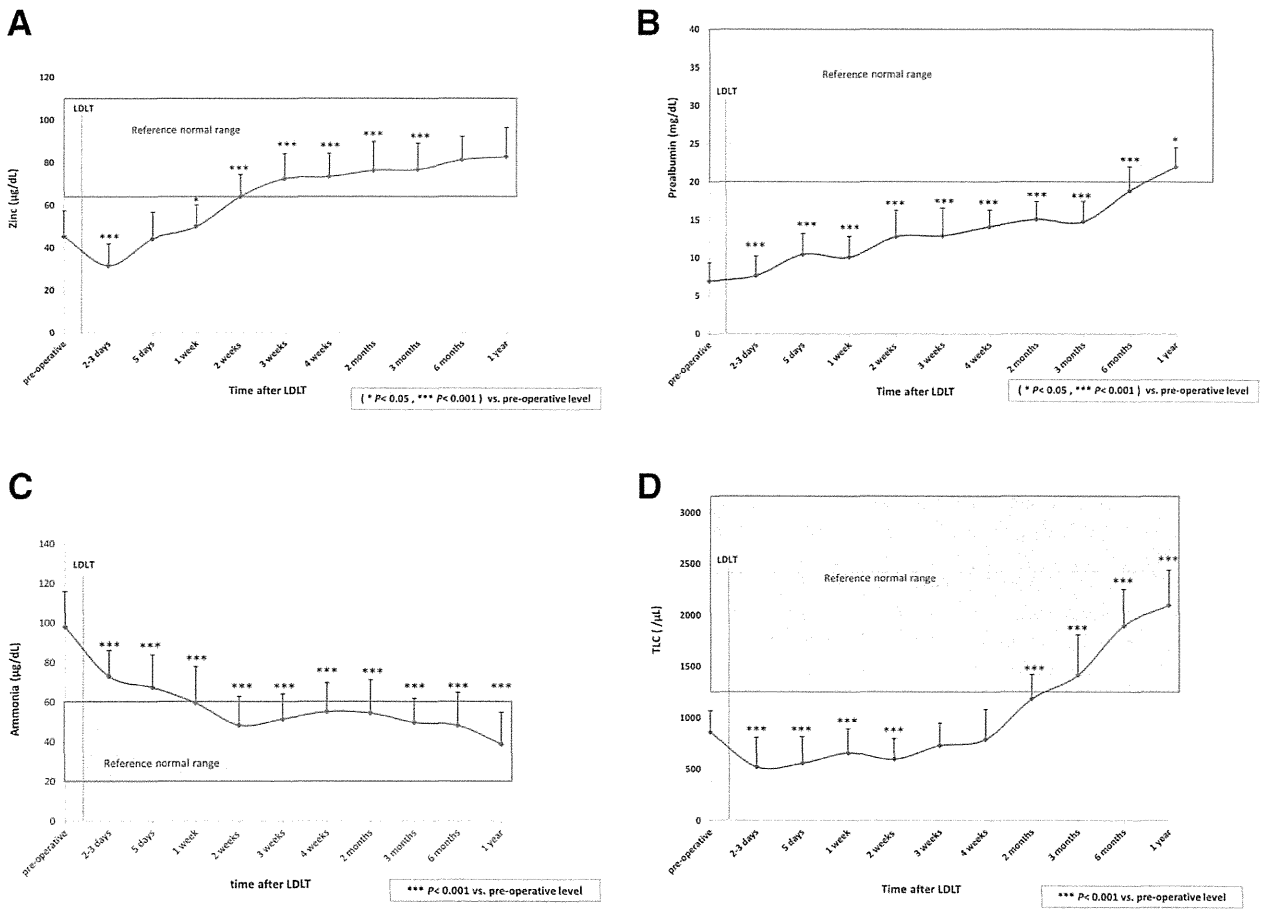


Figure 2. Time course of peritransplant changes of parameters: (A) zinc, (B) prealbumin, (C) TLC, (D) BCAA, (E) ammonia, (F) tyrosine, and (G) BTR.

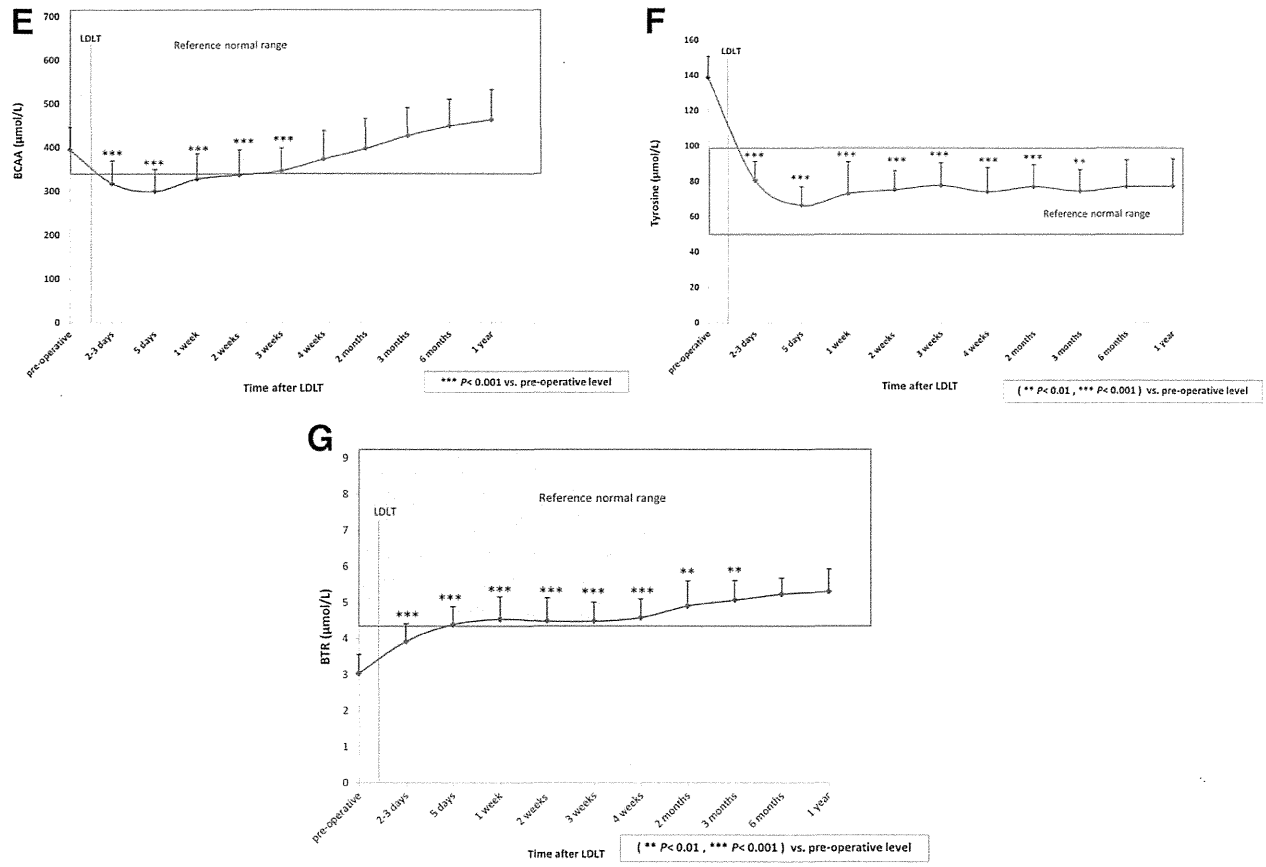


Figure 2. Continued.

w1 and continued to decrease slightly thereafter (Fig. 2C). The TLC level dropped shortly after LDLT, then gradually recovered to the normal level within 2 months after transplantation, and continued to increase thereafter (Fig. 2D). The BCAA level decreased over the first 5 days after LDLT to a subnormal level, then gradually increased until it normalized in w2, and further improved thereafter (Fig. 2E). The high pretransplant serum tyrosine level rapidly declined immediately after LDLT to return within the normal range by POD 2/3, then further decreased until POD 5, and remained relatively stable thereafter (Fig. 2F). Consequently, the BTR rose rapidly to normalize on POD 5, remained stationary for the next 3 weeks, and gradually improved thereafter (Fig. 2G).

Peritransplant Changes in the Parameters According to the GRWR: <0.8% Versus ≥0.8%

The backgrounds and peritransplant characteristics of the recipients with GRWR < 0.8% and those with GRWR ≥ 0.8% are given in Tables 1 and 2. There were no significant differences between the groups in age, sex, body mass index (BMI), CTP, MELD scores, etiology of disease, number of ABO-incompatible grafts, donor age, preoperative levels of the parameters examined, operative blood loss and transfusion units (erythrocyte concentrates), or cold and warm ischemia times.

There were no significant differences between the 2 groups with respect to zinc, prealbumin, TLC, or BCAA levels at any time point (Fig. 3A-D). Although the prealbumin and BCAA levels were close between the groups early after LDLT, at a longer time period after surgery, the GRWR ≥ 0.8% group showed somewhat persistent yet insignificant increases in prealbumin and BCAA levels in comparison with the levels in the GRWR < 0.8% group.

Ammonia and tyrosine levels declined faster and normalized earlier in the GRWR ≥ 0.8% group. The ammonia level significantly dropped from 98.6 ± 15.5 and 97.0 ± 17.7 μg/dL before LDLT to 46.0 ± 13.1 and 48.8 ± 17.1 μg/dL at w2 in the GRWR ≥ 0.8% group and the GRWR < 0.8% group ($P < 0.001$ and $P < 0.001$), respectively, with a significantly greater mean ratio of reduction in the GRWR ≥ 0.8% group versus the GRWR < 0.8% group ($P = 0.01$). The ammonia level was significantly lower in the GRWR ≥ 0.8% group versus the GRWR < 0.8% group on PODs 2 and 3 ($P = 0.001$) and remained decreased, although nonsignificantly, thereafter (Fig. 3E). The tyrosine level significantly dropped in the GRWR ≥ 0.8% group and

TABLE 1. Patient Characteristics

	GRWR ≥ 0.8% (n = 141)	GRWR < 0.8% (n = 67)	*P* Value
Donor age (years)	43.4 ± 11.9	41.0 ± 10.9	0.21
Recipient age at transplantation (years)	51.3 ± 12.5	48.9 ± 14.6	0.25
Sex: male/female (n/n)	65/76	33/34	0.77
BMI on admission (kg/m^2)	22.9 ± 4.3	23.8 ± 4.7	0.17
Underlying disease (n)			
HCC on top of viral hepatitis B or C	35	17	0.93
Viral hepatitis B/C-related cirrhosis	34	12	0.44
PBC/PSC	23	11	0.99
ALF	9	6	0.50
Biliary atresia after Kasai operation	8	6	0.38
Alcoholic cirrhosis	7	4	0.76
Metabolic diseases	4	3	0.54
NASH	5	2	0.83
Autoimmune hepatitis	3	1	0.76
Others	13	5	0.59
ABO compatibility (n)			0.35
Identical/compatible	98	42	
Incompatible	43	25	
Preoperative CTP classification: A or B/C	48/93	21/46	0.75
Preoperative MELD score	19.8 ± 8.5	21.7 ± 10.5	0.17
Baseline levels of parameters			
Zinc (μg/dL)	44.9 ± 10.5	46.4 ± 12.4	0.59
Prealbumin (mg/dL)	6.8 ± 2.3	7.3 ± 2.9	0.54
BCAA (μmol/L)	388.7 ± 49.9	402.7 ± 60.2	0.38
Tyrosine (μmol/L)	145.3 ± 13.3	151.5 ± 12.6	0.60
BTR	3.4 ± 0.5	3.5 ± 0.4	0.96
TLC (/μL)	852.3 ± 216.6	886.6 ± 213.0	0.78
Ammonia (μg/dL)	98.6 ± 15.5	97.0 ± 17.7	0.85

TABLE 2. Surgical Variables

Variable	GRWR ≥ 0.8% (n = 141)	GRWR < 0.8% (n = 67)	*P* Value
Graft type			<0.001
Left lobe	48	52	
Right lobe, including a posterior segment graft	93*	15	
Graft weight (g)	571.1 ± 163.6	427.5 ± 114.5	<0.001
Surgical duration (minutes)	919 ± 138	987 ± 181	0.35
Blood loss (mL)	9598 ± 3155	9769 ± 3190	0.92
Intraoperative erythrocyte transfusion (U)	20.9 ± 10.6	20.8 ± 12.6	0.74
Cold ischemia time (minutes)	57.3 ± 17.2	82.4 ± 13.1	0.64
Warm ischemia time (minutes)	39.9 ± 12.1	46.9 ± 17.3	0.39

*Including 1 domino graft.

the GRWR < 0.8% group from 135.3 ± 13.3 and 141.5 ± 12.6 μmol/L before LDLT to 59.7 ± 13.3 and 75.5 ± 13.7 μmol/L on POD 5 ($P < 0.001$ and $P < 0.001$), respectively, with a significantly higher mean ratio of reduction in the GRWR ≥ 0.8% group ($P = 0.02$). The tyrosine level was significantly lower in the GRWR ≥ 0.8% group versus the GRWR < 0.8% group on PODs 2 and 3 ($P = 0.001$) and remained decreased, although nonsignificantly, thereafter (Fig. 3F).

Consequently, the BTR increased faster and normalized earlier in the GRWR ≥ 0.8% group versus the GRWR < 0.8% group: it increased significantly from 3.0 ± 0.5 and 3.1 ± 0.4 before LDLT to 4.8 ± 0.5 and 3.9 ± 0.5 on POD 5 ($P < 0.001$ and $P = 0.02$), respectively, with a significantly greater mean ratio of increase ($P = 0.1$) in the GRWR ≥ 0.8% group. The BTR remained significantly higher in the GRWR ≥ 0.8% group versus the GRWR < 0.8% group during the first postoperative month [on PODs 2/3 and 5 and in w1, w2, and w3 ($P < 0.001$) and in w4 ($P = 0.002$)] and remained increased, although nonsignificantly, thereafter (Fig. 3G).

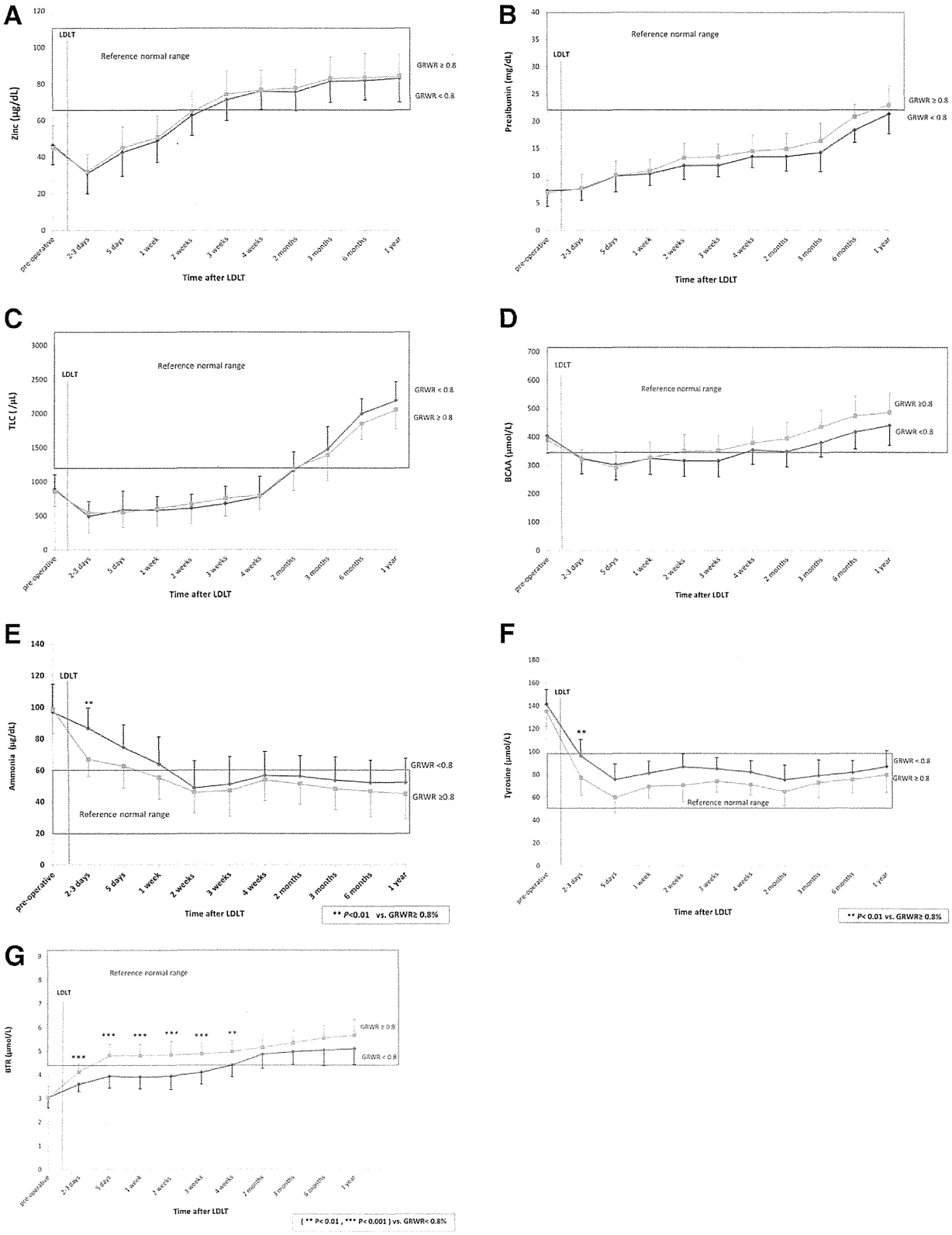


Figure 3. Time course of peritransplant changes of parameters according to GRWR (<0.8% versus ≥0.8%): (A) zinc, (B) prealbumin, (C) TLC, (D) BCAA, (E) ammonia, (F) tyrosine, and (G) BTR.

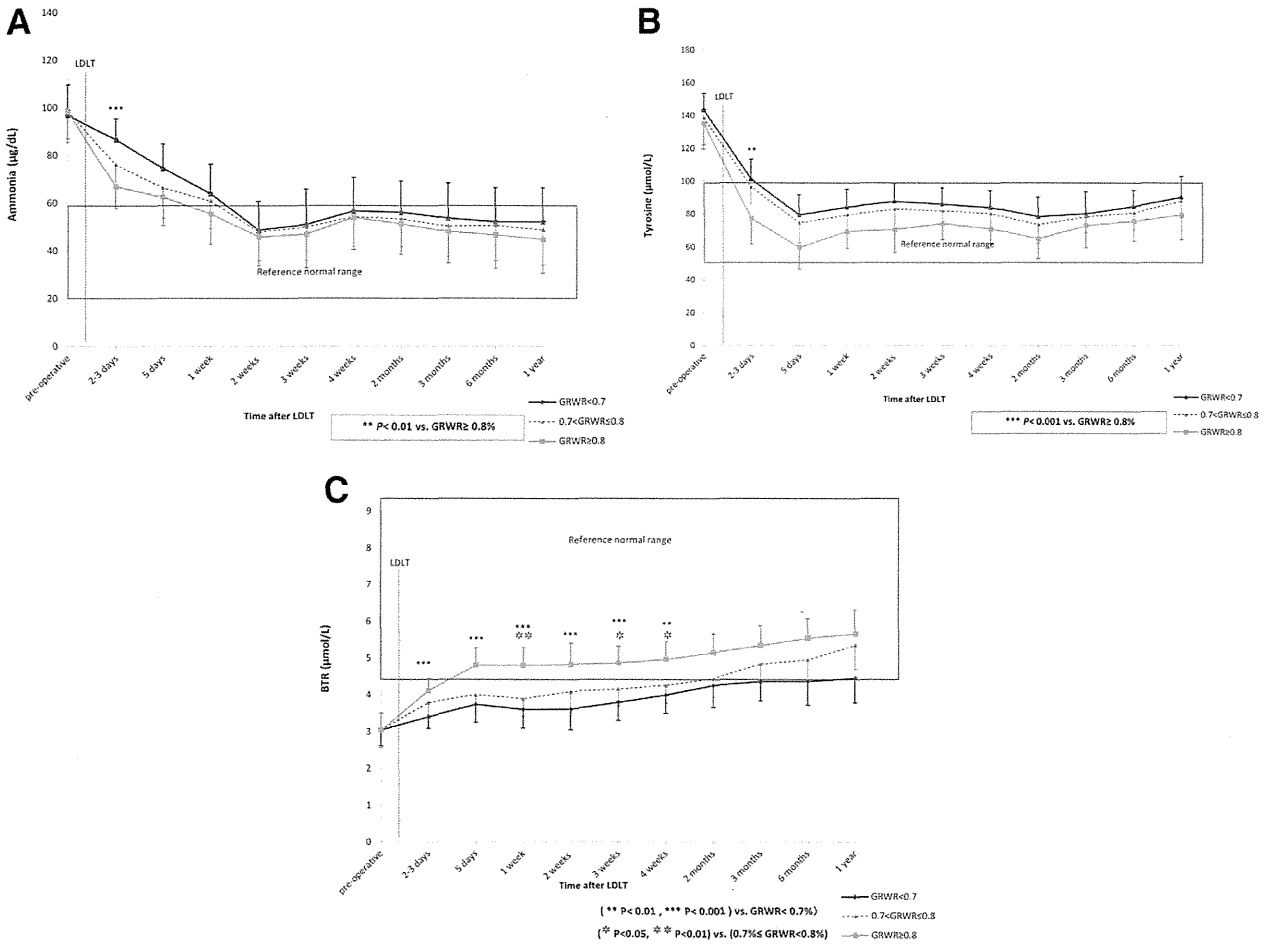


Figure 4. Comparison of time course of peritransplant levels of (A) ammonia, (B) tyrosine, and (C) BTR among patients with GRWR < 0.7%, between 0.7% and 0.8%, and ≥ 0.8%.

Peritransplant Changes in the Parameters According to the GRWR: <0.7% Versus 0.7% to 0.8% Versus ≥0.8%

Ammonia and tyrosine levels were significantly lower in the GRWR ≥ 0.8% group versus the GRWR < 0.7% group on POD 2/3 ($P < 0.001$ and $P = 0.001$, respectively) and remained decreased, although the difference did not reach significance (Fig. 4A,B). Levels of BTR were significantly higher in the group with GRWR ≥ 0.8% versus the group with GRWR < 0.7% during the first postoperative month [PODs 2/3 and 5 and w1, w2, and w3 ($P < 0.001$) and w4 ($P = 0.001$)] and was also significantly higher than that in the group with GRWR between 0.7% and 0.8% at w1, w3, and w4 ($P = 0.002$, $P = 0.01$, and $P = 0.04$, respectively; Fig. 4C). No other parameters differed significantly among the 3 groups at any of the time points analyzed.

Peritransplant Changes in the Parameters According to Preoperative CTP

Baseline preoperative zinc and prealbumin levels were significantly higher, whereas those of tyrosine and ammonia were significantly lower, in the group with CTP class A versus the group with class C ($P < 0.001$, $P < 0.001$, $P = 0.04$, and $P = 0.03$, respectively). Preoperative zinc and prealbumin levels were significantly higher in the group with class A versus the group with class B ($P = 0.04$ and $P < 0.001$, respectively). In contrast, none of the other parameters significantly differed among the 3 groups at any posttransplant time point examined.

Peritransplant Changes in the Parameters in ALF Recipients and Other Recipients

Preoperative baseline levels of ammonia, tyrosine, and prealbumin were significantly higher, whereas that of BTR was significantly lower, in the group with ALF versus the group without ALF ($P = 0.03$, $P = 0.01$, $P = 0.002$, and $P < 0.001$, respectively). Otherwise, preoperative levels of all other parameters did not significantly differ between the groups at any posttransplant time point analyzed.

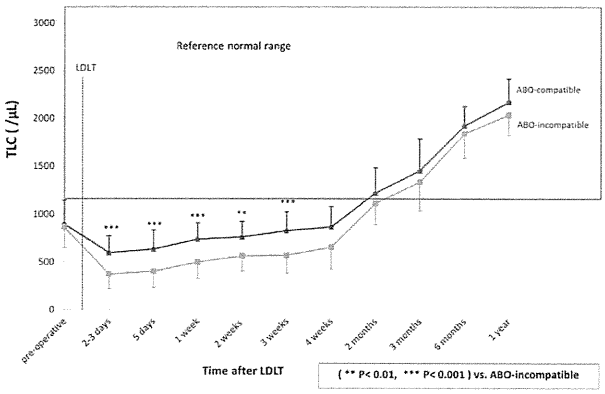


Figure 5. Time course of peritransplant changes of TLC in ABO-compatible and ABO-incompatible groups.

Peritransplant Changes in the Parameters in ABO-Incompatible and ABO-Compatible Recipients

Levels of zinc, prealbumin, BCAA, tyrosine, BTR, and ammonia did not significantly differ between the ABO-incompatible and ABO-compatible groups at any time point. However, TLC was significantly lower in the ABO-incompatible group versus the compatible group during the first 3 postoperative weeks [PODs 2/3 and 5, w1 and w3 ($P < 0.001$) and w2 ($P = 0.006$)] and remained low, although the difference was not significant (Fig. 5).

Risk Factor Analysis for Post-LT Survival

Univariate analysis revealed that none of the preoperative nutritional/metabolic parameters was a significant risk factor for posttransplant mortality (Table 3).

DISCUSSION

This is the first study to provide long-term collective profiling of nutritional/metabolic parameters in LT recipients. LDLT recipients tend to fall into a severe posttransplant catabolic phase because of the invasiveness of the operative procedure and the necessity for regeneration of the partial liver graft.[7] This might explain the temporarily decreased zinc and BCAA levels during the early postoperative period. Significance and increased utilization of zinc and BCAA for liver regeneration have been reported,[2,27] with the levels recovering later in the patient's course after surgery, regardless of the graft size, with the shift to an anabolic state. Presumably, the improved zinc level also followed the improvement in its absorption and decrease in its diuretic-induced urinary excretion after LT.

In the present study, the TLC level showed a prolonged decline during the initial posttransplant catabolic phase, presumably as a result of immunosuppressive therapy, and this may indicate the importance of an early, immunomodulating

TABLE 3. Univariate Analysis of Factors Affecting Posttransplant Patient Survival

Variable	Overall Survival (%)	*P* Value
Recipient age		
<60 years (n = 147)	86	0.38
≥60 years (n = 61)	92	
Donor age		
<50 years (n = 147)	91	0.48
≥50 years (n = 61)	84	
Sex		
Male (n = 98)	91	0.57
Female (n = 110)	84	
Original disease		
HCC (n = 52)	82	0.37
Non-HCC (n = 156)	90	
ABO blood type		
Compatible (n = 140)	91	0.24
Incompatible (n = 68)	82	
CTP score		
A or B (n = 69)	92	0.57
C (n = 139)	83	
MELD score		
<20 (n = 123)	91	0.77
≥20 (n = 85)	82	
GRWR		
<0.8% (n = 67)	88	0.79
≥0.8% (n = 141)	90	
Graft		
Right (n = 108)	89	0.55
Left (n = 100)	85	
Operative time		
<12 hours (n = 51)	89	0.08
≥12 hours (n = 157)	84	
Operative blood loss		
<10 L (n = 138)	92	0.09
≥10 L (n = 70)	82	
Pretransplant zinc level		
<40.5 μg/dL (n = 99)	84	0.73
≥40.5 μg/dL (n = 109)	89	
Pretransplant prealbumin level		
<5.6 mg/dL (n = 97)	83	0.34
≥5.6 mg/dL (n = 111)	91	
Pretransplant BCAA level		
<372.2 μmol/L (n = 99)	81	0.58
≥372.2 μmol/L (n = 109)	86	
Pretransplant BTR		
<2.8 (n = 100)	81	0.76
≥2.8 (n = 108)	86	
Pretransplant tyrosine		
<132 μmol/L (n = 100)	88	0.10
≥132 μmol/L (n = 108)	84	
Pretransplant TLC		
<700/μL (n = 100)	86	0.68
≥700/μL (n = 108)	86	
Pretransplant ammonia level		
<89 μg/dL (n = 104)	91	0.51
≥89 μg/dL (n = 104)	85	

enteral diet. Then, TLC gradually improved in parallel with an increase in lymphocyte proliferation upon recovery from protein-energy malnutrition and tapering of the immunosuppressive therapy.[4] The comparatively suppressed TLC in ABO-incompatible recipients during the first 3 weeks after transplantation might be attributable to the addition of immunosuppressants such as rituximab approximately 2 weeks before LT and complete B-cell elimination approximately 3 weeks after administration.[28]

Although CTP classification is one of the best tools for predicting mortality in patients with cirrhosis, one of its main limitations is the lack of an assessment of the nutritional and functional status.[29] Recovery of nutritional/metabolic parameters after successful LDLT occurred regardless of the pretransplant CTP class.

BCAA escape hepatic extraction with primary muscle uptake.[8] Thus, BCAA recovery regardless of graft size after the initial posttransplant decline might be attributed mainly to an improvement in cirrhosis-induced disturbances of muscular amino acid metabolism, namely, the hyperammonemia-activated glutamine synthesis, with a subsequent decrease in BCAA utilization and catabolism in skeletal muscle.[30] However, an influence of preoperative BCAA supplementation on baseline BCAA levels and levels in the early postoperative period should be also considered.

Tyrosine and ammonia levels decreased immediately after LDLT, presumably because of improvements in the visceral uptake capacity and hepatic metabolism. However, possible influences of preoperative malnutrition, preexisting extrahepatic shunts, or enteral nutrition cannot be excluded. Consistently, tyrosine clearance significantly improved 2 to 3 days after transplantation,[31] and ammonia levels improved within the first month after LDLT.[32] The tyrosine level was stabilized in the long term after LDLT, probably because of the improved graft hemodynamics and decreased basal proteolysis. The significant drop in ammonia and tyrosine levels seen with GRWR > 0.8% might be expected because of the greater liver mass for detoxifying or metabolizing these substrates.

Some limitations must be borne in mind. First, this was a retrospective, single-center study with an observational protocol. We gradually improved the perioperative nutritional regimen on the basis of our most recent findings to include preoperative BCAA and early post-LDLT enteral nutrition with an immunomodulating enteral diet enriched with hydrolyzed whey peptide. Therefore, a prospective analysis is needed to confirm the present findings. However, the study scale would be sufficient for follow-up of 208 recipients with diverse indications and under homogeneous immunosuppression regimens. Second, we were not able to collect all data at all time points. The exact duration and the amount of BCAA given in the preoperative nutritional therapy protocol varied among the individual patients, but because this was a retrospective study, these factors could not be adjusted. Third, graft function is dependent not only on size but also on graft quality. However, all grafts used had an L/S ratio $\geq$ 1.1, and both donor age and ischemia times were insignificantly different; therefore, large and small grafts were of nearly the same quality. Moreover, the baseline pretransplant parameter levels were insignificantly different. Fourth, we could not assess liver regeneration rates because neither CT nor magnetic resonance scanning was routinely performed at designated posttransplant follow-up visits. Fifth, many therapeutic interventions may have short-term effects on the functional development of hepatocytes or graft regeneration or directly alter the course of the parameters. However, we calculated the slopes within the first year after LT, when most patients received similar traditional therapies and the same perioperative nutritional therapy.

In conclusion, graft size had little impact on the recovery of nutritional parameters except for the ammonia and tyrosine levels. Further prospective studies are warranted to elucidate the role of nutritional parameters in the assessment of graft function and survival.

REFERENCES

1. Stickel F, Inderbitzin D, Candinas D. Role of nutrition in liver transplantation for end-stage chronic liver disease. Nutr Rev 2008;66:47-54.
2. Marchesini G, Fabbri A, Bianchi G, Brizi M, Zoli M. Zinc supplementation and amino acid-nitrogen metabolism in patients with advanced cirrhosis. Hepatology 1996;23: 1084-1092.
3. Shenkin A. Serum prealbumin: is it a marker of nutritional status or of risk of malnutrition? Clin Chem 2006; 52:2177-2179.
4. Nagai S, Yoshida A, Kohno K, Altshuler D, Nakamura M, Brown KA, et al. Peritransplant absolute lymphocyte count as a predictive factor for advanced recurrence of hepatitis C after liver transplantation. Hepatology 2014; 59:35-45.
5. Goldbecker A, Buchert R, Berding G, Bokemeyer M, Lichtinghagen R, Wilke F, et al. Blood-brain barrier permeability for ammonia in patients with different grades of liver fibrosis is not different from healthy controls. J Cereb Blood Flow Metab 2010;30:1384-1393.
6. Michitaka K, Hiraoka A, Kume M, Uehara T, Hidaka S, Ninomiya T, et al. Amino acid imbalance in patients with chronic liver diseases. Hepatol Res 2010;40:393-398.
7. Yoshida R, Yagi T, Sadamori H, Matsuda H, Shinoura S, Umeda Y, et al. Branched-chain amino acid-enriched nutrients improve nutritional and metabolic abnormalities in the early post-transplant period after living donor liver transplantation. J Hepatobiliary Pancreat Sci 2012; 19:438-448.
8. Tietge UJ, Bahr MJ, Manns MP, Boker KH. Hepatic amino-acid metabolism in liver cirrhosis and in the long-term course after liver transplantation. Transpl Int 2003; 16:1-8.
9. Humar A, Kosari K, Sielaff TD, Glessing B, Gomes M, Dietz C, et al. Liver regeneration after adult living donor and deceased donor split-liver transplants. Liver Transpl 2004;10:374-384.
10. Peng CJ, Wang XF, Li B, Wei YG, Yan LN, Wen TF, et al. Efficacy of middle hepatic vein reconstruction in adult

right-lobe living donor liver transplantation. Hepatobiliary Pancreat Dis Int 2010;9:135-138.

11. Umeda Y, Yagi T, Sadamori H, Matsukawa H, Matsuda H, Shinoura S, et al. Effects of prophylactic splenic artery modulation on portal overperfusion and liver regeneration in small-for-size graft. Transplantation 2008;86:673-680.
12. Yoshizumi T, Taketomi A, Uchiyama H, Harada N, Kayashima H, Yamashita Y, et al. Graft size, donor age, and patient status are the indicators of early graft function after living donor liver transplantation. Liver Transpl 2008;14:1007-1013.
13. Hori T, Ogura Y, Ogawa K, Kaido T, Segawa H, Okajima H, et al. How transplant surgeons can overcome the inevitable insufficiency of allograft size during adult living-donor liver transplantation: strategy for donor safety with a smaller-size graft and excellent recipient results. Clin Transplant 2012;26:E324-E334.
14. Kaido T, Mori A, Ogura Y, Hata K, Yoshizawa A, Iida T, et al. Lower limit of the graft-to-recipient weight ratio can be safely reduced to 0.6% in adult-to-adult living donor liver transplantation in combination with portal pressure control. Transplant Proc 2011;43:2391-2393.
15. Iwasaki M, Takada Y, Hayashi M, Minamiguchi S, Haga H, Maetani Y, et al. Noninvasive evaluation of graft steatosis in living donor liver transplantation. Transplantation 2004;78:1501-1505.
16. Morioka D, Egawa H, Kasahara M, Ito T, Haga H, Takada Y, et al. Outcomes of adult-to-adult living donor liver transplantation: a single institution's experience with 335 consecutive cases. Ann Surg 2007;245:315-325.
17. Inomata Y, Uemoto S, Asonuma K, Egawa H. Right lobe graft in living donor liver transplantation. Transplantation 2000;69:258-264.
18. Takada Y, Ueda M, Ito T, Sakamoto S, Haga H, Maetani Y, et al. Living donor liver transplantation as a second-line therapeutic strategy for patients with hepatocellular carcinoma. Liver Transpl 2006;12:912-919.
19. Inomata Y, Tanaka K, Egawa H, Uemoto S, Ozaki N, Okajima H, et al. The evolution of immunosuppression with FK506 in pediatric living-related liver transplantation. Transplantation 1996;61:247-252.
20. Egawa H, Ohdan H, Haga H, Tsuruyama T, Oike F, Uemoto S, Ozawa K. Current status of liver transplantation across ABO blood-type barrier. J Hepatobiliary Pancreat Surg 2008;15:131-138.
21. Kaido T, Ogawa K, Fujimoto Y, Ogura Y, Hata K, Ito T, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. Am J Transplant 2013;13:1549-1556.
22. Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al.; for ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN guidelines on enteral nutrition: liver disease. Clin Nutr 2006;25:285-294.
23. Shimomura Y, Murakami T, Nagasaki M, Honda T, Goto H, Kotake K, et al. Regulation of branched-chain amino acid metabolism and pharmacological effects of branched-chain amino acids. Hepatol Res 2004;30S:3-8.
24. Kaido T, Mori A, Ogura Y, Hata K, Yoshizawa A, Iida T, et al. Impact of enteral nutrition using a new immunomodulating diet after liver transplantation. Hepatogastroenterology 2010;57:1522-1525.
25. Kaido T, Mori A, Oike F, Mizumoto M, Ogura Y, Hata K, et al. Impact of pretransplant nutritional status in patients undergoing liver transplantation. Hepatogastroenterology 2010;57:1489-1492.
26. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. BMJ 1995;310:170.
27. Pescovitz MD, Mehta PL, Jindal RM, Milgrom ML, Leapman SB, Filo RS. Zinc deficiency and its repletion following liver transplantation in humans. Clin Transplant 1996;10:256-260.
28. Raut V, Uemoto S. Management of ABO-incompatible living-donor liver transplantation: past and present trends. Surg Today 2011;41:317-322.
29. Montano-Loza AJ. Clinical relevance of sarcopenia in patients with cirrhosis. World J Gastroenterol 2014;20:8061-8071.
30. Holecek M. Branched-chain amino acids and ammonia metabolism in liver disease: therapeutic implications. Nutrition 2013;29:1186-1191.
31. Shanbhogue RL, Bistrian BR, Lakshman K, Crosby L, Swenson S, Wagner D, et al. Whole body leucine, phenylalanine, and tyrosine kinetics in end-stage liver disease before and after hepatic transplantation. Metabolism 1987;36:1047-1053.
32. Urano E, Yamanaka-Okumura H, Teramoto A, Sugihara K, Morine Y, Imura S, et al. Pre- and postoperative nutritional assessment and health-related quality of life in recipients of living donor liver transplantation. Hepatol Res; doi:10.1111/hepr.12263.

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Case Report

Safe and effective treatment with daclatasvir and asunaprevir in a liver transplant recipient with severe cholestatic hepatitis C

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Severe cholestatic hepatitis C (SCH) is a unique variant of recurrent hepatitis C that occurs after liver transplantation. Unfortunately, the prognosis of SCH is poor, and interferon (IFN) therapy has been reported to not improve the prognosis. We herein report a case of progressive SCH with acute cellular rejection (ACR) and bacterial infection, which was successfully treated using IFN-free therapy with daclatasvir and asunaprevir. A 43-year-old man was diagnosed with SCH and mild ACR at day 48 after liver transplantation, and IFN-free therapy with daclatasvir and asunaprevir was started. Although he experienced catheter-related bacteremia on the first day, the IFN-free therapy was safely continued, which immediately caused his liver function to improve. His bilirubin levels decreased from 11.1 to 2.1 mg/dL and serum hepatitis C virus RNA levels became undetectable after 4 weeks of the treatment. This case indicates that IFN-free therapy for progressive SCH with acute cellular rejection and bacterial infection is safe and effective, and may improve the outcomes of hepatitis C virus positive transplant recipients.

Key words: asunaprevir, cholestatic hepatitis, daclatasvir, hepatitis C, liver transplantation, tacrolimus

INTRODUCTION

SEVERE CHOLESTATIC HEPATITIS C (SCH) is a unique variant of recurrent hepatitis C that occurs after liver transplantation in 2–9% of hepatitis C virus (HCV) positive liver transplant recipients.[1,2] SCH typically occurs within the first 6 months after liver transplantation, and is characterized by high serum levels of bilirubin, alkaline phosphatase (ALP) and γ-glutamyltransferase (γ-GT), as well as extremely high serum HCV RNA levels. In patients with SCH, perisinusoidal fibrosis rapidly progresses to cirrhosis and graft failure, resulting in a poor prognosis. The histological findings are characterized by extensive hepatocyte ballooning degeneration, spotty acidophilic bodies, Kupffer cell hypertrophy and prominent cholestasis. Unfortunately, antiviral therapy with an interferon (IFN)-containing regimen does not improve the prognosis for SCH,[3] although a recent case of SCH was successfully treated using IFN-free anti-HCV therapy with sofosbuvir and daclatasvir.[4] That case exhibited the histological features of SCH, although jaundice and other complications were absent. Therefore, the safety and efficacy of emergent IFN-free therapy remain unknown for patients who have progressive SCH with complications (e.g. rejection and infection). Here, we describe a case of progressive SCH with acute cellular rejection (ACR) and bacterial infection, which was successfully treated using IFN-free therapy with daclatasvir and asunaprevir.

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CASE REPORT

A 43-YEAR-OLD MAN underwent living donor liver transplantation (LDLT), with his sister as the donor, for HCV-related cirrhosis. Liver biopsies at 18 and 29 days after the LDLT revealed mild-to-moderate ACR, which was treated by increasing the dose of tacrolimus. As his aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, γ-GT and bilirubin levels were elevated to 115 IU/L, 107 IU/L, 661 IU/L, 850 IU/L and 3.2 mg/dL, respectively, liver biopsy was performed again at 48 days after the LDLT. The liver biopsy revealed hepatocyte ballooning degeneration, spotty acidophilic bodies,

moderate cholestasis, perisinusoidal fibrosis and findings of mild ACR. The serum HCV RNA levels were 7.9 logIU/mL, which were evaluated using real-time polymerase chain reaction-based quantitation, and his bilirubin level was elevated to 9.5 mg/dL. Therefore, we diagnosed the patient with SCH and mild ACR.

As the efficacy of dual therapy with peginterferon and ribavirin for SCH after liver transplantation is limited, and IFN would further aggravate the ACR, we started the patient on IFN-free therapy with daclatasvir (60 mg/day) and asunaprevir (200 mg/day) at day 56 after the LDLT. The HCV genotype was 1b, and resistance-associated substitutions at L31 and Y93 in the NS5A region, and at Q80, R155, D168 and V170 in the NS3 region of the HCV genome were not detected prior to treatment. On the first day of anti-HCV treatment, he had a fever of 38.6°C, with elevated white blood cell counts, and *Serratia marcescens* was detected in his blood sample; therefore, we diagnosed him with bacteremia caused by a peripheral venous catheter infection. The catheter was removed, antibiotics (tazobactam and piperacillin) were started and the bacterial infection subsequently resolved.

During the treatment for bacteremia, the anti-HCV therapy was continued, which immediately caused his serum AST, ALT, ALP and γ-GT levels to decrease; his AST, ALT and ALP levels subsequently normalized after a 4-week course of the therapy. In addition, although his bilirubin levels increased to 11.1 mg/dL on the day after initiating the treatment, they subsequently decreased to 2.1 mg/dL after 4 weeks of the treatment (Fig. 1a). His serum HCV RNA levels also dramatically decreased in the first week of treatment (to 3.9 logIU/mL), and became undetectable after 4 weeks of the treatment. The blood concentrations of tacrolimus was adjusted to trough levels of 5–7 ng/mL, by using therapeutic drug monitoring, after the daclatasvir and asunaprevir administration, although the concentration/dose (C/D) ratio for tacrolimus was elevated over the first 4 days (Fig. 1b). Thereafter, the C/D ratio decreased, and we were forced to increase the dose of tacrolimus.

At the last follow up, he was undergoing week 16 of the anti-HCV treatment. His AST, ALT, ALP, γ-GT and bilirubin levels were within the normal ranges, and serum HCV RNA remained undetectable (Fig. 1a).

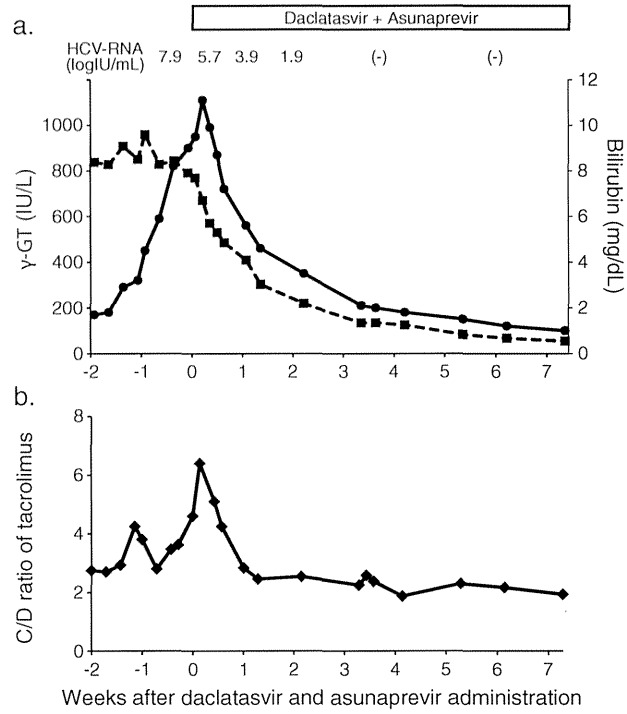

Figure 1 Clinical course of a patient with severe cholestatic hepatitis C and acute cellular rejection, who was treated with daclatasvir and asunaprevir. (a) Bilirubin (mg/dL) and γ-glutamyltransferase (γ-GT, IU/L) levels are indicated by the solid and dotted lines, respectively. The box indicates the duration of daclatasvir and asunaprevir treatment, and the serum hepatitis C virus (HCV) RNA levels (logIU/mL) are shown as values or (-), which indicates undetectable levels. (b) The concentration/dose (C/D) ratio for tacrolimus (ng/mL per mg) is indicated by the solid line.

DISCUSSION

THE SAFE AND effective use of daclatasvir and asunaprevir for SCH with ACR and bacterial infection in the present case indicates that the management of recurrent hepatitis C has dramatically changed with the introduction of direct-acting antiviral agents (DAA). IFN-free therapy can now be safely used, even for patients with rejection and infection. In addition, the rapid decline in serum HCV RNA levels, which can be achieved in most patients using this IFN-free therapy,[5] results in the rapid improvement of SCH.

Although the drug–drug interaction between calcineurin inhibitors and DAA would typically be an issue in transplant recipients, we were able to adjust the blood concentration of tacrolimus to the proper levels by using therapeutic drug monitoring. The C/D ratio for tacrolimus was elevated over the first 4 days and then decreased. This initial elevation appears to have been caused by the interaction of daclatasvir and asunaprevir with tacrolimus, as daclatasvir and asunaprevir are metabolized by the enzyme CYP3A, which is also responsible for the metabolism of tacrolimus. The mechanism for the subsequent

decrease in tacrolimus concentration during effective antiviral therapy may be due to increased tacrolimus metabolism, given the patient's improved liver function.[6,7]

As IFN-based therapy is risky for patients with bacterial infection (due to the possibility of IFN-induced neutropenia), it is typically difficult to continue IFN treatment in patients with a bacterial infection. However, we were able to safely continue IFN-free therapy with the treatment for the bacterial infection.

No resistance-associated variants were detected in the NS5A and NS3 regions of the HCV genome before we treated the patient. However, pre-existing NS5A L31M/V and/or Y93H variants are known to be associated with subsequent poor virological outcomes after daclatasvir and asunaprevir treatment.[5] In addition, it has been reported that most patients who had these resistance-associated HCV variants before the treatment also had undetectable HCV RNA during the treatment, and that 40% of the patients achieved a sustained virological response.[5] Therefore, the emergent use of IFN-free treatment for SCH would have been effective for the patient, even if he had pre-existing resistance-associated HCV variants. Even if the patient experienced a virological breakthrough during the treatment, or viral relapse after the treatment, he would have been able to receive several treatment options, including IFN-containing regimens, as the patient had recovered from the SCH, ACR and bacterial infection.

Therefore, we believe that IFN-free therapy for progressive SCH with rejection and bacterial infection is safe and effective, and may improve the outcomes of HCV positive transplant recipients. Based on the present case, we recognized that a new era has arrived in the treatment of recurrent hepatitis C after liver transplantation.

REFERENCES

1 Narang TK, Ahrens W, Russo MW. Post-liver transplant cholestatic hepatitis C: a systematic review of clinical and pathological findings and application of consensus criteria. *Liver Transpl* 2010 Nov **16**: 1228–35.
2 Terrault N. Liver transplantation in the setting of chronic HCV. *Best Pract Res Clin Gastroenterol* 2012 Aug **26**: 531–48.
3 Ong JP, Younossi ZM, Gramlich T *et al.* Interferon alpha 2B and ribavirin in severe recurrent cholestatic hepatitis C. *Transplantation* 2001 May 27 **71**: 1486–7.
4 Fontana RJ, Hughes EA, Bifano M *et al.* Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C. *Am J Transplant* 2013 Jun **13**: 1601–5.
5 Kumada H, Suzuki Y, Ikeda K *et al.* Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. *Hepatology* 2014 Jun **59**: 2083–91.
6 Kugelmas M, Osgood MJ, Trotter JF *et al.* Hepatitis C virus therapy, hepatocyte drug metabolism, and risk for acute cellular rejection. *Liver Transpl* 2003 Nov **9**: 1159–65.
7 Ueda Y, Kaido T, Uemoto S. Fluctuations in the concentration/dose ratio of calcineurin inhibitors after simeprevir administration in patients with recurrent hepatitis C after liver transplantation. *Transpl Int* 2015 Feb **28**: 251–2.

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ORIGINAL ARTICLE

Liver transplantation for advanced hepatocellular carcinoma in patients with Child-Pugh A and B

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Abstract
Purpose To investigate the outcomes of living donor liver transplantation for advanced hepatocellular carcinoma in Child-Pugh A/B patients and the usefulness of our expanded selection criteria, the Kyoto criteria.
Methods A total of 82 recipients with a Child-Pugh class A ($n = 27$) or B ($n = 55$) status having either multiple hepatic nodules or solitary tumors ≥5 cm in size treated between February 1999 and August 2012 were enrolled in this study.
Results The overall recurrence rate was significantly less for the Child-Pugh B patients than for the Child-Pugh A patients ($P = 0.042$), while the survival rates did not differ. In the Child-Pugh A and B patients, the survival rate was significantly greater, while the recurrence rate was lower among the patients meeting the Kyoto criteria than those exceeding these criteria ($P = 0.006$, $P = 0.001$, $P = 0.032$ and $P < 0.001$, respectively). In the Child-Pugh B patients, the overall survival and recurrence rates did not differ between the patients treated with and without pretreatment for hepatocellular carcinoma. In the Child-Pugh B patients treated with pretreatment, the overall survival rate was significantly greater, while the recurrence rate was lower among the patients meeting the Kyoto criteria than those exceeding these criteria ($P < 0.001$, $P < 0.001$, respectively).
Conclusions Living donor liver transplantation performed within the Kyoto criteria achieves excellent overall survival and recurrence rates, especially for Child-Pugh B patients, even those with advanced hepatocellular carcinoma.

Keywords Advanced hepatocellular carcinoma · Kyoto criteria · Pretreatment · Child-Pugh class A and B

Introduction

The consensus-based guidelines proposed by the Japanese Society of Hepatology [1, 2] took into consideration the current status in Japan, where liver resection for hepatocellular carcinoma (HCC) is safe, with <1 % mortality, especially in patients with a good hepatic reserve, and cadaveric donors for liver transplantation (LT) are difficult to identify, in association with concerns about the safety of live donors.

According to these guidelines, LT is the treatment of choice for decompensated Child-Pugh class (CP) C patients with a limited tumor burden meeting the Milan criteria. In contrast, those with a comparatively preserved liver function, namely CP class A or B patients, usually receive different conventional treatments, including hepatic resection and radiofrequency ablation, with curative intent; whereas unlike the guidelines adopted at Western transplant centers, LT is considered only as a final resort when uncontrollable recurrence occurs after repeated curative treatment [3, 4].

Hepatic resection offers 5-year rates survival similar to those of LT for early HCC in patients with well-compensated CP A cirrhosis composed of a single nodule up to 5 cm [5], albeit with unsatisfactory survival and high recurrence rates in cases with larger sized tumors or multiple

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hepatic nodules [6]. Therefore, the optimal management for advanced HCC, i.e., solitary tumors of ≥5 cm or multiple nodules in CP B or A patients, remains controversial.

We have been using expanded selection criteria for LDLT for HCC, since 2007 (Kyoto criteria: tumor number of ≤10 and maximal diameter of each tumor of ≤5 cm on pretransplant imaging, plus a pretransplant serum des-gamma-carboxy prothrombin (DCP) level of ≤400 mAU/mL [7]), which are more morphologically liberal than the Milan criteria [8]. In the present study, the outcomes of LDLT for advanced HCC in CP A/B patients and the usefulness of our expanded selection criteria were investigated. Moreover, the effect of pretreatment for HCC on the outcomes after LT was examined.

Methods

Patients

A total of 203 adult (age ≥18 years) patients underwent LDLT for HCC at Kyoto University Hospital between February 1999 and August 2012. The CP classifications were C, B, and A for 95, 78 and 30 patients, respectively. Ninety-five patients with CP C were excluded. The tumor morphology was evaluated using contrast-enhanced multi-detector computed tomography within 1 month before LDLT. Twenty-six patients with single tumor nodules less than 5 cm in maximal diameter were then excluded. The study thus comprised 82 patients with a CP classification of A ($n = 27$) or B ($n = 55$) having either solitary tumor of ≥5 cm or multiple hepatic nodules. The study protocol was approved by the Ethics Committee of Kyoto University in accordance with the Declaration of Helsinki of 1996.

The patients' profiles and pretransplant clinical characteristics are shown in Table 1. Preoperative imaging showed that 55 patients (CP A, $n = 16$ and CP B, $n = 39$) met the Kyoto criteria, while 27 (CP A, $n = 11$ and CP B, $n = 16$) patients did not. The preoperative measurements of the serum DCP levels have been described in detail elsewhere [9].

Sixty-seven of the 82 patients (82 %), including all of the 27 patients classified as having a CP A status (100 %) and 40 of the 55 patients classified as having a CP B status (73 %), had a history of previous treatment for HCC before LDLT using various non-transplant modalities, including transarterial chemoembolization (TACE), percutaneous ablation therapy, combined TACE and ablation therapy or hepatic resection. Of the patients with CP A class, seven patients received TACE, two patients received percutaneous ablation therapy, 10 patients received a combination of these approaches and eight patients underwent hepatic resection with other treatments. As for the patients with a CP B class, 12 patients received TACE, six patients received percutaneous ablation therapy, 16 patients received a combination of these approaches and six patients underwent hepatic resection with other treatments (Table 2). These treatments were not performed as a bridge to transplantation or for downstaging, but with the intent to perform curative treatment. Patients with uncontrolled recurrent HCC were subsequently referred to our department for salvage LDLT as a second-line treatment [9]. The final evaluation of the tumor morphology was performed using contrast-enhanced multi-detector computed tomography within one month before LDLT.

Table 1 Patient profiles and pretransplant clinical characteristics

Variable	Value
Donor age (year)	46 (19–64)[a]
Recipient age (year)	56 (22–69)[a]
Gender (male/female)	63/19
Etiology of cirrhosis	
Hepatitis C virus	41
Hepatitis B virus	28
Hepatitis C/B virus	5
Alcohol	2
Others	6
ABO compatibility	
Compatible/incompatible	60/22
Child-Pugh classification	
A/B	27/55
MELD score	12 (6–24)[a]
DCP	59 (5–20,600)[a]
AFP	53 (0.9–212,220)[a]
Milan criteria (met/exceeding)	30/52
Kyoto criteria (met/exceeding)	55/27
Tumor size (cm)	2.5 (0.3–22.5)[a]
No. of tumor nodules	3 (2–186)[a]

Tumor characteristics are those found on the preoperative imaging

AFP alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *MELD* model for end-stage liver disease

[a] Data are given as median values (range)

Table 2 Previous treatments for hepatocellular carcinoma before transplantation

	CP A ($n = 27$)	CP B ($n = 55$)
Pretreatment (−)	0	15
Pretreatment (+)	27	40
TACE+ ablation	10	16
TACE	7	12
Ablation	2	6
Hepatic resection	8	6

TACE transarterial chemoembolization

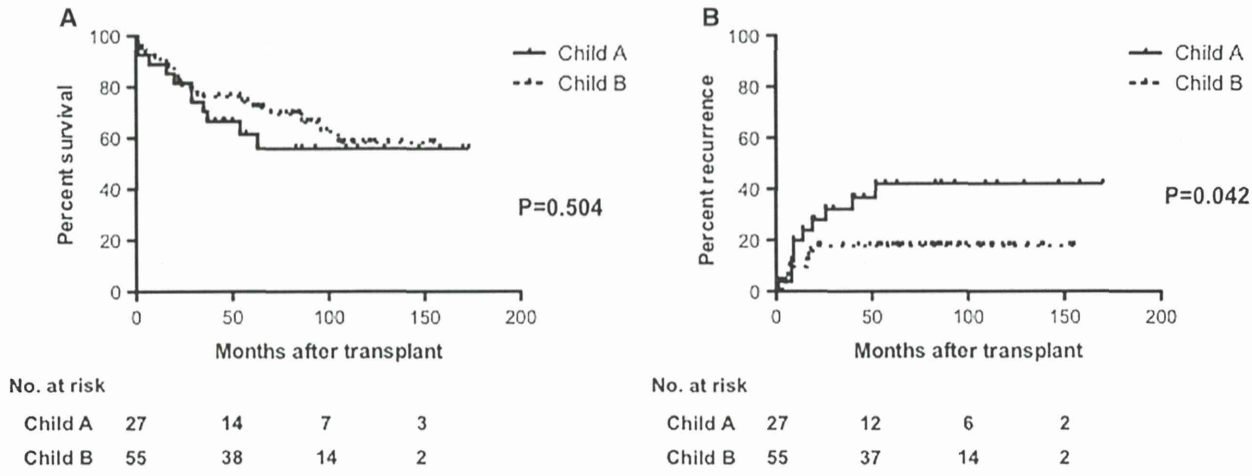

Fig. 1 Overall survival (**a**) and recurrence (**b**) rates in the Child-Pugh A and B patients

Until December 2006, our primary institutional selection criteria for LDLT for HCC included any size or number of tumors, provided that there were no distant metastases or gross vascular involvement on preoperative imaging. Since 2007, we have been using the Kyoto criteria as described [9].

The selection criteria for the recipients, as well as the surgical techniques for the donor and recipient operations, have been described in detail elsewhere [10–13]. Immunosuppressive treatment usually consisted of tacrolimus and low-dose steroids, as described previously [14, 15]. All patients received intravenous antimicrobial prophylaxis with ampicillin (0.5 g) and cefotaxime (0.5 g) twice daily for 3 days starting 30 min before surgery. No patients were switched to treatment with mammalian target of rapamycin inhibitor.

The median follow-up period in all 82 patients was 63 (range 1–173) months.

Parameters analyzed

The overall survival and recurrence rates were investigated first in all patients according to the CP classification (CP A vs. CP B) and then according to the Kyoto criteria (exceeding Kyoto vs. within Kyoto) within each of the CP A and B classes.

Owing to their good hepatic reserve, all patients classified as CP A patients were found to have a previous history of non-transplant treatment for HCC. Therefore, the overall survival and recurrence rates according to whether the patient received a non-transplant treatment modality for HCC before LDLT (Pre-Tx+ vs. Pre-Tx−) were examined only in CP B patients. Then, in those with a CP B classification who received pretreatment, the overall survival and recurrence rates were examined according to the Kyoto criteria (exceeding Kyoto vs. within Kyoto).

Statistical analysis

The cumulative overall survival and recurrence rates were calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. A two-tailed P value of <0.05 was considered to be significant. All statistical data were generated using the JMP 5.0.1 software program (SAS Institute, Cary, NC, USA) and Prism 6.02 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Overall survival and recurrence rates after LDLT according to the CP classification

The 5-year overall survival for the 27 patients with CP A (61 %) did not differ from that for the 55 patients with CP B (74 %; $P = 0.504$; Fig. 1a). The 5-year recurrence rate was significantly less for the patients with CP B (18 %) than for the patients with CP A (42 %; $P = 0.042$; Fig. 1b). Of the 10 CP A patients who died, seven died of recurrence; and of the 14 CP B patients who died, nine had recurrence.

Overall survival and recurrence rates after LDLT in patients with CP A or B based on the Kyoto criteria

The 5-year overall survival in patients with CP A was significantly greater for the 16 patients falling within the Kyoto criteria (88 %) than for the 11 patients exceeding the criteria (27 %; $P = 0.006$; Fig. 2a). The 5-year recurrence rate in the patients with CP A was significantly less for the patients falling within the Kyoto criteria (27 %) than for the patients exceeding these criteria (66 %; $P = 0.032$; Fig. 2b).

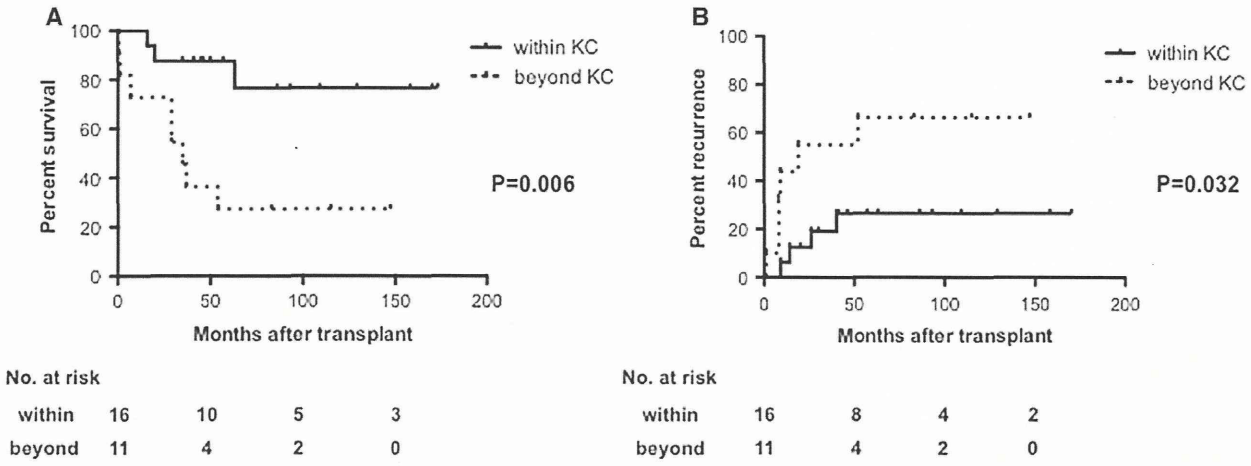

Fig. 2 Overall survival (**a**) and recurrence (**b**) rates in the Child-Pugh class A patients based on the Kyoto criteria. *KC* Kyoto criteria

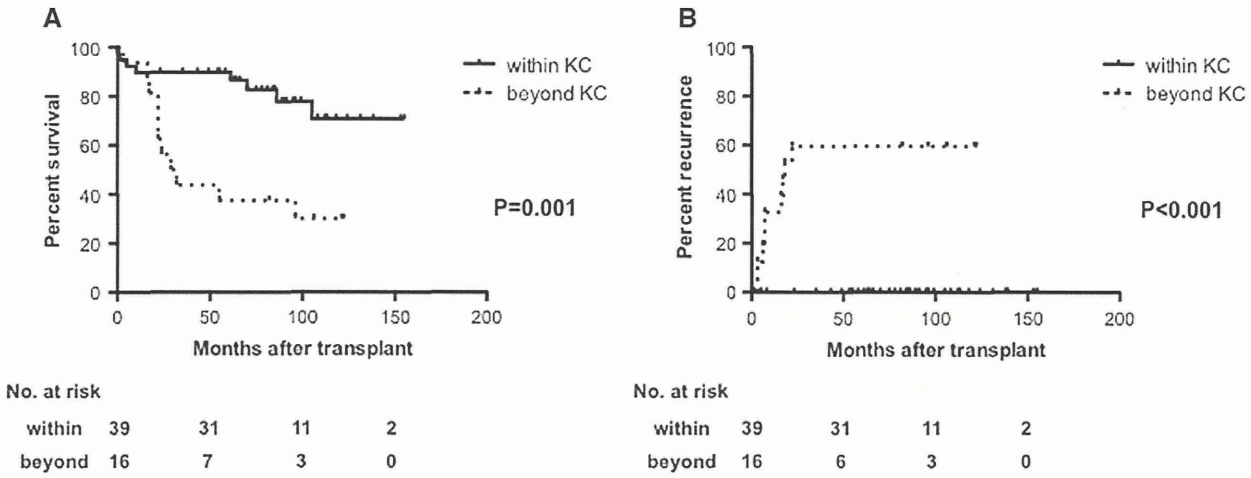

Fig. 3 Overall survival (**a**) and recurrence (**b**) rates in the Child-Pugh class B patients based on the Kyoto criteria. *KC* Kyoto criteria

The 5-year overall survival in the patients with CP B was significantly greater for the 39 patients falling within the Kyoto criteria (90 %) than for the 16 patients exceeding the criteria (38 %; $P = 0.001$; Fig. 3a). The 5-year recurrence rate in the patients with CP B was significantly less for the patients falling within the Kyoto criteria (0 %) than for the patients exceeding these criteria (60 %; $P < 0.001$; Fig. 3b).

Overall survival and recurrence rates after LDLT in the patients with CP B according to pretreatment for HCC

The long-term overall survival rates in the patients with CP B did not differ between the patients with ($n = 40$) and without ($n = 15$) pretreatment (5-year rates, 72 and 80 %, respectively; $P = 0.616$; Fig. 4a). The 5-year recurrence rates in the patients with CP B did not differ between the patients with and without pretreatment (21 and 8 %, respectively; $P = 0.239$; Fig. 4b).

Overall survival and recurrence rates after LDLT in the CP B patients with previous treatment for HCC according to the Kyoto criteria

The 5-year overall survival in the patients with CP B was significantly greater for the 29 patients falling within the Kyoto criteria (93 %) than for the 11 patients exceeding the criteria (22 %; $P < 0.001$; Fig. 5a). The 5-year recurrence rate in the patients with CP B was significantly less for the patients falling within the Kyoto criteria (0 %) than for the patients exceeding these criteria (80 %; $P < 0.001$; Fig. 5b).

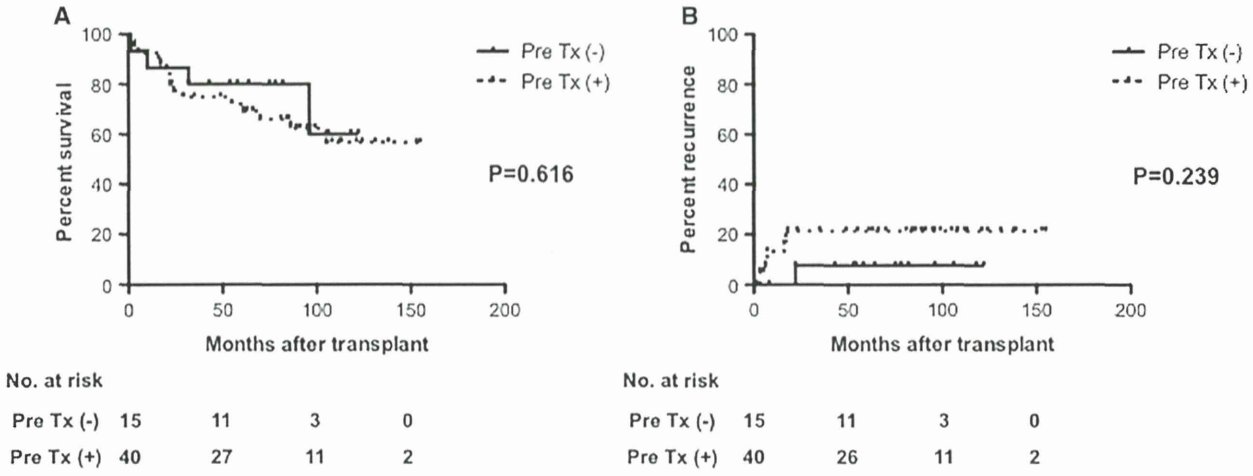

Fig. 4 Overall survival (**a**) and recurrence (**b**) rates in the Child-Pugh class B patients according to pretreatment. *Pre-Tx* pretreatment

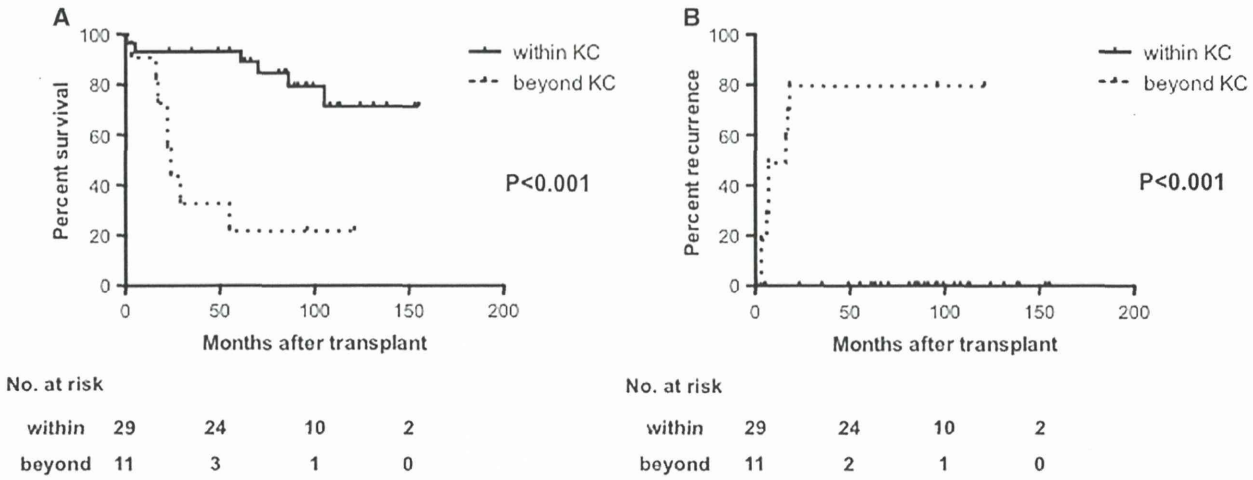

Fig. 5 Overall survival (**a**) and recurrence (**b**) rates in the Child-Pugh class B patients who received pretreatment based on the Kyoto criteria. *KC* Kyoto criteria

Discussion

Liver cirrhosis and HCC related to chronic hepatitis C virus infection are currently the most common indications for LT [16]. LDLT for HCC has achieved favorable survival rates, especially with the advent of recent operative techniques and perioperative management [17–19]. In Western transplant centers, LT is the treatment of choice for HCC meeting the Milan criteria in cases of CP class B or A cirrhosis [20]. In contrast, in Japan today, LT is considered only for such patients after uncontrollable recurrence occurs following repeated curative non-transplant treatment, such as TACE, percutaneous ablation therapy, combined TACE and ablation therapy or hepatic resection [2]. In these patients, the application of the Kyoto criteria achieves favorable outcomes after LDLT for HCC patients with a CP A/B classification having either a solitary tumor of $\geq$5 cm or multiple liver nodules, with even a null long-term recurrence rate and excellent overall survival rate, specifically in patients with CP B.

Many patients may survive long term after resection of HCC, without tumor recurrence. Moreover, it is arguable whether subjecting a live donor to the small but definite risk of mortality from live donor hepatectomy is ethically acceptable when the patient has the treatment option of resection, even though left lobe graft LDLT can significantly reduce the burden on the donor [20, 21]. Therefore, to reduce the use of scarce liver grafts, hepatic resection as

the initial treatment and transplantation as a salvage treatment in cases of tumor recurrence or liver failure may be the optimal treatment strategy for patients with early HCC and CP A cirrhosis. However, in borderline decompensated cirrhotic CP B patients with advanced HCC, i.e., large tumors of ≥5 cm or multiple liver nodules, it may be beneficial to consider LDLT earlier, especially when considering the aforementioned excellent survival and recurrence rates after LDLT using the Kyoto criteria. Moreover, as the status of CP B changes to decompensation, approximately 53 % of the patients who meet the Milan criteria no longer meet the Milan criteria after 2 years [22, 23]. In other words, these patients easily drop off the Milan criteria due to tumor progression when non-transplant conventional treatments are being repeatedly performed, each of which has its own morbidity and mortality risks, even in those with CP A/B cirrhosis [24]. A previous study showed that only 52 % of recurrent HCC tumors after resection detected on regular postoperative surveillance remain potentially transplantable according to the Milan criteria [25].

In the united network of organ sharing in the United States, candidates with HCC meeting the criteria for LT are even now given priority beyond their degree of hepatic decompensation, resulting in a shortened wait list time and decreased dropout rate [26]. In Japan, LDLT is mainly practiced with a relatively fixed waiting time [7] and represents a good source of organs; thus, it can be used to effectively reduce dropout to tumor progression when considered at the right time in such patients.

Neither the overall survival nor the recurrence rates differed between the patients with and without pretreatment among the CP B patients. Therefore, HCC pretreatment is not a contraindication and does not jeopardize the results of LDLT in such patients [8]. Moreover, in the pretreated patients, overall survival, as well as the recurrence rates, among the patients meeting the Kyoto criteria showed significantly better outcomes compared with those exceeding the Kyoto criteria. The application of the Kyoto criteria may eliminate the need for neoadjuvant therapy via TACE, which is occasionally performed to downstage tumors outside of the Milan criteria at the time of diagnosis.

A few limitations must be borne in mind when considering the findings of the present study. First, this was a retrospective, single-center study. Moreover, the study scale was relatively small (82 patients), although the median follow-up period (63 months) was sufficient, which would lend weight to the conclusions. A nationwide, multicenter study is thus necessary to confirm the findings of the present study. Second, a comparative study between LT and other treatments, including hepatectomy or ablation therapy in CP A/B patients using propensity score-matching, is needed to verify the usefulness of LT for these patients.

In conclusion, it is beneficial to consider LDLT within the Kyoto criteria earlier in CP B patients with advanced HCC, rather than postponing the procedure until uncontrollable recurrence occurs after repeated curative treatment.

Conflict of interest The authors of this manuscript have no financial support or conflicts of interest to disclose as described by Surgery Today.

References

1. Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, et al. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis. 2011;29:339–64.
2. Japan Society of Hepatology. Clinical practice guidelines for hepatocellular carcinoma (2013 version) (In Japanese). Tokyo: Kanehara; 2013.
3. Takahashi S, Kudo M, Chung H, Inoue T, Nagashima M, Kitai S, et al. Outcomes of nontransplant potentially curative therapy for early-stage hepatocellular carcinoma in Child-Pugh stage A cirrhosis is comparable with liver transplantation. Dig Dis. 2007;25:303–9.
4. Graf D, Vallböhmer D, Knoefel WT, Kröpil P, Antoch G, Sagir A, et al. Multimodal treatment of hepatocellular carcinoma. Eur J Intern Med. 2014;25:430–7.
5. Jiang L, Liao A, Wen T, Yan L, Li B, Yang J. Living donor liver transplantation or resection for Child-Pugh A hepatocellular carcinoma patients with multiple nodules meeting the Milan criteria. Transpl Int. 2014;27:562–9.
6. Sapisochin G, Castells L, Dopazo C, Bilbao I, Minguez B, Lázaro JL, et al. Single HCC in cirrhotic patients: liver resection or liver transplantation? Long-term outcome according to an intention-to-treat basis. Ann Surg Oncol. 2013;20:1194–202.
7. Kaido T, Takada Y, Uemoto S. Usefulness of the Kyoto criteria as selection criteria for living donor liver transplantation for hepatocellular carcinoma. Liver Transpl. 2010;16:538–40.
8. Kaido T, Ogawa K, Mori A, Fujimoto Y, Ito T, Tomiyama K, et al. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. Surgery. 2013;154:1053–60.
9. Fujiki M, Takada Y, Ogura Y, Oike F, Kaido T, Teramukai S, et al. Significance of des-gamma-carboxy prothrombin in selection criteria for living donor liver transplantation for hepatocellular carcinoma. Am J Transplant. 2009;9:2362–71.
10. Takada Y, Ito T, Ueda M, Sakamoto S, Haga H, Maetani Y, et al. Living donor liver transplantation as a second-line therapeutic strategy for patients with hepatocellular carcinoma. Liver Transpl. 2006;12:912–9.
11. Morioka D, Egawa H, Kasahara M, Ito T, Haga H, Takada Y, et al. Outcomes of adult-to adult living donor liver transplantation: a single institution's experience with 335 consecutive cases. Ann Surg. 2007;245:315–25.
12. Inomata Y, Uemoto S, Asonuma K, Egawa H. Right lobe graft in living donor liver transplantation. Transplantation. 2000;69:258–64.
13. Ito T, Kiuchi T, Egawa H, Kaihara S, Oike F, Ogura Y, et al. Surgery-related morbidity in living donors of right-lobe liver graft: lessons from the first 200 cases. Transplantation. 2003;76:158–63.
14. Inomata Y, Tanaka K, Egawa H, Uemoto S, Ozaki N, Okajima H, et al. The evolution of immunosuppression with FK 506 in

pediatric living related liver transplantation. Transplantation. 1996;61:247–52.
15. Egawa H, Ohdan H, Haga H, Tsuruyama T, Oike F, Uemoto S, Ozawa K. Current status of liver transplantation across ABO blood-type barrier. J Hepatobiliary Pancreat Surg. 2008;15:131–8.
16. Takada Y, Uemoto S. Living donor liver transplantation for hepatitis C. Surg Today. 2013;43:709–14.
17. Hammad A, Kaido T, Uemoto S. Perioperative nutritional therapy in liver transplantation. Surg Today. 2015;45:271–83.
18. Ikegami T, Shirabe K, Yoshiya S, Soejima Y, Yoshizumi T, Uchiyama H, et al. One-step reconstruction of the right inferior hepatic veins using auto-venous grafts in living donor liver transplantation. Surg Today. 2013;43:769–76.
19. Wang B, He HK, Cheng B, Wei K, Min S. Effect of low central venous pressure on postoperative pulmonary complications in patients undergoing liver transplantation. Surg Today. 2013;43:777–81.
20. Poon RT. Liver transplantation for solitary hepatocellular carcinoma less than 3 cm in diameter in Child A cirrhosis. Dig Dis. 2007;25:334–40.
21. Taniguchi M, Shimamura T, Todo S, Furukawa H. Small-for-size syndrome in living-donor liver transplantation using a left lobe graft. Surg Today. 2014. doi:10.1007/s00595-014-0945-x.
22. Vitale A, Boccagni P, Brolese A, Neri D, Srsen N, Zanus G, et al. Progression of hepatocellular carcinoma before liver transplantation: dropout or liver transplantation. Transplant Proc. 2009;41:1264–7.
23. Soejima Y, Taketomi A, Yoshizumi T, Uchiyama H, Aishima S, Terashi T, et al. Extended indication for living donor liver transplantation in patients with hepatocellular carcinoma. Transplantation. 2007;83:893–9.
24. Moon DB, Lee SG, Hwang S. Liver transplantation for hepatocellular carcinoma: single nodule with Child-Pugh class A sized less than 3 cm. Dig Dis. 2007;25:320–8.
25. Hu RH, Ho MC, Wu YM, Yu SC, Lee PH. Feasibility of salvage liver transplantation for patients with recurrent hepatocellular carcinoma. Clin Transplant. 2005;19:175–80.
26. Yao FY, Bass NM, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: lessons from the first year under the Model of End-Stage Liver Disease (MELD) organ allocation policy. Liver Transpl. 2004;10:621–30.

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ORIGINAL ARTICLE

Portal vein reconstruction in adult living donor liver transplantation for patients with portal vein thrombosis in single center experience

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Abstract

Background Liver transplantation (LT) used to be contraindicated in patients with portal vein thrombosis (PVT). In comparison to deceased donor LT, living donor LT (LDLT) still presents additional difficulties in determining appropriate vein grafts and overcoming small-for-size syndrome. Here, we introduce our LDLT strategies and assess their outcomes in adult patients with pre-existing PVT.

Methods We performed 282 consecutive adult LDLTs between April 2006 and December 2011. Forty-eight patients (17%) had pre-existing PVT (grade I; 15, II; 20, III; 12, IV; 1).

Results Our preferred treatments for PVT were thrombectomies/thromboendovenectomies in 30 patients, replaced grafts in seven, jump grafts in seven, renoportal anastomosis in one and no surgical intervention owing to minimal thrombosis in three. Post-transplant portal vein complications occurred in eight of 48 (17%) cases, which were treated by surgery, anticoagulation therapy, and/or interventional radiology. Post-transplant survival rates of patients with preexisting PVT at 1 year and 5 years were comparable to a PVT-free cohort (1 year; 81% vs. 77%, 5 years; 81% vs. 73%).

Conclusions The excellent survival rates in patients with PVT who underwent LDLT could be attributed to our strategies, which included surgical techniques and timely treatment of postoperative complications.

Keywords Living donor liver transplantation · Portal vein thrombosis · Reconstruction · Vein graft

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Introduction

End-stage liver cirrhosis is often associated with concomitant portal vein thrombosis (PVT) caused by portal hypertension, escaped blood flow to collateral vessels, and coagulopathy [1, 2]. Yerdel et al. reported that patients with high-grade PVT had more difficulties during surgery, more postoperative complications, and higher in-hospital mortality rates after deceased donor liver transplantations (DDLTs) [3]. As adequate portal vein (PV) flow is essential for proper liver graft function following transplantation, many reports have introduced surgical procedures such as thrombectomy, jump graft implantation, renoportal anastomosis, portocaval hemitransposition, and PV arterialization [4–14] to ensure sufficient portal blood flow to liver grafts. It is necessary to decide on the course of action during surgery, and to take special care when performing PV reconstruction for patients with PVT. It is more difficult to find appropriate vein grafts and reconstruct the PV in living donor liver transplantations (LDLTs) than in DDLTs. Few papers have reported systematic strategies regarding LDLTs and outcomes in patients with PVT [9, 15–17]. Here, we introduce our current strategy of LDLT for PVT patients while considering the following factors: the extent/localization of the thrombus according to Yerdel's classification, hemodynamics, intraoperative control of PV pressure, and the postsurgical management of complications. We collected retrospective clinical data, and analyzed the outcomes obtained using the management strategies outlined herein in adult LDLT for patients with PVT.

Materials and methods

Patients

Between April 2006 and December 2011, 282 consecutive adult LDLTs were performed in Kyoto University Hospital.

PVT was diagnosed using preoperative imaging techniques and based on the intraoperative findings. Dynamic multidetector computed tomography (MD-CT) was extensively used in evaluating PVT [2], while magnetic resonance imaging (MRI) was performed in patients with renal dysfunction or a contraindication against the contrast medium used in MD-CT. PVT was found in 48 (17%) of 282 patients who underwent adult LDLTs carried out at our institution. The overall patient follow-up period for all patients ranged from 7 days to 6.7 years (mean ± SD; 3.2 ± 2.2 years), and the medial follow-up period for surviving patients was 4.4 years (mean ± SD; 4.1 ± 1.7 years).

Strategy for PV reconstruction

We determined possible surgical strategies based on preoperative images, which included the identification of available vein grafts based on the extent of PVT according to Yerdel's classification grade. Candidate veins for grafting in LDLT included the recipient's external iliac vein, internal jugular vein, PV, and left renal vein.

Thrombectomy, thromboendovenectomy, or replacing PV trunk with vein grafts for grade I/II PVT

We initially tried complete thrombectomy or eversion thromboendovenectomy for grade I/II PVT that was limited to the PV trunk. We performed a simple anastomosis between the original PV and the PV of the donor liver (Fig. 1). In rare cases involving grade III PVT, thrombectomy was successfully performed using the pull-through technique, as previously reported [9]. When we found stenosis in the PV trunk above the confluence of the splenic vein, we resected it and replaced it with a vein graft taken from the recipient's external iliac or internal jugular vein. When portosystemic shunts such as splenorenal shunts, gastroesophageal shunts, and mesocaval shunts are identified on preoperative imaging, these collateral vessels are interrupted to prevent blood from being redirected away from the transplant [18, 19], i.e. when a rejection occurred, the compliance of the liver graft would worsen and the portal blood flow would redirect into portosystemic shunts, resulting in deteriorating, insufficient portal blood flow to the liver graft.

Jump grafts for grade III PVT

When superior mesenteric vein (SMV) blood flow was patent, and PVT that reached the confluence of the splenic vein could not be removed by thrombectomy, we used a jump graft between the SMV and the donor's PV using the recipient's iliac or jugular vein (Fig. 2). Although the anterior route to the pancreas was longer than the posterior route [20], the former was easier to handle during anastomosis.

Renoportal anastomosis for grade IV PVT

When the SMV as well as the PV trunk was obstructed by a thrombus, and all the portal blood flowed into the left renal vein through splenorenal shunts, we cut the left renal vein on the left side of the inferior vena cava, and interposed a vein graft between the recipient's left renal vein and the PV of the donor liver graft in an end-to-end fashion (Fig. 3).

Algorithm for portal pressure control

An algorithm for portal pressure control in LDLT has been previously reported [21]. Briefly, during surgery, PV pressure is monitored with a catheter inserted in the jejunal mesenteric

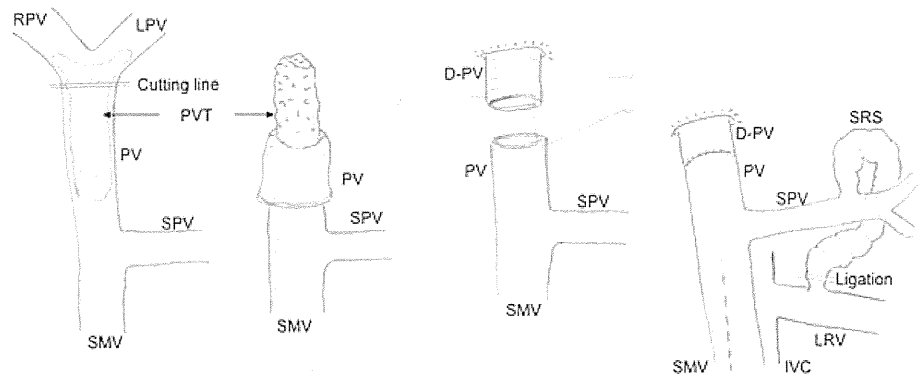

Fig. 1 Scheme of eversion thromboendovenectomy. When portal vein thrombosis (PVT) is limited to the portal vein (PV) trunk, the first treatment of choice is an eversion thromboendovenectomy and a simple anastomosis between the recipient's PV and the donor PV. The portosystemic shunt should be interrupted to prevent blood "stealing" after transplantation. *D-PV* donor portal vein, *IVC* inferior vena cava, *LPV* left portal vein, *LRV* left renal vein, *PV* portal vein, *PVT* portal vein thrombus, *RPV* right portal vein, *SMV* superior mesenteric vein, *SPV* splenic vein, *SRS* splenorenal shunt