Conclusions PBC patients are at high risk of waiting list mortality in the current allocation system. MELD-based allocation could reduce this risk.

Keywords: Child–Turcotte–Pugh · Liver transplantation · Model for End-Stage Liver Disease

Introduction

Liver transplantation is the only curative treatment option with excellent long-term results in patients with end-stage liver diseases. At present, the number of patients waiting to undergo liver transplantation is increasing in Japan, as well as in both Europe and the United States. However, many patients are dying on the waiting list because of the donor organ shortage. For example, recent waiting list mortality was reported as being 22.8 % in the United States [1]. Management of liver transplant waiting lists is aimed at minimizing waiting list deaths by prioritization of those with a higher mortality risk, and by ensuring allocation of available organs to these patients. Therefore, prioritization and allocation decisions require the accurate prediction of the survival probability of patients.

The indications for liver transplantation include a wide variety of liver diseases, including viral hepatitis, autoimmune hepatitis, cholestatic disease, metabolic disorders, and hepatic neoplasms. Because each type of liver disease has disease-specific therapeutic options and associated risk of complications, liver disease etiology can influence the patient's natural disease course and risk of death. Moreover, disease-specific clinical tools are widely used to determine prognosis in patients with primary biliary cirrhosis (PBC) [2, 3] and primary sclerosing cholangitis [4]. However, it is uncertain whether patients waiting for liver transplantation have a disease-specific risk for waiting list mortality, and whether the ability of the currently used allocation system to assess the urgency of transplantation could be generalized to every patient with heterogeneous etiology.

By consensus, a disease severity index used to allocate liver donor organs should be able to predict the probability of death in patients with end-stage liver diseases of heterogeneous etiology. In the United States, where a large number of patients are registered for liver transplantation, the Child–Turcotte–Pugh (CTP) score [5] was initially applied to assess the severity of liver disease in the United Network for Organ Sharing (UNOS) allocation algorithms, because of its simplicity and recognized ability to assess prognosis in patients with heterogeneous chronic liver disease. Subsequently, a number of studies have demonstrated the accuracy of the Model of End-Stage Liver Disease (MELD) score [6] in predicting short-term mortality risk in patients with end-stage liver disease [7–9]. Since February 2002, the MELD score has therefore been used as a UNOS criterion for allocating organs to patients waiting for liver transplantation [10].

On the other hand, in the countries with a small number of registrations for liver transplantation, a system of prioritization based on a detailed clinical review, which includes CTP score, MELD score, and other disease-specific prognostic scores, as well as patients' demographics, laboratory data, and disease histories, by a small number of expert clinicians is likely to be used to judge disease severity and potential mortality accurately. This clinical judgment-based prioritization of patients awaiting liver transplantation was initiated in October 1997 in Japan and, at present, little information is available concerning the prognostic ability of this allocation system.

The aims of the present retrospective study were: (1) to clarify the disease-specific risk for waiting list mortality in patients waiting for liver transplantation; and (2) to compare the current system of waiting list prioritization and organ allocation in Japan with the MELD and CTP scoring systems with regard to the risk in PBC patients, who have the highest risk of waiting list mortality.

Patients and methods

Patients and liver allocation policy in Japan

This was a nationwide retrospective cohort study. We used the Japan Organ Transplant Network (JOT)/the Assessment Committee of Indication for Transplantation database to identify all patients listed for deceased donor liver transplantation in Japan between October 15, 1997 and August 31, 2011. We excluded patients who were less than 18 years of age because they had a spectrum of primary diagnoses substantially different from those of patients older than 18 years. We also excluded patients listed for retransplantation to ensure that all observations represented unique individuals. Finally, we excluded patients who were diagnosed with acute liver failure because these patients rarely have chronic liver disease and are assigned the highest priority.

For JOT registration, the demographic, clinical, and laboratory data including CTP score, MELD score, or disease-specific prognostic score of all candidates are reviewed, and each candidate is assigned a clinical priority by the Assessment Committee of Indication for Transplantation (four physicians, five surgeons, and one pediatrician). The priority of candidates is represented by a medical point system, in which points are awarded according to estimated survival: 9 points for estimated survival <30 days, 6 points for <180 days, 3 points for

<360 days, and 1 point for ≥360 days. In patients with hepatocellular carcinoma, the points were determined only by the degree of hepatic decompensation. Additional points are awarded according to ABO blood group compatibility: 1.5 points for an identical blood group and 1 point for a compatible blood group. Patients with higher total points have a higher priority for donor liver allocation. For patients with identical points, waiting time is a liver allocation measure.

Age of the patient, blood type, etiology of liver disease, and medical point at listing were available for all the patients. Detailed demographic, clinical, laboratory data, including CTP score and MELD score at the time of listing, were available only in patients registered since June 22, 2006. The CTP score uses two clinical variables (ascites and encephalopathy), and three laboratory parameters (serum bilirubin and albumin levels and prothrombin time). Each variable is assigned a score from 1 to 3, with the aggregate score representing the CTP score [5]. Although the original CTP score used different criteria for total bilirubin level between patients with cholestatic disease and those with other etiologies, the criteria for the CTP score in the current Japanese allocation system did not change according to the etiology of liver disease. The MELD score was calculated using the most recent version of the formula documented on the UNOS website [11]: $9.57 \times \log_e$(creatinine mg/dL) $+ 3.78 \times \log_e$(bilirubin mg/dL) $+ 11.2 \times \log_e$(international normalized ratio [INR]) + 6.43, rounded to the nearest integer. Liver disease etiology was not incorporated in this version of the formula. Laboratory values less than 1.0 were set to 1.0 and the maximum serum creatinine was set to 4.0 mg/dL. The serum creatinine was set to 4.0 mg/dL if the patients had received dialysis at least twice within the week prior to the serum creatinine test. The MELD score was not capped at a score of 40. In PBC patients, the spontaneous survival predicted by the updated Mayo model was calculated as described previously [3].

Outcome

The patients' follow-up ended on 30 September 2011. The primary endpoint "waiting list mortality" or "waiting list death" was a combination of death and removal from the waiting list because the patient became too sick for transplantation or was otherwise medically unsuitable. We considered patients who were removed from the transplant list on account of clinical deterioration to be equivalent to patients who died, because these chronic liver diseases are almost uniformly fatal in the short term without transplantation. All other outcomes were censored, with the most common censoring events being transplantation or list removal due to an improvement in the patient's condition resulting in the patient no longer requiring transplantation.

Statistical analysis

Cox proportional hazards ratios (HRs) with 95 % confidence intervals (CI) for waiting list mortality were estimated with univariate models using age, gender, blood type, etiology of liver disease, as well as multivariate models using age and etiology of liver disease. To compare patients' characteristics between chronic hepatitis C virus (HCV) infection and PBC, we used the Mann–Whitney *U* test for numerical variables or the chi-square test for categorical variables. The HRs with 95 % CI for waiting list mortality of PBC patients were adjusted for each disease severity index, such as medical point, CTP score, and MELD score by bivariate Cox proportional hazards models. The rates of survival were estimated by the Kaplan–Meier method, and compared by log-rank test. All analyses were conducted using IBM SPSS version 19 (IBM SPSS, Chicago, IL, USA). A P value below 0.05 was considered to be statistically significant.

Results

Patient characteristics and outcome

A total of 1,407 patients were listed for deceased donor liver transplantation through the JOT registry during the study period. Of these patients, 1,295 (92.0 %) were aged ≥18 years. The etiology of liver disease in these subjects is shown in Table 1. The most prevalent diagnoses in patients ≥18 years were HCV infection (254 of 1,295, 19.6 %), hepatitis B virus infection (157 of 1,295, 12.1 %), and PBC (156 of 1,295, 12.0 %), and these accounted for 43.7 % of all patients ≥18 years. Of 1,295 patients, 239 were excluded from the study: 142 for acute liver failure and 97 for repeat liver transplant. Thus, a total of 1,056 patients formed the study cohort. In the study cohort, 64 % of patients were men and the median age of all patients was 51 years (range, 18–69 years). At listing, 78 patients were registered at medical point 1, 297 at point 3, 682 at point 6, and 29 at point 9. A flow diagram of the patient outcomes is shown in Fig. 1. At the end of study period, 313 patients were still listed and 743 had been removed from the list, with 267 removed for liver transplantation, 378 for death, and 98 for other reasons, including 54 who were too sick, 11 for improvement in their condition, and 33 for an unknown reason. Of the 267 patients who received liver transplantation, only 81 cases were able to receive deceased donation in Japan, and this accounted for 10.9 % of all patients removed from the list. Waiting list mortality, a combination of death and becoming too sick for transplantation, accounted for 58.1 % of all the patients removed from the list.

Factors associated with waiting list mortality

In univariate analysis, age, biliary atresia, PBC, hepatocellular carcinoma, metabolic diseases, polycystic diseases, and vascular diseases showed statistically significant association with waiting-list mortality. In multivariate analysis, age (HR 1.04; 95 % CI 1.03–1.05, $P < 0.001$), PBC (HR 1.79; 95 % CI 1.34–2.39, $P < 0.001$), and polycystic diseases (HR 0.27; 95 % CI 0.10–0.73, $P = 0.01$) were independently associated with waiting list mortality (Table 2). Hence, PBC patients had a 79 % higher risk of waiting list mortality compared with HCV patients with adjustment for age.

Table 1 Etiology of liver disease

	Total (n = 1,407)	≥18 years (n = 1,295)	<18 years (n = 112)
Cholestatic diseases	381	325	56
BA	93	48	46
PBC	156	156	0
PSC	105	99	6
Caroli disease	8	7	1
Others	18	15	3
Hepatocellular diseases	567	565	2
HCV	254	254	0
HBV	157	157	0
HCV and HBV	8	8	0
Alcoholic	48	48	0
AIH	22	22	0
NASH	25	25	0
Cryptogenic cirrhosis	53	51	2
HCC	76	76	0
Acute liver failure	163	142	21
Graft failure	121	97	24
Vascular disease	12	12	0
Metabolic disease	62	53	9
Polycystic disease	24	24	0
Others	1	1	0

AIH autoimmune hepatitis, *BA* biliary atresia, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *NASH* non-alcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

Waiting list mortality of PBC patients

The Kaplan–Meier waiting list survival curves for all PBC and HCV patients are shown in Fig. 2. The 1- and 2-year survival probabilities in HCV patients were 63 and 49 %, respectively (median 631 days, 95 % CI 355–907 days), whereas those in PBC patients were 51 and 33 %, respectively (median 392 days, 95 % CI 283–500 days); the differences between them represented a statistically significant difference (log-rank test, $P < 0.001$). Detailed demographic and clinical characteristics were available in 189 of 254 HCV patients and 81 of 156 PBC patients who were registered after June 2006. A comparison of the characteristics of patients with PBC and HCV is shown in Table 3. In comparison with HCV patients, PBC patients were younger and predominantly female. Patients with PBC had significantly higher platelet counts and serum bilirubin values, and lower INR and serum creatinine values. Neither the CTP score nor the medical point at listing was different between the groups. Conversely, the MELD score at listing was significantly higher in patients with PBC than in those with HCV. In addition, the median of the updated Mayo risk score was 9.4 in the PBC patients, and this predicted 1- and 2-year spontaneous survival rates of 74 and 54 %, respectively.

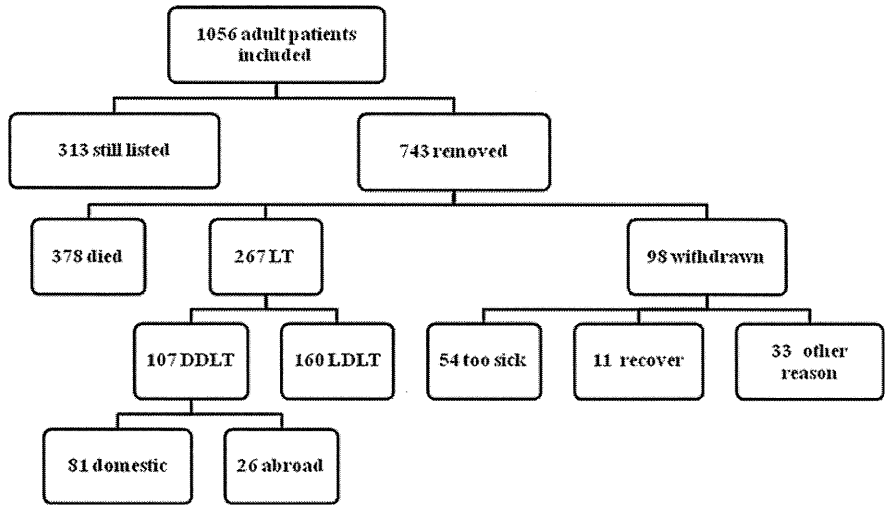

Fig. 1 Flow diagram of patient outcomes. *DDLT* deceased donor liver transplantation, *LDLT* living donor liver transplantation, *LT* liver transplantation

Table 2 Univariate and multivariate analysis of variables associated with waiting list mortality

Variables	Univariate			Multivariate		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Age (per year of age)	1.04	1.03–1.05	<0.001	1.04	1.03–1.05	<0.001
Male gender	0.93	0.77–1.13	0.48			
Blood type						
A	1.00	Reference				
B	1.07	0.83–1.43	0.61			
O	1.13	0.90–1.43	0.29			
AB	1.26	0.90–1.77	0.17			
Etiology						
HCV	1.00	Reference				
BA	0.40	0.22–0.72	0.002			
PBC	1.62	1.21–2.16	0.001	1.79	1.34–2.39	<0.001
PSC	0.79	0.54–1.17	0.24			
HBV	0.77	0.56–1.05	0.10			
Alcohol	0.95	0.59–1.53	0.83			
AIH	0.77	0.34–1.74	0.52			
NASH	1.11	0.76–1.63	0.59			
HCC	1.46	1.05–2.05	0.003			
Metabolic disease	0.40	0.22–0.75	0.004			
Polycystic disease	0.26	0.10–0.70	0.008	0.27	0.10–0.73	0.01
Vascular disease	0.009	0.01–0.67	0.002			
Others	0.70	0.34–1.43	0.33			

AIH autoimmune hepatitis, *BA* biliary atresia, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HR* hazard ratio, *NASH* non-alcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

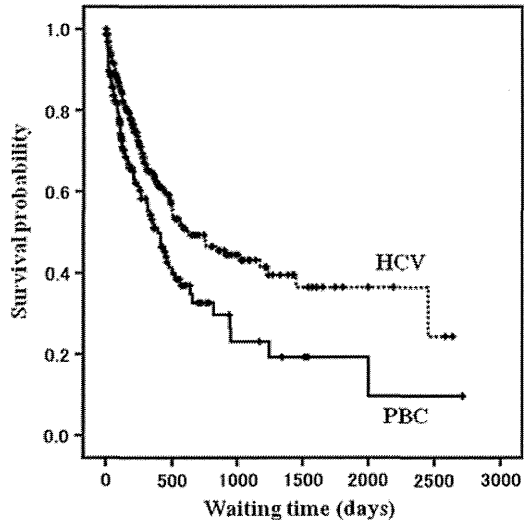

Fig. 2 Kaplan–Meier curves comparing the cumulative waiting list survival probability of patients with chronic hepatitis C (HCV, $n = 254$) and primary biliary cirrhosis (PBC, $n = 156$)

Table 3 Comparison of patient characteristics between HCV and PBC

Variable	HCV ($n = 189$)	PBC ($n = 81$)	*P* value
Age (years)	55 (29–69)	52 (27–69)	0.02[a]
Gender (male/female)	143/46	15/66	<0.001[b]
Platelet count ($\times 10^4/\mu L$)	6.0 (1.7–49.0)	10.2 (2.2–42.3)	<0.001[a]
Albumin (g/dL)	2.8 (1.8–4.4)	2.8 (1.4–4.2)	0.96[a]
Total bilirubin (mg/dL)	2.7 (0.4–39.8)	7.2 (0.7–41.2)	<0.001[a]
Creatinine (mg/dL)	0.78 (0.4–7.4)	0.67 (0.37–2.83)	<0.001[a]
Prothrombin time (%)	54.7 (11.0–103.0)	62.2 (16.0–120.0)	0.001[a]
INR	1.51 (0.98–6.24)	1.32 (0.91–4.31)	0.001[a]
MELD score	15 (7–52)	17.5 (8–39)	0.002[a]
CTP score	10 (6–15)	10 (5–15)	0.27[a]
Medical point (1, 3/6, 9)	54/135	22/59	0.81[b]

Data are shown as median (range). Data were available for patients who were listed after June 22, 2006

CTP Child–Turcotte–Pugh, *HCV* hepatitis C virus, *INR* international normalized ratio, *MELD* model of end-stage liver disease, *PBC* primary biliary cirrhosis

[a] Mann–Whitney *U* test

[b] Chi-square test

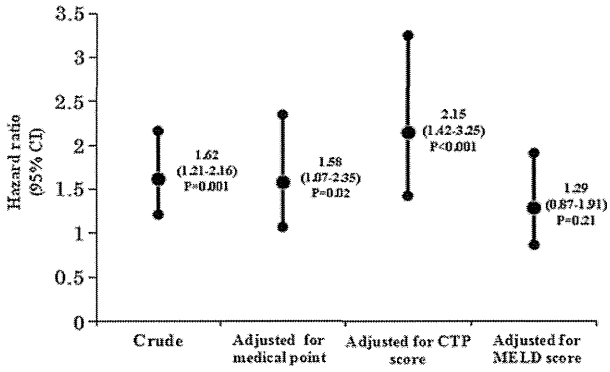

Fig. 3 Adjusted risk of waiting list mortality for patients with primary biliary cirrhosis compared with patients with chronic hepatitis C

To examine which disease severity index was able to assess the risk of PBC patients accurately, we estimated their relative hazards with adjustment for each index. We did not estimate age-adjusted relative hazard because age was not included in the allocation measures. Figure 3 indicates the crude and disease severity index-adjusted HR for waiting list mortality of PBC patients with reference to HCV patients. In univariate analysis, PBC patients were at 62 % (HR 1.62; 95 % CI 1.21–2.16, $P = 0.001$) increased risk of waiting list mortality

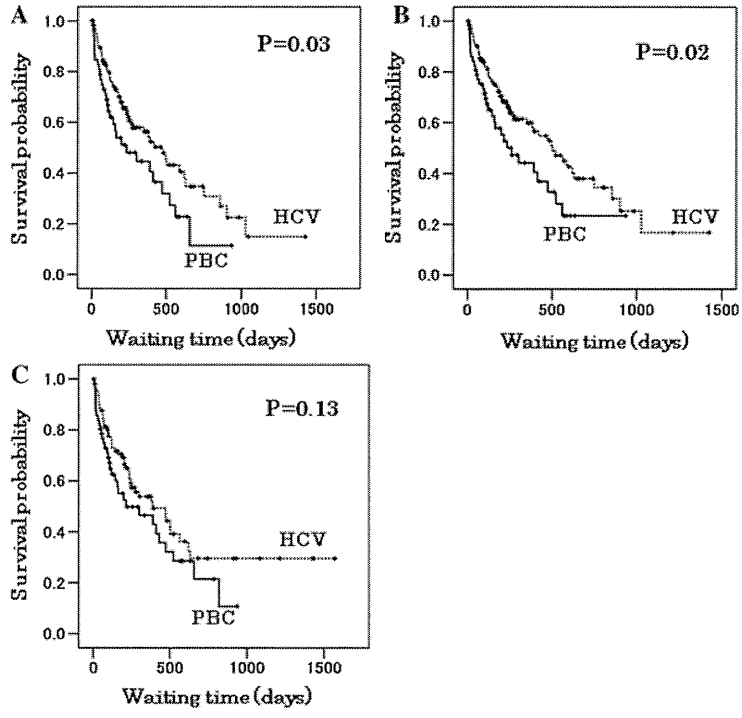

Fig. 4 Kaplan–Meier curves comparing the cumulative waiting list survival probability of patients with chronic hepatitis C (HCV) and primary biliary cirrhosis (PBC). Patients stratified medical point = 6 (**a**), and Child–Turcotte–Pugh score ≥10 (**b**), and Model of End-Stage Liver Disease (MELD) score ≥15 (**c**)

compared with HCV patients. In bivariate analysis, the medical point-adjusted HR of waiting list mortality of PBC patients was significantly higher than that of HCV patients (HR 1.58; 95 % CI 1.07–2.35, $P = 0.02$). The CTP score-adjusted HR also showed a significantly increased risk of waiting -list mortality in PBC patients (HR 2.15; 95 % CI 1.42–3.25, $P < 0.001$). However, the MELD score-adjusted HR did not show a statistically significant risk of waiting list mortality in PBC patients (HR 1.29; 95 % CI 0.87–1.91, $P = 0.21$).

Waiting list survival of patients with HCV and PBC was compared with stratification by each of the disease severity indices (Fig. 4). Patients with medical point 6, for which most PBC and HCV patients were registered, showed a significantly shorter waiting list survival for PBC patients than of HCV patients (median 261 vs. 503 days, $P = 0.02$). In patients with CTP score ≥10, the score classified as C, the shorter waiting list survival of PBC patients was also significant (median 235 vs. 475 days, $P = 0.03$). On the other hand, when they were selected by MELD ≥15, the score indicating patients who can be expected to achieve improved survival with liver transplantation [12], there was no significant difference in the waiting list survival rate between them ($P = 0.13$).

Discussion

The result of this study clearly indicated that the most common reason for removal from the waiting list in Japan was "waiting list death", which was a combination of death and becoming too sick for transplantation. The waiting list death included 58.1 % of all the patients removed from the list. In the United States, a recent report indicated that waiting list death was the reason for removal from the list in 25.9 % of adult patients [1]. Although this report included patients with acute liver failure and re-transplantation, high waiting list mortality in Japan was evident. Thus, the high mortality rate on the liver transplant waiting list is a major challenge in Japan. Moreover, severe donor organ shortage in Japan should contribute to the high waiting list mortality [13]; an improved organ allocation policy will be necessary to cause a decrease in waiting list death.

In this study, we found that PBC patients had a significantly higher risk of waiting list mortality compared with patients with other etiologies in the JOT registry. Since PBC is currently the third most common diagnosis in the JOT registry for liver transplantation, poor waiting list survival of PBC patients would contribute to the high waiting list mortality in Japan. PBC is a cholestatic liver disease that causes bile duct deterioration and progresses slowly to a terminal phase characterized by hyperbilirubinemia, signs of decompensated cirrhosis, ascites, and variceal bleeding. Only one type of medical therapy, involving the use of ursodeoxycholic acid (UDCA), is now widely recognized to improve the prognosis of PBC patients. Many studies have shown that UDCA therapy not only improves biochemical indices, but also delays histologic progression and improves survival without transplantation [14–16]. However, evidence has also accumulated that the

favorable effect of UDCA therapy is limited to patients with early-stage disease. In histologically advanced patients or biochemical non-responders, the transplant-free survival rate of UDCA-treated patients was not different from spontaneous survival [16, 17]. This means that PBC patients have no effective medical therapeutic option to prolong their survival when they have progressed to end-stage liver disease, and liver transplantation remains the only hope of a cure [18, 19]. PBC patients in our cohort also showed a consistently poor survival of a median period of 392 days.

The reason why PBC patients have a higher risk for waiting list mortality compared with patients with other etiologies of chronic liver disease is not clearly understood. Interestingly, PBC patients were younger, and their INR and serum creatinine levels were lower than for HCV patients at registration. This indicated that neither age nor liver and renal function at registration alone caused poor waiting list survival of PBC patients; the registration of PBC patients was not later than that for HCV patients. The rate of disease progression and lethal complications might be involved in their short waiting list survival rate. Moreover, the actual waiting list survival rate in PBC patients was not greater than the updated Mayo score-predicted spontaneous survival rate. This observation indicated that the PBC patients on the waiting list were refractory to the medical therapy and their waiting list survival suddenly deteriorated. Further analyses, particularly on the cause of death, are required to clarify the pathophysiology of PBC patients who have progressed to end-stage liver disease.

In general, deceased donor livers are allocated for transplantation on the basis of "sickest first", i.e., those who are more likely to die without a liver transplantation are assigned the highest priority. Therefore, the disease severity index used in the liver allocation system should consider the urgency of PBC patients for liver transplantation. However, our results have clarified the inability of the currently used Japanese allocation system to identify the risk of PBC patients. The medical point-adjusted HR of PBC patients revealed that they were at 58 % increased risk of waiting list mortality compared with HCV patients. In addition, the CTP score-adjusted HR showed that PBC patients were at 115 % increased risk for waiting list mortality. Thus, it is not only the current allocation system but also the CTP score-based allocation that cannot capture the risk for waiting list mortality in PBC patients. On the other hand, we found that the MELD score-adjusted HR of PBC patients lost statistical significance, and stratification by MELD score revealed comparable survival curves between patients with PBC and HCV. These results indicated that PBC patients had a similar risk of waiting list mortality compared with patients with other etiologies when they were stratified by MELD score. At the time of registration, the patients with HCV and PBC had different characteristics; however, only the MELD score accurately evaluated their disease severity, and therefore, MELD-based allocation would adequately assign priority to the patients according to their risk of waiting list mortality. Thus, our results demonstrated that the MELD score was superior to both the current Japanese allocation and CTP score-based allocation for ranking patients in the JOT registry by their risk of waiting list mortality.

In addition, patients should be re-evaluated according to their chronological change of hepatic failure to improve allocation. However, most patients with chronic liver disease were waiting at medical point 6 as an upper limit, because the highest priority at medical point 9 was generally awarded to the patients with acute liver failure or early graft failure in the current Japanese allocation system. Therefore, the current allocation system did not completely reflect the chronological change in the degree of liver failure. Thus, the MELD score, which was expressed numerically as a continuous variable with a wide dynamic range in the evaluation of hepatic decompensation, would have an advantage over the medical point system for assessing the chronological change in patients' risk of death.

In conclusion, this study demonstrated that patients with PBC, the third most common indication for liver transplantation in Japan, have a high risk for waiting list mortality in the current Japanese allocation system. The allocation system should be changed to accurately prioritize the patients with a higher mortality risk; MELD-based allocation would be suitable for this purpose and could reduce the waiting list mortality of PBC patients.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. OPTN/SRTR 2010 Annual Data Report. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2011. Available at: http://www.srtr.org/annual_reports/2010/. Accessed 3 Sept 2012.
2. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: model for decision making. Hepatology. 1989;10:1–7.
3. Murtaugh PA, Dickson ER, Van Dam GM, Malinchoc M, Grambsch PM, Langworthy AL, et al. Primary biliary cirrhosis: prediction of short term survival based on repeated patients visits. Hepatology. 1994;20:126–34.
4. Dickson ER, Murtaugh PA, Wiesner RH, Grambsch PM, Fleming TR, Ludwig J, et al. Primary sclerosing cholangitis: refinement

and validation of survival models. Gastroenterology. 1992;103: 1893–901.
5. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646–9.
6. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000; 31:864–71.
7. Kamath PS, Wiesner R, Malinchoc M, Kremers W, Therneau TM, Kosbery CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–70.
8. Forman LM, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from Child to MELD. Mayo End-stage Liver Disease. Hepatology. 2001;33:473–5.
9. Said A, Williams J, Holden J, Remington P, Gangnon R, Musat A, et al. Model for end-stage liver disease score predicts mortality across a broad spectrum of liver disease. J Hepatol. 2004;40: 897–903.
10. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124:91–6.
11. Organ distribution: allocation of livers. Available at: http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_8.pdf. Accessed 3 Sept 2012.
12. Murray KF, Carithers RI Jr. AASLD practice guidelines: evaluation of the patient for liver transplantation. Hepatology. 2005; 41:1–26.
13. Japan Organ Transplant Network. Available at: http://www.jotnw.or.jp/datafile/index.html in Japanese. Accessed 3 Sept 2012.
14. Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC study group. N Engl J Med. 1994;330:1342–7.
15. Corpechot C, Carrat F, Bonnand AM, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. Hepatology. 2000;32:1196–9.
16. Corpechot C, Carrat F, Bahr A, Chretien Y, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. Gastroenterology. 2005;128: 297–303.
17. Corpechot C, Abenavoli L, Rabahi N, Chretien Y, Andreani T, Johanet C, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008;48:871–7.
18. Markus BH, Dickinson E, Grambsh P, Fleming TR, Mazzaferro V, Klintmalm GB, et al. Efficacy of liver transplantation in patients with primary biliary cirrhosis. N Engl J Med. 1989;320: 1709–13.
19. Kim WR, Wiesner RH, Therneau TM, Poterucha JJ, Porayko MK, Evans RW, et al. Optimal timing of liver transplantation for primary biliary cirrhosis. Hepatology. 1998;28:33–8.

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Switching From Tacrolimus to Cyclosporine A to Prevent Primary Biliary Cirrhosis Recurrence After Living-Donor Liver Transplantation

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Recurrence of primary biliary cirrhosis (PBC) after liver transplantation has been shown to negatively affect graft and patient survival. Recently, protective effects of cyclosporine A against PBC recurrence after liver transplantation have been reported. Participants were 4 patients who underwent living-donor liver transplantation (LDLT) for end-stage liver disease due to PBC. Tacrolimus was used for initial immunosuppression, and this was switched to cyclosporine A at least 3 months after liver transplantation. Targeted trough level of cyclosporine A was 20 times that of tacrolimus. We assessed liver and renal function, as well as antimitochondrial M2 antibody for recipients prior to LDLT, as well as before and after switching immunosuppressive agents. Patients were 1 man and 3 women, and they were ages 45 to 47 years at LDLT. Timing of switching from tacrolimus to cyclosporine A was 13, 3, 7, and 4 months respectively after liver transplantation, and all 4 patients have been on cyclosporine A without adverse effects at 20 to 46 months after transplantation. In 2 of 4 patients who had high titers of antimitochondrial M2 antibody before transplantation, antibody titer did not elevate after LDLT. In the other 2 patients without elevation of antimitochondrial M2 antibody, the titer did not turn positive. Switching from tacrolimus to cyclosporine A was possible without medical problems, and all patients exhibit no recurrence of PBC. Cyclosporine A may be useful for prevention of PBC recurrence after LDLT.

Key Words: Primary biliary cirrhosis – Living-donor liver transplantation – Immunosuppression – Recurrence

Primary biliary cirrhosis (PBC) has been one of the most common indications for liver transplantation in adults. Recurrence of PBC after liver transplantation has been shown to negatively affect graft and patient survival. Recently, protective effects of cyclosporine A (CyA) against PBC recurrence after liver transplantation have been reported.[1,2] Corticosteroids after liver transplantation may

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Table 1 Clinical variables before liver transplantation, and before and after switching from tacrolimus to cyclosporine A

	Patient 1			Patient 2			Patient 3			Patient 4		
	Pre-LT	Before	After	Pre-LT	Before	After	Pre-LT	Before	After	Pre-LT	Before	After
Anti-M2 antibody, U/mL	<5	<5	<5	<5	<5	<5	149	66	66	155	47	94
AST, U/mL	167	15	13	112	15	18	112	103	20	132	19	21
ALT, U/mL	51	9	6	78	9	8	43	163	15	83	22	15
Total bilirubin, mg/dL	12.0	0.8	0.6	2.2	0.4	0.3	19.6	2.1	0.9	19.0	0.6	0.6
Albumin, g/dL	2.8	3.8	4.5	3.0	3.3	3.9	2.7	3.5	4.0	2.3	3.7	4.1
PT-INR	1.2	1.0	1.0	1.2	1.0	1.0	1.2	1.0	1.0	1.2	1.0	1.0
Creatinine, mg/dL	0.4	0.74	0.76	0.48	0.65	0.78	0.5	0.62	1.02	0.68	1.19	1.37

ALT, alanine aminotransferase; AST, aspartate aminotransferase; pre-LT, before liver transplantation; PT-INR, prothrombin time–international normalized ratio.

be important to prevent recurrence of PBC.[3] We retrospectively assessed the outcome of switching from tacrolimus to CyA in patients who underwent living-donor liver transplantation (LDLT) for PBC.

Patients and Methods

Participants were 4 patients who underwent LDLT for end-stage liver disease due to PBC at Jikei University Hospital from 2008 to 2009. Tacrolimus and steroids were used for initial immunosuppression, and these were switched to CyA, steroids, and/or mycophenolate mofetil at least 3 months after liver transplantation. The targeted trough level of CyA was 20 times that of tacrolimus. We assessed liver function, renal function, antimitochondrial M2 antibody, and PBC recurrence among recipients before LDLT, and before and after switching immunosuppressive agents.

Results

Patient 1

The recipient was a woman age 45 years at LDLT who had received a diagnosis of PBC at age 36 years. The donor was the woman's 45-year-old husband. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the recipient's Model for End-Stage Liver Disease (MELD) score was 18, and her Child-Pugh score was 10. Immunosuppressive agent was switched from tacrolimus to CyA at 22 months after LDLT without medical problems or PBC recurrence (Table 1). Antimitochondrial M2 antibody remained negative after LDLT. After LDLT, the patient was treated with insulin for diabetes mellitus due to adverse effects of tacrolimus.

Patient 2

The recipient was a woman age 44 years at LDLT who had received a diagnosis of PBC at age 30 years. The donor was the woman's 48-year-old older brother. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the recipient's MELD score was 11, and her Child-Pugh score was 9. Immunosuppressive agent was switched from tacrolimus to CyA at 3 months after LDLT without medical problems or PBC recurrence (Table 1). Antimitochondrial M2 antibody remained negative after LDLT.

Patient 3

The recipient was a woman age 47 years at LDLT who had received a diagnosis of PBC at age 38 years. The donor was an 18-year-old daughter. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the MELD score was 20, and the Child-Pugh score was 10. Immunosuppressive agent was switched from tacrolimus to CyA at 7 months after LDLT. Recipient had a high titer of antimitochondrial M2 antibody before LDLT; antibody titer did not elevate after LDLT (Table 1). At 20 months after LDLT, liver biopsy was performed for liver dysfunction. Liver biopsy specimen revealed moderate late cellular rejection (isolated central perivenulitis) and mild acute cellular rejection [rejection activity index (RAI) = 2; P1 B1 V0] without PBC recurrence (Fig. 1A).

Patient 4

The recipient was a man age 46 years at LDLT who had received a diagnosis of PBC at age 43 years. The donor was the man's 43-year-old younger sister. ABO blood type–identical LDLT was performed

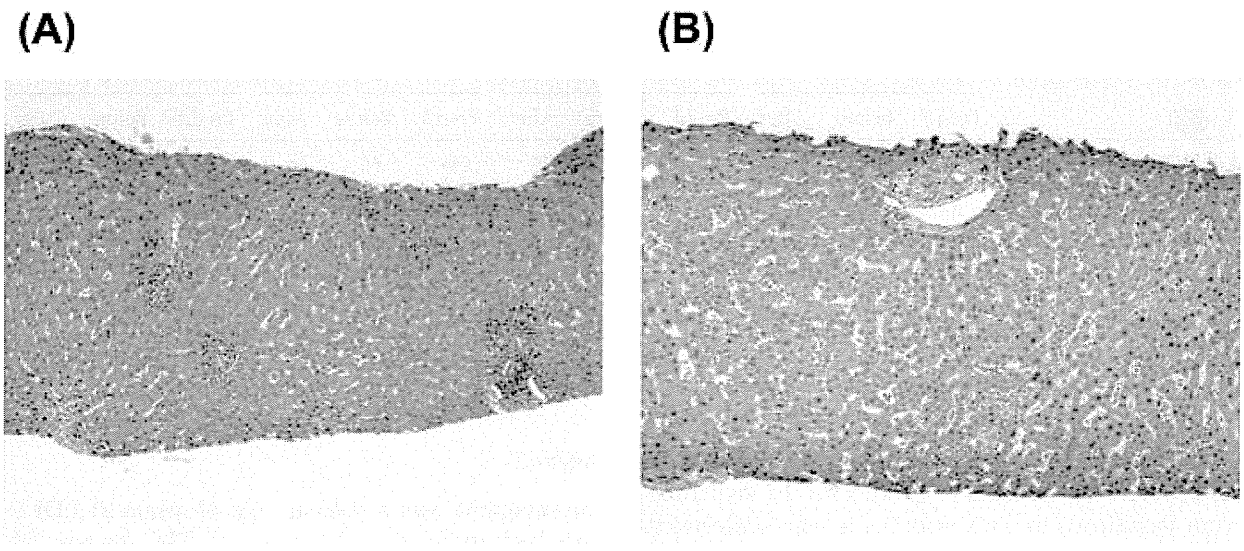

Fig. 1 (A) Liver biopsy specimen for liver dysfunction at 20 months after LDLT for patient 3 revealed moderate late cellular rejection (isolated central perivenulitis) and mild acute cellular rejection (RAI = 2; P1 B1 V0) without PBC recurrence. (B) Liver biopsy specimen for liver dysfunction at 8 months after LDLT for patient 4 revealed moderate acute cellular rejection (RAI = 4; P1 B2 V1) without PBC recurrence.

using the right lobe graft. At LDLT, the recipient's MELD score was 20, and his Child-Pugh score was 12. Immunosuppressive agent was switched from tacrolimus to CyA at 4 months after LDLT. Recipient had a high titer of antimitochondrial M2 antibody before LDLT; antibody titer did not elevate after LDLT (Table 1). At 8 months after LDLT, liver biopsy was performed for liver dysfunction. Liver biopsy specimen revealed moderate acute cellular rejection (RAI = 4; P1 B2 V1) without PBC recurrence (Fig. 1B).

Discussion

With the recent improvements in surgical, anesthetic, and microbiological techniques; the development of immunosuppressive agents; and increasing experience and better patient selection, better outcomes for liver transplantation for end-stage liver disease have been achieved. Liver transplantation is the treatment choice for patients with end-stage liver disease due to PBC; however, the incidence of recurrent PBC increases progressively, and histologic recurrent PBC is reported in approximately one third of patients by 10 years after liver transplantation.[1–6] The pathogenesis of PBC remains uncertain, and the perioperative clinical variables associated with recurrence of PBC after liver transplantation are not completely elucidated.

Despite the era effect of immunosuppressive agents, a major conclusion of most reports in patients who underwent liver transplantation for PBC is that the use of CyA is associated with a lower incidence of PBC recurrence in comparison with tacrolimus.[1–6] However, mechanisms of CyA for prevention of PBC recurrence are unknown. Conversely, tacrolimus is considered as a potent immunosuppressive agent with regard to mortality and graft loss at 1 year, as well as acute rejection.[7] Switching from tacrolimus as the primary immunosuppressive agent for PBC after liver transplantation to CyA as a maintenance immunosuppressive agent may enable safe prevention of PBC recurrence, as well as better outcomes.

Conclusions

Switching from tacrolimus to CyA was possible without sequelae, and all patients exhibit no recurrence of PBC. CyA may be useful for prevention of PBC recurrence after LDLT.

References

1. Montano-Loza AJ, Wasilenko S, Bintner J, Mason AL. Cyclosporine A protects against primary biliary cirrhosis recurrence after liver transplantation. *Am J Transplant* 2010;**10**(4):852–858

2. Liermann Garcia RF, Evangelista Garcia C, McMaster P, Neuberger J. Transplantation for primary biliary cirrhosis: retrospective analysis of 400 patients in a single center. *Hepatology* 2001;**33**(1):22–27
3. Neuberger J, Portmann B, Macdougall BR, Calne RY, Williams R. Recurrence of primary biliary cirrhosis after liver transplantation. *N Engl J Med* 1982;**306**(1):1–4
4. Charatcharoenwitthaya P, Pimentel S, Talwalkar JA, Enders FT, Lindor KD, Krom RA *et al.* Long-term survival and impact of ursodeoxycholic acid treatment for recurrent primary biliary cirrhosis after liver transplantation. *Liver Transpl* 2007;**13**(9): 1236–1245
5. Guy JE, Qian P, Lowell JA, Peters MG. Recurrent primary biliary cirrhosis: peritransplant factors and ursodeoxycholic acid treatment post-liver transplant. *Liver Transpl* 2005;**11**(10): 1252–1257
6. Levitsky J, Hart J, Cohen SM, Te HS. The effect of immunosuppressive regimens on the recurrence of primary biliary cirrhosis after liver transplantation. *Liver Transpl* 2003;**9**(7):733–736
7. McAlister VC, Haddad E, Renouf E, Malthaner RA, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. *Am J Transplant* 2006;**6**(7):1578–1585

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Original Article

Pre- and postoperative nutritional assessment and health-related quality of life in recipients of living donor liver transplantation

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Aim: The nutritional state of living donor liver transplantation (LDLT) recipients is one of the most important factors affecting postoperative outcome. Although the assessment of health-related quality of life (HRQOL) is of increasing importance, few studies have examined this in conjunction with LDLT recipient nutritional state.

Methods: Ten LDLT recipients with end-stage liver disease were recruited for this study. Measurements of energy expenditure, anthropometrics and laboratory data were performed before and 1, 6 and 12–24 months after LDLT. HRQOL was measured by using the 36-item Short-Form (SF-36) before and 1, 3, 6 and 12–24 months after LDLT.

Results: The preoperative value of non-protein respiratory quotient (npRQ) was 0.796 ± 0.026 and it increased significantly after the operation. Serum non-esterified fatty acid (NEFA) levels were high in the preoperative state, but had significantly decreased 1 month after the operation. A negative correlation between npRQ and NEFA was observed throughout the study period. Cholinesterase and albumin levels improved to normal levels within 6 and 12–24 months, respectively. The recovery of the physical component summary of the SF-36 was observed after the improvement of all domains of laboratory data and energy metabolism based on the nutritional state.

Conclusion: This study demonstrated that the recovery of metabolic function, laboratory data and HRQOL in LDLT recipients are variable, and it took more than 6 months to normalize the liver protein synthetic capacity and physical HRQOL score periods. Therefore, long-term nutritional support is required in LDLT recipients.

Key words: energy metabolism, living donor liver transplantation, non-protein respiratory quotient, nutritional assessment, quality of life

INTRODUCTION

LIVER TRANSPLANTATION IS the accepted treatment for patients with end-stage liver disease (ESLD). The outcome for liver transplantation patients has improved markedly in recent years as a result of advances in immunosuppressive protocols, preservation techniques and postoperative management.[1] In Japan, a total of 4292 living donor liver transplantations (LDLT) have been performed in 2006, and 2621 of these were adult-to-adult LDLT. The overall 3- and 5-year patient survival rates were 73.8% and 70.4%, respectively.[2]

Living donor liver transplantation recipients' malnutrition was found to be associated with increased length of stays in the intensive care unit (ICU), mortality and total hospital charges.[3,4] Therefore, adequate nutritional management and therapy are required to avoid malnutrition and the associated risks. However, there have been few studies which have performed nutritional assessment of LDLT patients.

The majority of patients with ESLD have decreased respiratory quotient (RQ) and increased resting energy expenditure (REE).[5,6] Low RQ is associated with decreased glucose oxidation and increased fat oxidation[7] and is indicative of starvation, such as which can

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occur after an overnight fast due to a lack of glycogen storage. For this reason, an increase in non-protein RQ (npRQ) values can be used as a marker of recovery in chronic liver disease patients.[8] Tajika *et al.*[9] also found that the npRQ represented an independent risk factor for survival in cirrhotic patients as individuals with a lower npRQ had a worse prognosis. Hypermetabolism may contribute to the protein energy malnutrition (PEM) associated with liver disease[10] as an increased REE has been reported in cirrhotic patients.[5] However, a definitive connection cannot be made as other reports have described normal or decreased REE.[7,11] In addition, a longitudinal study reported that postoperative hypermetabolism peaked on day 10 after transplantation, and continued to the hypermetabolic state over the following 6 months.[12] By 12 months post-transplant, there was no longer a difference between the measured and predicted basal metabolic rates.[13] Despite these studies, very little information is available which describes REE and RQ changes over the long term after LDLT.

The goal of transplantation is not only to ensure patient survival, but also to return a similar state of health as was enjoyed before the disease. This requires achieving a balance between the functional efficacy of the graft and the patient's physical and psychological integrity. The assessment of the health-related quality of life (HRQOL) is increasingly used as an outcome measure when evaluating medical procedures.[14] Although numerous studies have reported significantly improved HRQOL compared with the preoperative state,[15,16] the precise timing of the improvement is often debated. In addition, most studies that have investigated HRQOL following LDLT have not included measurements of energy metabolism, which is the basis of nutritional therapy, such as RQ.

In this study, we therefore performed nutritional assessment, including energy metabolism based on nutritional state, laboratory data and HRQOL, in both the pre- and postoperative states of LDLT recipients.

METHODS

Patients

THIS STUDY WAS conducted at Tokushima University Hospital. Ten recipients and eight control subjects were recruited for the study. The study design was approved by the ethical committee of Tokushima University Hospital. Written informed consent was obtained from each patient.

Anthropometric and food intake data

Bodyweight (BW) and body mass index (BMI) were measured under fasting conditions using a TBF-102 body composition meter (Tanita, Tokyo, Japan). Before LDLT, the dry weight was calculated by deducting an estimated weight for ascites in patients with ascites. Dieticians interviewed the amount of food eaten (meals + snacks), and asked the dietary intake by 24-h recall method and calculated energy intake. Under a dietitian's advice, a recommended energy intake of 30–35 kcal/kg was adjusted depending on their activity, with a protein intake of 1.0–1.2 g/kg and fat intake of below 50 g/day. Patients with inadequate food intake received supplemental enteral nutrient. A dietitian checked BW at every measurement day by indirect calorimetry and instructed on maintaining adequate BW.

Laboratory data

Serum biochemical parameters (white blood cells [WBC], red blood cells [RBC], hemoglobin [HGB], platelets [PLT], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [T-bil], direct bilirubin [D-bil], γ-glutamyltransferase [GGT], total protein [TP], albumin [Alb], cholinesterase [ChE], ammonia [NH_3] and C-reactive protein [CRP]) were measured prior to and 1, 6 and 12–24 months after LDLT. Blood samples were taken to determine the concentrations of fasting blood glucose (FBG) and non-esterified fatty acids (NEFA) at the indirect calorimetry measurements.

Energy measurements

Measurements of energy expenditure were made before and 1, 6, and 12–24 months after LDLT. Indirect calorimetry measurements were carried out at 07.30 hours after overnight fasting using an AE-300S respiratory gas analyzer (Minato Medical Science, Osaka, Japan). The O_2 consumption and CO_2 production rates were calculated, and once an equilibrium steady state was achieved, these values were used to calculate the REE. The basal energy expenditure (BEE) was estimated according to the equation reported by Harris and Benedict,[17] and the ratio of REE to BEE was expressed as the %REE. Urine was collected to assay the amount of nitrogen excretion. The npRQ was calculated from measurements of the daily urinary nitrogen excretion.

HRQOL

Questionnaires were completed prior to and 1, 3, 6 and 12–24 months after LDLT. HRQOL was assessed by the Short-Form Version 2 (SF-36v2)[18,19] which consists of

eight categories, including physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). It also includes two summary areas, with one representing a physical component summary (PCS) and the other a mental component summary (MCS). The raw scores were linearly transformed with standard scoring algorithms yielding scores that were then further adjusted using a Japanese norm-based scoring system to generate normalized scores with a mean (standard deviation) of 50 ± 10 (norm-based scores [NBS]).[20]

Statistical analysis

All data are expressed as mean ± standard error. Statistical analyses were performed using SPSS for Windows, version 16.0 (SPSS, Chicago, IL, USA). Repeated measures ANOVA with subsequent Dunnett's test were used to assess postoperative changes from the preoperative state. Differences between recipients and control subjects were analyzed with the use of Student's *t*-test. QOL score of LDLT recipient before and after LDLT was compared with healthy control subjects at baseline using Student's *t*-test with Bonferroni correction. Pearson's correlation coefficient analysis and simple regression were used to assess the relationship between npRQ and serum NEFA levels. *P*-values of less than 0.05 were considered statistically significant.

RESULTS

Patients

THE CHARACTERISTICS OF the LDLT patients and control subjects are listed in Table 1. LDLT was performed using the left and caudate lobe for all patients. The severity of postoperative complications was graded according to the Clavien–Dindo classification. Continuous hemodiafiltration was performed in case 7 at 13 days after LDLT, because the patient was complicated with acute renal failure (grade IV-a). Case 1 suffered from supraventricular arrhythmia and case 3 suffered from hemophagocytic syndrome (grade II). Other patients did not have severe complications after LDLT (grade I). None of the patients required reoperation for complications arising from the transplant operation. No patients suffered long-term complications associated with LDLT, such as biliary tract stricture and chronic rejection. The control group consisted of eight healthy individuals who donated part of the liver.

Table 1 Characteristics of LDLT recipients and control subjects

Case	Sex	Age (years)	Bodyweight (kg)	Body mass index (kg/m^2)	MELD score	Child–Pugh		Diagnosis	Period in ICU (days)	Period in hospital (days)	Graft	
						Grade	Score				(g)	GV/SLV (%)
1	M	55	54.5	20.8	16.0	C	13	LC (HCV)/HCC	7	46	396	34.2
2	M	55	67.9	24.3	24.5	C	10	LC (HBV)/FH	7	72	515	41.3
3	F	52	52.9	23.8	12.6	C	11	LC (HCV)/HCC	12	50	510	47.8
4	M	56	61.3	20.5	14.5	C	13	LC (HBV)	7	44	450	36.8
5	M	66	50.1	17.9	14.0	B	9	LC (HCV)/HCC	11	35	420	37.8
6	F	57	52.5	22.7	18.5	C	12	LC (non-B, non-C)	7	50	460	45.6
7	F	59	63.4	27.1	17.8	C	13	LC (HCV)	25	85	385	33.9
8	F	38	57.0	22.5	13.1	C	10	LC (HBV)/HCC	8	37	390	35.2
9	F	56	83.9	28.7	16.3	C	10	LC (HCV)/HCC	6	70	520	37.5
10	F	57	55.9	21.6	27.2	C	11	LF (autoimmune)	8	73	370	32.1
Recipient (n = 10)	M4/F6	55.1 ± 2.2	59.9 ± 3.2	23.0 ± 1.0	17.4 ± 1.5		11.4 ± 0.5		9.8 ± 1.8	56.2 ± 5.5	441.6 ± 20.5	38.2 ± 1.8
Control (n = 8)	M7/F1	48.8 ± 4.8	58.6 ± 1.9	20.9 ± 0.6								

Values are expressed as mean ± standard error.
FH, fulminant hepatitis; GV/SLV, graft volume/standard liver volume; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; LC, liver cirrhosis; LF, liver failure; MELD, model for end-stage liver disease.

Table 2 Body composition and energy intake

	Control	Before LDLT	After LDLT		
			1 month	6 months	12–24 months
Body composition					
BW (kg)	58.6 ± 1.9	59.9 ± 3.2	56.5 ± 3.6	56.0 ± 2.0	59.6 ± 3.9
BMI (kg/m^2)	20.9 ± 0.6	23.0 ± 1.0	21.7 ± 1.3	21.1 ± 0.6	22.8 ± 1.1
Energy intake					
Total (kcal/day)	1996 ± 71	1570 ± 102†	1736 ± 173	1823 ± 125	1873 ± 101
per kg of BW (kcal/kg per day)	34.3 ± 1.7	26.8 ± 4.0†	31.5 ± 1.4	33.2 ± 0.1	31.2 ± 0.1

Values are expressed as mean ± S.E.
$^\dagger P < 0.05$ vs control value (unpaired Student's *t*-test).
BMI, body mass index; BW, bodyweight; LDLT, living donor liver transplantation.

Body composition and dietary intake

Table 2 lists the measurement data for BW, BMI and dietary intake. The mean BW decreased 3.4 ± 1.4 kg in the first month after the operation. An identical trend was observed for BMI. However, there were no significant differences in BW and BMI among postoperative measurements compared with the preoperative values.

The patient preoperative dietary intake was 26.8 ± 4.0 kcal/kg per day, while the postoperative dietary intake was 31.5 ± 1.4, 33.2 ± 0.1 and 31.2 ± 0.1 kcal/kg per day at 1, 6 and 12–24 months, respectively, after LDLT. The postoperative values also did not significantly differ from those obtained before the transplant.

Laboratory data

The serum of LDLT recipients and control patients were subjected to various biochemical analyses (Table 3). The WBC count did not differ significantly at each postoperative time point compared with preoperative value. However, the RBC count and HGB levels had not returned to normal levels after 12–24 months, while the PLT numbers significantly increased in all periods after LDLT. Both T-bil and D-bil were higher in preoperative measurements compared with normal levels, but they had returned to normal levels after 6 months. Although GGT did not significantly differ at most postoperative time points compared with the preoperative value, it increased during the first 6 months after LDLT. After an initial decrease, TP returned to normal levels after 6 months. Alb was significantly higher in both the 1- and 6-month measurements after LDLT, but it returned to the lower limit of normal levels after 12–24 months. FBG did not significantly change at each postoperative point compared with the preoperative value. Although the amount of NH_3 was higher in the preoperative sample compared with normal levels, it significantly decreased in all periods after LDLT. ChE significantly increased after LDLT from its initially low level in the 6- and 12–24-month serum samples and had reached normal levels after 6 months. The preoperative levels of NEFA were higher than the normal levels and significantly decreased after the operation. In addition, simple regression analysis revealed a negative correlation between npRQ and serum NEFA concentrations for samples regardless of when they were collected ($r = -0.624$, $P < 0.001$; Fig. 1).

Nutritional metabolism

Although there was a great variability in the anthropometric and laboratory data between individuals, the preoperative mean of the npRQ value was consistently low (0.796 ± 0.026). However, it increased to 0.888 ±

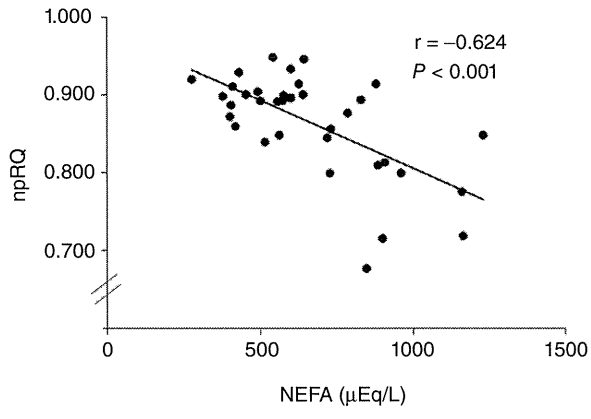

Figure 1 Relationship between npRQ and serum NEFA levels. ($P < 0.001$; Pearson's correlation coefficient analysis). NEFA, non-esterified fatty acids; npRQ, non-protein respiratory quotient.

Table 3 Laboratory data in LDLT recipients and control subjects

	Control	Before LDLT	After LDLT		
			1 month	6 months	12–24 months
WBC (/μL)	6163 ± 826	4440 ± 1217	6470 ± 1391	5478 ± 797	5544 ± 665
RBC ($\times 10^6$/μL)	4.28 ± 0.13	3.19 ± 0.18†	3.19 ± 0.15	3.89 ± 0.28*	4.10 ± 0.30*
HGB (g/dL)	12.5 ± 0.5	10.8 ± 0.5†	10.6 ± 0.5	12.0 ± 0.8	12.9 ± 0.9*
PLT ($\times 10^4$/μL)	25.6 ± 1.7	7.3 ± 1.6†	29.5 ± 4.2*	22.6 ± 2.9*	22.5 ± 1.7*
AST (IU/L)	17 ± 1	71 ± 18†	61 ± 26	30 ± 8	29 ± 7
ALT (IU/L)	17 ± 3	42 ± 12	62 ± 17	23 ± 6	16 ± 2
T-bil (mg/dL)	0.8 ± 0.1	9.5 ± 4.0	2.7 ± 1.4	0.9 ± 0.1*	1.0 ± 0.1*
D-bil (mg/dL)	0.1 ± 0.0	4.8 ± 2.8	1.4 ± 1.1	0.2 ± 0.1	0.1 ± 0.0
GGT (IU/L)	25 ± 5	30 ± 5	105 ± 18	112 ± 66	74 ± 31
TP (g/dL)	6.8 ± 0.1	6.3 ± 0.3	5.7 ± 0.1*	6.6 ± 0.1	7.1 ± 0.1*
Alb (g/dL)	3.9 ± 0.1	2.4 ± 0.1†	3.4 ± 0.1*	3.7 ± 0.2*	4.0 ± 0.1*
ChE (IU/L)	292 ± 22	77 ± 14†	132 ± 12*	299 ± 6*	309 ± 21*
NH_3 (μg/dL)	39 ± 4	91 ± 12†	43 ± 2*	41 ± 5*	35 ± 4*
CRP (mg/dL)	0.15 ± 0.08	0.64 ± 0.19†	0.74 ± 0.17	0.22 ± 0.08	0.29 ± 0.15
ICG15R (%)	5.1 0.9	45.4 ± 3.2†			
FBG (mg/dL)	94 ± 3	106 ± 9	89 ± 4	106 ± 8	113 ± 6
NEFA (μEq/L)	402 ± 42	1002 ± 112†	630 ± 66*	602 ± 17*	501 ± 45*

Values are expressed as mean ± standard error.
*$P < 0.05$ vs preoperative value (Dunnett's multiple comparison test).
†$P < 0.05$ vs control value (unpaired Student's *t*-test).
Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ChE, cholinesterase; CRP, C-reactive protein; D-bil, direct bilirubin; FBG, fasting blood glucose; GGT, γ-glutamyltransferase; HGB, hemoglobin; ICGR15, retention rate of indocyanine green in 15 min; LDLT, living donor liver transplantation; NEFA, non-esterified fatty acids; NH_3, ammonia; PLT, platelet; RBC, red blood cell; T-bil, total bilirubin; TP, total protein; WBC, white blood cell.

0.011, 0.895 ± 0.009 and 0.892 ± 0.010 at 1, 6 and 12–24 months, respectively, after the operation, which represented a significant difference when compared to the preoperative value (Fig. 2). In addition, although the npRQ was lower in the recipient group than the control group prior to LDLT, there was no significant difference between these groups after LDLT.

In this study, the %REE (86.4 ± 4.3) in the preoperative state was similar with the values determined for the control group. After LDLT, the %REE increased to 92.3 ± 2.8% during the first month, and significantly increased to 98.7 ± 3.1% and 98.3 ± 2.6% at 6 and 12–24 months, respectively, after the operation.

HRQOL

During the preoperative period, the mean HRQOL scores for all of the represented scales were below the control group and Japanese NBS. One physical (PF) and two psychological (VT and SF) components were significantly improved after 12–24 months compared with the preoperative values (Fig. 3). Although the PCS was also significantly improved after 12–24 months, this score remained lower than the control group and Japanese NBS. In contrast, the MCS did not differ at each time point compared with the control group and Japanese NBS.

DISCUSSION

AS THE LIVER plays a central role in fuel and energy metabolism, protein-energy malnutrition is common in patients with liver cirrhosis due to abnormal fuel metabolism. Energy metabolism is unbalanced in patients with a poor nutritional status, as demonstrated by increased and decreased rates of lipid and glucose oxidation, respectively. In this study, the npRQ of the patients prior to LDLT was initially low; however, it significantly increased after the operation. Thus, patients had more calories derived from fat and fewer calories derived from carbohydrates before LDLT due to decreased glycogen storage as a result of liver disorder and is consistent with a previous report.[10] Moreover, a decreased npRQ in the fasting state in cirrhotic patients would induce an elevation of serum NEFA concentra-

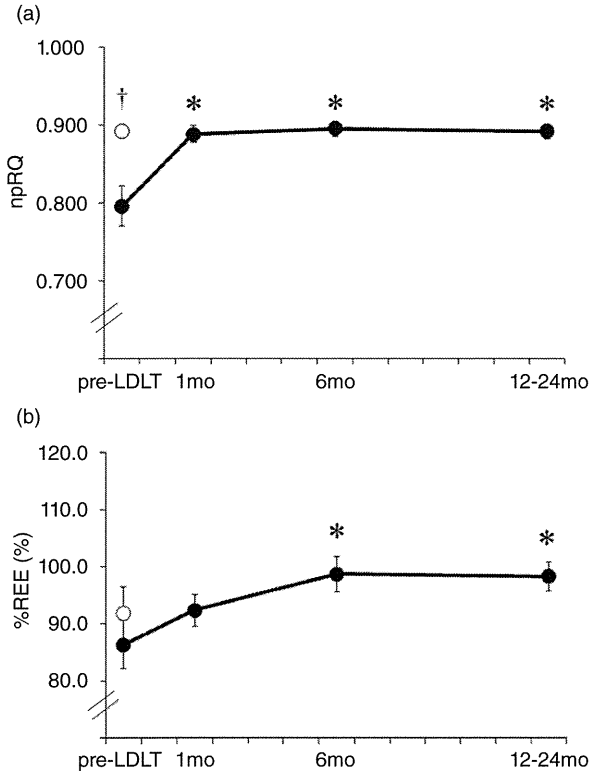

Figure 2 (a) npRQ and (b) %REE before and after LDLT. Open squares indicate control; filled squares indicate LDLT recipients. Values are expressed as mean ± standard error. $*P < 0.05$ vs preoperative value (Dunnett's multiple comparison test). $\dagger P < 0.05$ vs control value (unpaired Student's *t*-test). %REE, resting energy expenditure/basal energy expenditure; LDLT, living donor liver transplantation; npRQ, non-protein respiratory quotient. -○-, control: -●-, LDLT recipients.

tions by diminishing glucose oxidation and decrease glycogen stores in the liver and skeletal muscle.[5] Although the mean NEFA value was high before LDLT, it was significantly lower at all postoperative time points compared with the preoperative value. Moreover, a negative correlation was observed between npRQ and NEFA. For the diagnosis of npRQ, however, indirect calorimetry is required so that in daily practice most clinicians cannot use this approach. Taken together, these results suggest that the assessment of serum NEFA concentrations is a useful predictor of npRQ values, without the need for time-consuming indirect calorimetry measurements.

We also assessed changes in the laboratory data of blood serum associated with LDLT. The parameters of liver detoxification capacity, such as NH_3 and T-bil levels, immediately improved after transplantation. However, the length of time for the ChE and Alb levels, which indicate hepatic protein synthetic capacity, to improve to normal levels required 6 and 12–24 months, respectively. In a previous study, measuring the ChE activity showed liver function, which was useful for determining the prognosis of patients during the post-transplantation[21] and recovery period, which also agreed with past reports.[22] Although the mean npRQ was lower in the recipient group than the control group before LDLT, there was no significant difference between these groups 1 month after the transplantation. These results

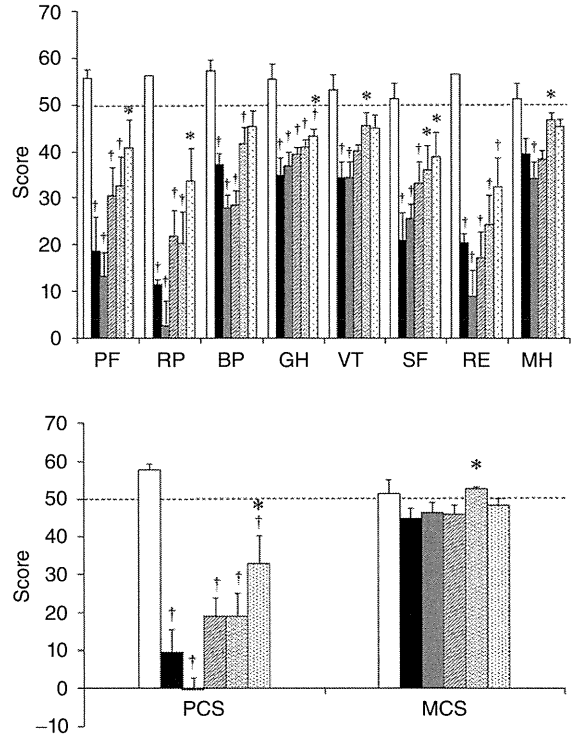

Figure 3 Normalized SF-36 scores at pre- and post-LDLT. Values are expressed as mean ± standard error. $*P < 0.05$ vs preoperative value (Dunnett's multiple comparison test). $\dagger P < 0.05$ vs control value (unpaired Student's *t*-test with Bonferroni correction). Fifty is the reference score of the general population. BP, bodily pain; GH, general health; LDLT, living donor liver transplantation; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; SF-36, 36-item Short-Form; VT, vitality. □, control: ■, pre-LDLT; ▩, 1 month; ▨, 3 months; ▧, 6 months; ⊡, 12–24 months.

indicate that the patients' glycogen storage capacity improved to a comparable level with healthy subjects quite quickly after LDLT. Thus, although the liver detoxification and glycogen storage capacities were improved at an early postoperative period, a much longer recovery period is required to improve the hepatic protein synthetic capacity, as indicated by serum ChE and Alb levels. Therefore, these results strongly suggest that long-term nutritional management of at least 24 months is necessary in LDLT recipients.

As patients with cirrhosis have been reported to have either increased,[10] normal[7,11] or decreased[7] resting metabolic rates, this issue remains controversial. Although we have previously reported that the measured energy expenditure in Child–Pugh class A patients was typically higher than control subjects,[6] in the present study, a clear conclusion could not be reached because both hypo- and normal metabolism were observed in the liver cirrhosis patients. The variability observed in the results between these studies may have originated from differences in the degree of severity, individual variation and primary disease etiology. Thus, based on these existing variables, it would be appropriate to extend the metabolic analyses to include more cases in future studies to resolve this issue.

We also evaluated the progression of HRQOL effects before and after LDLT with the use of the Short-Form health survey, known as the SF-36, which is currently the principal tool used for reporting HRQOL changes by managed-care plans. It is also the most frequently used survey in clinical trials for a variety of interventions in a number of disorders.[19] The HRQOL of patients with severe liver cirrhosis (Child–Pugh class C) as assessed using the SF-36 were lower than those of patients with mild to moderate liver cirrhosis (Child–Pugh class A and B), as previously reported.[23–25] In this study, most patients were of Child–Pugh class C before LDLT. During the preoperative period, the patient scores for all eight scales were below the Japanese NBS, with the PCS representing the lowest value (Fig. 3). Although the HRQOL scores improved after LDLT, they tended to score below the general population in most areas even after 12–24 months, which is a trend that has been reported previously.[26] Although the PCS remained lower than the Japanese NBS, it displayed remarkable recovery within 12–24 months after LDLT. Among the factors that can affect the perception of HRQOL after LDLT, recurrent hepatitis C virus (HCV) infections and post-transplant complications were reported in previous studies to be of importance.[27,28] However, HCV did not recur in our patients after LDLT and helps explain why all HRQOL scores improved after LDLT. Our patients did not display remarkable depression on the MCS though the pre- and postoperative periods, and this may be attributed to the feeling of rebirth these patients experienced by having survived a serious illness and the greater well-being that might have accompanied this change. In addition, the recovery of PCS was observed only after all domains of laboratory data and energy metabolism based on the nutrition state were also improved. Therefore, the improvement of HRQOL encompasses a comprehensive index of progress after LDLT.

In conclusion, this study has demonstrated differences in the recovery time of nutritional metabolism function, serum biochemical data and HRQOL in LDLT patients. In particular, hepatic protein synthesis capacity and the physical score in HRQOL were shown to require a long recovery period. Therefore, it is proposed that long-term, adequate and careful nutritional care for a minimum of 2 years is required in LDLT patients. In the present study, the observed npRQ values of LDLT patients in the preoperative state were lower than the control group. As the RQ decreases after overnight fasting due to glycogen depletion in patients with liver cirrhosis, it is recommended that frequent meals and a late evening snack be consumed to correct fasting starvation in the morning.[29] The observed decrease in the npRQ in the preoperative state was thought to be due to insufficient glycogen storage in the liver. In addition, a long recovery time after LDLT is needed to improve the hepatic protein synthesis capacity. As current research indicates that branched-chain amino acid (BCAA) supplementation after hepatectomy promotes rapid improvement of protein metabolism,[30] the administration of BCAA after LDLT may be beneficial for patients' nutritional state.

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REFERENCES

1 Starzl TE, Demetris AJ, Van Thiel D. Liver transplantation (2). *N Engl J Med* 1989; **321**: 1092–9.

2 Society TJLT. Liver Transplantation in Japan: registry by the Japanses Liver Transplantation Sciety. *Jpn J Transplant* 2008; 423–26.
3 Pikul J, Sharpe MD, Lowndes R, Ghent CN. Degree of preoperative malnutrition is predictive of postoperative morbidity and mortality in liver transplant recipients. *Transplantation* 1994; **57:** 469–72.
4 Harrison J, McKiernan J, Neuberger JM. A prospective study on the effect of recipient nutritional status on outcome in liver transplantation. *Transpl Int* 1997; **10:** 369–74.
5 Schneeweiss B, Graninger W, Ferenci P *et al.* Energy metabolism in patients with acute and chronic liver disease. *Hepatology* 1990; **11:** 387–93.
6 Yamanaka H, Genjida K, Yokota K *et al.* Daily pattern of energy metabolism in cirrhosis. *Nutrition* 1999; **15:** 749–54.
7 Merli M, Riggio O, Romiti A *et al.* Basal energy production rate and substrate use in stable cirrhotic patients. *Hepatology* 1990; **12:** 106–12.
8 Fan CL, Wu YJ, Duan ZP, Zhang B, Dong PL, Ding HG. Resting energy expenditure and glucose, protein and fat oxidation in severe chronic virus hepatitis B patients. *World J Gastroenterol* 2008; **14:** 4365–9.
9 Tajika M, Kato M, Mohri H *et al.* Prognostic value of energy metabolism in patients with viral liver cirrhosis. *Nutrition* 2002; **18:** 229–34.
10 Müller MJ, Böker KH, Selberg O. Are patients with liver cirrhosis hypermetabolic? *Clin Nutr* 1994; **13:** 131–44.
11 Mullen KD, Denne SC, McCullough AJ *et al.* Leucine metabolism in stable cirrhosis. *Hepatology* 1986; **6:** 622–30.
12 Plank LD, Metzger DJ, McCall JL *et al.* Sequential changes in the metabolic response to orthotopic liver transplantation during the first year after surgery. *Ann Surg* 2001; **234:** 245–55.
13 Shanbhogue RL, Bistrian BR, Jenkins RL, Randall S, Blackburn GL. Increased protein catabolism without hypermetabolism after human orthotopic liver transplantation. *Surgery* 1987; **101:** 146–9.
14 Testa MA, Simonson DC. Assesment of quality-of-life outcomes. *N Engl J Med* 1996; **334:** 835–40.
15 Bravata DM, Olkin I, Barnato AE, Keeffe EB, Owens DK. Health-related quality of life after liver transplantation: a meta-analysis. *Liver Transpl Surg* 1999; **5:** 318–31.
16 Younossi ZM, McCormick M, Price LL *et al.* Impact of liver transplantation on health-related quality of life. *Liver Transpl* 2000; **6:** 779–83.
17 Harris JA, Benedict FG. *Biometric Studies of Basal Metabolism in Man*. Washington: Carnegie Institute of Washington, 1919.
18 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30:** 473–83.
19 Fukuhara S, Ware JE, Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. *J Clin Epidemiol* 1998; **51:** 1045–53.
20 Fukuhara S, Suzukamo Y. *Manual of SF-336v2 Japanese Version*. Kyoto: Institute for Health Outcome & Process Evaluation Research, 2004.
21 Jankowski J. Liver transplantation in patients with alcoholic cirrhosis. *BMJ* 1990; **301** (6748): 390.
22 Stockmann M, Konrad T, Nolting S *et al.* Major influence of liver function itself but not of immunosuppression determines glucose tolerance after living-donor liver transplantation. *Liver Transpl* 2006; **12:** 535–43.
23 Marchesini G, Bianchi G, Amodio P *et al.* Factors associated with poor health-related quality of life of patients with cirrhosis. *Gastroenterology* 2001; **120:** 170–8.
24 Bryan S, Ratcliffe J, Neuberger JM, Burroughs AK, Gunson BK, Buxton MJ. Health-related quality of life following liver transplantation. *Qual Life Res* 1998; **7:** 115–20.
25 Younossi ZM, Boparai N, Price LL, Kiwi ML, McCormick M, Guyatt G. Health-related quality of life in chronic liver disease: the impact of type and severity of disease. *Am J Gastroenterol* 2001; **96:** 2199–205.
26 Painter P, Krasnoff J, Paul SM, Ascher NL. Physical activity and health-related quality of life in liver transplant recipients. *Liver Transpl* 2001; **7:** 213–19.
27 De Bona M, Ponton P, Ermani M *et al.* The impact of liver disease and medical complications on quality of life and psychological distress before and after liver transplantation. *J Hepatol* 2000; **33:** 609–15.
28 Desai R, Jamieson NV, Gimson AE *et al.* Quality of life up to 30 years following liver transplantation. *Liver Transpl* 2008; **14:** 1473–9.
29 Yamanaka-Okumura H, Nakamura T, Takeuchi H *et al.* Effect of late evening snack with rice ball on energy metabolism in liver cirrhosis. *Eur J Clin Nutr* 2006; **60:** 1067–72.
30 Togo S, Tanaka K, Morioka D *et al.* Usefulness of granular BCAA after hepatectomy for liver cancer complicated with liver cirrhosis. *Nutrition* 2005; **21:** 480–6.

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ORIGINAL ARTICLE

Effects of a whey peptide-based enteral formula diet on liver dysfunction following living donor liver transplantation

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Abstract
Background and aims Whey protein, a protein complex derived from milk is well known as a functional food with a number of health benefits. MEIN® (Meiji Dairies Co., Tokyo Japan) is a functional liquid-type nutritional diet containing whey-hydrolyzed peptide. In this study, we examined the effects of MEIN® on postoperative liver dysfunction in patients who underwent living donor-related liver transplantation (LDLT).
Methods Sixteen adult patients transplanted between 2005 and 2011 at our institute were evaluated retrospectively. In MEIN group ($n = 8$), administration of MEIN® was started around 14 days after liver transplantation when serum liver enzymes were re-elevated, while MEIN® was not administered in the control group ($n = 8$) who did not have postoperative liver dysfunction.
Results In the preoperative clinical characteristics, the model for end-stage liver disease score in the MEIN group was significantly lower than that in the control group. The graft-to-recipient body weight ratio in the MEIN group was lower than that in the control group. Elevation of enzymes in the liver function tests such as alanine aminotransferase and total bilirubin, and C-reactive protein in the MEIN group had significantly improved, and became almost normal values which were the same as those in the control group.
Conclusion These findings suggest that administration of whey-hydrolyzed peptide attenuates the post-transplant liver dysfunction and may avoid an unnecessary liver biopsy.

Keywords Liver transplantation · Whey peptide · Acute cellular rejection · Enteral nutrition

Abbreviations

AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
CRP	C-reactive protein
CT	Computed tomography
GRWR	Graft-to-recipient body weight ratio
HBV	Hepatitis B virus
HCV	Hepatitis C virus
LDLT	Living related donor liver transplantation
LPS	Lipopolysaccharide
MRCP	Magnetic resonance imaging
MELD	Model for end-stage liver disease
T-Bil	Total bilirubin

Introduction

After liver transplantation, the levels of liver enzymes, such as aspartate aminotransferase (AST), and alanine aminotransferase (ALT), are often elevated due to acute cellular rejection, the recurrence of virus hepatitis, portal vein thrombosis, hepatic artery thrombosis, hepatic vein obstruction, bile duct complications, drug-induced liver injury, and various types of infection [1, 2]. The presence of vessel thrombosis or obstruction and bile duct complications can be determined by imaging modalities, such as ultrasonography (US), dynamic computed tomography

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