Table 1 Reasons not indicated for transplantation

Variables	Patients ($n = 81$)
Recipient-related reasons	55 (68%)
Declined to undergo transplantation	6 (7%)
Lack of abstinence	17 (21%)
Medically not indicated	23 (29%)
Others	9 (11%)
Donor-related reasons	26 (32%)
No volunteer donor	11 (13%)
Medical ineligibility	15 (19%)

Table 3 Reasons for mortality and rejection in 8 patients

No.	Causes of mortality	Causes of rejection
1	LF	No volunteer donor
2	LF	Medically not indicated
3	LF	Declined to undergo LT
4	LF	Lack of abstinence
5	Bleeding of esophageal varices	Medically not indicated
6	LF	Medically not indicated
7	HCC	Medically not indicated
8	LF	No volunteer donor

All liver failures were caused by chronic ALD or alcoholic liver cirrhosis.
HCC, hepatocellular carcinoma; LF, liver failure; LT, liver transplantation.

[10–13] vs 9 [7–13], $P < 0.0025$). The Model for End-Stage Liver Disease (MELD) score was not significantly different between the two groups. The alcohol consumption history variables, such as High-Risk Alcoholism Relapse scale, duration of heavy drinking, average daily drinking, lifetime alcohol consumption and previous alcohol treatment, were also not significantly different between the two groups. The reasons for death and rejection in the mortality group are shown in Table 3. Causes of death were liver failure due to chronic ALD or alcoholic liver cirrhosis ($n = 6$), bleeding of esophageal varices ($n = 1$) and hepatocellular carcinoma ($n = 1$).

Table 4 shows the characteristics of 13 patients with decompensated liver cirrhosis due to ALD who underwent LDLT. The median Child–Pugh score was 11 (range, 7–12) and MELD score was 19 (10–23). Alcoholic liver cirrhosis in three patients (cases 2, 9 and 11) was caused by a relatively small amount of lifetime alcohol consumption (0.59 ton, 0.34 ton and 0.58 ton). Patients with ALD comprised 3% (13/400) of adult LDLT recipients. This proportion was similar to that of LT in Japan, 3.5% of adult recipients (134/3796), reported by the Japanese Liver Transplantation Society.[1] Long-term survival after LT for the ALD group ($n = 13$; median follow-up period [range], 38 months [2.1–111]) and non-ALD group ($n = 387$; 88 months [0.2–197]) is shown in Figure 2. The 1-, 3- and 5-year overall survival rates were 100%, 91% and 91% in the ALD group, respectively, and 90%, 86% and 83% in the non-

Table 2 Comparison between 6-month abstinence group and mortality within 6 months of referral group

Variables	Abstinence ($n = 21$)	Mortality ($n = 8$)	*P*-value
Male sex	15 (81%)	6 (75%)	0.62
Age (years)†	51 (35–65)	54 (41–64)	0.56
Child–Pugh score†	9 (7–13)	12 (10–13)	0.025
A (5–6)	0	0	
B (7–9)	10 (48%)	0	
C (10–15)	11 (52%)	7 (100%)	
MELD score†	17 (10–25)	20 (10–23)	0.49
HRAR scale†	2 (1–4)	2 (2–3)	0.69
0–3	20 (95%)	7 (100%)	
4–6	1 (5%)	0	
Duration of heavy drinking (years)†	27 (15–44)	32 (30–40)	0.14
Average daily drinking‡ (g)†	108 (44–360)	81 (44–144)	0.20
Lifetime alcohol consumption‡ (ton)†	1.3 (0.3–3.0)	1.0 (0.5–1.6)	0.27
Previous alcohol treatment†	0 (0–1)	0	0.55

†Median (range). ‡As ethanol.
HRAR, High-Risk Alcoholism Relapse; MELD, Model for End-Stage Liver Disease.

Table 4 Characteristics of 13 patients who underwent liver transplantation

No.	Age (years)	Sex	HCC	Child–Pugh score	MELD score	Drinking (g/day)†	Duration (years)	HRAR scale	Alcohol consumption (ton/life)†
1	52	M	y	7	10	144	30	2	1.6
2	44	M	n	11	20	64	25	2	0.59
3	57	M	y	9	14	108	30	2	1.2
4	65	M	n	7	14	88	30	2	1.2
5	43	M	n	12	19	360	20	4	2.6
6	36	F	n	10	17	176	15	2	0.96
7	65	M	n	11	23	88	44	2	1.4
8	62	M	y	9	18	122	40	3	1.8
9	41	F	n	9	20	44	21	1	0.34
10	51	M	n	8	10	144	28	3	1.5
11	45	F	n	12	14	64	25	2	0.58
12	51	M	y	9	14	80	25	2	0.73
13	56	F	y	9	14	100	25	2	0.90
Median	52			11	19	99	30	2	1.2
Range	35–64			7–12	10–23	44–240	15–40	2–3	0.55–1.6

†As ethanol.
HCC, hepatocellular carcinoma; HRAR, High-Risk Alcoholism Relapse; MELD, Model for End-Stage Liver Disease.

ALD group, respectively. Overall survival did not differ significantly between groups ($P = 0.460$). One patient in the ALD group died from recurrence of hepatocellular carcinoma. The rate of alcohol relapse after LT was 8% ($n = 1/13$, patient no. 1 in Table 4) in our series; however, this patient achieved re-sobriety after participating in an abstinence program.

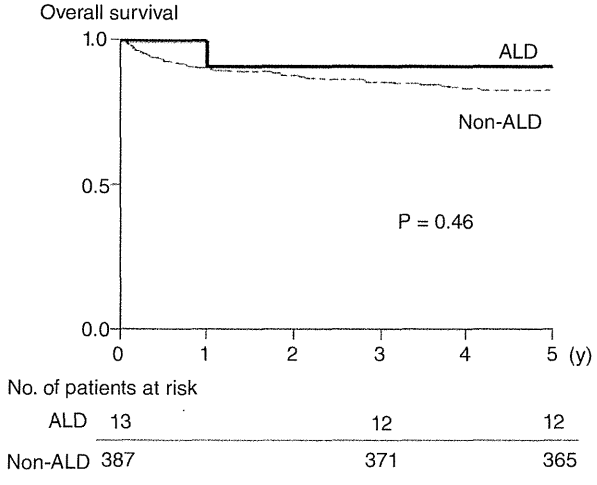

Figure 2 Long-term overall survival rates of liver transplant patients calculated from the time of surgery. ALD, alcoholic liver disease.

DISCUSSION

THE FINDINGS OF the present study demonstrated that LT for ALD within our indication criteria achieved good long-term survival and abstinence rates after LT. An abstinence period of at least 6 months before LT as an indication criterion for LDLT was acceptable to avoid re-drinking after LT and to confirm the possibility of recovery from liver failure.

The Japanese Liver Transplantation Society reported overall survival rates for ALD patients of 81.3% at 1 year, 78.5% at 3 years and 75.7% at 5 years.[1] Similar survival rates for ALD patients were reported in Europe (84% at 1 year, 78% at 3 years and 73% at 5 years)[2] and the USA (92% at 1 year, 86% at 3 years and 5 years).[14] LT for ALD patients within our indication criteria is supported by our findings, as the survival rates for those in our series (100% at 1 year, 91% at 3 years and 91% at 5 years) were higher compared to the three reports mentioned above. Despite the lack of a commonly accepted definition, the rate of alcohol relapse is reported to be relatively high, ranging 11.9–45.6%,[15–17] compared to the present findings (8%).

Mathurin *et al.* reported that early LT without an abstinence period can improve survival in patients with a first episode of severe alcoholic hepatitis.[18] Despite different objectives (treating chronic ALD in our series vs acute ALD in Mathurin *et al.*'s series) and different approaches (LDLT prevailing in East Asia regions vs

DDLT),[19] 21% of ALD patients in our study could not abstain from drinking alcohol before and/or after LT (Table 1). Graft failure and loss induced by re-drinking[7] might be missed if LT without an abstinence period were indicated based on optimism for sobriety after LT. Moreover, abstinence before LT allows for an observation period to confirm recovery from liver failure, avoiding unnecessary LT and the potential risks to the donors,[20] because 5% of ALD patients showed non-impaired liver function after 6-month abstinence (Fig. 1). It may be difficult to predict if ALD patients will achieve abstinence and be eligible for the next treatment step or die prior to transplantation, however, because no variables were found that distinguished the abstinence group from the mortality group without Child–Pugh score (Table 2). Indeed, even a relatively small amount of alcohol consumption can cause ALD requiring LT (Table 4). As for predictors of post-LT relapse, length of abstinence of more than 6 months is supported as necessary for selecting a patient for LT;[15,21–23] however, Mackie *et al.* and Veldt *et al.* suggested that LT could be considered after as little as 3 months of abstinence.[16,24] Based on the above points, a fixed period of abstinence, such as 6 months, should be required as an indication criterion for LT, although our data are insufficient for determining how many months of abstinence are necessary.

One of the drawbacks of this study is that, due to the limited number of cases (ALD group, $n = 13$, 13%), our data are not adequate to conclude whether and how long of an abstinence period is required. In addition, a short median follow-up period (38 months) in our series may overestimate the survival rates, because Cuadrado *et al.* reported that the mean interval from transplantation to alcohol relapse, which caused a significant decline in survival rates, was 47.5 months with a range of 5.0–86.9 months.[7] Another limitation related to our indication criteria is that a fixed period of abstinence may lead to an increase in waitlist mortality. To achieve a consensus on the pre-LT abstinence period for ALD, a well-organized randomized controlled trial is needed to determine rules supported by evidence.

In conclusion, an abstinence period of at least 6 months allows for the appropriate prediction of alcohol relapse after LT and selection of recovery from liver failure. LDLT for ALD within our criteria allows for acceptable compliance and sufficient survival benefit after LT, providing results that are complementary with the benefits of recipients and potential risks of donors.

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Original Article

Quality of life after adult living donor liver transplantation: A longitudinal prospective follow-up study

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Aim: Patient survival after living donor liver transplantation (LDLT) has improved, but improvement of the health-related quality of life (HRQOL) of LDLT recipients is also an important issue. The aim of this study was to assess the HRQOL of LDLT recipients from the preoperative period to 18 months following transplantation by prospectively evaluating Short Form-36 Version 2 (SF-36v2) scores.

Methods: Complete longitudinal SF-36v2 scores were collected from 35 consecutive LDLT recipients prior to surgery and at 3, 6, 12 and 18 months after transplantation.

Results: HRQOL scores were severely impaired in all dimensions preoperatively. Although the scores improved significantly up to 18 months after transplantation, they remained lower than those of healthy controls in the majority of domains. Impaired scores preoperatively were significantly associated with severity of liver disease represented by a higher Model for End-Stage Liver Disease (MELD) score and Child–Turcotte–Pugh class C, and scores in such patients improved significantly after LDLT in every dimension at 12 months, indicating that the greater the impairment at the pretransplant stage, the greater the improvement in both physical and mental conditions. Preoperative lower HRQOL scores and higher MELD scores were independently associated with significant physical and mental score gains during the first year after LDLT.

Conclusion: The findings of the present study may facilitate the development of measures aimed at improving recipient's post-transplant life and establishing realistic expectations for LDLT recipients.

Key words: health-related quality of life, liver transplantation, living donor liver transplantation, quality of life, recipient, Short Form-36

INTRODUCTION

LIVING DONOR LIVER transplantation (LDLT) is now a widely accepted and established treatment of choice for end-stage liver disease. An updated Japanese national survey reported 83.4% patient survival at 1 year and 76.9% patient survival at 5 years post-transplant.[1] Because of the improved patient survival in LDLT, a simple survey of mortality and morbidity after transplantation is no longer sufficient for providing an appropriate overview of the effects of medical care and interventions, as in deceased donor liver transplantation (DDLT).[2]

Health-related quality of life (HRQOL) is a quantitative conversion of a patient's self-assessment of the quality of the physical, functional, social and psychological dimensions of his/her life. Outcomes and interventions of the HRQOL survey are based on patient-driven objectives, priorities, interpretations and satisfaction, rather than solely physician-based medical objectives, such as mortality, morbidity and long-term survival. Thus, HRQOL research presents a challenging goal for clinicians to develop an analysis that can be standardized and applied to large patient populations.

Although several studies of a recipient's HRQOL after transplantation[3–8] have been reported for patients undergoing DDLT, those for patients undergoing LDLT

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are scarce.[9] The present study focuses on assessing HRQOL in patients with severe liver disease requiring LDLT in the preoperative period and for up to 18 months following transplantation, prospectively evaluating the longitudinal HRQOL scores using the Short Form-36 Version 2 (SF-36v2) questionnaire.

METHODS

Patients

A PROSPECTIVE, LONGITUDINAL, single-center study was planned to investigate HRQOL scores before and after LDLT. Between May 2006 and October 2009, 61 LDLT were performed in our institution. All recipients were recruited and assessed for inclusion. One recipient declined participation in this study. Nine patients presented with significant hepatic encephalopathy and were excluded from the study. Informed consent was obtained from the remaining 51 recipients. Finally, complete longitudinal data collection for 35 patients was completed during the scheduled period and included in the analysis (Fig. 1).

Methods

Health-related quality of life scores were evaluated using the SF-36v2 questionnaires[10,11] prior to surgery and at 3, 6, 12 and 18 months after transplantation. The 36 questions (items) are distributed across eight health-related dimensions: physical functioning (PF, 10 questions); physical role (PR, four questions); bodily pain (BP, two questions); general health (GH, five questions); vitality (VT, four questions); social functioning (SF, two questions); emotional role (ER, three questions); and mental health (MH, five questions on perceptions of health transition). These scales are scored from 0–100, with higher scores being more positive, like less pain and less limitation. Additionally, physical component summary (PCS) and mental component summary (MCS) scales were also calculated as weighted composites of the scaled scores from each of the eight dimensions.[11] The data were entered into a computer to determine the raw scale score for all multi-item scales and transformed to norm-based scores. Norm-based scores achieved the same mean values of 50 and a standard deviation of 10 in the general Japanese population for all eight scales, and were also used at the outset for PCS and MCS, to facilitate interpretation.[12–14]

Questionnaires were given to patients directly prior to each testing session or were collected by mail-in survey, and each patient completed the self-administered HRQOL questionnaires independently. This study was conducted in accordance with the Declaration of Helsinki, and was approved by the Institutional Review Board of Tokyo University Hospital. The protocol was explained to eligible patients, and written informed consent was obtained from all patients before enrollment. Our surgical techniques and immunosuppressive

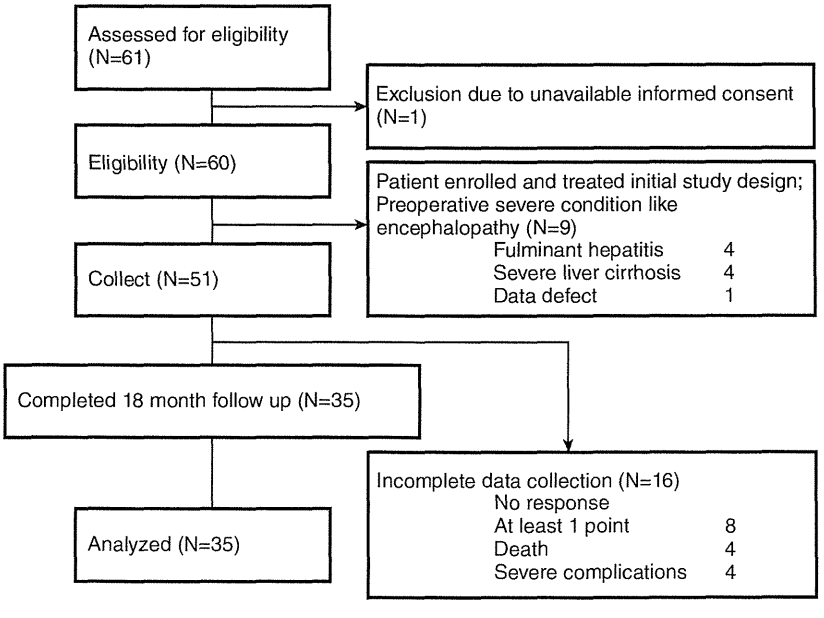

Figure 1 Flow diagram of patient inclusion and exclusion.

regimens (methylprednisolone plus tacrolimus) after LDLT are described elsewhere.[15,16]

Outcome measures

Health-related quality of life scores of all dimensions were measured and analyzed at the pretransplant period, and at 3, 6, 12 and 18 months after LDLT. The difference in the scores at each postoperative assessment was analyzed and compared with that from the pretransplant period. Recipient characteristics, including sex, age, etiology of primary disease, Model for End-Stage Liver Disease (MELD) score, Child–Turcotte–Pugh (CTP) classification, relationship with donor and post-transplant complication, were assessed for association with the preoperative, 12-month and 18-month HRQOL scores of each dimension. Score gains, defined as the difference between the 12-month score and the preoperative score of each dimension, were calculated and assessed for relevance with the aforementioned recipient characteristics. In addition, independent factors affecting pretransplant and 12-month score, and score gains were investigated as for two representing dimensions, PCS and MCS. Complications were defined as any postoperative morbidity requiring redo surgery or interventional treatments during the survey.

Statistical analysis

Values are expressed as the mean with/without standard deviation or median with range as appropriate. Comparisons were performed using one-way ANOVA and Student's *t*-tests, Scheffé's technique for multiple comparisons or the non-parametric Kruskal–Wallis test as appropriate. Multiple regression analysis was performed to investigate independent factors, in which categorization of continuous values was based on receiver-operator curve (for pretransplant scores) or mean value (for age and MELD scores). A *P*-value less than 0.05 was considered statistically significant. Statistical analysis was performed using computer software JMP ver. 5.1 (SAS Institute, Raleigh, NC, USA).

RESULTS

Patient characteristics and pretransplant HRQOL

PATIENT CHARACTERISTICS ARE summarized in Table 1. The population comprised 13 men and 22 women with a median age of 49 years (range, 18–65). The median MELD score was 15 (range, 3–33). The indications for LDLT included hepatitis C virus (HCV) cirrhosis ($n = 12$) and hepatitis B virus (HBV) cirrhosis, including hepatocellular carcinoma (HCC, $n = 12$), cholestatic disease ($n = 6$), alcohol-induced cirrhosis ($n = 2$), acute liver failure ($n = 2$) and others ($n = 7$).

Table 1 Recipient demographics ($n = 35$)

Characteristics	*n*
Sex (male : female)	13:22
Age (years) (range)	49 (18–65)
Etiology of liver disease	
Viral hepatitis	18 (12 HCV, 6 HBV)
Hepatocellular carcinoma	12 (9 HCV, 3 HBV)
Cholestatic disease	6 (5 PBC, 1 AIH)
Alcohol-induced	2
Acute liver failure	2
Others	7
MELD scores	15 (3–33)
Child–Turcotte–Pugh classification	
Class A	1
Class B	13
Class C	19

AIH, autoimmune hepatitis; HBV, hepatitis B; HCV, hepatitis C; PBC, primary biliary cirrhosis; MELD, Model for End-Stage Liver Disease.

The pretransplant HRQOL was severely impaired. All SF-36 dimensions except BP were significantly lower than those of the Japanese healthy norm by more than 20% (Fig. 2). BP and MH were significantly lower in patients with a higher preoperative MELD score, and PR, BP and PCS were significantly lower in CTP class C patients, indicating that the more impaired the liver function, the lower the HRQOL. Additionally, GH was significantly lower in HCV positive recipients, while SF was significantly higher, compared to those negative for HCV (Table 2).

SF-36 scores over time after LDLT

Scores in all dimensions increased over time, except for PR and SF at 3 months, and increased continuously or reached a plateau at 18 months after transplantation. Scores in every dimension were significantly improved at more than 6 months after transplantation (Fig. 2). BP, VT, MH and MCS scores reached levels comparable with the norm, while PF, PR, GH, SF, ER and PCS levels remained significantly lower than the norm at more than 12 months after transplantation (Fig. 2).

Patients with higher preoperative MELD score achieved significantly higher scores in PR, GH, VT, SF, ER, MH, PCS and MCS at 12 months and in PF, PR, GH, VT, SF, ER, MH, PCS and MCS at 18 months after trans-

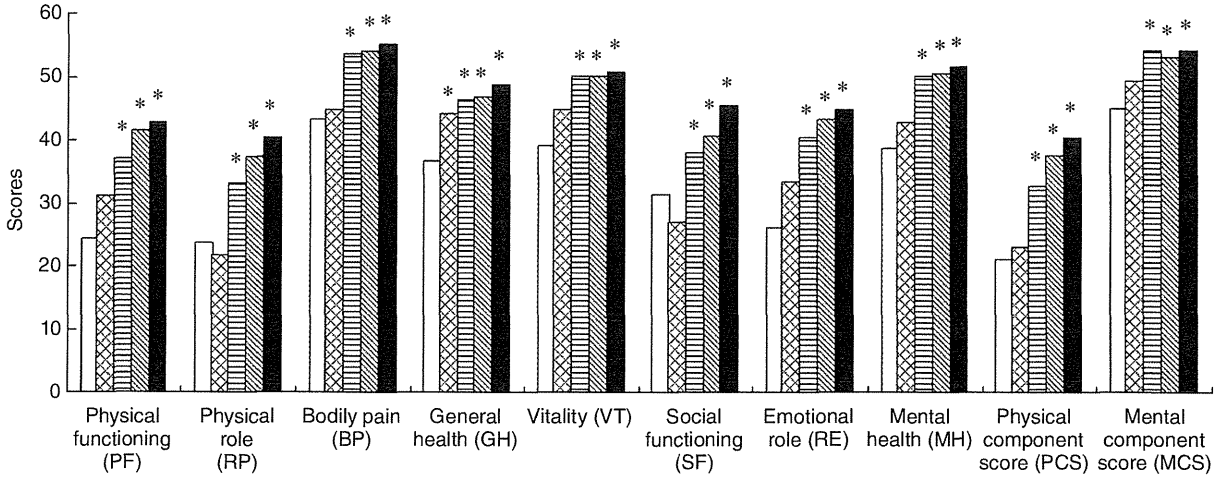

Figure 2 Short Form-36 scores of each dimension preoperatively, and at 3, 6, 12 and 18 months after living donor liver transplantation. *Significant difference compared with the preoperative score ($P < 0.05$). □, 0 months; ⊠, 3 months; ▤, 6 months; ▨, 12 months; ■, 18 months.

plantation than those with lower preoperative MELD scores. Similarly, patients in preoperative CTP class C achieved significantly higher scores in GH and SF at 12 months and in GH, VT, SF and MCS at 18 months (Tables 3,4).

Score gains in SF-36 scores over time after LDLT

The difference between the score in each dimension at 12 months after transplantation and the preoperative score was assessed. Patients with a higher preoperative MELD score gained significantly higher scores in PR, BP, VT, SF, ER, MH and MCS, while gains in the remaining dimensions (PF, GH and PCS) also tended to be higher (Table 5). Similar results were observed in the CTP classification analysis, in which class C patients gained higher scores in all dimensions, achieving a significant difference in PF, PR, BP and PCS (Table 5). Patients experiencing some complication during the post-transplant period showed a significantly lower gain in BP.

Multivariate regression analysis was performed to assess factors affecting the preoperative and 12-month scores, and the score gain in the PCS and MCS dimensions which are coverall domains (Table 6). Higher MELD score was independently associated with lower preoperative MCS score, while it was inversely associated with higher MCS score at 12 months. In the analysis of score gains, only pretransplant lower PCS score was proved to be an independent factor for score gain in the PCS dimension, while pretransplant lower MCS score and higher MELD score were both independent factors for score gain in the MCS dimension, indicating that patients with worse pretransplant condition achieved significantly greater score gains following transplantation.

Relationship between recipient and donor

The relationship between the recipient and donor is one of the most conspicuous factors in LDLT compared to DDLT, and could be associated with postoperative HRQOL in recipients. No differences were observed, however, in any dimension at 12 and 18 months after transplantation with respect to the relationship between the recipient and donor, while child recipients grafted from their parents showed a significantly lower score gain in PF, PR, VT and PCS compared with those grafted from a conjugal counterpart, sibling or child (Tables 3–5).

DISCUSSION

TO THE BEST of our knowledge, this is the first longitudinal analysis of LDLT recipient HRQOL with prospectively collected data. Consistent with the study on DDLT recipients, the scores were significantly impaired before transplantation, and significantly increased over time (for 18 months) after transplantation, but still remained below the level of healthy controls in most dimensions.

Table 2 SF-36 scores before living donor liver transplantation

	Pretransplant SF-36 scores																			
	PF	*P*	PR	*P*	BP	*P*	GH	*P*	VT	*P*	SF	*P*	ER	*P*	MH	*P*	PCS	*P*	MCS	*P*
Overall ($n = 35$)	24.6		23.9		43.4		36.8		39.1		31.4		26.2		38.7		21.1		45.1	
Age, years																				
<50 ($n = 13$)	24	0.905	26.6	0.731	42.4	0.744	39.6	0.107	42.7	0.237	31.3	0.564	31.4	0.235	43.4	0.077	21.9	0.973	48.5	0.2
≥50 ($n = 22$)	24.9		22.6		43.9		35.1		37		31.4		23.2		35.9		20.6		43.1	
Sex																				
Female ($n = 13$)	23.4	0.891	18.7	0.169	42.9	0.932	39.1	0.338	38.4	0.723	27.2	0.184	22.9	0.242	35.8	0.272	17.4	0.453	44.9	0.72
Male ($n = 22$)	25.2		26.9		43.6		35.4		39.5		33.8		28.2		40.4		23.2		45.3	
MELD score																				
<15 ($n = 14$)	27.2	0.593	26.7	0.22	**50.2**	**0.028**	35.2	0.483	41.4	0.493	33.4	0.474	29.7	0.139	**43.3**	**0.042**	24.3	0.443	47.6	0.424
≥15 ($n = 19$)	22.6		21.8		**38.2**		37.9		37.3		29.8		23.6		**35.3**		18.7		43.3	
CTP class																				
A and B ($n = 14$)	32.7	0.073	**33**	**0.017**	**52.5**	**0.007**	37.3	0.8	41	0.589	34.1	0.361	30.1	0.127	41.3	0.301	**31**	**0.02**	45	0.788
C ($n = 19$)	19.1		**18**		**37.3**		36.4		37.8		29.5		23.6		37		**15**		45.2	
HCV																				
No ($n = 23$)	23.6	0.714	24.8	0.834	43.9	0.834	**39.7**	**0.015**	39.5	0.767	**28.5**	**0.048**	25.7	0.674	38.4	0.793	20.8	0.945	45.4	0.835
Yes ($n = 12$)	26.4		22.1		42.2		**31.1**		38.2		**36.8**		27.1		39.4		21.6		44.5	
HCC																				
No ($n = 23$)	22.2	0.383	24.5	0.958	44	0.753	38.4	0.091	39.9	0.601	39.4	0.176	25.9	0.575	37.6	0.612	20.3	0.808	45.4	0.972
Yes ($n = 12$)	29		22.7		42		33.6		37.4		35.2		26.8		40.9		22.5		44.6	

Data is presented as means. Non-parametric Kruskal–Wallis test. Bold texts indicate the statistically significant difference between the groups.
BP, bodily pain; CTP, Child–Turcotte–Pugh; ER, emotional role; GH, general health; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MCS, mental component summary; MELD, Model for End-Stage Liver Disease; MH, mental health; PCS, physical component summary; PF, physical functioning; PR, physical role; SF, social functioning; SF-36, Short Form-36; VT, vitality.

Table 3 SF-36 scores at 12 months after living donor liver transplantation

	SF-36 scores 12 months after transplant																			
Overall ($n = 35$)	PF12 41.5	*P*	PR12 37.3	*P*	BP12 53.9	*P*	GH12 46.8	*P*	VT12 50	*P*	SF12 40.6	*P*	ER12 43.1	*P*	MH12 50.4	*P*	PCS12 37.6	*P*	MCS12 53	*P*
Age, years																				
<50 ($n = 13$)	45.9	0.121	38.1	0.959	55	0.794	48.1	0.515	51.9	0.362	41.4	0.729	44.2	0.707	49.5	0.986	40.3	0.495	52.9	0.838
≥50 ($n = 22$)	38.8		36.9		53.2		46.1		48.8		40.1		42.5		50.9		36		53.1	
Sex																				
Female ($n = 13$)	44	0.904	38.9	0.959	55.6	0.601	49.7	0.145	53.5	0.118	44.4	0.283	44.8	0.986	52	0.668	39.5	0.824	55.8	0.12
Male ($n = 22$)	39.9		36.4		52.9		45.1		47.9		38.2		42.1		49.5		36.5		51.3	
MELD score																				
<15 ($n = 14$)	36.8	0.162	**30.1**	**0.012**	52.2	0.496	**41.1**	**0.002**	**44.3**	**0.006**	**32.1**	**0.001**	**37.6**	**0.047**	**45.6**	**0.02**	**31.7**	**0.02**	**48.2**	**0.007**
≥15 ($n = 29$)	44.9		**42.8**		55.2		**51.2**		**54.2**		**46.9**		**47.2**		**54**		**42**		**56.6**	
CTP class																				
A and B ($n = 14$)	39	0.475	34.3	0.326	54.9	0.63	**43.3**	**0.043**	46.7	0.1	**35.5**	**0.045**	41.4	0.689	47.8	0.23	35.6	0.354	50	0.121
C ($n = 19$)	43.1		39.4		53.2		**49.3**		52.1		**43.9**		44.2		52.1		38.9		55	
HCV																				
No ($n = 23$)	42.1	0.833	39	0.463	54.8	0.523	48.7	0.117	52.4	0.086	41.4	0.764	44.2	0.662	51.2	0.613	38.6	0.509	54.5	0.164
Yes ($n = 12$)	40.2		34.1		52.1		43.4		45.4		39		41		48.9		35.7		50.2	
HCC																				
No ($n = 23$)	42.9	0.598	37.7	0.875	54.8	0.523	48.8	0.091	51.6	0.263	40.8	0.916	42	0.598	49.6	0.793	38	0.781	53.6	0.651
Yes ($n = 12$)	39.7		36.6		52.1		43		46.9		40.1		45.3		52		36.2		51.7	
Complications																				
No ($n = 21$)	42.4	0.799	37.6	0.968	56.2	0.135	46.2	0.761	50	0.946	40.5	0.918	43.6	0.845	50.9	0.636	38.5	0.866	53	0.973
Yes ($n = 14$)	40		36.9		50.4		47.8		50		40.7		42.3		49.7		36.2		53	
Relationship																				
Conjugal ($n = 13$)	49.2	NS	42.3	NS	57	NS	49	NS	52.9	NS	42.9	NS	48.1	NS	53.2	NS	44.4	NS	53.9	NS
Parent ($n = 4$)	41.9		34.1		53.9		41.9		50.3		42.3		43.9		50.4		36.5		52.8	
Child ($n = 12$)	33.1		31.8		49.5		47		47.2		36.8		37.8		47.1		30		52.3	
Sibling ($n = 6$)	41.1		39.8		55.9		45.3		49.2		41.2		42.4		50.9		38.8		52.5	

Data is presented as means. Non-parametric Kruskal–Wallis test or Scheffé's technique. Bold texts indicate the statistically significant difference between the groups.
BP, bodily pain; CTP, Child–Turcotte–Pugh; ER, emotional role; GH, general health; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MCS, mental component summary; MELD, Model for End-Stage Liver Disease; MH, mental health; NS, not significant; PCS, physical component summary; PF, physical functioning; PR, physical role; SF, social functioning; SF-36, Short Form-36; VT, vitality.

Table 4 SF-36 scores at 18 months after living donor liver transplantation

	SF-36 scores 18 months after transplant																			
	PF18	*P*	PR18	*P*	BP18	*P*	GH18	*P*	VT18	*P*	SF18	*P*	ER18	*P*	MH18	*P*	PCS18	*P*	MCS18	*P*
Overall ($n = 35$)	44.6		40.4		56.0		50.2		51.7		45.8		46.2		52.1		41.4		55.0	
Age, years																				
<50 ($n = 13$)	46.3	0.213	41.3	0.871	57.1	0.673	50.9	0.634	52.3	0.483	47.1	0.321	47.1	0.804	51.8	0.893	44.3	0.532	56.0	0.911
≥50 ($n = 22$)	40.8		38.9		54.8		48.1		50.8		44.1		46.5		52.9		38.9		54.7	
Sex																				
Female ($n = 13$)	44.9	0.872	40.8	0.903	58.1	0.492	51.2	0.291	53.8	0.482	48.1	0.789	46.6	0.824	53.8	0.562	43.7	0.722	58.6	0.651
Male ($n = 22$)	43.9		39.4		54.2		48.7		50.9		44.2		45.1		51.7		39.5		54.3	
MELD score																				
<15 ($n = 14$)	**37.8**	**0.03**	**33.1**	**0.006**	55.8	0.782	**40.7**	**0.001**	**43.2**	**0.008**	**38.1**	**0.001**	**39.1**	**0.021**	**47.6**	**0.013**	**32.7**	**0.001**	**50.1**	**0.009**
≥15 ($n = 29$)	**50.1**		**47.8**		58.2		**57.2**		**56.2**		**52.1**		**54.3**		**58.3**		**46.3**		**59.9**	
CTP class																				
A and B ($n = 14$)	40.6	0.108	38.4	0.112	55.8	0.798	**44.8**	**0.02**	**45.9**	**0.043**	**40.1**	**0.031**	41.4	0.689	49.3	0.346	40.5	0.723	**50.7**	**0.031**
C ($n = 19$)	45.8		42.7		57.5		**54.1**		**56.5**		**49.8**		44.2		55.4		42.3		**57.9**	
HCV																				
No ($n = 23$)	45.3	0.792	42.7	0.531	57.3	0.672	51.2	0.298	51.7	0.159	47.3	0.583	47.8	0.387	54.2	0.492	42.1	0.173	57.4	0.519
Yes ($n = 12$)	43.2		38.5		55.5		48.4		48.7		43.8		44.1		50.1		39.8		53.6	
HCC																				
No ($n = 23$)	45.3	0.723	41.7	0.652	57.5	0.630	50.6	0.301	52.1	0.891	46.1	0.722	44.8	0.392	51.6	0.623	42.8	0.395	57.9	0.409
Yes ($n = 12$)	42.6		38.9		53.8		47.4		50.3		44.7		49.1		54.1		39.1		54.2	
Complications																				
No ($n = 21$)	44.1	0.832	41.2	0.874	59.7	0.397	49.6	0.691	52.1	0.751	46.1	0.942	46.8	0.761	53.1	0.467	41.9	0.924	55.2	0.941
Yes ($n = 14$)	46.3		39.7		55.3		51.2		51.1		45.7		45.3		50.9		40.8		54.9	
Relationship																				
Conjugal ($n = 13$)	52.1	NS	42.5	NS	60.1	NS	51.2	NS	52.3	NS	46.1	NS	50.4	NS	56.2	NS	47.1	NS	55.2	NS
Parent ($n = 4$)	48.4		39.1		55.1		44.8		51.4		44.8		48.2		52.3		40.1		53.9	
Child ($n = 12$)	35.1		34.8		51.4		44.5		50.7		39.9		40.2		49.2		36.9		55.4	
Sibling ($n = 6$)	39.8		35.8		50.1		49.1		50.2		47.1		41.9		51.4		39.3		54.2	

Data is presented as means. Non-parametric Kruskal–Wallis test or Scheffé's technique. Bold texts indicate the statistically significant difference between the groups.
BP, bodily pain; CTP, Child–Turcotte–Pugh; ER, emotional role; GH, general health; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MCS, mental component summary; MELD, Model for End-Stage Liver Disease; MH, mental health; PCS, physical component summary; PF, physical functioning; PR, physical role; SF, social functioning; SF-36, Short Form-36; VT, vitality.

Table 5 SF-36 score difference (gain) 12 months after living donor liver transplantation

	Score gain during first year (score at 12 months – pretransplant score)																			
	ΔPF	*P*	ΔPR	*P*	ΔBP	*P*	ΔGH	*P*	ΔVT	*P*	ΔSF	*P*	ΔER	*P*	ΔMH	*P*	ΔPCS	*P*	ΔMCS	*P*
Overall ($n = 35$)	16.9		13.4		10.5		10.1		10.9		9.2		16.8		11.7		16.5		7.9	
Age, years																				
<50 ($n = 13$)	21.9	0.365	11.6	0.657	12.7	0.356	8.5	0.584	9.2	0.745	10.1	0.757	12.8	0.372	6.1	0.321	18.5	0.263	4.4	0.651
≥50 ($n = 22$)	13.9		14.6		9.3		11		11.9		8.7		19.3		15		15.4		9.9	
Sex																				
Female ($n = 13$)	20.6	0.573	20.2	0.065	12.8	0.393	10.6	0.824	15.1	0.199	17.2	0.054	21.9	0.154	16.1	0.304	22.1	0.12	11	0.26
Male ($n = 22$)	14.7		9.5		9.2		9.8		8.4		4.5		13.9		9.1		13.3		6.1	
MELD score																				
<15 ($n = 14$)	9.6	0.205	**3.4**	**0.029**	**1.9**	**0.02**	5.8	0.051	**2.9**	**0.02**	**−1.3**	**0.02**	**7.9**	**0.035**	**2.3**	**0.009**	7.4	0.051	**0.59**	**0.015**
≥15 ($n = 19$)	22.3		**21**		**17**		13.2		**16.9**		**17**		**24**		**18.7**		23.4		**13.4**	
Child–Pugh																				
A and B ($n = 14$)	**6.3**	**0.05**	**1.5**	**0.014**	**2.4**	**0.045**	6	0.069	5.7	0.124	1.4	0.111	11.2	0.175	6.5	0.137	**4.8**	**0.009**	5	0.252
C ($n = 19$)	**24**		**21.5**		**16**		12.8		14.4		14.4		20.7		15.2		**24.3**		9.8	
HCV																				
No ($n = 23$)	18.5	0.531	14.3	0.601	10.9	0.741	8.9	0.497	12.8	0.338	12.9	0.104	18.5	0.442	12.8	0.393	17.8	0.476	9	0.366
Yes ($n = 12$)	13.8		11.9		9.9		12.3		7.2		2.2		13.8		9.5		14.1		5.7	
HCC																				
No ($n = 23$)	20.7	0.281	13.2	0.931	10.8	0.781	10.4	0.972	11.6	0.807	11.4	0.319	16.1	0.649	12.1	0.903	17.7	0.543	8.3	0.917
Yes ($n = 12$)	9.7		13.9		10.1		9.5		9.5		4.9		18.4		11.1		14.3		7.2	
Complications																				
No ($n = 21$)	18.3	0.774	17.6	0.225	**16.4**	**0.025**	10.9	0.533	12.3	0.437	10.6	0.709	17.6	0.747	12.3	0.624	19.9	0.259	8.6	0.662
Yes ($n = 14$)	14.8		7.3		**1.7**		8.9		8.8		7.1		15.8		10.8		11.5		6.8	
Relationship																				
Conjugal ($n = 13$)	18.7		19.2		17.5		10		10.9		11.6		22.2		10		23.5		6.3	
Parent ($n = 4$)	1.8	a	1.7	b	8		6.6		3.1	b	8.2		8.5		6.6		3.8	a	6.9	
Child ($n = 12$)	19.7		13.9		5.6		12.6		15.1		14.4		16.3		14.2		15.3		9.5	
Sibling ($n = 6$)	17.6		8		7.2		7.5		7.7		14.3		12.1		13.7		12.5		8.8	

a, significantly lower than other three groups; b, significantly lower than conjugal and child donor groups. Bold texts indicate the statistically significant difference between the groups.

Data is presented as means. (Δ [domain name] = [pretransplant score] – [score at 12 months]). Non-parametric Kruskal–Wallis test or Scheffé's technique.

BP, bodily pain; CTP, Child–Turcotte–Pugh; ER, emotional role; GH, general health; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MCS, mental component summary; MELD, Model for End-Stage Liver Disease; MH, mental health; PCS, physical component summary; PF, physical functioning; PR, physical role; SF, social functioning; SF-36, Short Form-36; VT, vitality.

Table 6 Factors associated with pretransplant score, 12-month score, and score gains in PCS and MCS

	Pretransplant PCS		Pretransplant MCS		PCS at 12 months		MCS at 12 months		ΔPCS		ΔMCS	
	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*
Age, years (older, ≥50)	1.053	0.89	−6.781	0.101	−4.445	0.468	1.194	0.685	−8.289	0.245	4.066	0.365
Sex (male)	6.182	0.399	−0.778	0.840	−0.526	0.928	−2.325	0.398	−4.354	0.508	−2.653	0.510
MELD (high, ≥15)	14.949	0.149	−11.262	0.044	13.6	0.125	10.484	0.010	13.332	0.182	20.273	0.001
CTP (class C)	−6.069	0.110	8.789	0.095	−2.941	0.734	−3.056	0.405	3.766	0.393	−9.591	0.080
HCV (positive)	−3.051	0.729	0.318	0.946	−3.704	0.599	−5.361	0.113	−0.392	0.960	−4.272	0.378
HCC (yes)	3.087	0.753	−0.550	0.916	6.720	0.398	4.878	0.195	8.897	0.317	8.048	0.145
Parental donor (yes)	NA	NA	NA	NA	−7.371	0.108	−12.287	0.062	−10.405	0.291	0.962	0.870
Pretransplant score (≥20 for PCS and ≥45 for MCS)	NA	NA	NA	NA	8.009	0.181	0.806	0.751	−21.555	0.003	−14.188	0.001
	R = 0.486, *P* = 0.235		R = 0.451, *P* = 0.338		R = 0.485, *P* = 0.345		R = 0.614, *P* = 0.053		R = 0.712, *P* = 0.009		R = 0.768, *P* = 0.001	

(Δ [domain name] = [pretransplant score] − [score at 12 months]). Linear regression analysis.
CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MCS, mental component summary; MELD, Model for End-Stage Liver Disease; NA, not applicable; PCS, physical component summary.

In accordance with previous studies,[5,8,17] the findings of the present study clearly indicated that HRQOL based on SF-36 scores in patients awaiting liver transplantation is severely compromised in comparison with the general population. It is not unexpected that the severity of liver disease would correlate with HRQOL scores, and the present study revealed that BP and MH were significantly lower in patients with a higher preoperative MELD score, and that PR, BP and PCS were significantly lower in CTP class C patients. Saab *et al.*[18] found that manifestations of decompensated liver disease at the pretransplant stage, such as ascites and/or encephalopathy, were significantly correlated with HRQOL scores, but detected no correlation between the severity of the liver disease (MELD score and CTP classification) and HRQOL scores in the same study. Estraviz *et al.*[19] showed that CTP classification was clearly correlated with pretransplant HRQOL scores in the majority of dimensions: CTP class A patients had significantly higher scores in the SF-36 PF, GH, VT, SF and MCS dimensions compared with CTP class C patients.

The etiology of liver disease also seems to affect pretransplant HRQOL scores.[18–20] Estraviz *et al.*[19] compared alcohol-induced, HBV, HCV, HCC and cholestatic etiologies of liver cirrhosis prior to liver transplantation. They found that RP and PCS scores were highest for HCC, followed by cholestatic disease, and viral (HBV/HCV) etiology, and lowest for alcohol-induced cirrhosis. For the VT, SF, ER, MH, GH and MCS dimensions, HRQOL scores were again highest for HCC and cholestatic patients, but patients with alcohol-induced cirrhosis had higher scores than patients with viral etiologies. In the present study, however, we found no meaningful difference in the SF-36 dimensions among etiologies.

Previous studies[5–7,21,22] and the present study, investigating HRQOL scores of recipients after liver transplantation, uniformly reported a significant increase in most dimensions over time. In many studies, as in our study, most HRQOL scores remained significantly lower in liver transplant recipients compared with healthy controls despite the significant increase in scores.[2,8,23] An exception to this was observed in the mental domains, where we observed scores that were higher than the Japanese norm. This same result was also reported by a Spanish group,[19] and could be attributed to a feeling of rebirth recipients experience by having survived a serious illness and the resulting feeling of greater well-being. A few authors reported that HRQOL is wholly the same as that of the general population.[8,20,24–26]

The pretransplant differences in HRQOL scores according to disease severity or etiology disappeared

over 6 months after liver transplantation. Moreover, 18 months after transplantation, patients with a higher MELD score achieved significantly higher scores in all dimensions (BP dimension did not reach significance) and, similarly, patients in preoperative CTP class C achieved significantly higher scores in GH, VT, SF and MCS in the present study. This was explained by the fact that the greater the impairment at the pretransplant stage, the greater the improvement in both physical and mental conditions. Accordingly, recipients with lower scores preoperatively had higher scores after liver transplantation, achieving scores comparable or even higher than those with higher preoperative scores. The considerable gains achieved by recipients with severely impaired scores preoperatively may not be entirely objective; that is, these gains may be representative of the "response shift" phenomenon, by which subjects with significant impairment reset their standards of health, minimizing their problems and maximizing small gains in their state compared with healthier individuals.[17,27]

As for etiology, some authors indicated viral disease,[18,28–30] HCC,[19] and alcohol-induced disease[31–34] as factors affecting post-transplant HRQOL scores and score gains, while others did not.[8,35–37] In our investigation of factors affecting HRQOL score gains after liver transplantation, we found no independent factor in the multivariate analysis, except for primary lower scores at the pretransplant stage.

Our findings that scores increased continuously or reached a plateau in every domain for up to 18 months after transplant conflict with the findings of previous studies.[5,6,38–40] A recent systematic review[2,4] found decreased scores in the mental health domain beyond 12 months after transplantation. A similar decrease in the mental component in long-term observation was reported by several authors,[19,23,41] and longer follow up in future studies is warranted.

Finally, we investigated the relationship between the recipient and donor with regard to HRQOL scores. Consistent with the findings reported by Jin *et al.*,[42] we found no difference in any dimension at 12 and 18 months after LDLT. A significantly lower score gain in PF, PR, VT and PCS was observed in recipients of their parents' livers in comparison with the other three types of relationships. In addition to the small sample size, all recipients were within the first degree of consanguinity in our study, and findings derived from the present results with regard to the influence of donor-recipient relationship on recipient HRQOL are therefore not conclusive.

The present study has several limitations. The most significant limitation of our study was the small number of patients. Additional studies with more cases are needed. Based on the study design, patients who were either disenchanted with the transplant program (incomplete data) or too ill to complete the questionnaire (too sick at pretransplant state or death after LDLT) may not be captured, which may result in critical bias. Medical complications such as acute rejection and metabolic/renal disorders which were not assessed in the study which may affect HRQOL in the long term. Finally, cultural, economic, social and educational influences, all of which could affect HRQOL, were not properly controlled or measured. These limitations could be solved in future study with a large cohort.

In conclusion, among patients with severe liver disease requiring LDLT, HRQOL significantly improves after transplantation to levels comparable to those of healthy controls in some dimensions. Both preoperative HRQOL scores and gains in HRQOL scores following LDLT were influenced by the severity of the liver disease. No significant intergroup differences in post-transplant quality of life were detected, as patients with the most severe disease achieved greater gains than those with less severe disease. Insight into recipients' HRQOL and factors affecting HRQOL may contribute to the development of measures aimed at improving recipients' post-transplant life and establishing realistic expectations for recipients.

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Original Article

Living-donor liver transplantation for autoimmune hepatitis and autoimmune hepatitis–primary biliary cirrhosis overlap syndrome

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Aim: Recurrent autoimmune hepatitis (AIH) following liver transplantation has been reported in 20–30% of cases, mainly of Western populations. The aim of this study was to review our experience of living-donor liver transplantation (LDLT) in Japanese patients with AIH.

Methods: Among 375 adult (age ≥18 years) LDLT performed at our center between 1996 and 2010, 16 (4.2%) were for patients with AIH ($n = 12$) or AIH–primary biliary cirrhosis overlap syndrome ($n = 4$). The patient and donor characteristics and post-transplantation course were reviewed.

Results: All recipients were female with a median age of 48 years (range, 21–58). Low-dose methylprednisolone and calcineurin inhibitors were continued in all patients. Acute cellular rejection occurred in 10 (63%), which was more frequent than in our overall series of 28.5% (107/375 cases). Overall survival rate was 81.2% at 5 years. At the end of the follow up (median, 6.0 years [range, 0.1–9.6]), 13 patients were alive with normal liver function tests (aspartate transaminase, 18 ± 5 IU/mL; alanine transaminase, 16 ± 8 IU/mL). None of the survivors exhibited liver function test results suspicious for recurrent AIH, which might indicate liver biopsy.

Conclusion: Survival after LDLT for AIH and overlap syndrome was excellent and there was no evidence of clinical recurrence. The recurrence rate of AIH after liver transplantation may differ among countries, and requires further investigation.

Key words: autoimmune hepatitis, living donor, overlap syndrome, recurrence

INTRODUCTION

AUTOIMMUNE HEPATITIS (AIH) is a chronic inflammatory liver disease with an unknown etiology.[1,2] In most cases, hepatitis responds well to the administration of corticosteroids and other immunosuppressive therapies.[1–4] In some cases, however, inflammation processes progress to a stage in which liver transplantation is necessary. AIH accounts for 1–3% of all liver transplantation for adults. Survival after liver transplantation is excellent in this disease group with 5- and 10-year survival rates of 72% and 65%, respectively.[5] Recurrence of AIH following liver transplantation, however, is reported in 20–30% of cases.[6–8] Diagnosis of recurrent AIH is based on clinical, serological, and histological findings compatible with AIH in patients with a pretransplantation diagnosis of AIH. Viral hepatitis and other mechanical causes should be ruled out.[9–11] Following a systematic review of 13 articles and 414 cases, Gautam *et al.* reported that AIH recurred in 22% of cases at 26 months (range, 14–55) after liver transplantation.[6] Recurrent AIH may develop to a severe form with some requiring re-transplantation.[11–13] Several factors are considered a risk for disease recurrence, for example human leukocyte antigen (HLA)-DR3, pediatric recipient or corticosteroid withdrawal.[9,14–16] Whether long-term use of corticosteroids prevents the recurrence of AIH, however, is unknown. In Japan, 60 of 5510 (1%) living-donor

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liver transplantations (LDLT) were performed for patients with AIH between 1989 and 2009.[17] The LDLT results are excellent with a 5-year survival rate of 78.1%.[17] At our institution, calcineurin inhibitors and maintenance corticosteroids are continued in all recipients unless contraindicated, and thus the clinical course and rate of recurrence are likely to be consistent. Here, we reviewed the long-term course after LDLT for AIH at our center.

METHODS

Patients

BETWEEN APRIL 1996 and June 2010, a total of 375 adults (age ≥18 years) received LDLT at the University of Tokyo. Of these 375, 16 (4.2%) were diagnosed with AIH. Diagnosis prior to transplantation was based on generally accepted criteria: presence of autoantibodies at a titer of 1:40 and higher; elevated transaminases and normal or only slightly elevated alkaline phosphatase; hypergammaglobulinemia or elevation of immunoglobulin (Ig)G; histology compatible with AIH; and lack of serological markers for viral hepatitis.[18] Patient medical records were retrospectively reviewed. Because the original diagnoses of AIH were made by referring physicians 4.2 years (range, 0.2–17.3) prior to transplantation, original diagnostic scores were not available in all cases. The revised criteria for the diagnosis of AIH and simplified diagnostic criteria for the diagnosis of AIH were retrospectively applied.[18,19] The sample of tissue at the diagnosis was available only in one case; explant liver specimens were used for histological score in the other 15 cases. For the overlap syndrome, at least two accepted criteria for primary biliary cirrhosis (PBC) and AIH were required.[20]

Histology

Explant liver specimens were reviewed by two independent pathologists and scored according to the revised criteria for the diagnosis of AIH. The feature of AIH was also described as "typical" or "compatible" according to the simplified diagnostic criteria for AIH. The feature of PBC and other findings were also noted. In case of disagreement on the findings, the specimen was re-reviewed and discussed. Post-transplant biopsies were reviewed in a blinded manner by two independent pathologists with the aim of diagnosis of acute cellular rejection (ACR) or other change. ACR was graded according to the Banff schema.[21]

Surgical procedure and immunosuppression therapy

Our selection criteria for live liver donors, surgical techniques and use of immunosuppressants for LDLT are described elsewhere.[22–24] The post-transplantation immunosuppression regimen consisted of steroid induction with tacrolimus or cyclosporin A.[25] The doses of each drug were gradually tapered for 6 months after LDLT. Methylprednisolone was tapered from 3 mg/kg on the first postoperative day to 0.05 mg/kg at the sixth postoperative month. A maintenance dose of 2–4 mg of methylprednisolone was continued in all patients, including patients with non-AIH diseases.

Liver biopsy is indicated for patients with elevated liver function test results, after excluding biliary tract complications and infection. Protocol biopsy is not performed at our center. ACR confirmed by liver biopsy was treated first with steroid recycling therapy. When the second episode of ACR occurred, steroid recycling therapy was repeated and mycophenolate mofetil (MMF) was added. Steroid-resistant ACR was treated with muromonab-CD3 (OKT3).

Statistical analysis

Differences between groups were analyzed by the Mann–Whitney *U*-test for continuous variables and the χ^2-test for categorical variables. The overall survival curve was generated by the Kaplan–Meier method and compared with the log–rank test. $P < 0.05$ was considered statistically significant. All patients were followed until death or 30 November 2010. The median follow-up period was 6.0 years (range, 0.1–9.6) after transplantation.

RESULTS

Patient characteristics

THERE WERE 16 LDLT recipients with AIH; all were female and the median age was 48 years (range, 21–58). Their age at the original diagnosis of AIH was 44 years (range, 17–58). All were presented as decompensated cirrhosis; the mean (range) of Model for End-Stage Liver Disease (MELD) score and Child–Pugh score prior to transplantation were 14 (6–35) and 10 (8–12) respectively. A summary of patient characteristics is shown in Table 1. Prior to liver transplantation, seven cases were treated with corticosteroid monotherapy, and two were treated with corticosteroid and azathioprine. The review of explant liver histology showed compatibility with or typical of AIH in all cases. When the

Table 1 Characteristics of the 16 patients

Case	Age at Dx	Age at LDLT	Duration of disease (years)	Treatment prior to LDLT	Pretransplantation diagnosis	ANA	SMA	AMA	IgG (mg/dL)†	Histology typical AIH	Histology typical PBC	IAIHG criteria[18]	PBC–AIH overlap syndrome[20]
1	48	48	0.3	PSL	s/o AIH	>1:80	–	+	2981	Compatible	Typical	9	Yes
2	41	49	9.9	PSL	AIH	>1:80	>1:80	–	1708	Typical	–	21	–
3	29	45	17.3	PSL	AIH	>1:40	–	–	1114	Compatible	–	11	–
4	34	34	0.6	PSL	s/o AIH	>1:80	–	–	1974	Compatible	–	13	–
5	17	29	12.9	PSL	AIH	–	>1:40	–	1397	Typical	–	16	–
6	47	47	0.4	–	s/o AIH	–	–	–	1713	Typical	–	17	–
7	58	58	0.2	–	s/o AIH	>1:80	–	–	n/a	Typical	Typical	14	Yes
8	38	46	8.6	UDCA	PBC	>1:40	–	+	1841	Typical	Typical	11	Yes
9	43	51	7.8	–	s/o AIH	–	–	+	1924	Typical	–	11	–
10	45	56	11.2	–	AIH	>1:80	–	–	3294	Typical	–	20	–
11	53	54	0.7	PSL + AZA	AIH	>1:80	–	–	3005	Typical	–	21	–
12	51	51	0.2	–	s/o PBC	>1:80	>1:40	+	3053	Typical	–	16	–
13	48	51	3.9	PSL + UDCA	PBC-AIH	>1:80	–	+	2729	Typical	Typical	10	Yes
14	18	21	3.4	PSL + AZA	AIH	>1:40	–	–	1541	Typical	–	15	–
15	21	32	11.9	PSL	AIH	>1:40	–	–	2082	typical	–	17	–
16	54	58	4.5	–	AIH	>1:80	–	–	1873	Typical	–	16	–

†Normal range: 870–1700 mg/dL.

AIH, autoimmune hepatitis; AMA, anti-mitochondrial antibody; ANA, antinuclear antibodies; AZA, azathioprine; Dx, treatment; IAIHG, International Autoimmune Hepatitis Group; IgG, immunoglobulin G; LDLT, living-donor liver transplantation; n/a, not available; PBC, primary biliary cirrhosis; PSL, prednisolone; s/o, suspect of; SMA, smooth muscle antibodies; UDCA, ursodeoxycholic acid.

revised AIH criteria were used, eight patients (50%) were identified as definite AIH and seven (44%) as probable AIH. Using the simplified criteria, seven patients (44%) were identified as definite AIH and three (19%) as probable AIH. There were five cases positive for AMA; four of those showed features of both AIH and PBC, and met the European Association for the Study of the Liver criteria for AIH–PBC overlap syndrome.

Transplantation

Living-donor liver transplantation was performed in all 16 cases; surgical duration was 831 ± 114 min and warm and cold ischemic times were 72 ± 28 and 86 ± 45 min, respectively. Recipient and donor information is summarized in Table 2. Donor relation was spouse in four, son in four, daughter in four, and one each for mother, father, brother or niece. The median donor age was 28 years (range, 18–62). Six recipients were positive for HLA-DR4 whereas none were positive for HLA-DR3. A left lobe graft with/or without caudate lobe was used in nine, right lobe graft in five and posterior graft in two. The graft size was 468 ± 104 g and the graft weight/standard recipient liver volume was 45 ± 9%. Mean weight of the explant liver was 801 ± 314 g. Two recipients received hepatitis B core antigen positive donor grafts and were treated with prophylactic hepatitis B Ig therapy.

Table 2 Patient and donor demographics

Case	Age at LDLT	Donor age	Donor relation	HLA-DR (recipient/donor)	Mismatch†
1	48	20	Daughter	n/a	NA
2	49	22	Son	4,9/4,–	2
3	45	50	Spouse	2,12/6,–	5
4	34	34	Spouse	4,6/1,2	4
5	29	57	Father	6,8/2,6	3
6	47	23	Son	1,4/4,–	1
7	58	29	Son	8,15/8,15	0
8	46	24	Niece	4,–/4,–	2
9	51	18	Daughter	15,–/9,15	2
10	56	62	Spouse	4,4/11,13	5
11	54	31	Son	1,14/4,14	3
12	51	21	Daughter	4,11/4,14	2
13	51	23	Daughter	8,15/8,13	3
14	21	51	Mother	8,15/8,13	2
15	32	27	Brother	14,15/9,15	2
16	58	58	Spouse	1,14/15,15	3

†HLA-A, -B and -DR loci were used to calculate total mismatch score of 0–6.
HLA, human leukocyte antigen; LDLT, living-donor liver transplantation; n/a, not available.

ACR

Occurrence and treatment of ACR are shown in Table 3. A total of 27 biopsy samples were taken from 13 recipients. Sixteen episodes of ACR occurred in 10 recipients (63%), which was more frequent than in our overall series of 28.5% (107/375 cases). The first episode of ACR occurred at a median of 14 days (range, 8–42) in AIH patients, whereas it occurred at a median of 17 days (range, 6–54) in non-AIH recipients. Frequency of ACR was higher among recipients who received grafts from non-blood-related donors (spouse, 4/4, 100%) than those who received blood-related grafts (6/12, 50%), although statistically not significant ($P = 0.074$). ACR occurred more frequently among patients with AIH alone (9/12, 75%) than those with AIH–PBC overlap (1/4, 25%), without statistical significance ($P = 0.074$). Occurrence of ACR was not significantly associated with donor sex ($P = 0.42$) or the duration of disease ($P = 0.63$). MMF was introduced in seven recipients and OKT3 in one.

Survival

Three recipients died at 1.7, 1.9 and 12.3 months after LDLT. The causes of death were unrelated to graft failure: rupture of gastric varices, pulmonary embolization and virus-associated hemophagocytic syndrome. The 1- and 5-year overall survival rates were 87.5% and 81.2%, respectively (Fig. 1).

Post-transplantation course and recurrence of AIH

At the end of the follow up, 13 patients were alive. Laboratory data and immunosuppressive therapy for 13 patients are summarized in Table 3. Corticosteroids were gradually tapered and maintained in all cases; in most cases, 2 mg or 4 mg of methylprednisolone was administrated p.o. at the last visit. One case (case 2) received treatment with 10 mg of prednisolone because of arthritis. In case 15, who was treated with a 6-mg dose of methylprednisolone, we cautiously tapered the methylprednisolone because of a 10-year history of steroid therapy prior to LDLT. Treatment with calcineurin inhibitors with or without MMF was also maintained. Patients were followed every 4–6 weeks at the University of Tokyo outpatient clinic. Following the first postoperative year, none of these 13 exhibited increased values in liver function tests, which might be an indication for liver biopsy. Based on the clinical and biochemical