ORIGINAL PAPER

Nagoya J. Med. Sci. **72**. 119 ~ 127, 2010

RISK FACTORS OF RECIPIENT RECEIVING LIVING DONOR LIVER TRANSPLANTATION IN THE COMPREHENSIVE ERA OF INDICATION AND PERIOPERATIVE MANAGEMENTS

MASATOSHI ISHIGAMI[1], YOSHIAKI KATANO[1], KAZUHIKO HAYASHI[1], AKIHIRO ITO[1], YOSHIKI HIROOKA[1], YASUHARU ONISHI[2], TARO NAKAMURA[2], TETSUYA KIUCHI[3] and HIDEMI GOTO[4]

[1]*Department of Gastroenterology, Nagoya University School of Medicine*
[2]*Department of Transplant Surgery, Nagoya University School of Medicine*
[3]*Department of Transplant Surgery, Nagoya University Graduate School of Medicine*
[4]*Department of Gastroenterology, Nagoya University Graduate School of Medicine*

ABSTRACT

Living donor liver transplantation (LDLT) has become one of the chief methods of saving patients with end-stage liver disease due to liver cirrhosis. Accumulation of knowledge about indication and perioperative managements improve outcome of this treatment. In this study, we elucidate the risk factors of LDLT, which still exist today. Sixty-one patients received LDLT in our institute between 2003 and 2009 were included in this study. Recipient age and sex, donor age and sex, etiology, preoperative model of end-stage liver disease (MELD) score, hepatocellular carcinoma (HCC), graft versus recipient weight ratio (GRWR), cold and warm ischemic time, operation time, blood loss, ABO compatibility, rejection, cytomegalovirus (CMV) infection, biliary stricture, and calcineurin inhibitor (FK506 or cyclosporin A) were the factors investigated. $p<0.05$ was considered as statistically significant in the proportional hazard model. In univariate analysis, the recipients' age ($p=0.024$) and rejection episode ($p=0.046$) were selected as significant risk factors. In multivariate analysis including the factors that showed $p<0.2$ (recipient age, GRWR, ABO compatibility, rejection episode) in univariate analysis, recipient age ($p=0.008$, HR: 1.40; 95% CI: 1.09–1.80) and rejection episodes ($p=0.002$, HR: 13.33; 95% CI: 2.53–71.43) were still selected as significant independent risk factors after LDLT. Recipient age was shown to be 1.40 times risk per 1 year older and the rejection episode was shown to be 13.33 times risk in the recent era with comprehensive indication and preoperative management for LDLT. Indication must be cautious for elderly patients, and prevention of rejection is crucial for the improvement of results for LDLT.

Key Words: Risk factors, LDLT, Liver cirrhosis, Prognosis, Indication

INTRODUCTION

Liver cirrhosis is an irreversible liver disorder. It causes severe complications such as refractory ascites,[1)] esophago-gastric varices,[2)] hepatic encephalopathy,[3)] and spontaneous bacterial peritonitis (SBP),[4)] and subsequently leads to death. Furthermore, cirrhosis confers a high risk for hepatocel-

Corresponding author: Masatoshi Ishigami, MD, PhD
Department of Gastroenterology, Nagoya University School of Medicine,
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Phone: +81-52-744-2190, Fax: +81-52-744-2178, E-mail: masaishi@med.nagoya-u.ac.jp

lular carcinoma (HCC)[5] and subsequently, death.

There are strategies for temporal management of these complications, but it is not possible to reverse cirrhosis with life-threatening complications without transplantation. In Japan, because of specific ethical considerations, deceased donor liver transplantation is extremely rare (averaging about 4 cases per year nationwide.),[6] 99% of liver transplants are from close relatives of the patients.[7] In non-Japanese Asian and Western countries, the number of deceased donors has not reached the number of patients on the waiting list. Thus, the number of living donor liver transplantations (LDLT) is gradually increasing because of the needs of the patients and their families who cannot wait for a caderveric donor due to their life-threatening conditions.[8-10]

So LDLT is now a critical option for saving lives of patients with liver cirrhosis or excluding liver related complications in patients with liver cirrhosis in Japan. But there is an essential risk related to liver resection for healthy donors.[11,12] Therefore, an explanation of LDLT's risks must be made to both recipients and donors who decide to receive this treatment option.

There is a wealth of cumulative knowledge about the indications and preoperative managements of LDLT: included are like Milan criteria for preventing the risk for recurrence of HCC,[13] and the knowledge of the correct graft size of donor liver for avoiding small for size syndrome,[14] the combination of nucleoside analogue and high-dose anti-HBs immunoglobulin (HBIg) to control HBV reactivation,[15,16] the use of preoperative plasma exchange, rituximab and direct infusion of immunosuppressants through portal vein or hepatic artery in ABO-incompatible donor cases.[17,18] The extent of safety has become assured and the comprehension of indications and preoperative managements are now becoming established.

In this study, we elucidate the risk factors which still exist in this recent comprehensive era of LDLT in our transplant program, and discuss ways to improve the present-day prognosis for patients with liver cirrhosis who undergo LDLT.

PATIENTS AND METHODS

Patients

Sixty-one adult patients (≧18 years old) who received LDLT due to liver cirrhosis between 2003 and 2009 were included in this study. Recipients were 37 males and 24 females; their average age was 51.7±9.9 years old (range: 19–63). Donors were thirty-six males and twenty-five females with the average age of 36.1±12.7 years (range: 20–60). Etiologies were twenty for hepatitis C virus (HCV), seventeen for hepatitis B virus (HBV), eleven for primary biliary cirrhosis (PBC), four for cryptogenic cirrhosis, three for primary sclerosing cholangitis (PSC), three for cholestatic liver cirrhosis, two for autoimmune hepatitis (AIH), and one for Wilson's disease. Thirty-two (52.5%) had hepatocellular carcinoma (HCC), and nine (14.8%) were ABO-type incompatible cases. Fifty-five cases (90.2%) received right lobe grafts and six cases (9.8%) received left lobe grafts. Mean blood loss was 7559.0±1019.3 ml, and mean operation time was 985.6±237.3 minutes. Fifteen patients (24.6%) experienced one or more rejection episodes.

Indication for LDLT in patients with liver cirrhosis

Principally, an indication for the recipients is a clinically diagnosed case of liver cirrhosis with model of end-stage liver disease (MELD) score≧15. If MELD score<15, liver-related complications like refractory ascites and repeated variceral bleeding were the indication of recipients. In HCC cases, hepatic failure as previously described or the presence of uncontrolled tumors by other treatments with or without hepatic complications, were the first consideration. And in the first years, if distant metastasis and vascular invasions were excluded in imaging studies, all

patients were included for indication. But in the past two years, Milan criteria (up to 5 cm of single tumors or up to 3 tumors not exceeding 3 cm) were strictly obeyed. ABO incompatible cases were not considered as a contraindication.

After the donor candidates were given detailed explanation several times by hepatologists and transplant surgeons, preoperative checks for donor candidates were done only if they still had a strong will to donate the partial liver after the risks of liver resection were explained. Principal exclusion criteria of the donors were (1) age>60 years old; (2) fatty liver diagnosed by liver-kidney contrast in ultrasound study, or liver/spleen ratio in CT; (3) remnant liver volume estimated to be less than 35% of total liver volume; and (4) graft-versus recipient weight ratio (GRWR) was estimated to be less than 0.7%.

Perioperative management of LDLT

Immunosuppression was started with a double therapy of steroids and a calcineurin inhibitor (CNI; FK506 or cyclosporin A). In some cases mycophenolate mofetil (MMF) was added to avoid renal injury by high concentrations of CNI. CNI blood levels were kept above 10 ng/ml of trough in the first month and at 5 ng/ml thereafter in FK506 (FK) cases. And in cases using cyclosporine A (CyA), 200 ng/ml in trough (C0) and 1000ng/ml concentrations 2 hours after administraion (C2) was maintained in the first month and 150 ng/ml in C0 and 500 ng/ml in C2 thereafter. Steroids were tapered and withdrawn within 3 months postoperatively in most cases, except for HCV-positive patients who were maintained with a low dose (2.5–5 mg/day) of prednisolone. Rejection was diagnosed according to liver histology, and once acute cellular rejection was diagnosed, a high-dose methylprednisolone was administered for 3 days. If patients were refractory to this treatment, OKT3 was used. In HBV-positive cases, a combination of nucleoside analogue beginning before transplantation and high-dose HBIg beginning at anhepatic phase were applied and continued after transplantation. In HCV-positive cases, because of the high recurrence of viremia and hepatitis, and rapid progression of fibrosis was seen after liver transplantation, protocol biopsies irrespective of liver enzyme in the blood test were performed at 1, 3, 6, 12, 18, 24, and 36 POM and further annually in most cases except in those who succumbed early. Once recurrent hepatitis was diagnosed, a combination treatment of pegylated interferon (PEG-IFN) and ribavirin was applied to eliminate the virus.

Statistical analysis

To analyze the factors associated with survival after LDLT in patients with liver cirrhosis in recent era, we selected the following as candidate risk factors: the recipients' age and sex, donors' age and sex, etiology (HBV/HCV/PBC/others), preoperative MELD score, existence of HCC, GRWR, cold ischemic time, warm ischemic time, operation time, blood loss, ABO compatibility, existence of rejection, perioperative cytomegalovirus (CMV) infection, biliary stricture, and CNI (FK or CyA).

To evaluate the hazard ratio (HR) of each factor and to select independent factors for predicting death after liver transplantation, the proportional hazard model was used. For analysis of survival comparison, Log-rank test was used. $p<0.05$ was considered statistically significant. All analyses were done with Stat View ver 5.0.

RESULTS

Significant and independent factors for risk of death after LDLT

In univariate analysis, higher recipient age (HR: 1.20; 95% confidence interval (CI): 1.03–1.42,

p=0.024) and existence of rejection episodes (HR: 3.37; 95% CI: 1.03–11.11, p=0.046) were selected as significant factors for risk of death after LDLT (Table 1). We then conducted multivariate analyses including factors shown to be p<0.2 in univariate analysis (recipient age, GRWR, ABO compatibility, and rejection). Higher recipient age (p=0.008, HR: 1.40; 95% CI: 1.09–1.80) and history of rejection (p=0.002, HR: 13.33; 95% CI, 2.53–71.43) were again selected

Table 1 Univariate analysis of risk factors after LDLT

		Hazard ratio (95% CI)	p
Recipient age		1	
	1 year older	1.20 (1.03–1.42)	0.024*
Recipient sex	Female	1	
	Male	1.10 (0.32–3.77)	0.875
Donor age		1	
	1 year older	1.01 (0.96–1.05)	0.704
Donor sex	Female	1	
	Male	1.06 (0.31–3.62)	0.925
Etiology	PBC	1	
	HBV	0.54 (0.08–3.81)	0.533
	HCV	1.20 (0.23–6.20)	0.827
MELD score			1
	1 point more	1.01 (0.92–1.11)	0.769
HCC	No	1	
	Yes	1.60 (0.47–5.46)	0.456
GRWR		1	
	1% more	3.77 (0.50–28.16)	0.196#
Cold ischemic time		1	
	1 minute more	1.00 (1.00–1.01)	0.488
Warm ischemic time		1	
	1 minute more	0.98 (0.90–1.07)	0.705
Operation time		1	
	1 minute more	1.00 (1.00–1.00)	0.793
Blood loss		1	
	1 ml more	1.00 (1.00–1.00)	0.522
ABO blood type	Incompatible	1	
	Compatible	0.51 (0.10–2.54)	0.408
	Identical	0.29 (0.07–1.27)	0.101#
Rejection	No	1	
	Yes	3.37 (1.03–11.11)	0.046*
CMV infection	No	1	
	Yes	0.57 (0.14–2.26)	0.420
Biliary stricture	No	1	
	Yes	1.55 (0.44–5.50)	0.500
Calcineurin inhibitor	FK506	1	
	Cyclosporin A	0.86 (0.19–4.01)	0.851

LDLT: living donor liver transplantation, 95% CI: 95% confidence interval
PBC: primary biliary cirrhosis, HBV: hepatitis B virus, HCV: hepatitis C virus, GRWR: graft versus recipient weight ratio, CMV: cytomegalovirus
*p<0.05, #p<0.2 and proceed to multivariate analysis

as significant independent factors for the risk of death after LDLT (Table 2).

Survival curve analysis after LDLT according to the existence of rejection episodes

Fig. 1 shows the comparison of survival curves after LDLT with and without the existence of rejection episodes. Patients without rejection showed 1, 3, and 5 years of survival, 91.4%, 81.8%, and 81.8%, respectively, and patients with rejection showed the results: 66.7%, 59.3%, and 59.3%, respectively (p=0.028).

These data show that rejection episode is correlated with the risk of death after LDLT, especially in early postoperative death. Therefore, the perioperative management to avoid rejection is one of the most important factors for improving the results of LDLT.

Table 2 Multivariate analysis of risk factors after LDLT

		Hazard ratio (95% CI)	p
Recipient age		1	
	1 year older	1.40 (1.01–1.80)	0.008**
GRWR		1	
	1% more	0.94 (0.04–25.11)	0.969
ABO blood type			
	Incompatible	1	
	Compatible	0.28 (0.02–3.30)	0.312
	Identical	0.20 (0.03–1.22)	0.081
Rejection	No	1	
	Yes	13.33 (2.53–71.43)	0.002**

LDLT: living donor liver transplantation, 95% CI: 95% confidence interval, GRWR: graft versus recipient weight ratio
**p<0.01

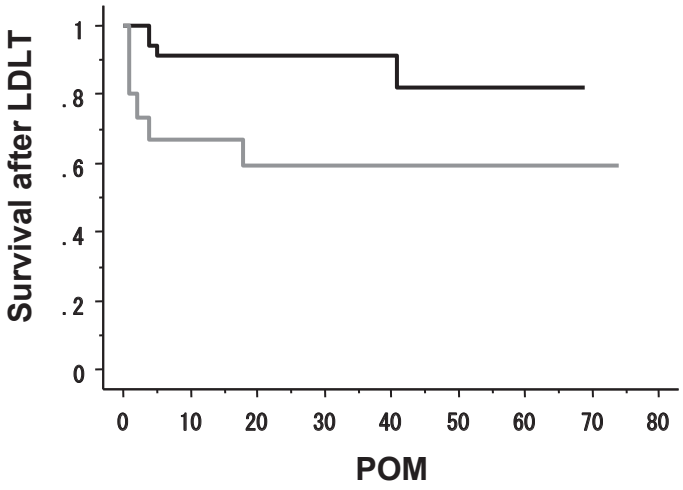

Fig. 1 Comparison of survival curves between patients with and without rejection episodes after living donor liver transplantation (LDLT) (p=0.028).
Black line indicates the survival curve of patients without rejection episodes and gray line indicates the survival curve of patients with rejection episodes. POM: postoperative months.

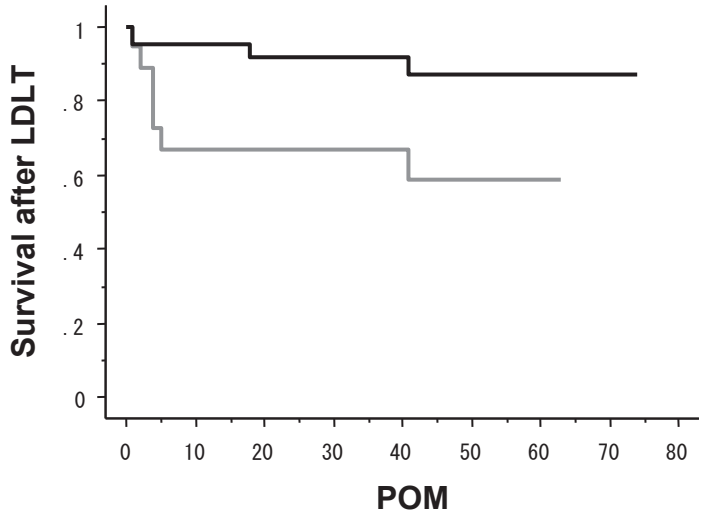

Fig. 2 Comparison of survival curves between patients ≧58 years old and <58 years old after living donor liver transplantation (LDLT) (p=0.010).
Black line indicates the survival curve of patients of <58 years old and gray line indicates the survival curve of patients of ≧58 years old. POM: postoperative months.

Survival curve analysis after LDLT according to recipient age

Fig. 2 shows a comparison of survival curves after LDLT depending on the recipients' age. Survival of patients ≧58 years old was 66.9%, 58.5%, and 58.5% in 1, 3, and 5 years after LDLT, respectively, and 95.1%, 92.1%, and 87.2% in patients of <58 years old (p=0.010), respectively.

These data show that older recipients have a definitely higher risk of death after LDLT. And collecting data from the survival curve comparison, recipient age ≧58 years was cautious for the indication of LDLT. Viewed from the proportional hazard model, for example, a 60-year-old recipient has an estimated risk of death 5.37 times greater, while a 65-year-old recipient has an estimated risk of death 28.93 times risk greater than that of a 55-year-old patients. Therefore, LDLT should be indicated cautiously for those 60 years or older, and patients older than 65 years could be a relative contraindication of LDLT in cirrhotic patients.

DISCUSSION

Recently, for patients with end-stage liver disease due to liver cirrhosis, LDLT has become one of the most important treatment options, especially in Japan, where deceased donor grafts are rarely received.[7] But a living liver donation has the essential problem that donors are healthy, and there are some definite risks to the donors in liver resection. To overcome this problem, donor selection should be conducted very cautiously and the establishment of safety not only for donors but also for recipients is crucial to explain the risks in order to obtain enough informed consent.

In this study, we tried to elucidate the risk factors of LDLT from the viewpoint of helping solve this problem for recipients. New knowledge about the risk factors for LDLT and improvement of perioperative managements has brought about better outcomes for LDLT in

recent years.

There are several reported preoperative risk factors to consider for the indication of liver transplantation: (1) liver function: both too early and too late for liver transplantation (estimated MELD score 15–30 was the proper indication of liver transplantation[19-21]); (2) graft size; GRWR<0.8% was a definite risk for LDLT[14]; (3) extent of HCC; Mazzaferro *et al.* reported that patients with tumors not exceeding 5 cm in single tumors, or up to 3 tumors not exceeding 3 cm each, showed good results in HCC recurrence compared with patients who exceeded this criteria after liver transplantation (Milan criteria).[13]

In the perioperative managements also, there are some valuable improvements in the liver transplant field: (1) ABO blood type incompatible donors; a definite risk to recipient compared with compatible and identical donors, but with recent advances in preoperative plasma exchanges and rituximab, and direct infusion of immunosuppressants via portal vein and/or hepatic artery, this kind of graft works well now, even by comparison to compatible or identical grafts.[17,18] (2) HBV-positive cases; with the recent introduction of the combination of nucleoside analogues and a high-dose HBIg, the rate of HBV reactivation decreased to 0–10%, and most cases were free from HBV recurrence and progressive disease after liver transplantation.[15,16] (3) HCV-positive cases; there is an accumulation of knowledge about unavoidable viral recurrences, the high rate of hepatitis recurrence, and the progression of liver fibrosis which is faster in transplanted patients. Serial protocol biopsies, irrespective of liver enzyme tests in blood, and the introduction of PEG-IFN and ribavirin, have brought some expected effects, especially in patients induced sustained viral response (SVR).[22,23]

To collect these knowledges, comprehensive indications and perioperative managements were established, and high-risk patients not clearly expected to benefit from LDLT tended to avoid this treatment option. We re-evaluated the LDLT risk factors for selected patients according to these policies, and we showed that rejection episodes and recipient ages remain the causes of death after LDLT.

Rejection is always an expectable complication because the non-self antigen-rich graft enters the recipient body and the immune reaction against it is unavoidable. Rejection itself is easy to control because of the advancement of immunosuppressants in most cases, but still a few patients died directly due to severe acute or chronic rejection. Furthermore, infection related to treatment with a high dose of strong immunosuppressants can also be a cause of death after liver transplantation. In fact, from observation of the survival curve, the early decline of survival is the most remarkable difference between patients with and without rejection. Therefore, diligent care for the avoidance of rejection, and tight monitoring of infection in patients treated with rejection are important from this standpoint.

Older recipients are a matter of debate for the indication of transplantation. Previous reports showed that short-term results of older recipients were not different from those of younger patients, but the outcome was worse in the long term if patients were divided by the age of 60.[24] Another report found that seniors older than 65 had an outcome worse than for those who are 60 to 65.[25]

But these findings were based on the data from deceased donor liver transplantation, and data from LDLT are scant. Living donor grafts are definitely smaller than whole grafts of deceased donors, and this could pose a considerable risk for poor outcomes in elderly patients. Indication of a high age limit is not agreed upon from one institute to another, but collectively from our study and previous reports, older patients with liver cirrhosis are risk factors for LDLT. We think that patients with liver cirrhosis who are older than 65 years are a relative contraindication of LDLT, considering the balance of risk to living donors and risk/benefit of the elderly recipients.

In conclusion, we evaluated the risk factors for LDLT in patients with liver cirrhosis in recent

era. Rejection episodes and older age of recipients were selected as significant independent factors for the risk of LDLT, so the indication of LDLT must be carefully considered in elderly patients. The administration of adequate immunosuppressants so as to avoid rejection is important for improving the outcome of LDLT even in the recent comprehensive era.

REFERENCES

1) Runyon BA. Management of adult patients with ascites caused by cirrhosis. *Hepatology*, 1998; 27: 264–272.
2) Imperiae TF, Chalasani N. A meta-analysis of endoscopic variceral ligation for primary prophylaxis of esophageal variceral bleeding. *Hepatology*, 2001; 33: 802–807.
3) Planas R, Ballaeste B, Alvarez MA, Rivera M, Montoliu S, Galas JA, Santos J, Coll S, Mollias RM, Solla R. Natural history of decompensated hepatitis C virus related cirrhosis. *J Hepatol*, 2004; 40: 823–830.
4) Caly WR, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. *J Hepatol*, 1993; 18: 353–358.
5) Chalasani N, Said A, Ness R, Hoen H, Lumeng L. Screening for hepatocellular carcinoma in patients with advanced cirrhosis. *Am J Gastroenterol*, 1999; 94: 2988–2993.
6) Dahlke MH, Popp FC, Eggert N, Hoy L, Tanaka H, Sasaki K, Piso P, Schlitt HJ. Differences in attitude toward living and postmortal liver donations in the United States, Germany, and Japan. *Psychomatics*, 2005; 46: 58–64.
7) Todo S, Furukawa H, Jim MB, Shimamura T. Living donor liver transplantation in adults: outcome in Japan. *Liver Transpl*, 2000; 6: S66–S72.
8) Broelssch CE, Malago M, Testa G, Valentin Gamazo C. Living donor liver transplantation in adults: outcome in Europe. *Liver Transpl*, 2000; 6: S64–S65.
9) Brown RS Jr, Russo MW, Lai M, Shiffmann ML, Richardson MC, Everhart JE, Hoofnagle JH. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med*, 2003; 348: 818–825.
10) Chen CL, Fan ST, Lee SG, Makuuchi M, Tanaka K. Living donor liver transplantation: 12 years experience in Asia. *Transplantaiton*, 2003; 75: S6–S11.
11) Surman OS. The ethics of partial-liver donation. *N Engl J Med*, 2002; 346: 1038
12) Umeshita K, Fujiwara K, Kiyosawa K, Makuuchi M, Satomi S, Sugimachi K, Tanaka K, Monden M. Japansese Liver Transplantation Society. Operative morbidity of living donors in Japan. *Lancet*, 2003; 362: 687–690.
13) Mazzaferro V, Regalia E, Doci R, Andreola S, Puvirenti A, Bozetti F, Monatto F, Ammantuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*, 1996; 334: 693–699.
14) Kiuchi T, Kasahara M, Uryuhara K, Inomata Y, Uemoto S, Asonuma K, Egawa H, Fujita S, Hayashi M, Tanaka K. Impact of graft size mismatching on graft prognosis in liver transplantation from live donors. *Transplantation*, 1999; 67: 321–327.
15) Markowitz JS, Martin P, Conrad AJ, Markmann JF, Seu P, Yersiz H, Goss JA, Scmidt P, Pakrasi A, Artinian L, Murray NG, Imagawa DK, Holt C, Goldstein LI, Stribling R, Bustill RW. Prophylaxis against hepatitis B recurrence following liver transplantation using combination lamivudine and hepatitis B immune globulin. *Hepatology*, 1998; 28: 585–589.
16) Marzano A, Salizzoni M, Debernardi-Venon W, Smedile A, Franchello A, Clancio A, Gentilcore E, Paintino P, Barbui AM, David E, Negro F, Rizetto M. Prevention of hepatitis B virus recurrence after liver transplantation in cirrhotic patients treated with lamivudine and passive immunoprophylaxis. *J Hepatol*, 2001; 34: 903–910.
17) Shimazu M, Kitajima M. Living donor liver transplantation with special reference to ABO-incompatible grafts and small-for-size grafts. *World J Surg*, 2004; 28: 2–7.
18) Yoshizawa A, Sakamoto S, Ogawa K, Kasahara M, Uryuhara K, Oike F, Ueda M, Takada Y, Egawa H, Tanaka K. New protocol of immunosuppression for liver transplantation across ABO barrier: the use of Rituximab, hepatic arterial infusion, and preservation of spleen. *Transplant Proc*, 2005; 37: 1718–1719.
19) Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. *Am J Transpl*, 2005; 5: 307–313.
20) Merion RM. When is a patient too well and when is a patient too sick for a liver transplant? *Liver Transpl*, 2004; 10: S69–S73.

21) Ishigami M, Honda T, Okumura A, Ishikawa T, Kobayashi M, Katano Y, Fujimoto Y, Kiuchi T, Goto H. Use of Model for End-Stage Liver Disease (MELD) score to predict 1-year survival of Japanese patients with cirrhosis and to determine who will benefit from living donor liver transplantation. *J Gastroenterol*, 2008; 43: 363–368.
22) Yimaz N, Shiffmann ML, Stravitz RT, Sterling RK, Luketic VA, Sanyal AJ, Mills AS, Contos MJ, Coterell A, Maluf D, Posner MP, Fisher RA. A prospective evaluation of fibrosis progression in patients with recurrent hepatitis C virus following liver transplantation. *Liver Transpl*, 2007; 13: 975–983.
23) Sharma P, Marrero JA, Fontana RJ, Greenson JK, Conjeevaram H, Su GL, Askari F, Sullivan P, Lok AS. Sustained virologic response to therapy of recurrent hepatitis C after liver transplantation is related to early virologic response and dose adherence. *Liver Transpl*, 2007; 13: 1100–1108.
24) Levy MF, Somasunder PS, Jennnings LW, Jung GJ, Molmenti EP, Fasola CG, Goldstein RM, Gonwa TA, Klintmalm GB. The elderly transplant recipient: a call for caution. *Ann Surg*, 2001; 233: 107–113.
25) Keswani RN, Ahmed A, Keefe EB. Older age and liver transplantation: a review. *Liver Transpl*, 2004; 10: 957–967.