Original Article

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Hepatitis B virus recurrence after living donor liver transplantation of anti-HBc-positive grafts: A 22-year experience at a single center

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Summary **The use of hepatitis B core antibody (anti-HBc)-positive grafts is one strategy for expanding the donor pool for liver transplantation (LT). The aim of this study was to determine the risk factors associated with hepatitis B virus (HBV) recurrence after living donor LT (LDLT) of anti-HBc-positive grafts. From January 1996 to December 2018, a total of 609 LDLT procedures were performed at our center. A retrospective review was performed for 31 patients (23 males and 8 females; median age = 47 years) who underwent LDLT for HBV-unrelated liver disease from anti-HBc-positive donors. The factors associated with HBV recurrence were evaluated and compared between the HBV recurrence and non-recurrence groups. The median follow-up period after LT was 135 months (range, 6-273 months). Four of 31 patients (12.9%) developed post-LT HBV recurrence. All four cases were HBV-naïve patients (anti-HBc-negative and Hepatitis B surface antibody-negative). The median interval between LDLT and HBV recurrence was 42 months (range, 20-51). The overall actuarial rates of HBV recurrence at 1, 3, 5, 10, and 20 years were 0%, 7.2%, 15.7%, 15.7%, and 15.7%, respectively. Although there were no significant differences between the HBV recurrence and non-recurrence groups, HBV recurrence tended to occur in HBV-naïve recipients ($P = 0.093$). HBV-naïve status may contribute to HBV recurrence after LDLT for HBV-unrelated liver disease from anti-HBc-positive donors. Careful monitoring for serological HBV markers is needed, particularly in this group.**

Keywords: Liver transplantation, HBV recurrence, anti-HBc, HBIG, HBV-naïve

1. Introduction

The current efforts to overcome the issue of organ shortage include the use of marginal liver grafts, such as those from hepatitis B core antibody (anti-HBc)-positive donors. In Japan, the prevalence of resolved hepatitis B virus (HBV) infection is 23.2%, which is much higher than that in Western countries (*1*). However, resolved HBV infections in donor livers may be reactivated in hepatitis B s antigen (HBsAg)-negative recipients due to post-liver transplantation (LT) immunosuppressive therapy. Ideally, in order to prevent HBV transmission, anti-HBc-positive donors should not be used at all. However, one possible strategy for expanding the donor pool is the use of anti-HBc-positive grafts for LT.

Previous studies have reported that, in the absence of any prophylaxis, the probability of HBV infection depends on the HBV serological status of the recipient (*2*). A variety of prophylactic strategies have been used in small patient series; however, an adequate consensus has not been reached (*3*). Prophylactic strategies that are currently used for LT from anti-HBc-positive donors vary from the administration of hepatitis B

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immunoglobulin (HBIG) or nucleoside/tide analogues (NAs) alone to combination therapy, depending on the liver transplant centers (*2,3*). We previously reported that HBIG monotherapy can prevent HBV infection from anti-HBc-positive donors (*4*). However, the recent practice guidelines indicate that lamivudine monotherapy is the most cost-effective treatment, due to the low rates of graft infection (< 3%) (*5,6*).

The aim of this study was to assess the incidence and risk factors associated with HBV recurrence in HBsAg-negative LDLT recipients of anti-HBc-positive grafts over a period of 20 years.

2. Methods

2.1. *Patients*

From January 1996 to December 2018, a total of 609 LDLT procedures were performed at the University of Tokyo Hospital. We retrospectively reviewed all demographics and radiologic and laboratory data, which had been gathered into a computerized database, collected over this period. All donors were HBsAg-negative. Among them, 55 (9.0%) were anti-HBc-positive donors. Of the recipients of anti-HBc-positive grafts, 33 were HBV-unrelated recipients. After 2 patients who were not followed up for at least 6 months were excluded, 31 patients were enrolled in this study (Figure 1). Patient data were censored at death or the time of the last follow-up.

The study protocol complied with the Good Clinical Practice Guidelines and the 1975 Declaration of Helsinki and was approved by the Institutional Review Board at the University of Tokyo Hospital.

2.2. *Immunoprophylaxis*

Postoperative prophylaxis consisted of HBIG monotherapy. HBIG was administered at 10,000 IU intravenously during the anhepatic phase. HBIG was administered once a month to keep the HBsAb level above 200 IU/L during the first year and above 100 IU/L thereafter (*4*).

2.3. *Immunosuppression protocol*

The details of the immunosuppression protocol are described elsewhere (*7*). The post-transplant immunosuppression regimen consisted of steroid and tacrolimus, both of which were tapered gradually. The targeted serum trough level of tacrolimus was 5 ng/mL, and methylprednisolone was prescribed at a dose of 0.05 mg/kg more than 1 year after LT.

2.4. *Serological monitoring*

The recurrence of the HBV was defined as the development of positive HBsAg and/or HBV DNA after LT (*2*). Standard biochemical tests of the liver function were performed at each follow-up visit. Measurements of HBsAg, Hepatitis B surface antibody (anti-HBs), and anti-HBc were carried out in the University of Tokyo Hospital using commercial chemiluminescent immunoassay (CLIA) kits in the ARCHITECT ANALYSER i2000 (Abbott Japan Co., Ltd., Tokyo, Japan). The sensitivity of the HBsAg assay ranged from 0.05 to 250 IU/mL. Specimens with an HBsAg value exceeding 250 IU/mL were diluted to 1:500 using a diluent recommended by the manufacturer, and the exact concentration of the samples has been measured since 2014. The sensitivity of the anti-HBs assay ranged from 6.0 to 1,000 mIU/mL. Until 2006, anti-HBc was measured using a microparticle enzyme immunoassay (MEIA, AxSYM System; Abbott Japan Co., Ltd.) in which samples with INH% values > 61% were regarded as positive, while those with values < 40% were regarded as negative. Between 2006 and 2008, anti-HBc was measured by a chemiluminescence enzyme-immunoassay (CLEIA) (Fujirebio, Tokyo, Japan), in which samples with INH% values > 50% were regarded as positive, while those with values < 50% were regarded as negative. Since 2008, anti-HBc was measured using the CLIA method, in which samples with S/CO values > 1.0 were regarded as positive, while those with values < 1.0 were regarded as negative. The HBV DNA levels were quantified with a transcription-mediated amplification assay (Mitsubishi Chemical Medience, Tokyo, Japan), which has a detection range of 3.7-8.7 log genome equivalents (LGE)/mL, until March 2004. Thereafter, all HBV DNA levels were quantified using the COBAS Amplicor HBV Monitor

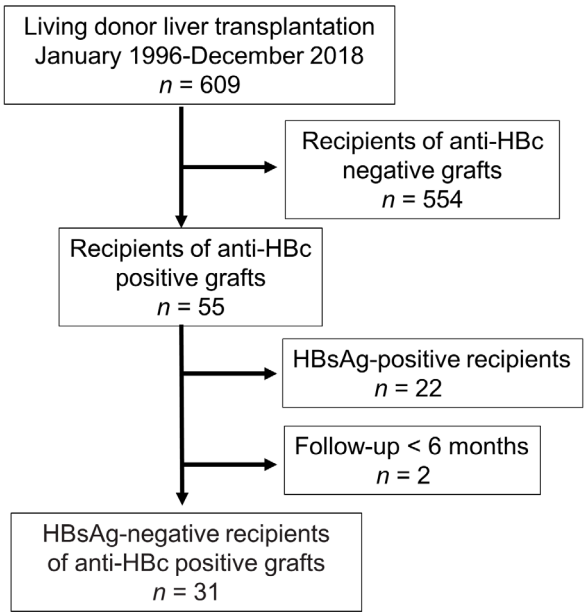

Figure 1. Flow diagram of the patients enrolled in the present study.

Test (Roche Diagnostics, Tokyo, Japan), which has a dynamic range of 2.6 to 7.6 log copies/mL, or COBAS TaqMan HBV Test v2.0 (Roche Diagnostics), which has a dynamic range of 2.1 to 9.0 log copies/mL (1.3 to 8.2 log IU/mL).

2.5. *Vaccination*

Among the subjects of the study, five patients were vaccinated in accordance with the one-year HBV vaccination protocol (*8*). After completion of the one-year vaccination protocol, patients were followed for an additional two years, with monthly measurements of the HBsAb titer and records of the required dose of HBIG for each patient in order to clarify the long-term efficacy of vaccination.

2.6. *Statistical analyses*

We assessed the cumulative incidence of HBV recurrence after LT and the overall survival with a Kaplan-Meier curve. We calculated the hazard ratios (HRs) for the time to HBV recurrence with the Cox proportional hazards model using each potential predictor as a covariate. The difference in the cumulative incidence of HBV recurrence was evaluated by the log-rank test. $p < 0.05$ was considered to indicate statistical significance, and $p < 0.1$ was considered to indicate a candidate potential predictor. Statistical analyses were performed using the SPSS statistics version 23.0 software package (SPSS Inc., Chicago, IL, USA).

Table 1. Patient demographics

Items	Recipients of anti-HBc-positive grafts ($n = 31$)
Age (years)	47 (0-64)
Sex, male/female	23/8
Primary disease	
HCV-cirrhosis	13 (42%)
Primary biliary cirrhosis	6 (19%)
Biliary atresia	4 (13%)
Alcoholic cirrhosis	3 (10%)
Others	5 (16%)
Pretransplant HBV status	
HBsAg positivity	0 (0%)
Anti-HBc/anti-HBs	
-/- (HBV naïve)	18 (58%)
+/+	6 (19%)
+/-	4 (13%)
-/+	3 (10%)
HBIG prophylaxis, yes/no	24/7
HBV vaccination, yes/no	5/26
Median follow-up period (months)	135 (6-273)

Qualitative variables are expressed as the numbers of patients, with percentages in parentheses, and quantitative variables are expressed as the medians, with ranges in parentheses. HCV, hepatitis C virus; HBV, hepatitis B virus; HBsAg, Hepatitis B surface Antigen; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; HBIG, hepatitis B immunoglobulin.

3. Results

3.1. *Patient demographics*

The patient characteristics are shown in Table 1. The population comprised 23 men and 8 women, with median age of 47 years old (range, 0-64 years old). Primary diseases for LT in these patients were hepatitis C virus-cirrhosis ($n = 13$), primary biliary cholangitis ($n = 6$), biliary atresia ($n = 4$), alcoholic cirrhosis ($n = 3$), and others ($n = 5$). At the time of transplantation, 18 were HBV-naïve (anti-HBc-negative and anti-HBs-negative), 6 were anti-HBc-positive and anti-HBs-positive, 4 were anti-HBc-positive, and 3 were anti-HBs-positive. The median follow-up period after LT was 135 months (range, 6-273 months).

3.2. *Risk factors for HBV recurrence after LDLT*

Four of the 31 patients (12.9%) developed post-LT HBV recurrence (Table 2). All cases of HBV recurrence were in HBV-naïve patients and those under HBIG prophylaxis. The overall actuarial rates of HBV recurrence after LT at 1, 3, 5, 10, and 20 years were 0%, 7.4%, 15.7%, 15.7%, and 15.7%, respectively (Figure 2). Although there were no significant differences between the HBV recurrence and non-recurrence groups, HBV recurrence tended to occur in HBV-naïve recipients (Log-rank, $P = 0.093$) (hazard ratio [HR] and confidence interval [CI]: not estimable due to non-

Table 2. The outcomes of patients with HBV recurrence after LT

No.	Age/ gender	Primary disease	Pre-LT HBV status Anti-HBs/ anti-HBc	Anti-HBc titer of donor (INH%)	HBV Prophylaxis	At the time of HBV recurrence				
						Duration from LT (months)	Anti-HBs (mIU/mL)	HBsAg (IU/mL)	HBV DNA (LC/mL)	Peak ALT (IU/l)
1	29/F	AIH	-/-	95	HBIG	35	15	26.67	> 7.6	116
2	53/M	PBC	-/-	92	HBIG, vaccination	20	90.7	1.18	8.9	186
3	52/M	Alcoholic	-/-	78	HBIG	49	15.7	197.04	3.9	125
4	47/M	PBC	-/-	91	HBIG	51	10	8.8	8.0	199

LT, liver transplantation; HBV, hepatitis B virus; Anti-HBs, hepatitis B surface antibody; Anti-HBc, hepatitis B core antibody; INH, inhibition; HBsAg, Hepatitis B surface Antigen; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; HBIG, hepatitis B immunoglobulin; LAM, lamivudine; ADV, adefovir; ETV, entecavir.

convergence) (Table 3). The cumulative rates of post-LT HBV recurrence in HBV naïve recipients (n = 18) at 1, 3, 5, 10, and 20 years were 0%, 12.2%, 25.7%, 25.7%, and 25.7%, respectively. By contrast, in the anti-HBc- and/or anti-HBs-positive recipients (n = 13), there were no cases of HBV recurrence throughout the follow-up period (Figure 3). In the 24 recipients receiving HBIG prophylaxis according to our center's protocol, there were no significant differences between the HBV recurrence group and the non-recurrence group (Table 4).

3.3. *The overall survival after LT*

The overall survival of the 31 recipients of anti-HBc-positive grafts at 1, 3, 5, 10, and 20 years were 96.6%, 89.7%, 85.9%, 81.1%, and 81.1%, respectively (Figure 4). During the study period, five recipients died: one from pulmonary embolism, and the remaining four from HBV-unrelated graft failure.

3.4. *Clinical course of the recipients with HBV recurrence*

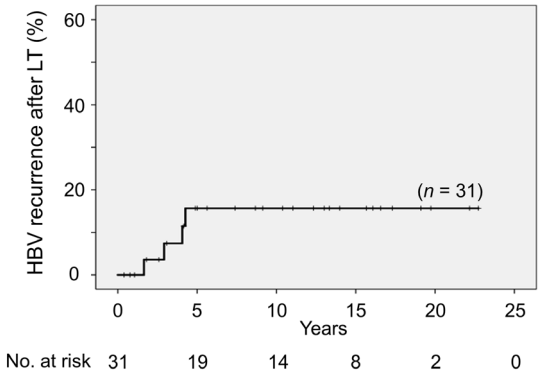

Figure 2. The cumulative overall rates of HBV recurrence after LDLT of anti-HBc-positive grafts.

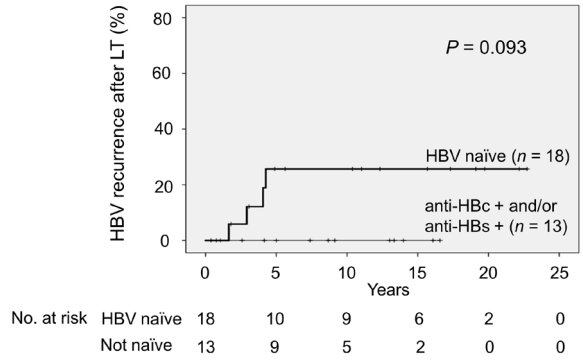

Figure 3. The cumulative rates of HBV recurrence after LDLT of anti-HBc-positive grafts.

Table 3. Predictive factors associated with HBV recurrence after LT

Items	HBV recurrence (n = 4)	HBV non-recurrence (n = 27)	HR	95% CI	P
Age, < 50/> 50 years	2/2	14/13	0.975	0.137-6.928	0.980
Sex, male/female	3/1	20/7	0.905	0.094-8.711	0.931
HBIG prophylaxis, yes/no	4/0	20/7	NE	NE	0.225
HBV vaccination, yes/no	1/3	4/23	0.639	0.066–6.154	0.699
Pre-LT HBV status					
HBV-naïve, yes/no	4/0	14/13	NE	NE	0.093
Anti-HBc positive, yes/no	0/4	10/17	NE	NE	0.148
Anti-HBs positive, yes/no	0/4	9/18	NE	NE	0.212

Qualitative variables are expressed as the numbers of patients, with percentages in parentheses, and quantitative variables are expressed as the medians, with ranges in parentheses. HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval; HBIG, hepatitis B immunoglobulin; LT, liver transplantation; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; NE, not estimable due to non-convergence.

Table 4. Predictive factors associated with HBV recurrence after LT under HBIG prophylaxis

Items	HBV recurrence (n = 4)	HBV non-recurrence (n = 20)	HR	95% CI	P
Age, < 50/> 50 years	2/2	8/12	0.572	0.080–4.068	0.576
Sex, male/female	3/1	14/6	1.359	0.141–3.093	0.791
HBV vaccination, yes/no	1/3	4/16	1.052	0.109–10.134	0.965
Pre-LT HBV status					
HBV-naïve, yes/no	4/0	10/10	NE	NE	0.106
Anti-HBc positive, yes/no	0/4	8/12	NE	NE	0.137
Anti-HBs positive, yes/no	0/4	7/13	NE	NE	0.224

Qualitative variables are expressed as the numbers of patients, with percentages in parentheses, and quantitative variables are expressed as the medians, with ranges in parentheses. HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval; HBIG, hepatitis B immunoglobulin; LT, liver transplantation; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; NE, not estimable due to non-convergence.

The clinical courses and outcomes of the recipients with HBV recurrence are shown in Table 2 and Figure 5. The median interval between LDLT and the development of HBV recurrence was 42 months (range, 20-51 months). At the time of HBV recurrence, anti-HBs titers were maintained at 10-90.7 mIU/mL despite positivity for HBsAg and HBV DNA. All cases of HBV recurrence were treated with lamivudine (LAM) or entecavir (ETV), with or without adefovir. No grafts were lost due to post-LT HBV recurrence-related events, and all cases were alive. Case 1 achieved HBsAg seroconversion after 18 months of LAM administration. In cases 2 and 3, HBsAg turned negative after 44 and 48 months of ETV administration respectively. However, HBsAg seroconversion was not achieved, and ETV was not discontinued. Case 4 remained HBsAg-positive throughout the study period. HBV DNA in these four cases was negative at the last follow-up.

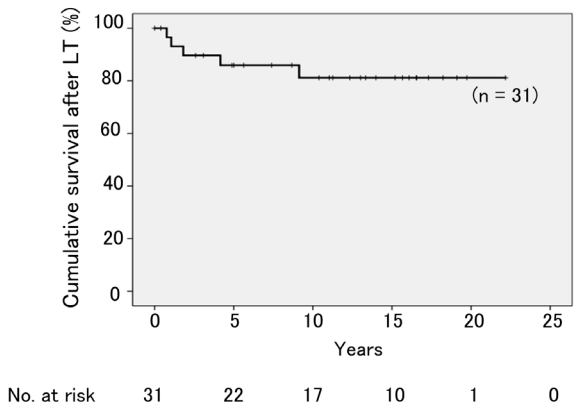

Figure 4. The cumulative survival in LDLT recipients.

3.5. *Outcomes of recipients not receiving HBIG prophylaxis*

Among the 31 patients, 7 did not receive HBIG prophylaxis according to our center's protocol after LDLT (Table 5). Of note, none of the 7 recipients developed HBV recurrence after a median interval of 160 months (range, 37-273 months) post-LT. At the time of transplantation, four were HBV-naïve, one was anti-HBs-positive, one was anti-HBc-positive, and one was anti-HBs-positive and anti-HBc-positive. Cases 1-4 were the patients who underwent LT before starting our HBIG prophylaxis protocol. Case 1 had achieved immunotorelance after LT and has since discontinued immunosuppressive drug use. Cases 2 and 3 were censored because of transfer to another hospital with no HBV recurrence. Cases 5-7 had incidentally not been administered HBIG prophylaxis; however, no patients had HBV recurrence under immunosuppression. They are now under close monitoring for HBV DNA according to the Japanese guideline for preventing HBV reactivation in patients receiving immunosuppressive therapy or chemotherapy (*9*).

3.6. *Vaccination*

All five vaccinated patients received HBIG prophylaxis

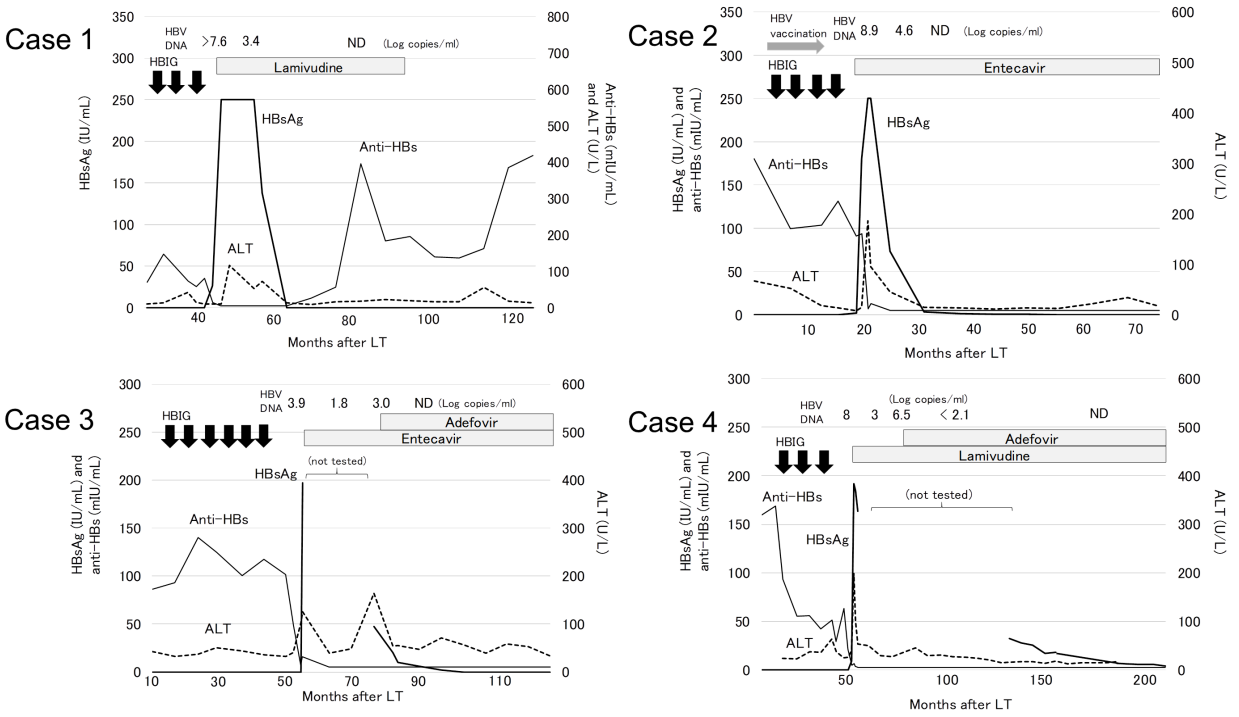

Figure 5. Clinical course of four patients with HBV recurrence after LDLT.

Table 5. Characteristics of patients without HBV prophylaxis

No.	Age/ gender	Primary disease	Pret-LT HBV status Anti-HBs (mIU/ml) / Anti-HBc (INH%)	Anti-HBc titer of donor	Immuno-suppression drug	Follow-up period (months)	HBV recurrence	Outcome
1	4/F	AGS	-/-	+	Withdrawal	273	None	Alive
2	0/M	BA	-/+	+	CyA	59	None	Transfer
3	0/M	BA	-/-	+	CyA	60	None	Transfer
4	8/M	BA	-/-	+	FK	266	None	Alive
5	46/M	PBC	150/-	51 INH%	FK	199	None	Alive
6	55/M	HCV	741/86	97 INH%	CyA	160	None	Alive
7	33/M	BCS	-/-	1.9 S/CO	FK	37	None	Alive

HBV, hepatitis B virus; LT, liver transplantation; Anti-HBs, hepatitis B surface antibody; Anti-HBc, hepatitis B core antibody; AGS, Alagille syndrome; BA, biliary atresia; PBC, primary biliary cholangitis; HCV, hepatitis C virus; BCS, Budd-Chiari syndrome; INH, inhibition; S/CO, sample/cut-off; CyA, cyclosporine; FK, tacrolimus.

(*8*). Of them, 2 showed a good response to the vaccination with an increase in the HBsAb titer (312 and 244 mIU/mL), and HBIG was discontinued successfully. However, the remaining three patients were poor responders, including one who had HBV recurrence after vaccination (Figure 5, case 2).

4. Discussion

It is well known that HBV infection can be reactivated in grafts from anti-HBc-positive donors at a frequency that is related to the HBV serological status of the recipient: in the absence of prophylaxis, this frequency was highest in HBV-naïve recipients (47.8%) and lowest in anti-HBc and/or anti-HBs positive recipients (1.4-13.1%) (*2*). However, with HBIG monoprophylaxis, the risk was decreased to 27% in HBV-naïve recipients and 0-5.8% in anti-HBc- and/or anti-HBs-positive recipients. Furthermore, with lamivudine monoprophylaxis, the risk was decreased to 3.4% in naïve recipients and 0-4% in anti-HBc- and/or anti-HBs-positive recipients (*2*).

In our center, HBIG monoprophylaxis has been the conventional strategy for LT from anti-HBc-positive donors (*4*). In the present study, the rate of HBV recurrence under HBIG monoprophylaxis was 16.7% (4 out of 24 patients) (Table 4), which was consistent with the findings of previous reports (*2*). Overall results showed that HBV recurrence tended to occur in HBV-naïve patients (Log-rank, $P = 0.093$) (Table 3). The rate of HBV recurrence was 22.2% (4 out of 18 patients) in the HBV-naïve group and 0% in the anti-HBc- and/or anti-HBs-positive group (0 out of 13 patients). These results are also consistent with those of previous reports (*2*).

Two main reasons have been proposed for HBV recurrence after LT: the discontinuation of HBIG (*10*) and the emergence of anti-HBs escape mutants (*11,12*). The mechanisms by which HBIG protects the transplanted liver against HBV reinfection are still unclear. One of the most prevalent theories is that HBIG protects naïve hepatocytes against HBV by blocking a putative HBV receptor (*13,14*). Previous studies have shown that recurrent hepatitis B during the first six months after LT develops mainly due to inadequate HBIG doses, whereas late recurrence is caused usually by the selection of immune escape mutants (*15-17*). The most common escape mutation is a glycine-to-arginine substitution at codon 145 of the HBV S protein (G145R) (*18*), which results in reduced binding to anti-HBs, allowing such viruses to escape neutralization by HBIG. In our study, 4 patients had HBV recurrence after a median interval of 42 months (range, 20-51 months) post-LT despite the continuous administration of HBIG. In that respect, our results suggest that all four of these cases may have had anti-HBs escape mutations. However, our study is limited by the fact that a sequence analysis of serum HBV DNA was not performed at the time of HBV recurrence.

In our study, seven recipients did not receive the HBIG prophylaxis protocol, as shown in Table 5. Remarkably, however, HBV recurrence did not occur in any of the seven cases. Cases 5 and 6 were patients who had adequate anti-HBs titers before LT (150 and 741 mIU/mL, respectively) (*19*). The latest EASL clinical practice guideline recommends that prophylaxis for HBV recurrence be performed immediately after LT if recipients do not have anti-HBs (*5*). Furthermore, Cholongitas *et al*. showed that recipients positive for both anti-HBc and anti-HBs represent a group that can safely receive anti-HBc-positive grafts without any post-transplant HBV prophylaxis (*2,20*). In that respect, cases 5 and 6 were recipients who did not need early HBV prophylaxis after LT. One proposed reason for this is that patients with resolved HBV infection have memory T-cells and various antibodies protecting against the proliferation of HBV, including anti-HBs-escape mutations (*16*). However, case 7, who did not have anti-HBs or anti-HBc, incidentally had not been receiving HBV prophylaxis and yet experienced no recurrence of HBV during the follow-up period. In that case, the anti-HBc titer of the donor was relatively low (1.9 S/CO). We previously reported that the titer of anti-HBc may reflect the potential activity of HBV,

even after HBsAg disappearance (*21*). The relationship between the anti-HBc titer of the donor and HBV recurrence after LT is still unclear, and further studies will be necessary to clarify this issue.

The feasibility of HBV vaccination in post-LT recipients is highly controversial. We previously reported that a limited number of patients were able to establish active immunity with our extended one-year vaccination protocol, and the clinical indication for HBV vaccination in LT recipients is currently minimal (*8*). Ishigami *et al*. reported that although the HBV vaccine is an effective substitute for prophylaxis against HBV reactivation after LT, frequent vaccination may be a risk factor for producing escape mutants (*12*). In our study, two of five patients demonstrated a good response to HBV vaccination. However, in Table 2 and Figure 5, case 2 developed HBV recurrence after receiving the HBV vaccination protocol. Although post-transplant HBV vaccination is an alternative that may provide a chance to discontinue prophylaxis by producing anti-HBs, close monitoring of serum HBV markers is needed. Furthermore, based on the fact that Japanese adults are not obligated to undergo HBV vaccination (*22*), pre-transplant HBV vaccination is crucial for potential recipients of LT in Japan (*19*).

In Japan, although the use of HBIG is associated with several issues, such as a high cost and the emergence of escape mutant, HBIG monotherapy is the dominant form of prophylaxis for HBV recurrence after LT from anti-HBc-positive donors (*4,16,23,24*). However, recent clinical practice guidelines of AASLD and EASL recommend the administration of antiviral therapy, such as LAM, ETV, tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF), as these antiviral drugs function as cost-effective treatments due to the low rates of HBV recurrence (< 3%) (*5,6,25*). We are still cautious for NAs especially in the young for the potential risk of the emergence of drug-resistant variants and unknown adverse reactions due to their long-term use.

There are some limitations associated with our study, including its retrospective design and relatively small sample size. However, to our knowledge, this study has the longest duration of follow-up among studies analyzing LDLT recipients with anti-HBc-positive grafts. Furthermore, our results indicated the possibility of a tailor-made prophylactic antiviral therapy for this specific group (*20,26*).

In conclusion, an HBV-naïve status may contribute to HBV recurrence after LDLT of anti-HBc-positive grafts. We should remain cautious concerning the risk of HBV recurrence, particularly in this group. In this respect, pre-transplant HBV vaccination should be recommended for candidate recipients of LT. Further multicenter studies are needed in order to standardize the prophylactic regimen for HBV recurrence after LT with anti-HBc-positive grafts.

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