Original Article

Risk factors for hepatitis B virus recurrence after living donor liver transplantation: A 22-year experience at a single center

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SUMMARY   The factors associated with hepatitis B virus (HBV) recurrence after living donor liver transplantation (LDLT) have not been fully clarified. The aim of this study was to determine the risk factors associated with HBV recurrence after LDLT. From January 1996 to December 2018, a total of 609 LDLT operations were performed at our center. A retrospective review was performed of 70 patients (male, $n = 59$; female, $n = 11$; median age = 54 years) who underwent LDLT for HBV-related liver disease. The virologic and biochemical data, tumor burden, antiviral and immunosuppressive therapy were evaluated and compared between the HBV recurrence and non-recurrence groups. Eleven of 70 patients (16%) developed post-LDLT HBV recurrence. The overall actuarial rates of HBV recurrence at 1, 3, 5, 10, and 20 years were 0%, 13%, 16.7%, 18.8%, and 18.8%, respectively. The median interval between LDLT and HBV recurrence was 57 months (range, 18-124 months). Based on the univariate and multivariate analyses, a serum HBV DNA level of ≥ 4 log copies/mL (hazard ratio [HR], 4.861; 95% confidence interval [95% CI], 1.172-20.165; $P = 0.029$), and hepatocellular carcinoma (HCC) beyond the Milan criteria (HR, 10.083; 95% CI, 2.749-36.982; $P < 0.001$) were independent risk factors for HBV recurrence after LDLT. In LDLT patients, high pre-LT HBV DNA levels and HCC beyond the Milan criteria were risk factors for HBV recurrence. With the current expansion of the LT criteria for HCC, we should remain cautious regarding the risk of HBV recurrence, particularly in these groups.

Keywords   living donor liver transplantation, HBV recurrence, HBV DNA, HCC, Milan criteria

1. Introduction

Hepatitis B is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) worldwide. In the era without effective prophylaxis, hepatitis B virus (HBV)-related disease was a relative contraindication for liver transplantation (LT) until the mid-1990s (*1*). Since the mid-1990s, several prophylaxis strategies for recurrent HBV have shown great progress (*2*), with the use of anti-hepatitis B immunoglobulin (HBIG) and nucleos(t)ide analogues (NAs). However, approximately 10% of transplanted patients still experience HBV recurrence (*3,4*). In previous studies, the factors associated with HBV recurrence were reported to include non-fulminant hepatitis B (*5*), a high pre-LT HBV DNA level (*6,7*), hepatitis B e antigen (HBeAg) positivity (*8*), immunosuppression from steroids and

systemic chemotherapy (*9*), and pre-LT HCC and post-LT HCC recurrence (*10-13*).

The aim of the present study was to assess the incidence and risk factors associated with HBV recurrence in living donor liver transplantation (LDLT) recipients over a 20-year period. We analyzed a retrospective series of patients who underwent LDLT for HBV-related liver disease, and evaluated their virologic and biochemical data, tumor burden, antiviral therapy, and immunosuppressive therapy.

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 demographic, radiologic and laboratory data, which were recorded in a computerized database in the study period. Among these patients, 70 (12%) patients underwent LDLT for HBV-related liver disease, and were enrolled in this study. Patient data were censored at death or at the time of the last follow-up examination.

The study protocol complied with the Good Clinical Practice Guidelines and the 1975 Declaration of Helsinki and was approved by the Research Ethics Committee/Institutional Review Board of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (project number 2158).

2.2. Immunoprophylaxis

Prior to 2008, prophylactic post-transplant treatment was based on HBIG (Hebsbulin-IH; Japan Blood Products Organization, Tokyo, Japan) monotherapy. After 2008, all patients were treated with a combination of HBIG and at least one NA agent (lamivudine, adefovir, entecavir, tenofovir or a combination thereof) for HBV prophylaxis after transplantation. HBIG (10,000 IU, intravenous) was administered during the anhepatic phase and just after the end of the operation. Thereafter, HBIG was administered to maintain hepatitis B surface antibody (anti-HBs) levels at > 1,000 IU/L for 3 months and > 500 IU/L within 1 year; finally, the HBsAb titer was maintained at 100-200 IU/L for > 1 year after transplantation.

2.3. Immunosuppression protocol

The details of the immunosuppression protocol are described elsewhere (*14*). The post-transplant immunosuppression regimen consisted of a steroid and a calcineurin inhibitor, such as tacrolimus or cyclosporine, with or without mycophenolate mofetil. The immunosuppressive dosing was adjusted according to the therapeutic drug levels and the renal function. Maintenance tacrolimus therapy after 6 months was targeted at a level of 5 ng/mL, and a cyclosporine trough level of 100 ng/mL was maintained, depending on the rejection profile. The monitoring of trough serum levels was conducted regularly as per protocol for the evaluation of toxicity and compliance and for dose adjustments. Methylprednisolone was prescribed at a dose of 0.05 mg/kg more than 6 months after LT.

2.4. Serological monitoring

HBV recurrence was defined as the development of hepatitis B surface antigen (HBsAg) positivity and/or HBV DNA positivity after LT (*15*). Standard biochemical tests of the liver function were performed at each follow-up visit. The measurement of HBsAg and anti-HBs was carried out in the University of Tokyo Hospital using commercial chemiluminescent immunoassay (CLIA) kits

in an 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 of > 250 IU/mL were diluted to 1:500 using a diluent recommended by the manufacturer. The exact concentrations of the samples have been measured since 2014. The sensitivity of the anti-HBs assay ranged from 6.0 to 1000 mIU/mL. 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 Test (Roche Diagnostics, Tokyo, Japan), which has a dynamic range of 2.6 to 7.6 log copies/ml, or a 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, 28 patients were vaccinated in accordance with the one-year HBV vaccination protocol (*16*). 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 LDLT and overall survival with a Kaplan-Meier curve analysis. We calculated the hazard ratios (HRs) for the time to HBV recurrence with a Cox proportional hazards model using each potential predictor as a covariate. *P* values of < 0.05 were considered to indicate statistical significance, and *p* values of < 0.15 were considered to indicate candidate potential predictors. All statistical analyses were performed using the SPSS statistics version 23.0 software package (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient demographics

The patient characteristics are shown in Table 1. The population included 59 men and 11 women, with median age of 54 years (range, 38-67 years). The median follow-up period after LT was 134 months (range, 1-226 months). HCC was present in 39 patients (56%). Among them, 37 patients with HCC were diagnosed by preoperative computed tomography or magnetic resonance imaging, whereas two patients were diagnosed incidentally by a pathological examination of

the explant. According to the explant pathology, HCC beyond the Milan criteria (no macrovascular invasion, a single tumor ≤ 5 cm, or up to three tumors ≤ 3 cm each) was present in 16 patients (41%). Pre-LT HCC

Table 1. The characteristics of the 70 patients with hepatitis B virus-related liver disease

Variable	
Age	54 (38-67)
Male/Female	59/11 (84%/16%)
HBsAg, +/-	69/1 (98%/2%)
HBeAg, +/-	14/56 (20%/80%)
HBV DNA (log copies/ml)	
< 2.6	49 (70%)
2.6-4.0	12 (17%)
> 4.0	9 (13%)
HCC, +/-	39/31 (56%/44%)
Milan criteria, within/beyond	23/16 (59%/41%), *n* = 39
Pre-LT treatment of HCC	
Resection/TACE/TACE+RFA or PEIT/RFA/PEIT/TAI/none	7/18/9/1/1/1/33
Pre-LT antiviral therapy	
LMV/LMV +ADV/TDF/ETV/None	39/4/1/15/11
HBV Prophylaxis	
HBIG/HBIG+NA	52/18 (74%/26%)
LMV/LMV+ADV/ETV	1/3/14 (5%/17%/78%), *n* = 18
Follow-up period (months)	134 (1-226)

Qualitative variables are expressed as the number of patients with the percentage in parentheses, and quantitative variables are expressed as the median, with the range in parentheses. ADV, adefovir; ETV, entecavir; HBeAg, hepatitis B e-antigen; HBIG, hepatitis B immunoglobulin; HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LAM, lamivudine; NA, nucleoside analogue; LT, liver transplantation; PEIT, percutaneous ethanol injection therapy; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion; TDF, tenofovir.

therapy was administered to 28 of the 39 patients with HCC (72%). Among them, 23 patients (64%) received a combination of local ablative therapy in the form of arterial chemoembolization, radiofrequency ablation and/or an ethanol injection prior to LDLT. Four patients (10%) underwent surgical resection of the tumor, and one patient (3%) received systemic chemotherapy prior to LDLT.

3.2. Risk factors for HBV recurrence after LDLT

Eleven of the 70 patients (16%) developed post-LT HBV recurrence. The overall actuarial rates of HBV recurrence after LDLT at 1, 3, 5, 10, and 20 years were 0%, 13%, 16.7%, 18.8%, and 18.8%, respectively (Figure 1A). Table 2 shows the results of the univariate and multivariate analyses of risk factors associated with HBV recurrence after LDLT. The univariate analyses revealed that the HCC beyond the Milan criteria (hazard ratio [HR], 7.592; 95% confidence interval [95% CI], 2.217-25.991; *P* = 0.001) was significantly associated with HBV recurrence. According to the multivariate analysis, serum pre-LT HBV DNA ≥ 4 log copies/mL (HR, 4.861; 95%CI, 1.172-20.165; P=0.029) and HCC beyond the Milan criteria (HR, 10.083; 95% CI, 2.749-36.982; *P* < 0.001) were independent risk factors for HBV recurrence after LDLT.

3.3. Pretransplant HCC and HCC recurrence

The cumulative HBV recurrence rate after LDLT in patients with HCC was higher (with marginal significance) than that in patients without HCC (*P* = 0.080) (Figure 1B). Meanwhile, the cumulative HBV
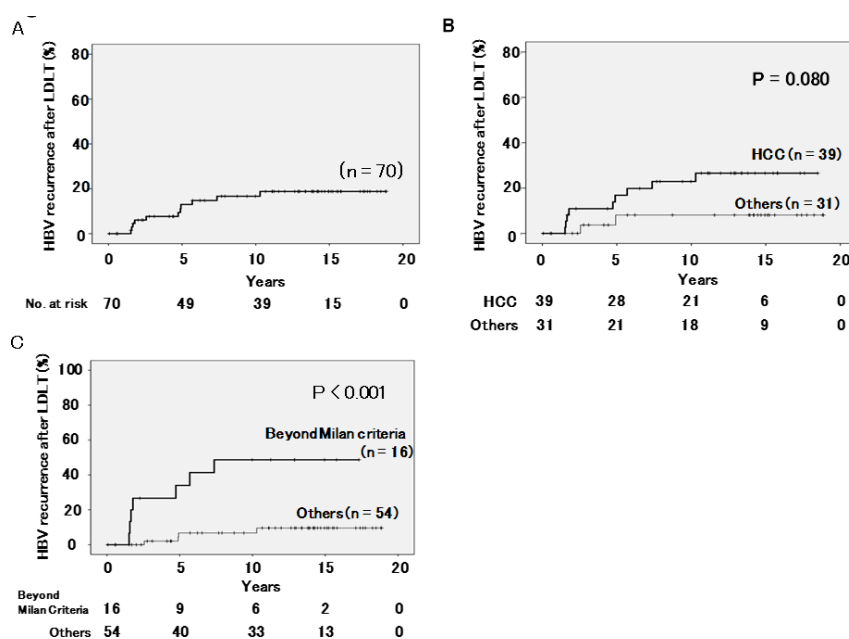

Figure 1. The cumulative rates of HBV recurrence after LDLT in recipients with HBV-related liver disease. (A) The overall analysis. **(B)** HCC versus others. **(C)** HCC beyond the Milan criteria versus others.

Table 2. Predictors of HBV recurrence after LT

Items	HBV recurrence (n = 11)	HBV non-recurrence (n = 59)	Univariate analysis			Multivariate analysis		
			HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age, ≥ 55 (years)	7	32	1.416	0.414-4.839	0.579			
Sex, male	11	48	NE	NE	0.155			
HBeAg, +	3	11	1.462	0.387-5.517	0.575			
HBV DNA ≥ 4 (LC/mL)	3	6	2.702	0.716-10.203	0.143	4.861	1.172-20.165	0.029
Vaccination, +	3	25	0.350	0.092-1.337	0.125			
HCC, +	9	32	3.602	0.778-16.676	0.101			
Milan criteria, beyond	7	9	7.592	2.217-25.991	0.001	10.083	2.749-36.978	< 0.001
Pre-LT HCC treatment, +	7	30	1.516	0.444-5.181	0.507			
CNI, FK	9	47	1.222	0.264-5.658	0.797			
Prophylaxis, HBIG	10	42	2.684	0.341-21.141	0.348			

CI, confidence interval; CNI, calcineurin inhibitor; FK, tacrolimus; HBeAg, hepatitis B e-antigen; HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; LC, log copies; LT, liver transplantation.

Table 3. Antiviral therapy administered and the outcomes of patients with HBV recurrence after LDLT

No.	Age (years), sex	HBeAg	HBVDNA (LC/mL)	Primary disease	Milan Criteria	HBV prophylaxis	HBV Recurrence (months)	HCC recurrence (months)	Outcome
1	56, M	-	ND	Cirrhosis	-	HBIG	59	-	Alive
2	39, M	+	4.0	Cirrhosis	-	HBIG	31	-	Alive
3	59, M	-	ND	HCC	Within	HBIG	124	-	Alive
4	48, M	+	4.9	HCC	Within	HBIG	59	-	Alive
5	55, M	-	ND	HCC	Beyond	HBIG	88	-	Alive
6	48, M	-	ND	HCC	Beyond	HBIG	68	-	Alive
7	52, M	+	5.2	HCC	Beyond	HBIG	57	-	Alive
8	53, M	-	3.7	HCC	Beyond	HBIG	20	14	Died
9	54, M	-	ND	HCC	Beyond	HBIG	18	19	Died
10	54, M	-	ND	HCC	Beyond	HBIG	18	20	Died
11	64, M	-	ND	HCC	Beyond	HBIG+ETV	21	22	Alive

ETV, entecavir; HBeAg, hepatitis B e-antigen; HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LC, log copies; LDLT, living donor liver transplantation; ND, not detected.

recurrence rate in patients with HCC beyond the Milan criteria was significantly higher than that in those with HCC within the Milan criteria (P < 0.001) (Figure 1C). Among 16 patients with HCC beyond the Milan criteria, 7 patients (44%) developed HBV recurrence after LDLT (Table 3, case 5-11), and recurrent HCC developed in 4 of these 7 patients (57%) (case 8-11). In case 8, the tumors were beyond the Milan criteria at LDLT, and HCC recurred as lung metastasis at 14 months after transplantation. Despite the administration of chemotherapy, the HCC had grown, and HBV reappeared at 20 months after transplantation (Figure 2A). In case 9, there were uncountable HCC tumors, and the disease was beyond the Milan criteria at LDLT. At 18 months after transplantation, recurrent HBV was observed, and HCC recurred at 19 months after LDLT (Figure 2B). In case 10, there were 7 HCC tumors at LDLT. HBV reappeared at 18 months after transplantation, and HCC recurrence was observed as bone metastasis at 20 months after LDLT (Figure 2C). All 3 patients (cases 8-10) finally died of recurrent HCC, at 25, 33, 44 months after transplantation, respectively. Among the 4 patients with recurrent HCC, the remaining patient (case 11) was the only patient to survive. The tumors were beyond

the Milan criteria at LDLT, and HBV reappeared at 21 months after LDLT, despite combined therapy with HBIG and entecavir. HCC recurred as lung metastasis at 22 months after transplantation, and lung resection was performed. HBsAg disappeared after the operation and the patient had an uneventful postoperative course (Figure 2D).

3.4. Vaccination

HBV vaccination was indicated for patients with normal or near normal liver function test results with a low level of immunosuppression, and the follow-up period after LDLT was at least one year (*16*). All 28 vaccinated patients received HBIG monoprophylaxis. Among them, 2 showed a good response to the vaccination with an increase in the anti-HBs titer, and HBIG was successfully discontinued. However, the remaining 26 patients were poor responders, including 3 who developed recurrent HBV after vaccination.

3.5. Overall survival after LDLT

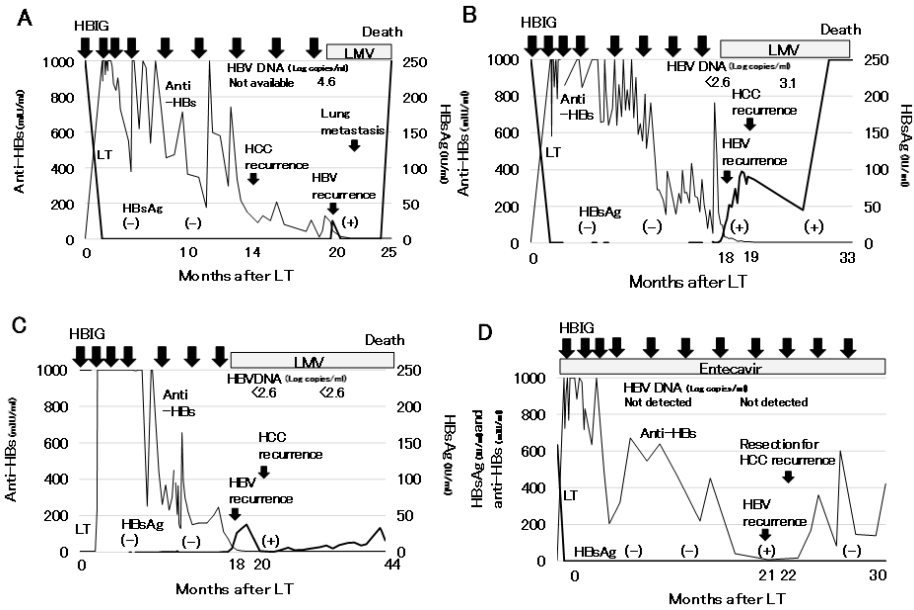The overall survival rates of the 70 recipients at 1, 3, 5,

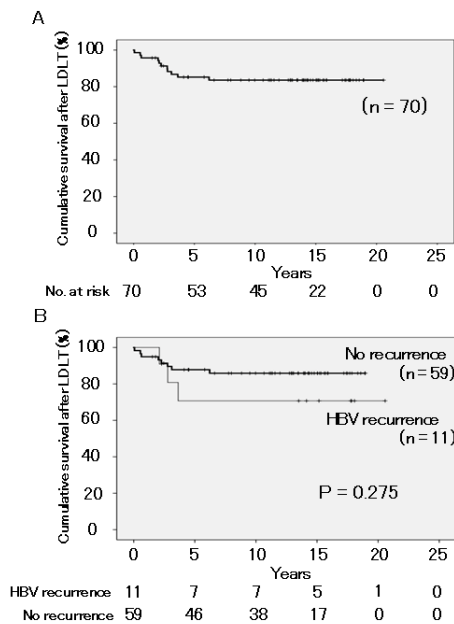**Figure 2. The clinical course of the patients with recurrent HBV after LDLT.**

Figure 3. The cumulative rates of survival in LDLT recipients.
(A) The overall analysis. **(B)** The patients with recurrent HBV versus those without.

10, and 20 years were 95.7%, 88.3%, 85.2%, 83.6%, and 83.6%, respectively (Figure 3A). During the study period, 11 recipients died: 5 from recurrent HCC, 2 from respiratory diseases, and the remaining 4 due to other reasons: graft failure due to hepatic vein stenosis, acute heart failure, cerebral hemorrhage, and colon cancer. The overall survival rate after LDLT was not significantly reduced in patients with recurrent HBV; the probability rates of survival at 1, 3, 5, 10, and 20 years were 100%, 80.8%, 70.7%, 70.7%, and 70.7%,

respectively, in patients with recurrent HBV and 94.9%, 89.6%, 87.8%, 85.9%, and 85.9%, respectively, in patients without recurrent HBV (*P* = 0.275) (Figure 3B).

4. Discussion

In our study, we demonstrated that pre-LT HBV DNA ≥ 4 log copies/mL and HCC beyond the Milan criteria were independent risk factors for the recurrence of HBV after LDLT. A high pre-LT HBV DNA level is well known to be a factor associated with the recurrence of HBV after LT (*6,7*). In this respect, our results were consistent with previous reports.

Previous studies have suggested an association between HCC and a higher risk of HBV recurrence after transplantation (*10-13*). Faria *et al.* reported that the presence of HCC at transplantation and HCC recurrence were independent risk factors for HBV recurrence (*10*). Furthermore, Saab *et al.* reported that pre-LT HCC and the recurrence of HCC after transplantation were associated with HBV reinfection and with decreased patient survival (*11*). Several mechanisms may be involved in the higher rate of HBV recurrence in HCC patients. Although the immunosuppression related to HCC recurrence may itself contribute to HBV recurrence, the direct relationship between the resection of metastasis and the disappearance of HBsAg suggests HBV replication in HCC metastasis (Figure 2D). Faria *et al.* demonstrated the presence of covalently closed circular DNA in both HCC cells and in non-tumor cells in explanted livers, suggesting that HBV replication may also occur in tumor cells (*10*). Furthermore, Bai *et al.* indicated that cccDNA and pgRNA are detected and represented HBV replication not only in non-HCC

tissues but also in HCC tissues (*17*). In the current era of highly effective prophylaxis against HBV, these finding suggests that HCC itself is the main factor of HBV prophylaxis failure.

Since the Milan criteria were proposed in 1996, liver transplantation has become widely accepted for HCC patients with favorable tumor morphology. However, because of the strict limitations in patient selection, the Milan criteria were recently challenged by several studies to expand the patient selection (*18-22*). In Japan, expanded criteria for LT for HCC patients were recently proposed. Based on a data analysis of the Japanese nationwide survey, the 5-5-500 rule (nodule size ≤ 5 cm in diameter, nodule number ≤ 5, and alfafetoprotein value ≤ 500 ng/mL) were established as new expanded LT criteria for HCC patients (*23*). Meanwhile, in our study, among 16 patients with HCC beyond the Milan criteria, 7 patients developed recurrent HBV. Furthermore, HCC beyond the Milan criteria was an independent risk factor for the recurrence of HBV after LDLT. These results suggest that although it is crucial to widely accept HCC patients, the expansion of the Milan criteria is a double-edged sword with regard to the risk of HBV recurrence. Meanwhile, HCC recurrence occurred in 4 of these 7 patients with recurrent HBV (Table 2, case 8-11). It is noteworthy that HBV recurrence preceded HCC recurrence in 3 of 4 cases (Figure 2B, C, D). Especially in case 11, HCC recurrence was suspected at the time of HBV recurrence based on previous reports and our own experience, and resection for lung metastasis could be performed at an early stage (Figure 2D). Vatansever et al. reported that the HBV and HCC recurrence are closely related in patients who underwent LT due to HBV-associated HCC (*24*). They also insisted that the HBV recurrence after LT increases the risk of HCC recurrence. Therefore, they concluded that the HBV recurrence may be used as a predictor in forecasting the HCC recurrence. Whether HBV recurrence can be a definite predictor of the recurrence of HCC after LT is a matter of debate, however, these results should not be missed and require confirmation by further investigations.

The present study was associated with several limitations, including its retrospective design and relatively small sample size. However, to our knowledge, this is the first paper to call attention to the relationship between the expansion of the Milan criteria and HBV recurrence after LT. Furthermore, this study has the longest follow-up period among LDLT studies analyzing recipients with HBV-related liver disease.

In conclusion, HCC beyond the Milan criteria were independent risk factors for the recurrence of HBV in LDLT patients. In this era with the expansion of the LT criteria for HCC, we should remain cautious with regard to the risk of HBV recurrence, particularly in these groups. Further multicenter studies are needed in order to evaluate our results prospectively.

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