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Long-term outcomes of liver transplantation using grafts from donors with active hepatitis B virus replication: a multicenter cohort study

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Purpose: Liver grafts from donors with HBV infection contributed to expanding the donor pool under the hepatitis B immunoglobulin and antiviral agents (nucleos(t)ide analogues) in the HBV-endemic area. We report long-term outcomes of liver transplantations (LTs) using grafts from donors with active or chronic HBV infection.
Methods: Overall, 2,260 LTs performed in 3 major hospitals in Seoul from January 2000 to April 2019 were assessed for inclusion. Twenty-six grafts (1.2%) were obtained from HBsAg (+), HBeAb (+), or HBcAb (+) donors, and recipient outcomes were retrospectively reviewed. Donor and recipient demographics and transplantation outcomes were analyzed.
Results: Sixteen deceased donor LTs were performed using active HBsAg (+) grafts. Ten other LTs were sourced from 10 living donors. There was no significant difference in survival in patients who received deceased donor LTs compared with that in those who underwent LT with non–hepatitis virus-infected grafts. Fourteen patients who were followed up for >5 years were stable, and no difference in hepatocellular carcinoma recurrence rate was observed 5 years after transplantation between transplants from donors with and those without HBV.
Conclusion: Considering long-term outcomes, liver grafts from donors with active HBV replication can be safely used for LT.
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Key Words: Hepatitis B virus, Hepatocellular carcinoma, Liver transplantation, Marginal graft, Outcome

INTRODUCTION

Liver transplantation (LT) is widely recognized as a curative treatment for end-stage liver disease and hepatocellular carcinoma (HCC) [1,2]. While the demand for LT continues to increase, the disparity between supply and demand of available grafts has likewise increased [3]. To overcome the shortage of deceased donors, the use of living donor LTs (LDLTs) has become increasingly common, especially in Asia. Simultaneously, LT using safe marginal grafts has increased [4,5]. To support these efforts, strategies have been established for the safe use of marginal grafts including small-for-size liver grafts, old-aged donor grafts, ABO-incompatible grafts, grafts with steatosis, and virus-infected grafts.

HBV-related end-stage liver disease and HCC are the main indications for LT in East Asian areas where HBV infection

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is endemic, including Korea (3% prevalence in 2016) [6]. In these areas, the high prevalence of donors with HBV carrier status has made using liver grafts with inactive HBV infection necessary [7]. However, the possibility of HBV transmission or reactivation, or HCC recurrence after LT from an HBV are major issues that must be addressed. Nevertheless, attempts to use these grafts, following strict selection criteria and perioperative management protocols have continued. The current criteria include appropriate graft allocation, such that the recipient's prognosis is unaffected [8,9]; perioperative medication using hepatitis B immunoglobulin (HBIG) [10]; administration of antivirals to control HBV [11]; and regular surveillance for HBV reactivation or HCC occurrence.

Several previously published retrospective and prospective studies have approved the use of HBsAg (+) grafts with caution [6,12,13]. However, most of them were short-term retrospective studies (<5 years). Although HBV reactivation is commonly reported within 2–3 years posttransplantation, HCC occurrence needs to be monitored over a longer period, as several publications have reported HCC recurrence >5 years posttransplantation [14,15].

Therefore, this study investigated the long-term safety outcomes of LT with active and chronic HBV-infected liver grafts and the prevalence of HCC recurrence after LT.

METHODS

Study population and data collection

The electronic medical records of 2,260 patients who underwent LT at 3 major hospitals from January 2000 to April 2019 were retrospectively reviewed. Twenty-six patients (1.2%) who received liver grafts from donors positive for HBsAg, HBeAg, or HBV DNA were enrolled (Fig. 1). Demographics and other information about deceased donors were also collected from the Korean Network for Organ Sharing database. For LDLT donors, outpatient follow-up appointment records were reviewed to evaluate donor safety.

This study was approved by the Institutional Review Boards of each institution (No. H-2104-178-1214, No. 20-2021-17, and No. B-2108-705-403). The need for informed consent was waived by the review boards. This report complies with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for reporting observational studies.

HBV recurrence

The recurrence of HBV was defined as serum HBV DNA detection and increased HBV DNA levels after LT for HBsAg (+) recipients in whom HBsAg (+) grafts were transplanted.

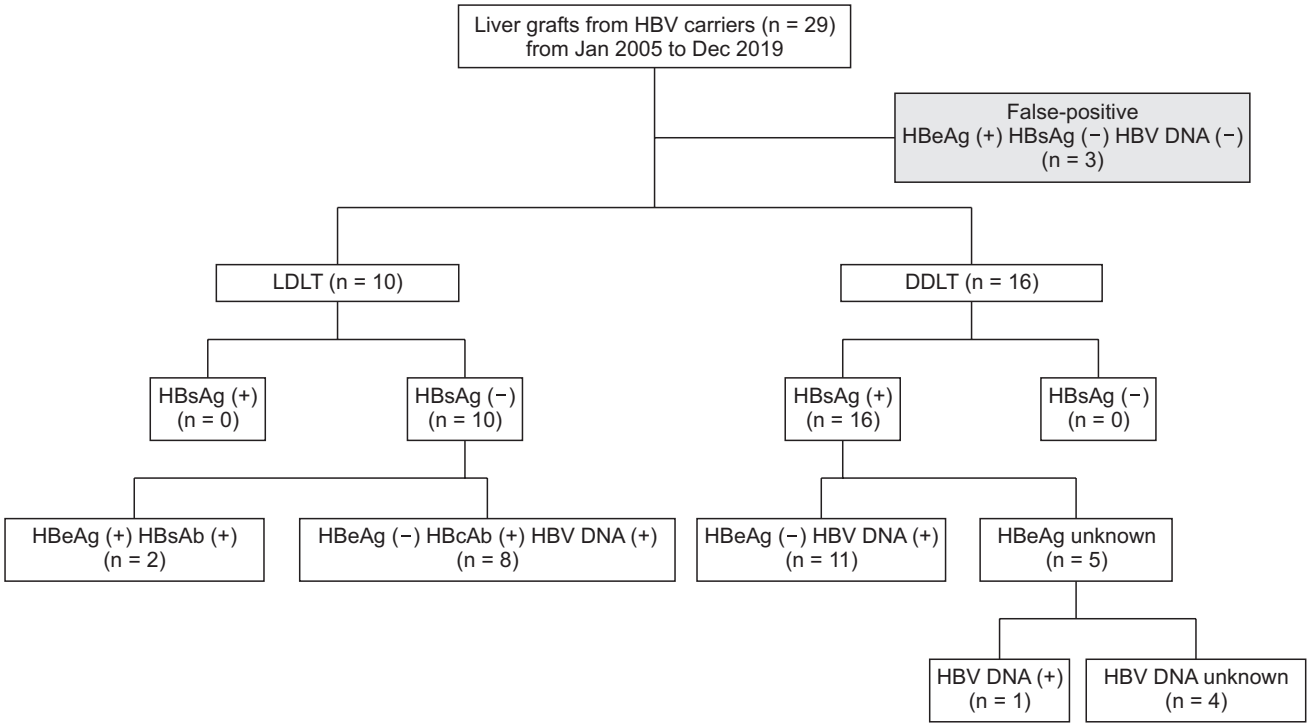

Fig. 1. Flow chart of the study population. Three patients were excluded as their serology results were considered to be false positives following consultation with a hepatologist. Twenty-six donors were regarded as having active (deceased donor liver transplantation, DDLT) or chronic (living donor liver transplantation, LDLT) HBV infection. All deceased donor liver transplantations used HBsAg (+) grafts. All living donors had chronic hepatitis with HBsAg (–) seroconversion. Serum liver enzyme levels were within the normal ranges in all donors.

Positive seroconversion of HBsAg was determined in patients who underwent transplantation using HBsAg (–) grafts. We schematized the HBV infection state of recipients to investigate changes in liver graft properties after LT [16]. Donors and recipients were divided into resolved, inactive, or chronic hepatitis groups based on their serologic status (HBsAg/Ab, HBeAg/Ab, and HBV DNA titer) and serum liver enzyme levels, determined by consultation with our hepatologist [17].

Immunosuppressant regimen

Basiliximab (Simulect, Novartis) 40 mg was used on the day of the operation and postoperative day 4 as the immunosuppression induction agent. Triple therapy regimens of tacrolimus, mycophenolate mofetil, and corticosteroids were used as maintenance immunosuppressive therapy. The target serum concentration of tacrolimus was 8–12 ng/mL for the first 6 months posttransplantation, and 6–8 ng/mL beyond 6 months post-LT.

Prophylaxis for HBV recurrence

Prophylaxis for HBV reactivation using intravenous HBIG (Hepabig, Green Cross) was initiated intraoperatively during the anhepatic phase (induction dose) and maintained (maintenance dose) in most cases (Fig. 2). An induction dose of 10,000 or 20,000 IU and maintenance dose of 10,000 IU was administered to recipients transplanted with HBsAg (+) grafts. After discharge, approximately 10,000 IU of HBIG was administered according to the serum HBsAb levels, which were measured

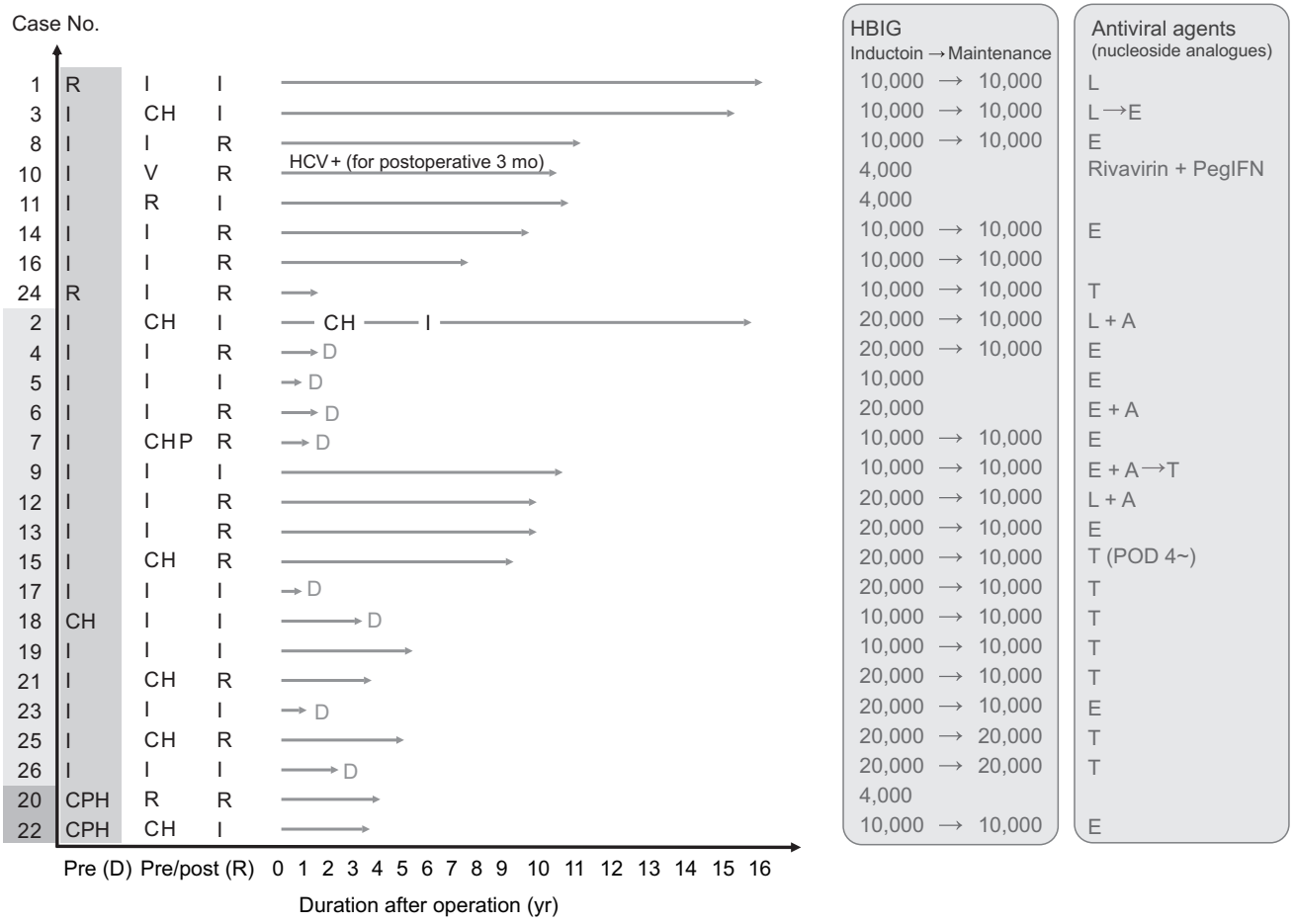

Fig. 2. HBV infection stage of donors and recipients, as well as transplantation outcomes and perioperative management of each patient. Eight donors with HBcAb (+) HBV DNA (+) were regarded as cases of resolving HBV, an immune-inactive stage with low viral replication. The other 2 donors had HBeAg (+) chronic HBV infection with HBsAg seroconversion. D is marked at the end of the arrow of deceased recipients. Hepatitis B immunoglobulin (HBIG) was administered as a maintenance dose after induction. The operator decided the dose based on the HBV infection statuses of the donor and recipient. The same principle was applied to dosages of antiviral agents. Pre (D) indicates the HBV infection stage of donors, pre (R) indicates that of recipients before transplantation, and post (R) indicates that of recipients after transplantation. R, resolution; I, inactive; CH, HBeAg (–) chronic hepatitis; V, vaccinated; CHP, HBeAg (+) chronic hepatitis; CPH, HBe-positive chronic hepatitis with HBV seroconversion; HCV+, HCV DNA positive; L, lamivudine; A, adefovir; E, entecavir; T, tenofovir; PegIFN, pegylated interferon a2a; POD, postoperative day.

regularly at the outpatient clinic. Nucleoside/nucleotide analogues (NAs) were also routinely used after LT.

Statistical analyses

IBM SPSS Statistics ver. 27.0 (IBM Corp.) was used for statistical analyses. The Student t-test was used to analyze continuous variables, and categorical variables were analyzed using the chi-square or Fisher exact test. The Kaplan-Meier method was used to evaluate and compare patient survival,

Table 1. Clinical characteristics of recipients

Variable	Data
No. of patients	26
Sex	
Male	13 (50.0)
Female	13 (50.0)
ABO blood group	
ABOc	26 (100)
O+	8 (30.8)
A+	11 (42.3)
B+	5 (19.2)
AB+	2 (7.7)
Type of LT	
DDLT	16 (61.5)
LDLT	10 (38.5)
Age (yr)	59.0 ± 10.1 (41.0–76.0)
Body mass index (kg/m^2)	23.5 ± 3.5 (17.8–30.8)
MELD score	19.9 ± 8.4 (9.5–37.5)
Gastrointestinal bleeding	5 (19.2)
Hepatic encephalopathy	8 (30.8)
Ascites	15 (57.7)[a]
Transplant indication	
Decompensated cirrhosis	11 (42.3)
HBV	9 (33.3)
HCV	1 (3.8)
PBC	1 (3.8)
Retransplantation	1 (3.8, chronic rejection)
HCC	14 (53.8)
HBV	12 (46.2)
HBV + HCV	1 (3.8)
MOVC	1 (3.8)
Diagnosis by imaging	14 (53.8)
Pathologic HCC	11 (42.3)
Meeting Milan criteria	8 (30.8)
Tumor marker	
α-FP (ng/mL)	22.5 ± 28.4 (1.0–95.2)
PIVKA (mAU/mL)[b]	34.6 ± 41.5 (5.0–199.0)

Values are presented as number only, number (%), or mean ± standard deviation (range).
LT, liver transplantation; DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; MELD, Model for End-Stage Liver Disease; PBC, primary biliary cirrhosis; HCC, hepatocellular carcinoma; MOVC, membranous obstruction of the inferior vena cava; PIVKA, prothrombin in vitamin K absence.
[a]spontaneous bacterial peritonitis = 3; [b]n = 24.

Table 2. Clinical characteristics of recipients with HCC in detail (n = 14)

Case No.	Pre-LT				Milan	Pre-LT treatment	Pathologic diagnosis				
	Size (cm)	Number	Sum (width + length)	VI			HCC	Size (cm)	Number	Sum (width + length)	VI
1	<1	2	<1	N	I	T	Yes	4.2	1	5.7	No
5	1.5	1	<3	Y	B	T	No				
6	<1	1	<1	Y	B	T/P	Yes	3.2	3	6.7	No
7	9.7	10	<10	N	B	O/T/H/R/P	Yes	3.3	>5	3.3	No
9	2.0	5	1.3	N	I	T/P	Yes	1.3	3	2.8	No
11	0.7	1	0.7	N	I	T	Yes	2.2	2	2.2	No
13	2.2	1	2.2	N	I	T	Yes	2.0	2	3.2	No
14	6.8	1	6.8	N	B		No[a]	5.0	1	5.0	No
17	2.8	2	3.8	N	I	T/R/RT	Yes	3.5	3	5.4	No
19	9.0	1	9.0	N	B	T/R/P	No	2.1	5	7.1	No
23	1.0	2	2.0	N	I	T	No				
24	0.0	0	0.0	N	I	T/R	No				
25	1.2	2	2.4	N	B	O/T/R	Yes	0.5	2	1.0	No
26	0.9	2	1.8	N	I	T/R	Yes	1.2	1	1.2	No

HCC, hepatocellular carcinoma; LT, liver transplantation; VI, vascular invasion; B, beyond; I, in; T, transarterial chemoembolization; P, percutaneous ethanol injection therapy; O, operation; H, hepatectomy; R, radiofrequency ablation; RT, radiotherapy.
[a]Intrahepatic cholangiocarcinoma.

Table 3. Serological status of donors and recipients

Case No.	Donor							Recipient							
	HBsAg	HBsAb	HBeAg	HBeAb	HBcAb (IgG)	HCV Ab	HBV DNA (IU/mL)	HBsAg	HBsAb	HBeAg	HBeAb	HBcAb (IgG)	HCV Ab	HBV DNA (IU/mL)	HDV Ab
1	–	87.3	–	–	+	–	<51.5	>250	0.08	–	+	+	–	58.1	
3	–	>1,000	–	+	+	–	136	>250	0	–	+	+	–	19,600	
8	–	>1,000	–	+	+	–	<20	3.3	0.4	–	+	+	–	63	–
10	–	2.37	–	+	+	–	<20	0.0	32.8	–	–	–	+		–
11	–	240.2	–	+	+	–	<20	0	5.5	–	+	+	–	0	–
14	–	414.2	–	+	+	–	<20	3,310.7	0.0	–	+	+	–	794	–
16	–	>1,000	–	+	+	–	<20	4,124.7	0.2	–	+	+	–	50	–
24	–	17.5	–	–	+	–	<20	2,636.1	0.8	–	–	+	–	0	–
2	230.0	–	–	+	+	–	30	>250	+	–	+	+	–	43,800	
4	210.1	–	–	+	+		Weakly (+)	0.0	+	–	–	+	–	0	
5	+	–	–	+				197.6	0.2	–	+	+	–	0	
6	5,043.0	–	–	+	+		44	8.2	32.4	–	–		–	<12	
7	>250	0.3	–	+	+	–	128	>250	96.3	+	–	+	1.04	42,700,000	
9	156.9	0.3	–	+	+	–	395	7.3	1.3	–	+	+	–	20	
12	+	–	–	+	+		1,050	952.6	+	–	–	+	–	243	–
13	+	–	–		+		1,000	18.5	0.1	–	+	+	12.59	331	
15	>250	–	–	+	+		Positive	3,214.8	+	–	+	+	–	8,970	–
17	+	0.0	–		+	–	<60	3,483.9	0.0	–	+	+	–	0	0.0002
18	+	0.0	–		+	–	6,870	4,064.9	0.6	–	+	+	–	1,760	–
19	+	+	–		+	–	139	2,010.4	0.0	–	+	+	–	0	–
21	+	–	–			–	14.9	1,462.8	3.2	–	+	+	–	2,016	–
23	+	–	–	+	+	–	1,320	710.8	0.7	–	+	+	1.50	<20	–
25	+	–	–		+	–	399	1.1	25.6	–	–	+	–	+	
26	+	–	–		+	–	Positive	1,593.2	<10.0	–	–	+	–	–	
20	–	316.6	+	–	+	–	0.0	0.0	27.9	–	+	+	–		–
22	–	30.2	+	–	–	97.8		5,100.7	0.0	–	+	+	–	214,327	–

+, positive; –, negative.
White row, HBcAb (+) HBV DNA (+); light gray row, HBsAg (+); dark gray row, HBsAb (+) HBeAg (+) chronic hepatitis.

and the log-rank test was used to compare survival curves. Statistical significance was set at the P-values of <0.05.

RESULTS

Demographics

The study included 10 LDLTs and 16 deceased donor LTs (DDLTs). All HBsAg (+) grafts were from deceased donors and were transplanted into recipients who had a history of HBV infection. Among recipients who received grafts from living donors, 2 received HBsAb (+) and HBeAg (+) grafts, and 8 received HBcAb (IgG) (+) and HBV DNA (+) grafts. The 8 donors who were HBcAb (+) and HBV DNA (+) were determined to be in the HBV immune-inactive stage with low viral replication.

The mean age of the recipients was 59.0 ± 10.1 years (Table 1). The male-to-female ratio was 1:1. The mean body mass index (kg/m^2) was 23.5 ± 3.5. The mean Model for End-Stage Liver Disease (MELD) score of the recipients before LT was 19.9 ± 8.4 (range, 9.5–37.5). There was no significant difference in MELD scores between DDLT and LDLT recipients (18.6 ± 7.0 vs. 20.7 ± 9.3, P = 0.150). The most common indication for LT was decompensated cirrhosis. Retransplantation was performed in 1 patient who had experienced chronic rejection after DDLT. Fourteen patients (53.8%) underwent LT for HCC. The numbers of HCC tumors ranged from 1 to 5, and the average tumor size was 3.96 ± 2.03 cm (range, 1.0–7.1 cm). Eight patients (30.8%) with HCC met the Milan criteria, and 6 exceeded the threshold Milan criteria (Table 2). Table 3 shows the serological statuses of donors and recipients. Cold ischemic time was shorter in the LDLT group (103.3 ± 44.8 minutes) than that in the DDLT group (264.4 ± 359.7 minutes) (Table 4). The graft-to-recipient weight ratio was 1.3 ± 0.4 in 8 LDLTs. Detailed information on each donor and recipient is presented in Tables 5 and 6.

Outcomes

Immediate postoperative complications (postoperative days, 1–29) were reported in 8 patients (30.8%). Severe complications (Clavien-Dindo classification, ≥IIIa) were reported in 4 patients. The most common complication was infection. Three patients (11.5%) had HCC recurrence, and all of them died

Table 4. Transplantation outcome: operation outcome for recipients

Variable	Data (n = 26)
Cold ischemic time (min), n = 23	201.3 ± 289.2 (35.0–1,470.0)
LDLT, n = 9	103.3 ± 44.8 (35.0–159.0)
DDLT, n = 14	264.4 ± 359.7 (44.0–147.0)
Warm ischemic time (min), n = 25	41.0 ± 17.2 (19.0–93.0)
GRWR, n=8	1.3 ± 0.4 (0.8–2.1)
Postoperative complication	
Immediate complication (<30 days)	8 (30.8)
Recipient severe complications, CD grade ≥ IIIa	3 (11.5)
Recipient hospital mortality	1 (3.8)
Type of complications	
Renal complication	2 (7.7)
Vascular anastomosis stenosis	2 (7.7)
Biliary complication	6 (23.1)
Cardiovascular complication	3 (11.5)
Infection	7 (26.9)
HCC recurrence	3 (11.5)[a]
De novo cancer[b]	1 (3.8)
Adhesive ileus	1 (3.8)
Neurologic complication	1 (3.8)[c]
Graft losses	0 (0)
Cause of death	8 (30.8)
Time to death (months)	20.0 ± 14.5 (2.0–47.3)
Septic shock[d]	4 (15.4)
De novo cancer	1 (3.8)
HCC recurrence	3 (11.5)

Values are presented as mean ± standard deviation (range) or number (%).
LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; GRWR, graft-to-recipient weight ratio; CD, Clavien-Dindo classification; HCC, hepatocellular carcinoma.
[a]Including 1 HCC-cholangiocarcinoma case; [b]Klastkin tumor; [c]temporal lobe epilepsy. [d]Causes of septic shock were duodenal ulcer perforation (n = 1), bile leak accompanying intraabdominal bleeding (n = 1), and pneumonia (n = 2).

Table 5. Recipient characteristics at the time of LTs (n = 26)

Case No.	Age (yr)	Sex	Blood type	BMI (kg/m^2)	Year of LT	Indication	HCC	MELD score	CPT score[a]	Pre-LT treatment[b]
1	49	Male	B+	21.7	2005	HBV	Yes	30.7	C14^{AB}	TACE^{1}
2	55	Male	AB+	30.1	2005	HBV	No	14.5	C10^{A}	
3	63	Female	O+	18.7	2006	HBV	No	22.4	C12^{AP}	
4	59	Male	B+	21.4	2007	HBV	No	32.8	B9^{B}	
5	41	Male	O+	25.5	2008	HBV	Yes	15.7	B8^{B}	TACE^{1}
6	76	Male	A+	21.7	2009	HBV	Yes	13.6	B9	TACE^{5} + PEIT^{5}
7	61	Male	A+	22.6	2009	HBV	Yes	21.1	A6	OP + intraoperative RFA + TACE^{13} + PEIT^{3}
8	53	Male	O+	22.7	2009	HBV	No	18.0	C10^{P}	
9	70	Male	O+	23.7	2010	HBV	Yes	15.38	B8	TACE^{10} + PEIT^{3}
10	56	Male	A+	27.3	2010	HCV	No	22.7	C13^{S}	
11	66	Male	A+	26.9	2010	MOVC	Yes	9.5	A6	TACE^{1}
12	52	Female	B+	23.7	2010	HBV	No	37.5	C12^{A}	
13	65	Female	A+	25.5	2010	HBV/HCV	Yes	15.0	C12^{A}	TACE^{5}
14	68	Female	B+	30.8	2011	HBV	Yes[c]	10.5	A6	
15	46	Male	O+	19.3	2011	HBV	No	32.29	C13^{AP}	
16	51	Female	O+	17.8	2013	ADPKD/HBV	No	15.86	B8^{A}	
17	44	Female	A+	20.1	2013	HBV	Yes	23.31	C10^{AP}	TACE^{8} + RFA^{1} + RTx for liver and lung metastasis
18	70	Female	A+	25.3	2015	TH/HBV	No	26.93	C13^{SP}	
10	73	Female	B+	24.6	2015	HBV	Yes	10.51	C10^{AB}	TACE^{5} + RFA^{2} + PEIT^{4}
20	57	Female	O+	30.0	2017	PBC	No	17.95	C10^{P}	
21	52	Male	B+	20.2	2017	HBV	No	34.97	C10^{AB}	
22	49	Female	B+	21.3	2017	HBV	No	26.0	C12^{S}	
23	76	Female	AB+	22.6	2018	HBV	Yes	15.22	B8^{AP}	TACE^{1}
24	71	Female	O+	23.6	2018	HBV	Yes	12.05	B8^{A}	TACE^{2} + RFA^{1}
25	52	Male	A+	20.3	2015	HBV	Yes	11.0	B9	OP + intraoperative RFA + RFA^{3} + TACE^{1}
26	60	Female	A+	24.8	2015	HBV	Yes	12.0	A6	TACE^{1} + RFA^{2}

LT, liver transplantation; BMI, body mass index; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; CPT, Child-Turcotte-Pugh; TACE, transarterial chemoembolization; OP, operation; PEIT, percutaneous ethanol injection therapy; RFA, radiofrequency ablation; RTx, radiotherapy; MOVC, membranous obstruction of inferior vena cava; ADPKD, autosomal dominant polycystic kidney disease; TH, toxic hepatitis; PBC, autosomal dominant polycystic kidney disease.
^{A}, ascites; ^{B}, gastrointestinal bleeding; ^{P}, portosystemic encephalopathy; ^{S}, spontaneous bacterial peritonitis.
[a]Symptoms in urgency. [b]Superscript numbers mean the numbers of treatment. [c]Intrahepatic cholangiocarcinoma.

owing to cancer. Bone metastasis was detected in patient 7 on postoperative day 340. Patient 17 was found to have HBV recurrence in the liver and perihepatic space on postoperative day 390. Patient 26 was diagnosed with HCC metastasis in the pleura, chest wall, diaphragm, and lung on postoperative day 249. All 3 patients remained inactive HBV carriers, and HBV DNA was absent despite HCC progression after LT. No graft loss was identified in any of the patients during the follow-up period. The most common cause of death was septic shock. All deaths occurred in recipients who received HBsAg (+) grafts (Table 7, Fig. 2). The last biopsy results showed that all rejections were appropriately treated, and that there was no chronic liver damage in the surviving recipients. Based on our definition of reactivation, no HBV reactivation was observed during the follow-up period.

The target serum HBsAb level for HBIG administration was over 200 IU/mL during the posttransplantation period. Only 4,000 IU of HBIG was used for induction in patients 10 and 11 because serum HBsAg could not be detected and their serum HBV levels were low (<20 IU/mL). Patients who received HBsAb (+) and HBeAg (+) grafts (n = 2) were also treated with HBIG. The recipient who was in the resolved stage at the time of transplantation received 4,000 IU for the first 3 days posttransplantation based on their serology (HBsAg [–], HBsAb [+], and HBcAb [+]). Another recipient with chronic HBV was administered 10,000 IU in the long term. All but 4 LT recipients were administered NAs to prevent HBV reactivation; NAs were strictly administered postoperatively to those who received HBsAg (+) grafts.

The mean follow-up duration was 82.6 ± 60.1 months, and the mean time to death was 20.0 ± 14.5 months (range, 2.0–47.3 months). The overall mortality rate was 30.8% (8 of 26), which was higher than the 18.6% mortality rate (387 of 2,076) among patients who received transplants from donors without HBV infection. However, there was no significant difference in patient survival (P = 0.250) (Fig. 3B). All living donors survived,

Table 6. Donor characteristics at the time of LT

Case No.	Age (yr)	Sex	Blood type	BMI (kg/m^2)	Type of LT	Cause of death	TB	PT/INR	CIT (min)	WIT (min)	Relationship with recipient
1	20	Male	B+	18.7	LDLT		0.6	1.32			Son
2	26	Male	B+		DDLT	tSAH + SDH			117	74	
3	34	Male	O+	20.9	LDLT		1.1	1.06	84	39	Son-in-law
4	28	Male	B+		DDLT	tSAH + ICH				72	
5	31	Female	O+		DDLT					45	
6	46	Female	A+		DDLT	Left MCA aneurysmal rupture			223	43	
7	55	Male	A+	20.7	DDLT	Post-TSA bleeding	0.6	1.17	323	93	
8	55	Female	O+	22.1	LDLT		0.6	1.02	159	35	Sister-in-law
9	37	Male	O+		DDLT	sSAH + ICH	0.9	1.23	1,470	30	
10	53	Male	A+	19.7	LDLT		0.6	0.94	151	50	Younger brother
11	34	Male	O+	24.3	LDLT		0.8	1.01	138	52	Son
12	52	Male	O+		DDLT	Seizure			242	35	
13	52	Female	A+		DDLT	tSAH + SDH			272	38	
14	29	Male	A+	26.2	LDLT		0.8	1.04	35	35	Son
15	48	Female	O+		DDLT	Anaphylactic shock			215	23	
16	58	Male	O+	20.3	LDLT		0.9	1.04	68	34	Spouse
17	46	Male	A+	27.8	DDLT	HIS			50	35	
18	46	Male	A+	20.0	DDLT	SAH			44	26	
19	58	Male	B+	22.0	DDLT	SAH			70	23	
20	61	Male	O+	27.1	LDLT		1.6	1.19	68	19	Spouse
21	16	Male	O+	23.8	DDLT	CA				32	
22	53	Female	O+	21.6	LDLT		0.5	0.94	84	25	Elder sister
23	61	Male	AB+	18.0	DDLT	tSDH			82	42	
24	44	Female	O+	20.0	LDLT		0.6	0.97	143	37	Daughter
25	52	Female	A+	23.6	DDLT	SAH	0.9	1.35	259	39	
26	40	Male	A+	34.6	DDLT	IVH	0.6	1.35	250	48	

LT, liver transplantation; BMI, body mass index; TB, total bilirubin; INR, international normalized ratio; CIT, cold ischemic time; WIT, warm ischemic time; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; tSAH, traumatic SAH; SDH, subdural hemorrhage; ICH, intra-cranial hemorrhage; MCA, middle cerebral artery; TSA, transsphenoidal approach; sSAH, spotaneous subarachnoid hemorrhage; HIS, hypoxic-ischemic encephalopathy; SAH, subarachnoid hemorrhage; CA, cardiac arrest; tSDH, traumatic SDH.
White row, HBcAb (+) HBV DNA (+); light gray row, HBsAg (+); dark gray row, HBsAb (+) HBeAg (+) chronic hepatitis.

and their most recent liver function test results were normal (Table 8).

DISCUSSION

Previous attempts to use chronic hepatitis or healthy HBV carrier grafts have shown outcomes comparable to those resulting from grafts from HBV-negative patients [12]. Development of antiviral agents with low resistance rates and HBIG has enabled the expansion of the LT donor pool to include HBV-infected graft tissue [18,19]. Moreover, other studies have reported that chronic hepatitis grafts may be safely transplanted to vaccinated recipients without a history of HBV infection [5]. Therefore, grafts from HBV-positive donors may even be considered in recipients without a history of HBV infection if perioperative immunization and NA and HBIG therapies are administered. According to the 2020 position statement and recommendations of the European Liver and Intestine Transplantation Association (ELITA), HBsAg (+) grafts may be used after an assessment of the risks and benefits for each recipient. Moreover, HBsAg (+) grafts should be considered whenever there is an option of indefinite prophylaxis with entecavir or tenofovir [20].

After a nationwide HBV vaccination program was started in 1983, the vertical transmission rate of HBV in Korea decreased [21], and the overall prevalence of HBsAg carriage has remained at 2.9% since 2010 (intermediate endemicity range, 2%–7%) [16]. However, data from 2016 demonstrated that the prevalence of HBsAg in older age groups has remained higher than that in younger age groups [6]. Thus, using grafts from donors with chronic or active HBV infection could potentially increase the donor pool.

Reactivation of HBV was initially defined based on classical criteria, including an increased HBV DNA titer and positive seroconversion of HBsAg. However, in recipients of HBsAg (+) grafts, HBV recurrence should be defined as an increase

Table 7. Transplantation outcome: detailed outcome of each patient

Case No.	Follow-up (mo)	Survival	Cause of death	Postoperative course	Last pathology	HBV reactivation	HCC recur
1	193.7	Yes			Postoperative 11 mo: no ACR	No	No
3	181.4	Yes			Postoperative 6 yr: no ACR diffuse ballooning	No	No
8	136.8	Yes			Postoperative 5 yr: no ACR mild portal fibrosis	No	No
10	130.8	Yes		Chronic hepatitis	Postoperative 3 mo: chronic HCV hepatitis	No	No
11	132.6	Yes		ACR (RAI = 2)	Postoperative 4 yr: no ACR mild spotty necrosis	No	No
14	118.7	Yes		ACR (RAI = 3)	Postoperative 8 days: ACR (RAI = 3)	No	No
16	93.9	Yes		ACR (RAI = 5→1)	Postoperative 5 yr: mild portal inflammation	No	No
24	26.7	Yes			No Bx	No	No
2	187.1	Yes			Postoperative 6 yr: no ACR	No	No
4	25.8	No	Septic shock due to duodenal ulcer perforation	Chronic rejection	Postoperative 2 yr: chronic cholangiohepatitis	Yes (No)	No
5	2.0	No	Septic shock		No Bx	No	No
6	23.2	No	Klastkin tumor	ACR (RAI = 2)	Postoperative 12 day: ACR (RAI = 2)	No	No
7	15.9	No	HCC recur	Lung metastasis	Postoperative 6 mo: no ACR with focal necrosis	Yes (No)	Yes[a]
9	133.9	Yes			Postoperative 21 mo: no ACR	Yes (No)	No
12	128.8	Yes			Postoperative 7 yr: no ACR minimal portal inflammation	No	No
13	128.4	Yes			Postoperative 3 yr: chronic HCV hepatitis	No	No
15	115.2	Yes			Postoperative 4 yr: no ACR mild portal inflammation	Yes (No)	No
17	7.1	No	HCC recur	HBsAg + chronic hepatitis	Postoperative 3 mo: cholestatic hepatitis	No	Yes[b]
18	47.3	No	Septic shock due to repeated SBP		Postoperative 11 mo: no ACR	Yes (No)	No
19	73.8	Yes			Postoperative 6 yr: no ACR diffuse ballooning	Yes (No)	No
21	47.3	Yes			Postoperative 5 yr: no ACR mild portal fibrosis	No	No
23	9.9	No	Septic shock due to aspiration pneumonia	ACR (RAI = 3)	Postoperative 3 mo: chronic HCV hepatitis	No	No
25	62.8	Yes		ACR (RAI = 4)	Postoperative 4 yr: no ACR mild spotty necrosis	No	No
26	28.8	No	HCC recur	ACR (RAI = 7)	Postoperative 8 days: ACR (RAI = 3)	No	Yes[c]
20	51.1	Yes			Postoperative 5 yr: mild portal inflammation	No	No
22	45.5	Yes				No	No

HBV reactivation was evaluated using 2 criteria. Six reactivation cases were observed when applying the conventional definition (HBsAg positive seroconversion and increase in serum HBV level). In contrast, no reactivation was identified when applying our criteria (notation in parentheses).
HCC, hepatocellular carcinoma; ACR, acute cellular rejection; RAI, rejection activity index; Bx, biopsy.
White row, HBcAb (+) HBV DNA (+); light gray row, HBsAg (+); dark gray row, HBsAb (+) HBeAg (+) chronic hepatitis.
[a]Recurred as bone metastasis at 340 days postoperatively. Palliative radiotherapy (RT) was done. [b]Recurred in the liver and perihepatic space at 390 days postoperatively. Peritoneal seeding was also accompanied. TACE (transarterial chemoembolization) was done twice. [c]Recurred at 249 days postoperatively and metastasis were found at pleura, chest wall, diaphragm, and lung. S7 segmentectomy combined diaphragmatic resection was done for palliation and TACE, chemotherapy, and RT were followed.

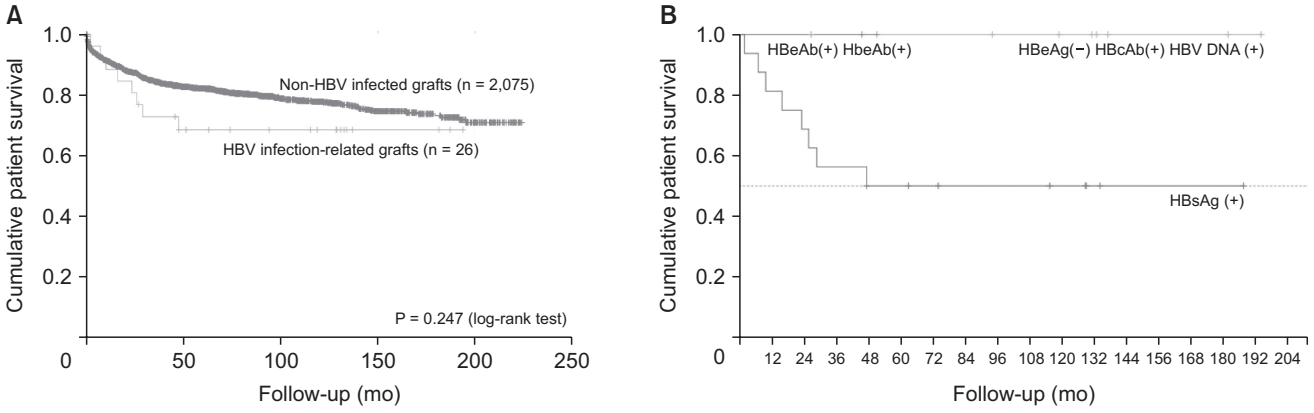

Fig. 3. Kaplan-Meier curve for recipient survival. (A) HBV infection status of the donor did not affect recipient survival (P = 0.247, log-rank test). (B) All reported deaths occurred in patients who received HbsAg (+) grafts.

Table 8. Transplantation outcome: living donor follow-up

Case No.	Survival	Intraoperative Bx	Follow-up (mo)	Latest LFT			
				AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TB (mg/dL)
1	Yes	No fatty change	12.4	21	17	88	1.1
3	Yes	M5m5	3.9	23	22	98	1.1
8	Yes	M1m3	4.2	22	15	87	0.4
10	Yes	M1m1, no fibrosis	3.9	28	15	101	0.6
11	Yes	No fatty change, no fibrosis	9.4	40	28	115	1.3
14	Yes	M20m20, no fibrosis	102.4	13	16	71	0.8
16	Yes	M5m1	74.2	23	24	53	1.0
20	Yes	M2m0	37.4	23	18	89	0.9
22	Yes	No fatty change, subcapsular fibrosis	47.6	26	12	73	0.7
24	Yes	M1m1, focal balloon change	29.1	21	25	48	1.2

Bx, biopsy; LFT, liver function test; M, macrovesicular fatty change (%); m, microvesicular fatty change (%); TB, total bilirubin.

in serum HBV DNA titer, because recipients have a persistent HBsAg (+) status [17]. HBeAg and HBV titers should also be monitored in these patients. In this study, recipient 2 was the only patient in the HBsAg (+) group in whom an increased HBV DNA titer was observed. The elevated HBV DNA titer in recipient 2 resolved spontaneously by 5 years postoperatively; their HBeAg test result was negative, and liver function test results were within the normal range. The results of this patient's most recent pathology tests at 6 years postoperatively were normal.

We described the stage of HBV infection after LT [22,23]. This staging addresses both HBV infection status and liver damage and seems to provide an accurate interpretation of the clinical aspects of HBV infection. Nevertheless, patients with chronic HBV infection may show various serologic profiles that do not clearly fit the criteria for chronic infection, especially in HBV-endemic areas. Therefore, we consulted with our hepatologist while classifying the infection stages of such patients. All donors and recipients were in varying stages of chronic hepatitis, except recipient 8, who was vaccinated before undergoing LT. LT recipients who survived were all classified as either inactive (n = 7) or resolved (n = 11), indicating that HBV was well controlled in these patients [24]. Living donors were classified as HBV resolving (n = 8, HBcAb [+] HBV DNA [+]/immune-inactive stage with low viral replication) or resolved (n = 2, HBsAb [+] HBeAg [+]) at the time of transplantation. The liver function test results were normal during the follow-up; this might indicate that liver donors with a stable HBV infection stage can safely donate their liver, even though major hepatectomy is known to be a major insult that may lead to an HBV flare-up, even in a healthy carrier.

HDV coinfection suppresses HBV recurrence in LT patients [25]. However, others have reported that recipients with HDV have poor prognosis owing to progression of HDV-inducing cirrhosis [26,27]. In addition, HDV may contribute to HCC recurrence and *de novo* HCC progression [25,27]. To improve surgical outcomes, clinicians must consider HDV infection status in both grafts and recipients when using grafts from HBV-positive donors, and screening for HDV should be a part of pre-LT assessments. The ELITA statement strongly suggests that HBsAg (+) grafts should be discharged when HDV is present in either the donor or the recipient [15].

Most deaths were reported approximately 2 years after LT. The relatively high mortality observed among patients transplanted with HBsAg (+) grafts seems to reflect the critically ill condition of patients undergoing DDLT. During the same period, HCC recurrence was reported, but no deaths were reported beyond 5 years after LT. Infection occurs most frequently at 2–4 years posttransplantation [28]. Early HCC recurrence is most common at 14–16 months postoperatively, although late recurrence may occur >5 years posttransplantation [14,15]. Saab et al. [28] reported that HBV recurrence does not directly affect transplantation outcomes. However, many other studies have shown that HBV infection and HCC recurrence are closely related [29,30]. In our study, 14 patients were followed up for >5 years; all were stable, and no increase in HCC recurrence rate was observed 5 years after transplantation. In addition, there was no difference in patient survival between those who underwent LT with HBV-infected grafts and those with non–HBV-infected grafts.

This study had a few limitations. First, the small patient cohort (n = 26) hindered clear interpretation of the results and prevented identification of risk factors affecting transplantation outcomes. Additionally, the lack of regular liver biopsies during follow-up restricted the accurate evaluation of long-term graft condition.

Nevertheless, the strengths of this study are its long-term evaluation of the safety of grafts from HBV-positive donors, and its introduction of HBV infection stage assessments for evaluating viral progression in the posttransplantation period. These assessments demonstrated that HBV recurrence and HCC risk were not significantly increased over the long term in LTs using HBV-infected grafts. In addition, grafts that are HBeAg (+), HBcAb (+), and HBV DNA (+) are considered safe to use in terms of long-term survival, HBV reactivation, and HCC recurrence. Furthermore, setting a standard management and follow-up schedule for transplantation using HBsAb (+), HBeAg (+), and HBcAb (+) HBV DNA (+) grafts is necessary to improve technique safety.

In conclusion, liver grafts from donors with active or chronic HBV infection can be safely used in the long term. Considering their comparable outcomes with HBV-negative donor grafts, they can be safely used in HBV-endemic areas to effectively expand donor pools.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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