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Kidney Transplantation From Hepatitis B Surface Antigen (HBsAg)–Positive Living Donors to HBsAg-Negative Recipients: Clinical Outcomes at a High-Volume Center in China

Xian-ding Wang,[1,2,a] Jin-peng Liu,[1,2,a] Tu-run Song,[1,2] Zhong-li Huang,[1,2] Yu Fan,[1,2] Yun-ying Shi,[3] Li-yu Chen,[4] Yuan-hang Lv,[5] Zi-lin Xu,[5] Xiao-hong Li,[6] Li Wang,[1,2] and Tao Lin[1,2]

[1]Department of Urology/Institute of Urology, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [2]Organ Transplantation Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [3]Department of Nephrology, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [4]Department of Infectious Diseases, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [5]West China School of Clinical Medicine, Sichuan University, Chengdu, Sichuan, China, and [6]Department of Health Statistics, West China School of Public Health, Sichuan University, Chengdu, Sichuan, China

(see the Editorial Commentary by Terrault on pages 1024–5.)

Background. Data on kidney transplantation (KTx) from hepatitis B surface antigen (HBsAg)–positive (HBsAg+) donors to HBsAg-negative (HBsAg–) recipients [D(HBsAg+)/R(HBsAg-)] are limited. We aimed to report the outcomes of D(HBsAg+)/R(HBsAg–) KTx in recipients with or without hepatitis B surface antibody (HBsAb).

Methods. Eighty-three D(HBsAg+)/R(HBsAg–) living KTx cases were retrospectively identified. The 384 cases of KTx from hepatitis B core antibody–positive (HBcAb+) living donors to HBcAb-negative (HBcAb–) recipients [D(HBcAb+)/R(HBcAb–)] were used as the control group. The primary endpoint was posttransplant HBsAg status change from negative to postive (-– →+).

Results. Before KTx, 24 donors (28.9%) in the D(HBsAg+)/R(HBsAg–) group were hepatitis B virus (HBV) DNA positive, and 20 recipients were HBsAb–. All 83 D(HBsAg+)/R(HBsAg–) recipients received HBV prophylaxis, while no D(HBcAb+)/R(HBcAb–) recipients received prophylaxis. After a median follow-up of 36 months (range, 6–106) and 36 months (range, 4–107) for the D(HBsAg+)/R(HBsAg–) and D(HBcAb+)/R(HBcAb–) groups, respectively, 2 of 83 (2.41%) D(HBsAg+)/R(HBsAg–) recipients and 1 of 384 (0.26%) D(HBcAb+)/R(HBcAb–) became HBsAg+, accompanied by HBV DNA-positive (P = .083). The 3 recipients with HBsAg–→+ were exclusively HBsAb–/HBcAb– before KTx. Recipient deaths were more frequent in the D(HBsAg+)/R(HBsAg–) group (6.02% vs 1.04%, P = .011), while liver and graft function, rejection, infection, and graft loss were not significantly different. In univariate analyses, pretransplant HBsAb–/HBcAb– combination in the D(HBsAg+)/R(HBsAg–) recipients carried a significantly higher risk of HBsAg–→+, HBV DNA–→+, and death.

Conclusions. Living D(HBsAg+)/R(HBsAg–) KTx in HBsAb+ recipients provides excellent graft and patient survivals without HBV transmission. HBV transmission risks should be more balanced with respect to benefits of D(HBsAg+)/R(HBsAg–) KTx in HBsAb-/HBcAb– candidates.

Keywords. HBsAg-positive living donors; donor-derived HBV transmission; HBsAg-negative recipients; kidney transplantation.

The scarcity of donor kidneys and the high mortality among dialysis patients have pushed the transplant community and some kidney transplantation (KTx) candidates to expand the acceptance criteria by accepting donors with certain concerns [1–5]. One such exploration focuses on the use of kidneys from hepatitis B surface antigen (HBsAg)–positive (HBsAg+) donors [6, 7]. Utilization of donors who are HBsAg+ can expand the donor pool, as 3.5% of the global population has serological evidence of HBsAg [8]. The prevalence of HBsAg+ in the general population varies widely depending on the geographic location, from less than 1% in Europe and North America to 7.18% in China [9]. Previously, HBsAg+ kidneys could be transplanted mainly to matched HBsAg+ recipients and seldom to HBsAg-negative (HBsAg–) recipients, primarily due to concerns for donor-derived hepatitis B virus (HBV) complications [10–12].

The existence of HBV immunity after vaccination or previous infection and the application of HBV prophylaxis have prompted consideration of HBsAg+ donors as a valuable opportunity for HBsAg– candidates (D[HBsAg+]/R[HBsAg–]) [13]. Underestimation of HBV transmission risk could lead to infection transmission to the recipient, whereas overestimation may

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[a]X. W. and J. L. contributed equally to this work.

Correspondence: T. Lin, Department of Urology/Institute of Urology, West China Hospital, Sichuan University. Number 37, Guoxue Alley, Chengdu, Sichuan, 610041 China (kidney1234@163.com).

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result in missed opportunities for KTx [14]. This subject is of particular interest in China where the HBsAg+ population is 93 million (with an estimated prevalence of 7.18%), meaning that 7.18% of potential donors are HBsAg+ [9, 15]. Excluding HBsAg+ donors significantly reduces the supply of kidney allografts.

The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Guideline suggested that HBsAg+ donors may be considered for HBsAg– recipients with HBV immunity [11]. According to the US Organ Procurement Transplant Network (OPTN) Annual Report, the proportions of D(HBsAg+)/R(HBsAg–) were 0.0% in deceased KTx recipients and 0.5% in living KTx recipients [16]. If the potential HBsAg+ donor is also HBV DNA positive, most centers currently do not consider D(HBsAg+)/R(HBsAg–) for living donation [17, 18]. Furthermore, data regarding D(HBsAg+)/R(HBsAg–) KTx in recipients without HBV immunity have never been reported. These 2 types of KTx are actually performed in our center. The present study aimed to report the clinical outcomes of KTx from HBsAg+ living donors (HBV DNA negative or positive) to HBsAg– recipients with or without HBV immunity.

METHODS

Data Collection

All living kidney donations and transplantations were approved by the Institutional Review Board of West China Hospital and the Health Commission of Sichuan Province, China. D(HBsAg+)/R(HBsAg–) recipients were additionally informed about the potential risks and benefits of D(HBsAg+)/R(HBsAg–) KTx, and then gave written informed consent. Living D(HBsAg+)/R(HBsAg–) KTx were retrospectively identified through the medical archives of West China Hospital from 1 January 2009 to 30 June 2017. D(HBsAg+)/R(HBsAg–) KTx were excluded, if (1) there was pretransplant hepatitis C virus infection, (2) it was an ABO incompatible KTx or (3) a deceased donor KTx.

D(HBsAg+)/R(HBsAg–) and HBsAg–/hepatitis B core antibody–positive (HBcAb+) donors to HBsAg–/hepatitis B core antibody–negative (HBcAb–) recipients (D[HBcAb+]/R[HBcAb–]) are the 2 possible sources of donor-derived HBV infection in organ transplantation [11, 19]. These 2 settings were also the main topics of HBV+ donors discussed in the published guidelines (eg, KDIGO and British guidelines) and multidisciplinary consensus recommendations [11, 17, 19]. However, it is now generally accepted that D(HBcAb+)/R(HBcAb–) KTx patients, especially when the recipients are hepatitis B surface antibody positive (HBsAb+), have negligible risk of transmitting HBV infection to the recipients and no excess risk of graft failure or morbidity [11]. Thus, in our study, D(HBcAb+)/R(HBcAb–) KTx patients were used as the control group of D(HBsAg+)/R(HBsAg–).

Medical records were thoroughly reviewed for donor/recipient baseline demographic, clinical, and immunological characteristics. HBV-associated characteristics such as pre- and posttransplant status of HBsAg, HBsAb, hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), HBcAb, HBV DNA, application of hepatitis B immunoglobulin (HBIG) and antiviral prophylaxis, and liver function were examined. Transplant-related outcomes including graft function, rejection, infection, graft loss, and death were also analyzed. If the recipients were alive and did not show any posttransplant HBV seroconversion, HBV serology and DNA quantification were tested at the last follow-up (September to December 2017). This study protocol was reviewed and approved by the Biomedical Ethics Committee of West China Hospital (no. 2019SHEN1179).

Statistical Analysis

The primary endpoint was posttransplant HBsAg status change from negative to postive (-–→+) in the recipient. HBsAb titers were classified into 4 grades: negative (<10 IU/L) and positive (10–100, 100–1000, >1000 IU/L). The change in HBsAb titer towards <10 →10–100→100–1000→>1000 IU/L was an upgrade, and towards >1000→100–1000→10–100→<10 IU/L was a downgrade. Abnormal liver function was defined as serum alanine aminotransferase (ALT) greater than 40 (female) or greater than 50 IU/L (male), or total bilirubin greater than 28 μmol/L, while active liver injury was ALT greater than 80 (female) or greater than 100 IU/L (male), or total bilirubin greater than 34 μmol/L.

Baseline characteristics and posttransplant complications between the 2 groups were compared using Student's *t*, chi-square, Fisher's exact, or Wilcoxon rank sum tests, as appropriate. If there were significant differences in some baseline characteristics, a sensitivity analysis was additionally used to explore the potential impact of these baseline characteristics on clinical outcomes. Graft and recipient survivals were estimated using the Kaplan-Meier method, and differences in survival were compared univariately using the log-rank test. Univariate analyses of potential pretransplant donor (HBsAg and HBV DNA levels) and recipient (age, gender, human leukocyte antigen [HLA] mismatch, HBV serology, HBV prophylaxis) risk factors influencing clinical outcomes (HBsAg–→+, HBV DNA–→+, HBcAb–→+, active liver injury, graft loss, death) were analyzed via the Fisher's exact test. All statistical analyses were conducted by R version 3.6.1 (R Foundation), with $P < .05$ being statistically significant.

RESULTS

Baseline Characteristics

During the study period, 83 D(HBsAg+)/R(HBsAg-) and 384 D(HBcAb+)/R(HBcAb-) patients were identified from 2071 living donor KTx cases at our institution, with a frequency of 4.0% and 18.5%, respectively. Before kidney donation, all living donors in the 2 groups displayed normal liver enzymes, total

Table 1. Baseline Demographic, Clinical, and Immunological Characteristics in the 2 Groups

	D(HBsAg+)/R(HBsAg−) (n = 83)	D(HBcAb+)/R(HBcAb−) (n = 384)	*P*
Donor			
Median (range) age, years	50 (31–66)	48 (20–66)	.302
Male, n (%)	39 (47.0)	132 (34.4)	.031
Living related, n (%)	83 (100)	384 (100)	
Recipient			
Median (range) age, years	32 (9–51)	28 (9–58)	.005
Male, n (%)	64 (77.1)	269 (70.1)	.197
Cause of end-stage renal failure, n (%)			
Glomerulonephritis	40 (48.2)	65 (16.9)	<.001
Non-glomerulonephritis	8 (9.6)	33 (8.6)	
Unknown	35 (42.2)	286 (74.5)	
Pre-emptive transplant, n (%)	6 (7.2)	28 (7.3)	1.000
Median (range) duration on dialysis, months	9 (0–120)	10 (0–96)	.182
Mean±SD HLA mismatch, n (A, B, DR, DQ)	4.04 ± 1.47	3.58 ± 1.27	.004
PRA >0, n (%)	27 (32.5)	96 (25)	.158
Second transplant, n (%)	0	1 (0.3)	1.000
Induction therapy, n (%)			
IL-2 receptor antagonist	49 (59.0)	231 (60.2)	.567
Anti-thymocyte globulin	18 (21.7)	66 (17.2)	
No induction	16 (19.3)	87 (22.7)	
Initial immunosuppression, n (%)			
Tac+MPA+Pred	78 (94.0)	366 (95.3)	.620
CsA+MPA+Pred	5 (6.0)	18 (4.7)	

Abbreviations: CsA, cyclosporin A; D(HBcAb+)/R(HBcAb−), hepatitis B core antibody–positive living donors to hepatitis B core antibody–negative recipients; D(HBsAg+)/R(HBsAg−), hepatitis B surface antigen–positive living donors to hepatitis B surface antigen–negative recipients; HLA, human leukocyte antigen; IL-2, interleukin 2; MPA, mycophenolic acid; PRA, panel reactive antibody; Pred, prednisone; SD, standard deviation; Tac, tacrolimus.

bilirubin, and coagulation function and had no evidence of liver cirrhosis by ultrasound. Table 1 details the baseline demographic, clinical, and immunological data for both groups. There were significant differences in donor sex, recipient age, cause of end-stage renal failure, and HLA mismatch between 2 groups.

Pre- and Posttransplant Hepatitis B Virus Status

Pre- and posttransplant HBV serology in the 2 groups are summarized in Table 2. Before KTx, there was a higher proportion of HBsAb+ in the recipients of the D(HBsAg+)/R(HBsAg−) group. For the 24 donors with pretransplant HBV DNA+ in the D(HBsAg+)/R(HBsAg−) group, the median DNA level was 1.20×10^3 IU/mL (range, 5.86×10 to 4.04×10^6 IU/mL). In the D(HBsAg+)/R(HBsAg−) group, the most common pretransplant HBV serology combination in the donors was HBsAg+, HBsAb−, HBeAg−, HBeAb+, and HBcAb+ (77

Table 2. Pre- and Posttransplant Hepatitis B Virus Serology in the 2 Groups

	D(HBsAg+)/R(HBsAg−) (n = 83)	D(HBcAb+)/R(HBcAb−) (n = 384)	*P*
Donors' pretransplant HBV serology, n (%)			
HBsAg+	83 (100)	0	<.001
<1000 IU/ml	35 (42.2)	0	
≥1000 IU/ml	48 (57.8)	0	
HBsAb+	3 (3.6)	283 (73.7)	<.001
HBeAg+	0	0	
HBeAb+	78 (94.0)	146 (38.0)	<.001
HBcAb+	82 (98.8)	384 (100)	.178
HBV DNA+	24 (28.9)	Unknown[a]	
Recipients' pretransplant HBV serology, n (%)			
HBsAg+	0	0	
HBsAb+	63 (75.9)	153 (39.8)	<.001
Titer, 10–100 IU/L	31 (37.3)	71 (18.5)	
Titer, >100 IU/L	32 (38.6)	82 (21.4)	.001
HBeAg+	0	0	
HBeAb+	34 (41.0)	1 (0.3)	<.001
HBcAb+	58 (69.9)	0	<.001
HBV DNA+	0	Unknown[a]	
Recipients' most recent HBV serology, n (%)			
HBV DNA− → +	2[b] (2.4)	1[c] (0.3)	.083
HBsAg− → +	2[b] (2.4)	1[c] (0.3)	.083
HBeAg− → +	1 (1.2)	1 (0.3)	.324
HBeAb− → +	4 (4.8)	0	.001
HBeAb + → −	4 (4.8)	1 (0.3)	.004
HBcAb− → +	7 (8.4)	10 (2.6)	.019
HBsAb titer downgrade	1 (1.2)	29 (7.6)	.027
HBsAb titer upgrade	13 (15.7)	15 (3.9)	.002

Abbreviations: ALT, alanine aminotransferase; D(HBcAb+)/R(HBcAb−), hepatitis B core antibody–positive living donors to hepatitis B core antibody–negative recipients; D(HBsAg+)/R(HBsAg−), hepatitis B surface antigen–positive living donors to hepatitis B surface antigen–negative recipients; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; −→+, change from negative to positive; +→−, change from positive to negative

[a]We did not test the pretransplant HBV DNA levels of the donors or recipients in the D(HBcAb+)/R(HBcAb−) group.

[b]Two D(HBsAg+)/R(HBsAg−) recipients developed posttransplant HBsAg+ accompanied by HBV DNA+. The first recipient (32-year-old male; pretransplant donor/recipient HBV serology) was HBV DNA−/−, HBsAg+/−, HBsAb−/−, HBeAg−/−, HBeAb+/−, HBcAb+/−. His HBV prophylaxis was lamivudine alone for 1.5 months. The recipient experienced a temporary increase in ALT, up to 163 IU/L 1 year after transplantation. He was then lost to follow-up during posttransplant years 1.5–5.5. He was found to have HBV DNA+ (5.02×10^4 IU/mL), HBsAg+, HBeAb+, HBcAb+, and ALT 55 IU/L when admitted due to pulmonary infection 5.5 years after transplantation. He received long-term entecavir monotherapy until he died of pulmonary infection 7 years after transplantation. The second recipient (24-year-old male; pretransplant donor/recipient HBV serology) was HBV DNA+ (1.14×10^3 IU/mL)/−, HBsAg +/−, HBsAb−/−, HBeAg−/−, HBeAb+/−, HBcAb+/−. His prophylaxis was HBIG 2000 IU and lamivudine for 2 months. He received a total of 1500 mg intravenous methylprednisolone to treat acute rejection 5 months after transplantation. He became HBV DNA+ (>5.00×10^7 IU/mL), HBsAg+, and HBcAb+ 6 months after transplantation. His total bilirubin level rapidly increased from 26 μmol/L at month 6 to 489 μmol/L at month 8 when he died of liver failure and pulmonary infection.

[c]One D(HBcAb+)/R(HBcAb−) recipient developed posttransplant HBsAg+ accompanied by HBV DNA+. The recipient was a 26-year-old male, and the pretransplant donor/recipient's HBV serology was HBV DNA unknown/unknown, HBsAg−/−, HBsAb−/−, HBeAg−/−, HBeAb−/−, HBcAb+/−. He did not receive any HBV prophylaxis. The recipient was found to have HBV DNA+ (3.53×10^4 IU/mL), HBsAg+, HBeAg+, HBcAb+, and ALT 11 IU/L 2 years after transplantation. He then received long-term entecavir monotherapy. Four months away from 9 years after transplantation, his HBV DNA level was 6.52×10^2 IU/mL, ALT was 26 IU/L, and he was found to have biopsy-proven antibody-mediated rejection, which was treated by increasing the doses of oral immunosuppressants. He died of liver failure with herpes simplex virus infection and HBV DNA active replication (4.63×10^5 IU/ml) 1 month away from 9 years after transplantation.

donors, 92.8%), and 22 of 77 (28.6%) were HBV DNA+; the most common combinations in the recipients was HBsAg–, HBsAb+, HBeAg–, HBeAb+, and HBcAb+ (27 recipients, 32.5%). No HBV prophylaxis was used in the D(HBcAb+)/R(HBcAb–) group, whereas all D(HBsAg+)/R(HBsAg–) recipients received prophylaxis. The HBV prophylaxis regimens based on donors' pretransplant HBsAg, HBV DNA, and recipients' pretransplant HBsAb levels are detailed in Table 3.

After a median follow-up of 36 months (range, 6–106 months) for the D(HBsAg+)/R(HBsAg–) group and 36 months (range, 4–107 months) for the D(HBcAb+)/R(HBcAb–) group, 2 of 83 D(HBsAg+)/R(HBsAg–) recipients and 1 of 384 D(HBcAb+)/R(HBcAb–) recipient became HBsAg+, accompanied by HBV DNA+ (P = .083) (Table 2).

Posttransplant Clinical Outcomes and Laboratory Parameters

Analysis of the posttransplant clinical complications indicated that D(HBsAg+)/R(HBsAg–) KTx had a higher incidence of recipient death (Table 4). One D(HBsAg+)/R(HBsAg–) recipient and 1 D(HBcAb+)/R(HBcAb–) recipient died of HBV-associated liver failure (detailed in the footnotes of Table 2). Posttransplant levels of ALT, total bilirubin, and creatinine and the estimated glomerular filtration rate were comparable, except that the D(HBsAg+)/R(HBsAg–) group had a lower total bilirubin level at 1 month (P = .020) and 24 months (P = .017) after transplantation. The 2 groups had no significant differences in graft survival at 1 year (98.8% vs 98.7%, P = .914), 3 years (97.6% vs 96.9%, P = .679), and 5 years (97.6% vs 95.3%, P = .376), or in recipient survival at 1 year (97.6% vs 99.2%, P = .209) and 3 years (97.6% vs 99.2%, P = .209), except for a relatively lower recipient survival at 5 years in the D(HBsAg+)/R(HBsAg–) group (95.2% vs 99.2%, P = .007).

Univariate Analyses of Potential Prognostic Factors on Transplant Outcomes

Univariate analyses of potential donor and recipient prognostic factors on posttransplant outcomes in the D(HBsAg+)/R(HBsAg–) group are shown in Table 5. The pretransplant HBsAb–/HBcAb– combination in the recipients carried the significantly higher risk of posttransplant HBsAg–→+, HBV DNA–→+, and recipient death. In the D(HBcAb+)/R(HBcAb–) group, HLA mismatch, recipient age, gender, and pretransplant HBsAb status (HBsAb– vs HBsAb+ or HBsAb– vs HBsAb titer 10–100 IU/L vs >100 IU/L) were univariately not predictive of posttransplant HBsAg–→+, HBV DNA–→+, HBcAb–→+, active liver injury, graft loss, or death.

Sensitivity Analysis

There were significant differences in some baseline parameters between the 2 groups (Tables 1 and 2), which are known risk factors for graft dysfunction and shortened graft survival [20, 21]. We first performed a sensitivity analysis via the Cochran-Mantel-Haenszel test stratified by these baseline parameters, and there was little change in posttransplant clinical complications after stratification. Then, we further adopted propensity score matching (PSM) of D(HBsAg+)/R(HBsAg–) patients with 83 cases from 384 D(HBcAb+)/R(HBcAb–) recipients, according to donor/recipient sex and age and the pretransplant recipients' status of HBsAb (<10 IU/L, 10–100 IU/L, >100 IU/L). As expected, after PSM, all baseline parameters were comparable, except for a higher HLA mismatch in the D(HBsAg+)/R(HBsAg–) group. The comparison results of transplant

Table 3. Hepatitis B Virus (HBV) Prophylaxis Based on Donors' Pretransplant Hepatitis B Surface Antigen (HBsAg) and HBV DNA and Recipients' Pretransplant Hepatitis B Surface Antibody Levels in the D(HBsAg+)/R(HBsAg–) Group

	HBIG[a]		Antiviral[b]	
	Yes	No	Yes	No
D(HBsAg+)/R(HBsAg–) recipients (n = 83), n (%)	42 (51)	41 (49)	65 (78)	18 (22)
Donors' pretransplant HBsAg level, n (%)				
<1000 IU/mL (n = 35)	11 (31)	24 (69)	28 (80)	7 (20)
1000–3000 IU/mL (n = 13)	9 (69)	4 (31)	12 (92)	1 (8)
>3000 IU/mL (n = 35)	22 (63)	13 (37)	25 (71)	10 (29)
Donors' pretransplant HBV DNA, n (%)				
Negative (n = 59)	19 (32)	40 (68)	42 (71)	17 (29)
Positive (n = 24)	23 (96)	1 (4.2)	23 (96)	1 (4)
Recipients' pretransplant HBsAb titer, n (%)				
Negative (n = 20)	11 (55)	9 (45)	15 (75)	5 (25)
Positive (n = 63)	31 (49)	32 (51)	50 (79)	13 (21)
10–100 IU/L (n = 30)	16 (53)	14 (47)	22 (73)	8 (27)
>100 IU/L (n = 33)	15 (45)	18 (55)	28 (85)	5 (15)

Abbreviations: D(HBsAg+)/R(HBsAg–), hepatitis B surface antigen–positive living donors to hepatitis B surface antigen–negative recipients; HBIG, hepatitis B immunoglobulin; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

[a]HBIG was infused as a single dose of 2000 IU immediately before transplantation.

[b]Antiviral was initiated on the first day posttransplant. Among the 65 recipients (78.3%) who received antiviral prophylaxis, 49 received 100 mg of lamivudine daily, whereas 16 were on 0.5 mg of entecavir daily. Antiviral duration was 1–3 months (due to the retrospective nature of our study, we cannot provide the exact duration of each recipient).

Table 4. Posttransplant Clinical Complications in the 2 Groups

	D(HBsAg+)/R(HBsAg–) (n = 83), n (%)	D(HBcAb+)/R(HBcAb–) (n = 384), n (%)	P
Delayed graft function	2 (2.4)	4 (1.0)	.290
Rejection	12 (14.5)	51 (13.3)	.776
Infection	34 (41.0)	121 (31.5)	.097
Abnormal liver function	29 (34.9)	154 (40.1)	.382
Active liver injury	8 (9.6)	43 (11.2)	.680
Malignancy	0	0	
Graft loss	4 (4.8)	19 (4.9)	.961
Recipient death	5 (6.0)	4 (1.0)	.011

Abbreviations: D(HBcAb+)/R(HBcAb–), D(HBcAb+)/R(HBcAb–), hepatitis B core antibody–positive living donors to hepatitis B core antibody–negative recipients; D(HBsAg+)/R(HBsAg–), D(HBsAg+)/R(HBsAg–), hepatitis B surface antigen–positive living donors to hepatitis B surface antigen–negative recipients.

Table 5. Univariate Analyses of Potential Pretransplant Donor and Recipient Risk Factors Influencing Transplant Outcomes in the D(HBsAg+)/R(HBsAg–) Group

	HBsAg– → +		HBV DNA– → +		HBcAb– → +		Active Liver Injury		Graft Loss		Death	
	Events	*P*	Events	*P*	Events	*P*	Events	*P*	Events	*P*	Events	*P*
Donors' pretransplant HBV factors, n (%)												
HBsAg level												
<1000 IU/mL (n = 35)	1 (2.9)	1.000	1 (2.9)	1.000	4 (11)	.448	2 (5.7)	.458	1 (2.9)	.635	3 (8.6)	.646
≥1000 IU/mL (n = 48)	1 (2.1)		1 (2.1)		3 (6.3)		6 (13)		3 (6.3)		2 (4.2)	
HBV DNA												
– (n = 59)	1 (1.7)	.497	1 (1.7)	.497	4 (6.8)	.407	4 (6.8)	.220	2 (6.7)	.575	3 (5.1)	.624
+ (n = 24)	1 (4.2)		1 (4.2)		3 (13)		4 (17)		2 (6.7)		2 (6.7)	
Recipients' pretransplant factors, n (%)												
Age												
≤40 years (n = 66)	2 (3.0)	1.000	2 (3.0)	1.000	6 (9.1)	1.000	7 (11)	1.000	3 (4.5)	1.000	5 (7.6)	.578
>40 years (n = 17)	0		0		1 (5.9)		1 (5.9)		1 (5.9)		0	
Gender												
Male (n = 64)	2 (3.1)	1.000	2 (3.1)	1.000	6 (9.4)	1.000	8 (13)	.188	4 (6.3)	.569	5 (7.8)	.584
Female (n = 19)	0		0		1 (5.3)		0		0		0	
HLA mismatch												
≤4 (n = 68)	2 (2.9)	1.000	2 (2.9)	1.000	6 (8.8)	1.000	7 (10)	1.000	2 (2.9)	.148	4 (5.9)	1.000
>4 (n = 15)	0		0		1 (6.7)		1 (6.7)		2 (13)		1 (6.7)	
HBsAb												
– (n = 20)	2 (10)	.056[a]	2 (10)	.056[a]	2 (10)	.673[a]	4 (20)	.091[a]	2 (10)	.244[a]	3 (15)	.088[a]
+ (n = 63)	0		0		5 (7.9)		4 (6.3)		2 (3.2)		2 (3.2)	
10–100 IU/L (n = 31)	0	.056[b]	0	.056[b]	3 (9.7)	.785[b]	1 (3.2)	.157[b]	2 (6.5)	.168[b]	1 (3.2)	.241[b]
>100 IU/L (n = 32)	0		0		2 (6.3)		3 (9.4)		0		1 (3.1)	
HBcAb												
– (n = 25)	2 (8.0)	.088	2 (8.0)	.088	7 (28)		4 (16)	.234	1 (4.0)	1.000	3 (12)	.158
+ (n = 58)	0		0		0		4 (6.9)		3 (5.2)		2 (3.4)	
HBsAb/HBcAb												
+/+ (n = 49)	0	.027	0	.027	0		3 (6.1)	.149	2 (4.1)	.365	2 (4.1)	.046
+/– (n = 14)	0		0		5 (36)	.407[c]	1 (7.1)		0		0	
–/+ (n = 9)	0		0		0		1 (11)		1 (11)		0	
–/– (n = 11)	2 (18)		2 (18)		2 (18)		3 (27)		1 (9.1)		3 (27)	
HBV prophylaxis, n (%)												
HBIG												
Yes (n = 42)	1 (2.4)	1.000	1 (2.4)	1.000	4 (9.5)	1.000	5 (12)	.713	2 (4.8)	1.000	3 (7.1)	1.000
No (n = 41)	1 (2.4)		1 (2.4)		3 (7.3)		3 (7.3)		2 (4.9)		2 (4.9)	
Antiviral												
Yes (n = 65)	2 (3.1)	1.000	2 (3.1)	1.000	6 (9.2)	1.000	7 (11)	.680	4 (6.2)	.572	4 (6.2)	1.000
No (n = 18)	0		0		1 (5.6)		1 (5.6)		0		1 (5.6)	

Abbreviations: D(HBsAg+)/R(HBsAg–), hepatitis B surface antigen–positive living donors to hepatitis B surface antigen–negative recipients; HBcAb, hepatitis B core antibody; HBIG, hepatitis B immunoglobulin; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HLA, human leukocyte antigen; –→+, change from negative to positive.

[a]Comparison between HBsAb– and HBsAb+ recipients.

[b]Comparison among HBsAb– and HBsAb titer 10–100 IU/L and >100 IU/L recipients.

[c]Comparison between HBsAb+/HBcAb– and HBsAb–/HBcAb– recipients

outcomes between D(HBsAg+)/R(HBsAg–) and D(HBcAb+)/R(HBcAb–) groups were consistent before and after PSM, except for recipient death (6.0% vs 1.0%, $P = .011$, before PSM; 6.0% vs 1.2%, $P = .216$, after PSM) and active liver injuries (9.6% vs 11.2%, $P = .680$, before PSM; 9.6% vs 2.4%, $P = .048$, after PSM). Possible explanations are that if the incidences were similar before and after PSM (eg, 1.0% and 1.2% for recipient death in the D[HBcAb+]/R[HBcAb–] group), the larger sample size usually had a higher test efficiency, and PSM sometimes accomplished the opposite of its intended goal—increasing imbalance and bias [22]. A prospective, well-controlled comparison of a larger series is necessary to clarify this issue.

DISCUSSION

Before our publication, the 2 largest series of D(HBsAg+)/R(HBsAg–) KTx were from China and Thailand [23, 24]. Jiang

et al [23] prospectively reported that 2 of 65 HBsAb+ recipients developed de novo HBsAg+ but neither developed severe liver dysfunction or died. Chancharoenthana et al [24] retrospectively analyzed the data of 43 recipients with HBsAb greater than 100 IU/L, and no posttransplant HBV seroconversion was detected. In our study, there was no HBV infection in 63 HBsAb+ recipients, further confirming the safety of D(HBsAg+)/R(HBsAg−) KTx in either natural (past HBV infection) or vaccine-induced HBsAb+ candidates. Furthermore, there were 4 recipients developing posttransplant HBeAb+ and 7 developing HBcAb+ without clinical sequelae. The development of the seroconversion remains to be elucidated, possibly representing re-expression or the consequences of occult HBV infection from the donor [25, 26].

Based on previous studies and our series, few cases of donor-derived HBV transmission have been reported in recipients with either past infection- or vaccine-induced HBV immunity [24]. In our study, there were 2 cases showing HBsAg−→+ among the 20 HBsAb− recipients, while no such cases were noted among the 63 HBsAb+ recipients. As there was no HBsAg−→+ among the HBsAb+/HBcAb+ (past infection) patients compared with the HBsAb+/HBcAb− (past vaccination or past infection with subsequent HBcAb clearance) patients, or among patients with an HBsAb titer of 10–100 IU/L compared with those with a titer greater than 100 IU/L, we were unable to identify the subgroup(s) possessing a higher level of protection against transmission in the D(HBsAg+)/R(HBsAg−) KTx setting. In any case, HBV vaccination should be recommended for D(HBsAg+)/R(HBsAg−) candidates without previous HBV infection− or vaccine-induced immunity [11]. However, the immune response to HBV vaccination in patients receiving dialysis is not as high as that of the general population: 48.6% were nonresponders (HBsAb <10 IU/L) and seroprotection (HBsAb ≥100 IU/L) was observed in 27.7% of patients [27]. Furthermore, 12 months after KTx, the HBsAb titers were not likely to be detected in 25% of HBsAb+ recipients [28]. On the contrary, in the present study, upgrades and downgrades of posttransplant HBsAb titers were more and less frequent in D(HBsAg+)/R(HBsAg−) recipients, indicating that D(HBsAg+)/R(HBsAg−) might possibly be an HBV "vaccination" in these recipients.

Besides HBV immunity, transmission risk is also influenced by prophylaxis [17]. Knowledge of HBV prophylaxis in organ transplantation has primarily been derived from liver transplantation [29–31]. However, the clinical characteristics of HBV transmission are somewhat different between liver and kidney transplantations. The concentration of HBV in the kidney is generally much lower than in the liver [32]. Meanwhile, liver recipients are commonly HBsAg+ and what concerns us is recipient-derived HBV transmission to the liver graft, whereas in KTx, we are more concerned about donor-derived HBV transmission to the recipient [33]. Up until now, there has been no generally accepted prophylactic regimen in KTx [17]. Berber et al [34] reported that 3 HBsAb+ recipients from deceased donors with HBsAg- (unknown of HBeAg and HBV DBA status) were treated with 1- to 3-year lamivudine without any HBV transmission. In Jiang et al's series [23], recipients received 400 IU HBIG on transplant day and 1 month after; if the donor was HBV DNA+, the recipient was treated with 400 IU HBIG weekly for 3 months and 100 mg lamivudine daily for 6 months. In Tuncer et al's study [35], neither HBIG nor an antiviral was utilized in 35 HBsAb+ recipients from HBV DNA-negative donors, and there were no HBV infections. Chancharoenthana et al [24] revealed that D(HBsAg+/no HBV viremia)/R(HBsAg−/HBsAb >100 IU/L) KTx without HBV prophylaxis provided comparable outcomes compared with those treated with lamivudine alone or lamivudine plus HBIG. Our prophylaxis regimen remains to be improved in HBsAb− recipients as there was 1 fatal HBV hepatitis at 8 months after KTx in an HBsAb− recipient with prophylaxis of 2000 IU HBIG and lamivudine for 2 months. Magiorkinis et al [36] reported a case of fulminant hepatitis in a recipient with HBsAb of 11.6 IU/L with HBIG and HBV vaccine prophylaxis, and molecular analysis revealed multiple mutations in open reading frames of HBV, highlighting the importance of evaluation of HBsAg+ donors for HBV mutants, as certain genotypes and mutants have been linked to HBV transmission, prophylactic resistance, and disease progression [37, 38]. However, we did not test for the possible HBV mutants in our patients. In non–liver recipients who are HBsAb−/HBcAb−, antiviral prophylaxis for up to 1 year has been suggested [13]. Currently, HBV genotyping and antiviral resistance will be tested in all our HBV DNA+ donors for possible mutant HBV infections, and HBsAb− recipients will receive antiviral prophylaxis for a minimum of 6 months.

To the best of our knowledge, our study represents the largest cohort of D(HBsAg+)/R(HBsAg−) KTx patients. Furthermore, our study had several unique characteristics compared with previous publications. First, most previous series were confined to KTx from deceased donors [23, 24], while our donors were all living. Second, according to US OPTN policy, HBeAg and HBeAb testing is not mandated for living donors. We routinely perform HBsAg, HBsAb, HbeAg, HbeAb, and HBeAb testing for all living donors (additional HBV DNA quantification for HBsAg+ donors). Third, 24 of 83 (28.9%) donors were HBV DNA+ compared with 7 of 65 (10.8%) in Jiang et al's and 1 of 43 (2.3%) in Chancharoenthana et al's series, respectively.

We also transplanted 20 HBsAg+ living kidneys into HBsAg−/HBsAb− recipients, which has never been reported in the literature. As discussed previously, 48.6% of dialysis patients receiving HBV vaccination were nonresponders (HBsAb <10 IU/L) [27]. For these nonresponders, if the HBsAg+ donor was the only living donor for them and we declined the living donor, these patients would otherwise have an indefinite waiting time for an HBsAg− deceased donor. Rarely, some patients might have had progressive illness (eg, uncontrollable heart failure) that rendered

them too sick to continue dialysis; therefore, they underwent D(HBsAg+)/R(HBsAg−) KTx without vaccination. In our view, the ethics of knowingly infecting recipients with HBV depends on the willingness of transplant clinicians to give greater weight to patients' autonomy than to minimizing iatrogenic HBV transmission [39]. Based on our univariate analyses, the pretransplant HBsAb−/HBcAb− combination in the recipients carried the significantly higher risk of posttransplant HBsAg−→+, indicating that past HBV infection− or vaccine-induced HBV immunity may be more important than the application of HBV prophylaxis for HBsAg−→+. The benefits of D(HBsAg+)/R(HBsAg−) KTx must be balanced to consider the relatively small but potentially catastrophic transmission in HBsAb−/HBcAb− recipients. HBsAb−/HBcAb− recipients should be given a thorough explanation prior to obtaining their informed consent and receive more intensive HBV prophylaxis and monitoring [40].

Our data are changing the clinical practice pattern for D(HBsAg+)/R(HBsAg−) living-donor KTx at our institution. All D(HBsAg+)/R(HBsAg−) candidates are discussed at our multidisciplinary meeting. Hepatitis B virus genotyping and antiviral resistance will be tested in HBV DNA+ donors for possible mutant HBV infections. HBsAb− candidates will receive a 4-dose series (40 μg/dose) of HBV vaccination on a 0-, 1-, 2-, and 6-month schedule. Immediately before KTx, if (1) HBsAb−/HBcAb−, the recipient will receive a single dose of 2000 IU HBIG and antiviral for 9–12 months; (2) HBsAb−/HBcAb+, a single dose of 2000 IU HBIG and antiviral for 6 months; (3) HBsAb titer between 10 and 100 IU/L, a single dose of 2000 IU HBIG and antiviral for 3 months; (4) HBsAb titer greater than 100 IU/L, antiviral for 1 month (donor HBV DNA+) or no prophylaxis (donor HBV DNA−). D(HBsAg+)/R(HBsAg−) recipients will be closely monitored for the possible chance of HBV infection by serological testing and HBV DNA measurement.

This study has several potential limitations. First, this was a single-center, retrospective cohort study. Second, there was a lack of protocol monitoring of posttransplant HBV serology and DNA. We were unable to reveal the natural history of donor-derived HBV transmission, and the actual transmission rate may be underestimated as some could have been transiently HBsAg+ with subsequent clearance by the recipient's immunity and prophylaxis. Third, information on donors' predonation antiviral treatment and recipients' pretransplant HBV vaccinations was unavailable in some donors and recipients. Fourth, all our donors were HBeAg− pretransplant, and our findings may not apply to HBeAg+ donors.

Conclusions

Living D(HBsAg+)/R(HBsAg−) KTx in HBsAb+ recipients provides excellent graft and patient survivals without HBV transmission. Although our study provides initial evidence of transplanting HBsAg+ kidneys into HBsAg−/HBsAb− recipients, the optimal choice and duration of prevention strategies for HBsAb− recipients merit further study. Understanding the incremental risk of HBV transmission in HBsAb−/HBcAb− recipients enables transplant clinicians to weigh the risk–benefit for individual candidates. Due to the worldwide organ shortage, D(HBsAg+)/R(HBsAg−) should not be an absolute contraindication to living kidney donation.

Notes

Author contributions. X. W., L. C., L. W., and T. L. designed the research. X. W., T. S., Z. H., Y. F., and T. L. wrote the article. X. W., J. L., Y. S., L. C., Y. L., and Z. X. collected the data. X. L. performed statistical analysis. X. W., J. L., Y. F., T. S., Y. S., L. W., and T. L. performed data analysis. X. W., T. S., Y. S., Y. L., Z. X., J. L, Y. F., Z. H., and T. L. contributed to data interpretation and intellectual content.

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