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Pretransplant Hepatitis B Viral Infection Increases Risk of Death After Kidney Transplantation

A Multicenter Cohort Study in Korea

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Abstract: Clinical outcomes in kidney transplant recipients (KTRs) with hepatitis B virus (HBV) have not been thoroughly evaluated. Here, we investigated recent posttransplant clinical outcomes of KTRs with HBV and compared them with KTRs with hepatitis C virus (HCV) and seronegative KTRs.

Of 3855 KTRs from April 1999 to December 2011, we enrolled 3482 KTRs who had viral hepatitis serology data; the patients were followed up for 89.1 ± 54.1 months. The numbers of recipients with HBV and HCV were 160 (4.6%) and 55 (1.6%), respectively. We analyzed the clinical outcomes, including overall mortality and graft failure, among patients who had undergone kidney transplantation.

Patients with HBV showed poorer survival ($P = 0.019$; adjusted hazard ratio [HR] = 2.370; 95% confidence interval [CI]: 1.155–4.865) than KTRs without HBV. However, the graft survival of patients with chronic hepatitis B did not differ from that of patients without HBV. Hepatic complications were the primary causes of mortality of KTRs with HBV. Mortality significantly correlated with a higher grade of inflammation ($P = 0.002$) and with the use of lamivudine or adefovir antiviral treatment ($P = 0.016$). HBV-positive KTRs treated with the new-generation antiviral agent entecavir showed improved patient survival compared with KTRs receiving lamivudine (log-rank $P = 0.050$). HCV did not affect patient survival; however, it increased the incidence of graft failure ($P = 0.010$; adjusted HR = 2.899; 95% CI: 1.289–6.519). KTRs with HCV had an increased incidence of acute rejection (log-rank $P = 0.005$, crude HR = 2.144; 95% CI: 1.341–3.426; $P = 0.001$).

KTRs with chronic hepatitis B may exhibit poor survival due to post-transplantation hepatic complications. Pretransplant histological liver evaluations and adequate antiviral management with potent nucleoside/nucleotide analogues are needed to improve the survival of KTRs with chronic hepatitis B even when liver function is within the normal range.

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Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, HbA1c = glycated hemoglobin, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HLA = human leukocyte antigen, HR = hazard ratios, KTR = kidney transplant recipient, PEG-IFN = pegylated-interferon.

INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the primary causes of liver disease in kidney transplant recipients (KTRs). Immunosuppression after kidney transplantation exacerbates the progression of liver disease to cirrhosis or hepatocellular carcinoma,[1,2] and affects patient and allograft survival. Nevertheless, controversy remains regarding how HBV and HCV infection differentially affect outcomes following transplantation.

A previous long-term study found that KTRs with HBV infection had an increased risk of mortality and allograft failure compared with KTRs without HBV infection.[3–5] A meta-analysis of observational studies also showed that hepatitis B surface antigen (HBsAg)-seropositivity was independently associated with patient death and graft survival after kidney transplantation.[6] However, these studies have limitations when evaluating the effect of antiviral therapy because the publication period was before the antiviral nucleoside/tide era or because

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the authors did not specify the percentage of antiviral therapy. Although several studies have reported the efficacy of antiviral agents in KTRs after the introduction of such agents, most studies enrolled a small number of patients over a relatively short period, making it difficult to determine the impact of antiviral treatment on transplant outcome.[7–9]

The impact of HCV infection has been reported in various studies. KTRs with HCV exhibit higher mortality than KTRs without HCV due to liver failure or cardiovascular disease.[10,11] However, recent studies did not support those findings, demonstrating that immunosuppressive regimens did not affect patient survival.[12,13] The conflicting results regarding patients with HCV infection may be attributable to the various effects of immunosuppressive agents, such as cyclosporine or mycophenolate, which are known to inhibit HCV replication and immune cell function.[13,14]

Considering the long natural history and the discordant reports on HBV and HCV infections after kidney transplantation, a more extensive evaluation is needed to determine the effects of antiviral therapy on transplant outcome. We compared the long-term outcomes of KTRs with chronic HBV or HCV infection with those of KTRs without viral hepatitis infection in an HBV-endemic country. We also investigated the significance of pretransplant liver biopsy and the effects of antiviral treatment in patients with HBV and HCV infections.

METHODS

Study Cohort

This multicenter cohort study included patients admitted to 4 tertiary hospitals: Seoul National University Hospital; Seoul National University Boramae Medical Center; Asan Medical Center, University of Ulsan College of Medicine; and Kyungpook National University Hospital. Patients aged over 18 years who underwent kidney transplantation between January 1997 and December 2011 were eligible for the study. Patients who underwent retransplantation or multiorgan transplantation were excluded from the analysis. Of the 3855 KTRs, 3484 were enrolled who had viral hepatitis serology data available. Chronic hepatitis B and C infections were defined as persistent positivity for hepatitis B surface antigen and antiHCV antibody for at least more than 6 months, respectively. All candidates for KTRs with chronic HBV infection were aimed to be treated with prophylactic antiviral drugs (nucleoside analogues) prior to or immediately after kidney transplantation.[15,16] Patients who were not treated with prophylactic antiviral agents were monitored regularly for HBV DNA titers and preemptively treated in case of newly detected or significant increases (>10-fold) in HBV DNA. In scenarios of HBV reactivation (an increase in HBV DNA above 2000 IU/mL and persistent elevation of ALT levels) after kidney transplantation, the patients were treated with nucleoside analogues.[17,18] All clinical investigations were approved by the institutional review board at each center and conducted in accordance with the guidelines of the 2008 Declaration of Helsinki.

Data Collection

Patient baseline information was obtained from a review of medical records. Transplant-related variables included age; sex; body mass index; primary cause of kidney failure; dialysis modality and duration; type of immunosuppressant; and history of pretransplant hypertension, ischemic heart disease, cerebrovascular disease, or liver cirrhosis. Pretransplantation laboratory values, including leukocyte, hemoglobin, serum albumin, glucose, cholesterol, high-sensitivity C-reactive protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and glycated hemoglobin (HbA1c), were collected. HBsAg and HCV antibody titers were assessed using chemiluminescent or enzyme microparticle immunoassay technology. The severity of liver cirrhosis was assessed based on the modified Child-Pugh classification.[19,20] The antiviral agent type and histological liver biopsy findings were obtained for patients with HBV and HCV infections. Donor-related variables, such as age, sex, donor type, matched human leukocyte antigen (HLA) number, and cross-match results, were also reviewed.

Outcomes

The patients were grouped according to their viral state and compared for primary and secondary outcomes. The primary outcomes were graft and patient survival rates. Graft failure was defined as a return to dialysis or preemptive kidney retransplantation. The secondary outcome was biopsy-proven acute rejection. We also reviewed the causes of graft failure and patient death.

Statistical Analysis

Continuous data are expressed as the means ± standard deviation. All continuous variables were tested for normality distribution using Q–Q plot and Kolmogorov–Smirnov tests. Comparisons between groups were performed using the χ^2 test or Fisher exact test for categorical data and an independent *t* test for continuous data. Graft and patient survival and acute rejection incidence between groups were determined and analyzed using the Kaplan–Meier method. In the survival analysis according to the prophylactic antiviral treatment, we did not compare the overall survival during the entire follow-up time; instead, we compared the 5-year survival to adjust for discrepancies in follow-up time between the groups. The hazard ratios (HRs) and confidence intervals (CIs) for primary and secondary outcomes were calculated with the Cox proportional hazards model adjusted for age, sex, diabetes mellitus, body mass index, donor type, primary renal disease, renal replacement therapy, hypertension, ischemic heart disease, immunosuppressive agents, and serum albumin levels. The statistical analysis was performed using the SPSS system for Windows, version 21.0 (IBM SPSS Inc, Chicago, IL). *P* values <0.05 were considered statistically significant.

RESULTS

KTR Characteristics According to Hepatitis Serology

A total of 3482 adult KTRs were enrolled in this study. One hundred sixty patients (4.6%) had HBV, and 55 (1.6%) had HCV. There were no patients with HBV and HCV coinfection. Figure 1A shows the increasing numbers of incident kidney transplants and illustrates the annual trend of the proportions of patients with HBV and HCV among KTRs. The proportion of patients with HBV (2.3–7.6%) was more than twice that of the proportion of KTRs with HCV (0.0–3.0%). Figure 1B describes the proportion of KTRs with HBV who received prophylactic antiviral treatment. Before 2001, approximately half of KTRs with HBV were not treated with prophylactic antiviral agents. The number of patients who received no prophylactic antiviral treatment continually decreased over time. Prior to 2007, lamivudine was the primary antiviral agent used to treat KTRs with HBV. Since 2008, increasing numbers of patients have been treated with entecavir.

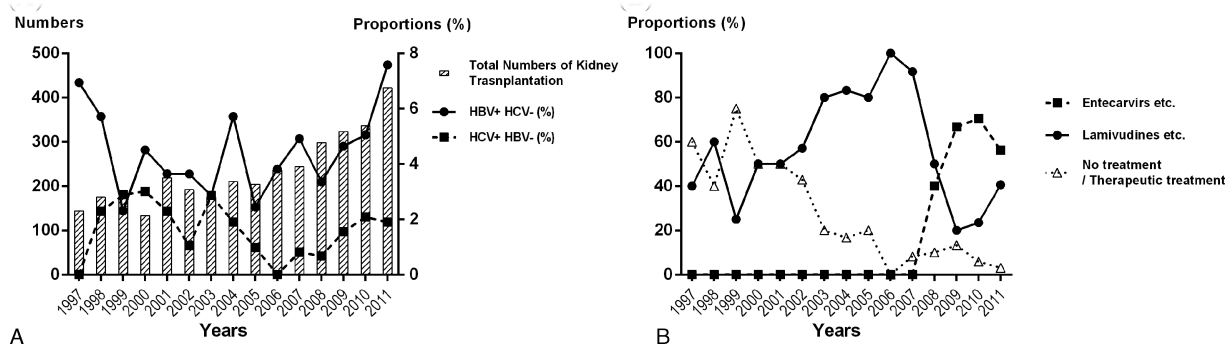

FIGURE 1. The annual trend of kidney transplantations and prophylactic antiviral treatment. A, Total kidney transplantations and proportion of kidney transplantation recipients with HBV and HCV. The number of kidney transplantations is continuously increasing. The proportion of kidney transplantation recipients with HBV is larger than that with HCV. B, Among KTRs with HBV, the number of patients who received no prophylactic antiviral treatment continually decreased over time. Prior to 2007, lamivudine was the primary antiviral agent used to treat KTRs with HBV. Since 2008, increasing numbers of patients have been treated with entecavir.

The demographic and clinical characteristics of KTRs according to their hepatitis B and C serology are summarized in Table 1. The age of KTRs with HBV (43.0 ± 10.8 years old) was higher than that of seronegative KTRs. KTRs with HBV showed a preponderance of males (80.0%) compared with KTRs with HCV (58.2%) and seronegative KTRs (58.9%). The body weight of the KTRs with HBV (63.1 ± 10.2 kg) was higher compared with those of the other groups; the body mass index did not differ between the groups. The proportion of patients with liver cirrhosis was higher in the groups of KTRs with HBV (5.6%) and HCV (1.8%) compared with seronegative KTRs (0.4%). The severity of cirrhosis did not differ between the groups. Comorbidities of diabetes, hypertension, and ischemic heart disease did not differ between the groups. None of the patients with HCV infection was diagnosed with cryoglobulinemia. The primary renal disease causes, pretransplant renal replacement therapy, and renal replacement therapy duration were also comparable between the groups. In the group of KTRs with HBV, the donor age (41.4 ± 12.0 years old) and the proportion of deceased donors (28.9%) were higher than those of the seronegative KTRs. Laboratory values of white blood cell counts, hemoglobin levels, glucose levels, C-reactive protein levels, serum creatinine levels, HbA1c levels, AST levels, and ALT levels did not differ between the groups. However, KTRs with HBV had low serum albumin levels (3.6 ± 0.6 g/dL) and low serum cholesterol levels (151.8 ± 39.8 mg/dL). The use of immunosuppressive calcineurin inhibitors and antimetabolites did not differ between the groups. However, the use of azathioprine was lower among KTRs with HBV ($P < 0.001$). The proportion of patients who received prophylactic antiviral treatment with nucleoside analogues in the HBV group was 80.6%. Pretransplant antiviral treatment with pegylated-interferon (PEG-IFN) with or without ribavirin (PEG-IFN 2, PEG-IFN, and ribavirin 2) was administered to 7.2% of the HCV group. The percentages of KTRs who underwent pretransplant liver biopsy were 77.5% in the HBV group and 62.0% in the HCV seropositive group ($P = 0.028$).

Survival and Causes of Mortality Among KTRs

KTR survival was compared among the groups using Kaplan–Meier curves (Figure 2). The numbers of deaths among KTRs with HBV, HCV, and seronegativity were 18 (11.3%), 3 (5.5%), and 121 (3.7%), respectively, during the mean follow-up duration of 89.1 ± 54.1 months. The cumulative 10-year survival rates of the KTRs with HBV, HCV, and negative serology were 83.6%, 91.8%, and 95.5%, respectively. Patients with HBV exhibited a poorer survival rate than did patients in the other groups ($P < 0.001$). The crude and adjusted hazard ratios (HRs) for mortality were analyzed using a Cox proportional hazards analysis, as shown in Table 2. Univariate analysis revealed that the crude HR of HBV seropositivity was 3.290 (95% CI: 2.005–5.399; $P < 0.001$). Patient age (HR: 1.062; 95% CI: 1.047–1.078; $P < 0.001$), diabetes mellitus (HR: 3.017; 95% CI: 2.117–4.300; $P < 0.001$), transplant donor type (deceased vs. living related; HR: 3.097; 95% CI: 2.085–4.598; $P < 0.001$), ischemic heart disease (HR: 3.478; 95% CI: 1.999–6.052; $P < 0.001$), and serum albumin levels (HR: 0.677; 95% CI: 0.498–0.919; $P = 0.012$) were significantly associated with mortality. Multivariate analysis indicated that the adjusted HR of HBV seropositivity was 2.370 (95% CI: 1.155–4.865; $P = 0.019$). The causes of mortality are compared in Table 3. Among the causes of mortality in patients with HBV, hepatic causes (44.4%), including hepatocellular carcinoma (6 patients), acute hepatic failure due to HBV reactivation (1 patient), and sclerosing cholangitis (1 patient), were significantly higher than other causes. There were no cases with HCV reactivation hepatitis or HCV-related hepatic mortality among the KTRs with HCV.

Risk of Mortality Among KTRs With HBV

We compared the demographic and laboratory characteristics of patients with HBV stratified by their mortality to investigate factors associated with mortality in HBV-positive patients (Supplementary Table 1, http://links.lww.com/MD/B3). Age, sex, body mass index, diabetes mellitus, transplant era, serum albumin levels, C-reactive protein levels, AST and ALT levels, cholesterol levels, and pretransplant HBV DNA titers did not differ according to mortality in HBV-positive patients. HBV-positive KTRs with mortality showed a higher grade of inflammation in liver biopsy (above mild inflammation, 7/11 [54.6%] vs. 32/113 [23.9%], $P = 0.002$), a tendency toward severe fibrosis or cirrhosis in liver biopsy (2/11 [18.2%] vs. 6/113 [5.3%], $P = 0.110$), less use of prophylactic antiviral treatment (11/18 [61.1%] vs. 118/142 [83.1%], $P = 0.070$), and a higher rate of antiviral treatment with lamivudine or adefovir (14/18 [77.8%] vs. 93/142 [56.3%],

TABLE 1. Patients' Characteristics According to Hepatitis Serology

	Total Patients (n = 3482)	HBV+HCV- (n = 160)	HBV-HCV- (n = 3267)	P^1	HCV+HBV- (n = 55)	P^2
Age, y	40.6 ± 12.9	43.0 ± 10.8	40.4 ± 13.0	0.003	43.9 ± 11.8	0.628
Body weight, kg	59.5 ± 12.4	63.1 ± 10.2	59.3 ± 12.5	<0.001	58.0 ± 12.4	0.008
BMI	22.1 ± 3.3	22.5 ± 3.1	22.1 ± 3.3	0.208	21.5 ± 3.1	0.055
Age of donor, y	39.3 ± 12.3	41.4 ± 12.0	39.2 ± 12.3	0.025	40.8 ± 12.4	0.743
Sex (male)	2084 (59.9%)	128 (80.0%)	1924 (58.9%)	<0.001	32 (58.2%)	0.001
Diabetes mellitus	580 (16.7%)	32 (20.0%)	534 (16.3%)	0.224	14 (25.5%)	0.395
Hypertension	2856 (82.0%)	138 (86.3%)	2676 (81.9%)	0.162	42 (76.4%)	0.087
Ischemic heart disease	130 (3.7%)	8 (5.0%)	121 (3.7%)	0.400	1 (1.8%)	0.309
Liver cirrhosis	22 (0.6%)	9 (5.6%)	12 (0.4%)	<0.001	1 (1.8%)	0.232
Child-Pugh Classification				0.652		0.788
Grade A		6 (66.7%)	9 (75.0%)		1 (100%)	
Grade B		1 (11.1%)	2 (16.7%)			
Grade C		2 (22.2%)	1 (8.3%)			
Donor type				0.037		0.608
Living related	1806 (51.9/53.7%)	70 (44.0%)	1716 (54.4%)		20 (37.7%)	
Living unrelated	765 (22.0/22.7%)	43 (27.0%)	708 (22.4%)		14 (26.4%)	
Deceased	795 (22.8/23.6%)	46 (28.9%)	730 (23.1%)		19 (35.8%)	
Primary renal disease				0.065		0.476
Diabetes mellitus	435 (12.5%)	31 (19.4%)	396 (12.1%)		8 (14.5%)	
Hypertension	230 (6.6%)	6 (3.8%)	219 (6.7%)		5 (9.1%)	
Glomerulonephritis	934 (26.8%)	40 (25.0%)	881 (27.0%)		13 (23.6%)	
Cystic disease	133 (3.8%)	3 (1.9%)	129 (3.9%)		1 (1.8%)	
Others	461 (13.2%)	21 (13.1%)	436 (13.3%)		4 (7.3%)	
Unknown	1289 (37.0%)	59 (36.9%)	1206 (36.9%)		24 (43.6%)	
Renal replacement disease (RRT)				0.514		0.678
Preemptive	229 (6.6/11.1%)	7 (7.4%)	218 (11.3%)		4 (10.3%)	
HD	1392 (40/67.3%)	64 (68.1%)	1299 (67.1%)		29 (74.4%)	
PD	378 (10.9/18.3%)	18 (19.1%)	355 (18.3%)		5 (12.8%)	
Others	70 (2.0/3.4%)	5 (5.3%)	64 (3.3%)		1 (2.6%)	
Duration of RRT, mo	27.7 ± 37.2	35.0 ± 45.6	26.8 ± 36.0	0.057	50.0 ± 57.1	0.184
Immunosuppression						
Calcineurin inhibitor				0.612		0.895
Tacrolimus	1651 (47.4/51.5%)	80 (55.6%)	1541 (51.2%)		30 (56.6%)	
Cyclosporin A	1537 (44.1/47.9%)	64 (44.4%)	1450 (48.2%)		23 (43.4%)	
Others	5 (0.1/0.2%)	0 (0.0%)	5 (0.2%)		0 (0.0%)	
No use	14 (0.4/0.4%)	0 (0.0%)	14 (0.5%)		0 (0.0%)	
Antimetabolite				<0.001		0.559
Mycophenolate	2199 (63.2/76.1%)	92 (76.7%)	2075 (76.2%)		32 (66.7%)	
Azathioprine	527 (15.1/18.2%)	14 (11.7%)	504 (18.5%)		9 (18.8%)	
Others	49 (1.4/1.7%)	9 (7.5%)	36 (1.3%)		4 (8.3%)	
No use	116 (3.3/4.0%)	5 (4.2%)	108 (4.0%)		3 (6.3%)	
Prophylactic antiviral treatment		129 (80.6%)			4 (7.2%)	
Liver biopsy		124 (77.5%)			31 (62.0%)	
Hb (/μL)	10.5 ± 1.8	10.4 ± 1.6	10.5 ± 1.8	0.840	10.8 ± 2.4	0.437
Albumin, g/dL	3.7 ± 0.6	3.6 ± 0.6	3.7 ± 0.6	0.047	3.8 ± 0.5	0.139
hs-CRP, mg/dL	0.55 ± 1.37	0.47 ± 0.99	0.55 ± 1.39	0.661	0.77 ± 1.60	0.296
AST, IU/L	20.4 ± 20.5	22.1 ± 13.2	20.1 ± 22.1	0.276	19.7 ± 7.5	0.106
ALT, IU/L	19.4 ± 31.5	20.8 ± 17.0	19.2 ± 34.4	0.564	18.7 ± 10.6	0.399
Cholesterol, mg/dL	163.3 ± 42.1	151.8 ± 39.8	163.9 ± 42.2	0.001	159.2 ± 43.3	0.291

The demographic and clinical characteristics of KTRs with HBV are compared with KTRs with seronegativity and KTRs with HCV.
P^1 represents the P values comparing the groups of KTRs with HBV and KTRs with seronegativity.
P^2 represents the P values comparing the groups of KTRs with HBV and KTRs with HCV.

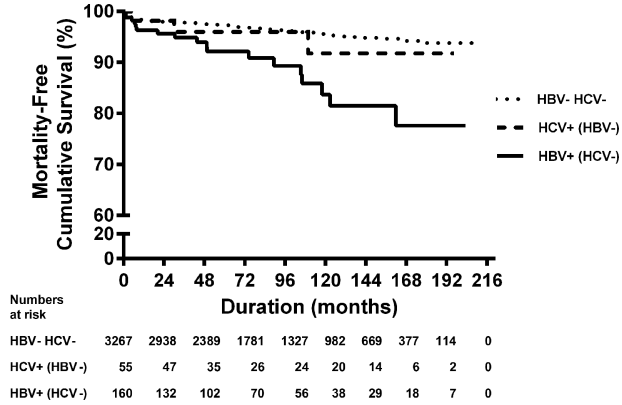

FIGURE 2. Patient survival is presented in a Kaplan–Meier survival plot. Kidney transplantation recipients with HBV show poorer overall survival (log-rank $P<0.001$) than those with HCV or negative hepatitis serology.

$P=0.016$) than those without mortality. When we compared the survival of KTRs with HBV according to their liver biopsy results, KTRs who exhibited liver inflammation on the liver biopsy showed a tendency toward poorer survival than those without liver inflammation (Figure 3A; log-rank, $P=0.070$). KTRs with severe fibrosis or liver cirrhosis showed significantly poorer survival than those without fibrosis (Figure 3B; log-rank, $P=0.047$). Patients who were treated with new-generation antiviral agents such as entecavir showed better survival than those who were treated with lamivudine or adefovir (Figure 3C; log-rank, $P=0.050$). The crude and adjusted HRs for mortality among KTRs with HBV are summarized in Table 4. Pretransplant histological findings of liver inflammation (adjusted HR: 3.804; 95% CI: 1.043–13.871; $P=0.043$) and severe fibrosis or cirrhosis (adjusted HR: 9.508; 95% CI: 1.467–61.608; $P=0.018$) were associated with increased mortality.

Graft Survival and Acute Rejection After Transplantation

The numbers of graft failures among KTRs with HBV, HCV, and seronegativity were 16 (10.0%), 14 (25.5%), and 292 (8.9%), respectively. A comparison of graft survival among the groups is shown in Figure 4A. Patients with HBV showed graft survival comparable to patients with negative hepatitis serology. However, patients with HCV showed a poorer graft survival rate compared with the other groups ($P<0.001$). The crude HR of HCV for graft failure was 3.105 (Table 2, 95% CI: 1.816–5.308; $P<0.001$), and the adjusted HR was 2.899 (95% CI: 1.289–6.519; $P=0.010$).

The causes of graft failure are compared in Table 3. The causes of graft failure did not differ between the groups ($P=0.254$). Acute rejection was the most common cause of graft failure in KTRs with HCV. Events of acute rejection are compared in Figure 4B. KTRs with HCV showed a significantly increased incidence of acute rejection (log-rank $P=0.005$; crude HR: 2.144 [1.341–3.426], $P=0.001$) compared with KTRs with HBV or seronegativity. In the subgroup analysis of KTRs with HCV, there was no significant difference in graft survival according to viral load of HCV (data not shown).

DISCUSSION

In this study, we compared the overall survival of KTRs and graft survival according to HBV and HCV serology using multicenter data from patients in an HBV-endemic country. HBV is prevalent in South Korea, and the prevalence of chronic hepatitis B infection (4–5%) is higher than that of HCV (1.68%).[21,22] HBV also had a high prevalence in our study participants, and the proportion of KTRs with HBV was more than 2-fold the proportion of KTRs with HCV. Despite studies on the prognosis of KTRs with HCV, the natural clinical course and prognosis of HBV infection after renal transplantation have not been thoroughly investigated, and the influence of HBV infection on the prognosis of KTRs remains controversial. This study investigated the prognosis of KTRs with HBV and made comparisons with KTRs with HCV and seronegative recipients.

In this study, KTRs with HBV showed poor overall survival compared with KTRs without HBV. KTRs with HBV have a potential risk of liver disease exacerbation due to immunosuppressive agents.[1,23] Progressive liver disease is a common adverse event in immunosuppression in KTRs with HBV.[24] Before the introduction of antiviral treatment among KTRs with HBV, the proportion of patients who experienced viral reactivation reached 30% (higher than the 5% incidence of

TABLE 2. Risk From Chronic Hepatitis B and C Infections for Mortality and Graft Failure

	Model 1*		Model 2†		Model 3‡	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Mortality						
HBV	3.290 (2.005–5.399)	<0.001	2.707 (1.586–4.619)	<0.001	2.370 (1.155–4.865)	0.019
HCV	1.485 (0.472–4.670)	0.499	1.251 (0.396–3.951)	0.703	1.171 (0.284–4.826)	0.827
Graft failure						
HBV	1.234 (0.746–2.042)	0.413	1.026 (0.598–1.762)	0.925	1.381 (0.545–3.499)	0.496
HCV	3.105 (1.816–5.308)	<0.001	2.738 (1.531–4.897)	0.001	2.768 (1.226–6.252)	0.014

HR = hazard ratio; 95% CI = 95% confidence interval.
*Unadjusted model; hazard ratios of chronic hepatitis B and C infections for mortality and graft failure were analyzed.
†Multivariate analysis included covariates of clinically significant factors including age, sex, diabetes mellitus, body mass index, and donor type.
‡Multivariate analysis included covariates of clinically significant factors that were included in Model 2 and statistically significant factors that showed *P* values below 0.10 in the univariate analysis. In the mortality analysis, the covariates of age, sex, diabetes mellitus, body mass index, primary renal disease, donor type, hypertension, ischemic heart disease, and antimetabolite immunosuppressive agents were adjusted. In the graft failure analysis, the covariates of age, sex, diabetes mellitus, body mass index, renal replacement therapy, donor type, hypertension, ischemic heart disease, antimetabolite immunosuppressive agent, and hemoglobin levels were adjusted.

TABLE 3. Cause of Death and Graft Failure According to Hepatitis Serology

	Total (n = 3482)	HBV+HCV- (n = 160)	HCV+HBV- (n = 55)	HBV-HCV- (n = 3267)
Cause of death (P <0.001)	142	18	3	121
Hepatic disease (+HCC)	9 (6.3%)	8 (44.4%)	0 (0.0%)	1 (0.8%)
Infections	45 (31.7%)	4 (22.2%)	1 (33.3%)	40 (33.1%)
Cardiovascular disease	23 (16.2%)	1 (5.6%)	1 (33.3%)	21 (17.4%)
Pulmonary disease	2 (1.4%)	0 (0.0%)	1 (33.3%)	1 (0.8%)
Gastrointestinal disease	2 (1.4%)	1 (5.6%)	0 (0.0%)	1 (0.8%)
Malignancy	10 (7.0%)	1 (5.6%)	0 (0.0%)	9 (7.4%)
Unknown	51 (35.9%)	3 (16.7%)	0 (0.0%)	48 (39.7%)
Cause of graft loss (P = 0.254)	322	16	14	292
Rejections	134 (41.6%)	6 (37.5%)	8 (57.1%)	120 (41.1%)
Primary disease recurrence	20 (6.2%)	1 (6.3%)	1 (7.1%)	18 (6.2%)
Chronic allograft nephropathy	13 (4.0%)	1 (6.3%)	0 (0.0%)	12 (4.1%)
Renal vascular disease	5 (1.6%)	0 (0.0%)	0 (0.0%)	5 (1.7%)
Other renal disease	10 (3.1%)	1 (6.3%)	0 (0.0%)	9 (3.1%)
Infections	23 (7.1%)	2 (12.5%)	1 (7.1%)	20 (6.8%)
Cardiovascular disease	3 (0.9%)	0 (0.0%)	1 (7.1%)	2 (0.7%)
Others/unknown	114 (35.4%)	5 (31.3%)	3 (21.4%)	106 (36.3%)

Causes of death differed according to hepatitis serology (χ^2 P <0.001). Causes of graft failure did not differ between groups (χ^2 P = 0.254).

natural viral reactivation).[1] In addition, among KTRs with HBV, 85% had histological deterioration of fibrosis or inflammation on the subsequent serial liver biopsy, 42% had chronic hepatitis, and 28% had cirrhosis at 66 months after kidney transplantation.[1] Before the 2000s, KTRs with HBV had markedly higher mortality after transplantation than KTRs without HBV due to progressive liver disease.[3] In a meta-analysis by Fabrizi et al,[25] KTRs with HBV were found to be associated with increased mortality and hepatocellular carcinoma. The induction of HBV clearance and an improvement in the prognosis of KTRs with HBV have been expected following the recent widespread use of preemptive or prophylactic antiviral treatment. Yap et al[9] reported that the 10-year survival of KTRs with HBV could be improved from 55% to 90% using antiviral treatment. Recent studies also reported no difference in survival according to HBV seropositivity.[26,27] However, despite the improvement of survival after antiviral treatment, studies with many participants and long follow-ups showed deleterious effects of HBV seropositivity on the overall survival of KTRs.[9,28,29]

The present study shows that KTRs with HBV had poorer overall survival due to death from hepatic causes, including HCC and acute hepatic failure from HBV reactivation. Increased mortality due to hepatic complications has been consistently reported in various studies. KTRs with HBV have a higher risk of HCC. Hoffman et al[2] reported that solid organ transplant recipients with HBV have a 9.7-fold higher risk of developing HCC. Reddy et al[27] revealed that hepatic failure was significantly increased among KTRs with HBV despite comparable overall mortality. Notably, in addition to the increased mortality due to liver-associated complications, our study revealed that a lack of antiviral treatment or the use of older-generation antiviral drugs, such as lamivudine or adefovir, was significantly associated with increased mortality. No mortality was experienced by any of the KTRs with HBV who were treated with entecavir in this study. The interesting difference

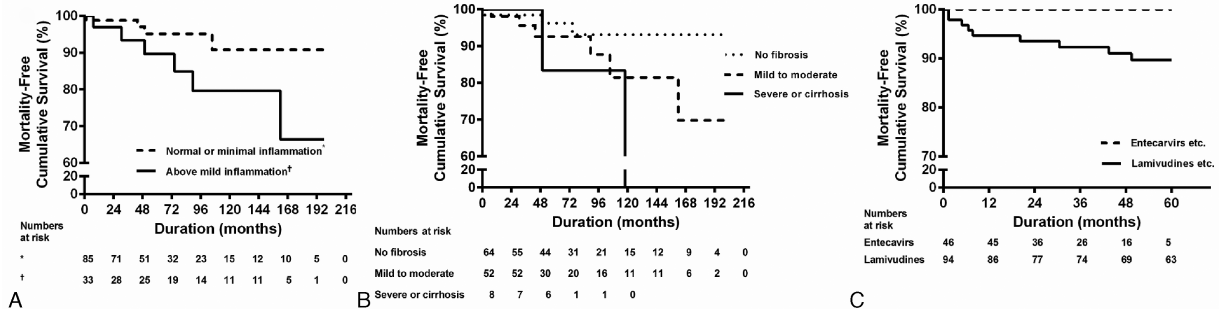

FIGURE 3. Patient survival among KTRs with HBV. A, Patient survival according to inflammation on liver biopsy. B, Patient survival according to fibrosis on liver biopsy. C, Patient survival according to antiviral treatment. KTRs who exhibited liver inflammation on the liver biopsy showed a tendency toward poorer survival than those without liver inflammation (log-rank, P = 0.070). KTRs who had severe fibrosis or liver cirrhosis showed significantly poorer survival than those without fibrosis (log-rank, P = 0.047). KTRs who were treated with new-generation antiviral agents such as entecavir showed better survival than those who were treated with lamivudine or adefovir (log-rank, P = 0.050). *Normal or minimal inflammation in liver biopsy, †above mild inflammation on liver biopsy.

TABLE 4. Cox Proportional Hazard Analysis for Mortality Among KTRs With HBV

	Univariate Analysis		Multivariate Analysis 1*		Multivariate Analysis 2†	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age	1.044 (1.000–1.089)	0.049	1.047 (0.976–1.124)	0.200	1.051 (0.979–1.127)	0.167
Sex (male)	0.464 (0.174–1.240)	0.126	0.286 (0.081–1.004)	0.051	0.243 (0.070–0.837)	0.025
Diabetes mellitus	1.250 (0.354–4.419)	0.729	1.175 (0.203–6.790)	0.857	1.442 (0.265–7.855)	0.672
Body mass index	1.079 (0.917–1.269)	0.359				
HBV titer (>2000 IU/mL)	0.594 (0.128–2.753)	0.594				
Antiviral treatment (vs. no treatment)	0.819 (0.264–2.539)	0.730				
Liver biopsy pathology						
Inflammation						
Normal or minimal inflammation	Reference		Reference			
Above mild inflammation	3.053 (0.858–10.871)	0.085	3.804 (1.043–13.871)	0.043		
Fibrosis						
No fibrosis	Reference				Reference	
Fibrosis, mild to moderate	2.683 (0.670–10.739)	0.163			3.321 (0.791–13.933)	0.101
Severe fibrosis or liver cirrhosis	7.858 (1.266–48.772)	0.027			9.508 (1.467–61.608)	0.018

*Multivariate analysis 1 included covariates for age, sex, diabetes mellitus, and liver inflammation on biopsy.
†Multivariate analysis 2 included covariates for age, sex, diabetes mellitus, and degrees of fibrosis on liver biopsy.

between lamivudine or adefovir and entecavir is likely related to the antiviral efficacy of the drugs. It is well known that the individual efficacies of entecavir and tenofovir are superior to those of lamivudine and adefovir in terms of the histological improvement rate, virological response, and alanine aminotransferase level normalization.[30,31] In HBV-infected KTRs, entecavir showed a higher virological response than lamivudine.[32] Efficient antiviral treatment may reduce HBV reactivation and prevent the histological and clinical hepatic deterioration after transplantation typically observed in KTRs with HBV. Therefore, all KTRs with HBV should be treated with potent antiviral drugs following recent guidelines.[33] Our study also revealed that inflammation or fibrosis on liver biopsy was significantly associated with increased mortality. Patients with HBV infection without overt clinical features of cirrhosis are recommended to undergo a liver biopsy as part of their pretransplantation evaluation to identify histological evidence of cirrhosis.[34] The present study found that liver inflammation or severe fibrosis/liver cirrhosis on biopsy is associated with mortality. These findings may support the importance of pretransplant liver biopsy and may be helpful when deciding the appropriate candidates for kidney transplantation and predicting posttransplant clinical outcomes among KTRs with HBV.

In this study, the graft failure of KTRs with HBV did not notably differ from that in the other groups. The impact of HBV on graft survival after kidney transplantation has been controversial. Fornairon et al[1] reported improved graft survival among KTRs with HBV. In contrast, Ridruejo et al[35] found that graft survival in KTRs with HBV was poorer than that in KTRs without HBV. In a meta-analysis of 6 older observational studies, Fabrizi et al[25] concluded that HBV infection was an independent risk factor for graft failure after kidney transplantation. However, recent studies have consistently reported that graft survival is not inferior in KTRs with HBV compared with

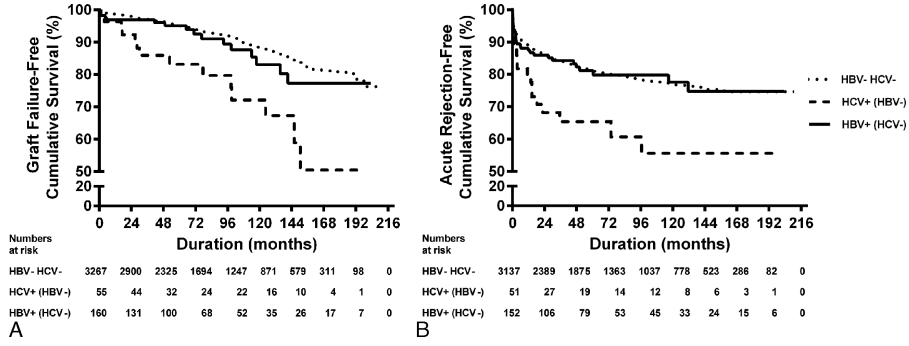

FIGURE 4. Graft survival and events free survival of acute rejection. A, Graft survival in patients with HCV was poorer (log-rank $P<0.001$) than in those with HBV or negative hepatitis serology. B, KTRs with HCV showed a significantly higher incidence of acute rejection (log-rank $P=0.005$; crude HR = 2.144 (1.341–3.426), $P=0.001$) than KTRs with HBV or seronegativity.

other KTRs without HBV.[24,27,36] There may be several explanations for the improvement in graft survival in KTRs with HBV. Antiviral treatment may have reduced graft failure. Reddy et al[27] investigated the prognosis of KTRs with HBV, including patient survival, hepatic failure, and graft survival, according to the era. Before 1995, graft survival in KTRs with HBV was poorer than in patients without HBV. However, after 1995, graft survival in KTRs with HBV did not differ from that in KTRs without HBV. Additionally, the risk of graft failure may have been overestimated due to KTRs with HBV and HCV coinfection in the meta-analysis.[25] Among the 6 observational studies that were included in the meta-analysis, only 2 (by Lee et al and Ridruejo et al) showed increased graft failure in KTRs with HBV.[35,37] These 2 studies enrolled KTRs with HBV and HCV coinfection who showed increased graft failure compared with KTRs with seronegativity. Because the high risk of graft failure among KTRs with HBV and HCV coinfection was included in the risk assessment of the meta-analysis, we can conclude that the risk of graft failure was overestimated in the previous meta-analysis.

In contrast with KTRs with HBV, our study demonstrated that KTRs with HCV had a similar survival rate but a lower graft survival rate compared with those without HCV. These differential effects of HCV on transplant outcome represent a somewhat different result in that most data have suggested shortened overall patient and graft survival in KTRs with HCV.[38,39] The limited number of KTRs with HCV and the limited follow-up duration in this study may explain the absence of an impact of HCV on patient survival. Most studies have revealed that HCV infection does not have a short-term impact but does have a long-term impact.[29] The increased mortality of KTRs with HCV has been explained by the progression of liver disease, hepatocellular carcinoma, and combined cardiovascular disease.[11] Mortality was found to be associated with various factors, such as histological liver biopsy findings, the acquisition time of HCV infection, and immunosuppressive regimen.[12,13,40] Our study did not fully stratify confounding factors for patient survival, such as liver biopsy and immunosuppression. It is also difficult to determine the impact of HCV on patient survival in a limited number of KTRs with HCV. However, our data suggest that graft survival in KTRs with HCV was lower than that of other groups. The exact mechanism of decreased graft survival in KTRs with HCV is not fully understood. Morales et al[41] described HCV infection as being associated with membranous glomerulonephritis and progressive renal function deterioration in KTRs. Although HCV infection could induce immune complex chronic glomerulonephritis in the graft,[42] it is suggested that decreased graft survival may be attributable to acute rejection in the present study. The incidence of acute rejection has been reported in several studies; however, the results are not consistent. The reason for increased acute rejection in HCV patients is unknown; however, it could be partly related to the under-immunosuppression of KTRs with HCV. Further studies investigating the impact of immunosuppression on the clinical course and progression of HCV infection in KTR are needed. Furthermore, we must consider the probable changes in disease progression and transplant outcomes as direct-acting antiviral agents are introduced into KTRs with HCV.[43]

The limitations of our study are related to its retrospective design. The prognostic value of pretransplant HBV DNA levels and liver biopsy may be underestimated because these tests are not conducted at a consistent interval prior to kidney transplantation. The effects of antiviral treatment may be underestimated due to a relatively high proportion of lamivudine use. In the analysis of survival according to the prophylactic antiviral treatment received, we could not fully demonstrate the beneficial effect of new-generation antiviral agents due to the considerable differences in follow-up time between groups. However, this study enrolled a relatively large number of KTRs with HBV and has the strength of a long follow-up. Unlike previous studies that failed to demonstrate increased mortality of KTRs with HBV due to relatively short follow-up,[27] this study showed increased mortality among KTRs with HBV to be closely associated with post-transplant liver-associated problems.

In conclusion, KTRs with chronic hepatitis B may have poor survival due to post-transplantation hepatic complications. Antiviral treatment in KTRs with HBV was associated with decreased mortality, and pretransplant histological inflammation on liver biopsy may affect post-transplant survival. A thorough pretransplant evaluation including liver biopsy and adequate antiviral treatment in KTRs with chronic hepatitis B will be needed even if liver function is within a normal range.

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