

A multicenter evaluation of hepatitis B reactivation with and without antiviral prophylaxis after kidney transplantation

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Social Media: Do kidney transplant patients require antiviral prophylaxis to prevent hepatitis B virus reactivation? Check out the results of our multicenter study here < [link to visual abstract](#)

Abstract

Background: Hepatitis B virus (HBV) reactivation in hepatitis B surface antigen (HBsAg)-negative and hepatitis B core antibody (anti-HBc)-positive kidney transplant recipients ranges between 1.4% and 9.6%. Limited evidence is available regarding routine antiviral prophylaxis and identifiable risk factors for HBV reactivation in this population.

Methods: In this multicenter retrospective study, we evaluated the prevalence of HBV reactivation in HBsAg-negative anti-HBc-positive kidney transplant recipients who did or did not receive antiviral prophylaxis. The primary outcome assessed the prevalence of HBV reactivation, defined as a positive HBV DNA by PCR of any viral load at or above the minimal detection level. The principal safety outcomes assessed 1-year graft survival, 1-year all-cause mortality, biopsy-proven acute rejection, and antibody-mediated rejection.

Results: One hundred and sixty-one patients met inclusion criteria and comprised two groups, antiviral prophylaxis ($n = 14$) and no antiviral prophylaxis ($n = 147$). Of patients who did not receive prophylaxis, only five (3.4%) experienced HBV reactivation, whereas one (7.1%) patient in the prophylaxis group experienced reactivation over a median follow-up of 1103 days ($p = .43$). Furthermore, there were no differences with respect to all secondary outcomes. Statistical analysis demonstrated delayed graft function to be a significant factor associated with HBV reactivation.

Conclusion: These study results suggest that the prevalence of HBV reactivation in HBsAg-negative anti-HBc-positive kidney transplant recipients is low, regardless of antiviral prophylaxis. Furthermore, there were no significant graft-related outcomes among those that did experience reactivation.

KEYWORDS

antiviral prophylaxis, hepatitis B, kidney transplantation

1 | BACKGROUND

The prevalence of hepatitis B virus (HBV) infection ranges from 2.2% to 20.9% in kidney transplant recipients and is associated with significant morbidity and mortality.¹⁻³ Therefore, assessing hepatitis B serologies in pre-transplant patients is vital to appreciate the potential risk of HBV reactivation post transplantation. Patients with chronic HBV present with serologies including positive hepatitis B surface antigen (HBsAg) and hepatitis B core IgG or total antibody (anti-HBc). These patients pose a high risk of HBV reactivation after kidney transplantation in the absence of antiviral prophylaxis, irrespective of HBV DNA levels.^{4,5} Patients who are anti-HBc IgG-positive but HBsAg-negative are either convalescent from HBV infection or have a false-positive anti-HBc.^{6,7} This patient population may be at risk for HBV reactivation after kidney transplantation. An isolated positive hepatitis B surface antibody (anti-HBs) is indicative of vaccination without HBV exposure. Recently vaccinated patients to hepatitis B may also develop transient detectable HBsAg; however, these patients are anti-HBc IgG-negative, indicating no history of chronic HBV.⁸

Reactivation of HBV after kidney transplantation can occur in those with previous HBV infection (anti-HBc IgG or anti-HBc total-positive), and ranges from mild and asymptomatic to severe liver failure or hepatocellular carcinoma.⁹ The risk of HBV reactivation in HBsAg-negative anti-HBc-positive kidney transplant recipients reported in the literature ranges between 1.4% and 9.6%.¹⁰⁻¹³ Despite recovery from initial hepatitis B infection, there lies a risk of reactivation of the virus due to its dormant nature, and the role of antivirals becomes less clear. HBV reactivation is evidenced by loss of HBV immune control in HBsAg-positive, anti-HBc-positive or HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy, an increase in HBV DNA, compared to baseline, and reverse seroconversion of HBsAg negative to positive.⁸ The risk of reactivation may be increased in patients on immunosuppressive therapy including chemotherapy and anti-rheumatic biologics. An even greater risk for HBV reactivation is present with the use of monoclonal antibodies such as rituximab.⁸

Current American Association for the Study of Liver Diseases (AASLD) guidelines recommend that HBsAg-negative anti-HBc-positive non-liver transplant recipients be monitored (alanine aminotransferase (ALT) and HBV DNA every 3 months for the first-year post transplantation) without prophylactic antiviral therapy, but alternatively antiviral therapy for can be considered.⁸ However, the guidelines do not delineate when to monitor versus when to use antiviral prophylaxis. The guidelines do recommend prophylaxis for HBsAg-negative, anti-HBc-positive patients receiving anti-CD20 monoclonal antibodies such as rituximab, which may be observed in non-liver transplant recipients receiving treatment for antibody-mediated rejection (AMR).⁸ Given the low risk of HBV reactivation in HBsAg negative anti-HBc-positive kidney transplant recipients, AASLD and the American Society of Transplantation Infectious Disease Community of Practice (AST ID COP) recommend against routine

antiviral prophylaxis.^{8,14} However, other authors recommend the use of antiviral prophylaxis in the setting of low anti-HBs titers or if HBsAg or HBV DNA becomes detectable.¹⁵

Data on HBV reactivation based on the use of antiviral prophylaxis and various patient risks such as lymphocyte-depleting agents and anti-HBs status is limited.^{12,13} Therefore, this multicenter study was conducted to evaluate the prevalence of HBV reactivation in HBsAg-negative and anti-HBc-positive kidney transplant recipients who did or did not receive hepatitis B antiviral prophylaxis, and to identify risk factors associated with HBV reactivation.

2 | METHODS

This was a multicenter retrospective cohort study of adult kidney transplant recipients from Keck Medicine of USC, Michigan Medicine, University Hospitals Cleveland Medical Center, and the University of Kentucky Healthcare. We included HBsAg-negative anti-HBc-positive kidney transplant recipients transplanted between January 2010 and January 2020 who were 18 years of age or older. Recipients were excluded if they had a history of previous transplant, were on immunosuppression at the time of transplantation, received a kidney transplant from an HBsAg-positive, HBV NAT-positive, or anti-HBc-positive donor, were HBsAg-positive at the time of transplant, were taking HBV antiviral therapy at the time of transplant, or had a known viral infection pre-transplant including human immunodeficiency virus or hepatitis C virus. We identified 259 potentially eligible patients; however, only 161 met inclusion criteria.

All data collection was performed through a manual chart review of the electronic health records. Data were collected at each individual institution and combined to create the study database. This study was approved by the Institutional Review Board of University of Southern California (HS-20-00867).

The primary outcome of the study was the prevalence of hepatitis B reactivation, defined as a positive HBV PCR of any viral load at or above the minimal detection level, in kidney transplant recipients receiving antiviral prophylaxis, compared to those not receiving antiviral prophylaxis targeted toward HBV. Secondary outcomes included 1-year graft survival (graft failure defined as a return to hemodialysis or re-transplant), 1-year all-cause mortality, biopsy-proven acute rejection (BPAR), and AMR.

IBM SPSS statistical software (version 28, SPSS) was used to conduct data analysis. Categorical data were compared using either a chi-square test or Fisher's exact test, and continuous data were compared using a two-tailed Student's *t*-test or Mann-Whitney *U*-test. A binary logistic regression was performed to identify factors associated with HBV reactivation. In addition to factors such as age and antiviral prophylaxis use, variables with $p < 0.2$ on univariate analysis were considered for inclusion in the multivariate model. A receiver operating characteristic (ROC) curve was produced to evaluate the sensitivity and specificity of the multivariate model.

3 | RESULTS

Baseline characteristics are represented in Table 1. One hundred and sixty-one patients were eligible for study inclusion: 147 patients in the non-hepatitis B prophylaxis group and 14 patients in the hepatitis B prophylaxis group. Of note, Asians represented 35.4% of the entire patient population. The mean age in years was 59.7 ± 9.8 and 58.1 ± 14.9 in the non-prophylaxis group and prophylaxis group, respectively. Other similarities between the two groups included the etiology of renal disease, most commonly being diabetes and hypertension or a combination of the two conditions. With respect to anti-HBs titers pre-transplant, 79.6% of patients who did not receive antiviral prophylaxis had reactive anti-HBs titers, compared to 78.6% in the group that did receive prophylaxis ($p > .99$). Induction immunosuppression used at the time of transplantation was similar between the groups. Rabbit anti-thymocyte globulin was used in 76.2% of patients in the non-prophylaxis group versus 71.4% of patients in the prophylaxis group ($p = .75$). Maintenance immunosuppression between the two groups was similar with a majority of patients in the entire cohort (82.6%) receiving triple maintenance immunosuppression with tacrolimus, mycophenolate, and prednisone. There was also no difference with respect to the usage of steroid maintenance immunosuppression between the two groups (87.8% vs. 92.9%; $p > .99$). All patients in the prophylaxis group received entecavir for hepatitis B prophylaxis, and the median duration of antiviral prophylaxis was 615 days, with three patients receiving indefinite prophylaxis.

As seen in Table 2, the overall prevalence of HBV reactivation in the entire study cohort was 3.7%. There was no statistically significant difference between the two cohorts with respect to the primary outcome of our study. Of the 147 patients who did not receive prophylaxis, only five (3.4%) experienced HBV reactivation, whereas one (7.1%) of 14 patients who did receive prophylaxis experienced reactivation ($p = .43$). This was over a median follow-up period of 1103 days for the entire cohort. The one patient who developed HBV reactivation in the prophylaxis group was on antiviral prophylaxis for 1064 days post transplantation before antiviral discontinuation. HBV reactivation occurred in this patient 504 days after discontinuation of antiviral prophylaxis.

With respect to all secondary outcomes, no differences were observed between the two cohorts (Table 2). Death-censored graft loss occurred in seven (4.8%) patients in the non-prophylaxis group, compared to zero patients in the prophylaxis group ($p > .99$). One-year all-cause mortality occurred in four (2.7%) patients in the non-prophylaxis group, compared to zero patients in the prophylaxis group ($p > .99$). BPAR occurred in 23 (15.8%) patients who did not receive prophylaxis, while only two (14.3%) patients in the hepatitis B prophylaxis group developed BPAR ($p > .99$). BPAR did not precede any of the six cases of HBV reactivation. Moreover, only one patient who experienced HBV reactivation 2 days after transplantation had an episode of BPAR diagnosed 1641 days post transplantation. This patient had Banff 1a acute cellular rejection and was treated with a cumulative dose of 1000 mg of intravenous methylprednisolone. Three patients in the non-prophylaxis group did experience AMR; however, they received

treatment with intravenous immune globulin (IVIG) with or without plasmapheresis, and no patient in either cohort received rituximab.

Table 3 summarizes the six HBV reactivation cases. The average age of patients who experienced HBV reactivation was 57 years, and 50% were Asian. Four patients had reactive anti-HBs titers pre-transplantation, with quantitative levels considered protective in the general patient population. Interestingly, most patients with HBV reactivation also had delayed graft function (83.3%), defined as return dialysis within 7 days of transplantation. Of the six patients who had HBV reactivation, only one received HBV antiviral prophylaxis, and the median time to HBV reactivation for the cohort was 232 days. The single patient who did receive HBV antiviral prophylaxis and experienced HBV reactivation had a total bilirubin of 1.8 mg/dl at the time of reactivation; however, it is important to note that the patient was diagnosed with Gilbert's syndrome and did not have hepatic complications. Importantly, one of the patients who did not receive antiviral prophylaxis went on to develop HBV reactivation, and subsequently Stage F3 liver fibrosis on the Metavir histological index of grading fibrosis, indicating severe liver fibrosis.

As demonstrated in Table 4, potential risk factors for HBV reactivation with a $p < .2$ on the univariate analysis included delayed graft function and IVIG use for the treatment of allograft rejection. These factors were included in a backward stepwise logistic regression model. HBV antiviral prophylaxis was also included in the model to determine if it truly influenced protection against HBV reactivation, despite the results of our primary outcome. Age has been shown to be a factor associated with HBV reactivation based on a previous study; therefore, it was also included in our model.¹² Our multivariate logistic regression model demonstrated that the absence of HBV prophylaxis did not predict the development of HBV reactivation in our patient population. However, delayed graft function was found to be a significant risk factor for HBV reactivation (OR 12.17 [1.22–121.99], $p = .03$). Our multivariate model generated an ROC curve with an area under the curve of 0.75 with a standard error of 0.09, demonstrating a fair model of fit.

4 | DISCUSSION

Our study reviewed the use of hepatitis B antiviral prophylaxis to no hepatitis B antiviral prophylaxis on the prevalence of HBV reactivation in HBsAg-negative anti-HBc-positive kidney transplant recipients at a multicenter level. There is no consensus on when to use antiviral prophylaxis in HBsAg-negative anti-HBc-positive kidney transplant recipients, and there is limited evidence identifying patients at high risk for HBV reactivation that may warrant prophylaxis.⁷ The results of our study concur with the recommendations provided by AASLD and AST ID COP in that antiviral prophylaxis targeted toward HBV may not be indicated in HBsAg-negative anti-HBc-positive kidney transplant recipients.

Despite being on immunosuppressive therapy, including greater than 70% of the cohort receiving rabbit anti-thymocyte globulin, the non-prophylaxis group in our study experienced a reactivation rate similar to the prevalence of HBV in the United States, which is less than

TABLE 1 Baseline demographics and clinical characteristics

	No hepatitis B prophylaxis (n = 147)	Hepatitis B prophylaxis (n = 14)	p-value
Age (years)	59.7 ± 9.8	58.1 ± 14.9	.70
Race			
Black	34 (23.1%)	2 (14.3%)	.74
Caucasian	44 (29.9%)	2 (14.3%)	
Asian	50 (34.0%)	8 (57.1%)	
Hispanic	14 (9.5%)	2 (14.3%)	
Other	5 (3.4%)	1 (7.1%)	
Indication for transplant			
Diabetes	49 (33.3%)	2 (14.3%)	.23
Hypertension	41 (27.9%)	2 (14.3%)	
IgA nephropathy	10 (6.8%)	0	
FSGS	7 (4.8%)	1 (7.1%)	
Polycystic kidney disease	7 (4.8%)	1 (7.1%)	
Diabetes and hypertension	18 (12.2%)	4 (28.6%)	
Other	15 (10.2%)	4 (28.6%)	
Donor type			
Living donor	29 (19.7%)	2 (14.3%)	> .99
Deceased donor	118 (80.3%)	12 (85.7%)	
Anti-HBs status			
Anti-HBs reactive	117 (79.6%)	11 (78.6%)	> .99
Quantitative anti-HBs	359.9 ± 366.6 (n = 117)	214.6 ± 311.9 (n = 11)	.23
Baseline liver enzymes			
AST (IU/L)	20.3 ± 9.5 (n = 134)	20.6 ± 9.2 (n = 13)	.89
ALT (IU/L)	19.4 ± 10.6 (n = 134)	20.8 ± 16.8 (n = 13)	.76
Alkaline phosphatase (IU/L)	112.8 ± 83.9 (n = 134)	94.3 ± 31.5 (n = 13)	.43
Total bilirubin (mg/dl)	0.4 ± 0.2	0.5 ± 0.2	.36
Delayed graft function	54 (36.7%)	4 (28.6%)	.77
Induction immunosuppression			
Anti-thymocyte globulin	112 (76.2%)	10 (71.4%)	.75
Basiliximab	24 (16.3%)	3 (21.4%)	.71
None	11 (7.5%)	1 (7.1%)	> .99
Maintenance prednisone immunosuppression	129 (87.8%)	13 (92.9%)	> .99
Antiviral agent utilized			
Entecavir	-	14 (100.0%)	-
Time to initiation of HBV prophylaxis (days)	-	3.0 [1-85.5]	-
Follow-up, days	1136.0 [659.5-1879.5]	962.0 [500.5-1517.8]	.33

Note: Data represented as n (%), median [interquartile range], or mean ± standard deviation.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; FSGS, focal segmental glomerulosclerosis; HBV, hepatitis B virus.

TABLE 2 Primary and secondary outcomes

Outcome	No hepatitis B prophylaxis (n = 147)	Hepatitis B prophylaxis (n = 14)	p-value
HBV reactivation	5 (3.4%)	1 (7.1%)	.43
Appropriate antiviral dosing	-	11 (78.6%)	-
Time to HBV reactivation (days)	108.0 [4.0–356.0]	1568.0	.29
Liver enzymes at time of reactivation (n = 4)			
AST (IU/L)	25.8 ± 12.2	25.0	.96
ALT (IU/L)	34.4 ± 26.0	26.0	.78
Alkaline phosphatase (IU/L)	74.0 ± 37.4	51.0	.60
Total bilirubin (mg/dl)	0.4 ± 0.1	1.8	< .001
One-year death censored graft survival	140 (95.9%)	14 (100.0%)	> .99
BPAR	23 (15.8%)	2 (14.3%)	> .99
Borderline	13 (56.5%)	1 (50.0%)	
Banff 1a	5 (21.7%)	0	
Banff 2a	3 (13.0%)	1 (50.0%)	
Banff 2b	1 (4.3%)	0	
Banff 3	1 (4.3%)	0	
Antibody-mediated rejection	3 (2.0%)	0	> .99
One-year all-cause mortality	4 (2.7%)	0	> .99

Note: Data represented as n (%), median [interquartile range], or mean ± standard deviation.

Abbreviations: HBV, hepatitis B virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BPAR, biopsy-proven acute rejection.

2%.¹⁶ Similarly, previous studies have demonstrated an HBV reactivation incidence ranging from 1% to 10% in this specific kidney transplant population.^{10–13,17} Given the historical data and the results of our study, we suggest that standard maintenance immunosuppression post kidney transplantation may not significantly increase the risk for HBV reactivation. However, it is important to note that our multicenter retrospective study did not evaluate overall glucocorticoid exposure, which future studies should aim to report. But it is the authors' opinion that since the median days to HBV reactivation in the non-prophylaxis group and the prophylaxis group were 108 and 1568 days, respectively, these patients would have been on minimal doses of oral prednisone. Although there seemed to be a trend toward a higher prevalence of HBV reactivation in the group that did receive hepatitis B antiviral prophylaxis (7.1%), compared to the non-prophylaxis group (3.4%), this was not statistically significant. Additionally, the sample sizes varied significantly between the groups, with only 14 patients in the prophylaxis group and 147 patients in the non-prophylaxis group, which may

have skewed the data. Interestingly, of the six patients experiencing HBV reactivation, only two patients had quantitative HBV viral loads. The HBV viral load of the remaining four patients, including one of the patients on antiviral prophylaxis, was detected but at the minimum detection level and was not quantified.

A group of Japanese investigators reviewed 52 patients with resolved HBV infection who underwent kidney transplantation and found that age and anti-HBc titer to be significant risk factors for HBV reactivation.¹² Our study did not evaluate anti-HBc titers, and we did not find age to be a significant risk factor for reactivation. However, we did find delayed graft function to be a significant predictor of HBV reactivation. This may be explained by the increased incidence of HBV acquired in dialysis centers.¹⁸ We acknowledge that our study was not powered to detect significant factors associated with HBV reactivation; however, our study contained a larger sample size than the study by Mei et al.¹² There were a few other notable differences observed between and within the groups. Of the 14 patients in the prophylaxis

TABLE 3 Demographic and clinical outcomes of HBV reactivation cases

Case	Age	Race	Anti-HBs status (quant, mIU/ml)	DGF	Induction IS	Antiviral ppx (Y/N)	Time to antiviral initiation (days)	Time to reactivation (days)	HBV viral load (IU/ml)	HBV flare*	Treatment of HBV infection	Liver compli-cation	1-year mortality
1	68	Asian	R (120.0)	Y	Basiliximab	Y	12	1568	<20	N	No antiviral treatment; HBV lab monitoring initiated	N	N
2	66	Asian	NR (< 2.5)	Y	ATG	N	7	4	22	N	Entecavir started on POD 7	N	N
3	62	Asian	R (86.9)	Y	ATG	N	ND	356	<20	N	No antiviral treatment; HBV lab monitoring initiated	N	N
4	61	Caucas:	NR (2.6)	Y	ATG	N	150	108	22	N	Entecavir started POD 150; switched to TAF POD 198	Y; fibro-sis stage F3# (diag-nosed POD 143); cir-rhosis	N
5	53	Hispanic	R (722.0)	Y	ATG	N	ND	1204	<10	N	ND	N	N
6	30	Black	R (230.0)	N	ATG	N	ND	2	<20	N	ND	N	N

Abbreviations: Anti-HBs, hepatitis B surface antibody; Quant, quantitative; DGF, delayed graft function; IS, immunosuppression; ppx, prophylaxis; HBV, hepatitis B virus; R, reactive; NR, non-reactive; ATG, anti-thymocyte globulin; Y, yes; N, no; POD, post-operative day; TAF, tenofovir alafenamide; ND, no data available.

*HBV flare defined as HBV reactivation plus an elevation in liver enzymes 2–3x the normal limit.

#Stage F3 liver fibrosis on the Metavir histological index of grading fibrosis, indicating severe liver fibrosis.

group who did not experience HBV reactivation, 10 (71.4%) had quantitative anti-HBs concentrations greater than 10 mIU/ml. It is established that anti-HBs concentrations of 10 mIU/ml or higher after vaccination provides protection against hepatitis B infection in immunocompetent patients. Furthermore, vaccines are recommended in immunocompromised patients to maintain anti-HBs concentrations of 10 mIU/ml or higher.¹⁹ Moreover, the results of a retrospective study of 1959 patients by Jeon et al. suggest that the presence of anti-HBs confers protection against HBV in patients undergoing kidney transplantation.¹⁷ Interestingly, of the five patients who experienced HBV reactivation in the non-prophylaxis group, three had reactive anti-HBs titers with concentrations of 86 mIU/ml, 722 mIU/ml, and 230 mIU/ml, well above the protective level defined of 10 mIU/ml. Although our study is limited in size, the results suggest that protective anti-HBs concentrations in immunocompromised kidney transplant recipients may not be protective as they are in immunocompetent individuals.

While the reactivation rate appeared higher in the group receiving hepatitis B prophylaxis, it is important to note that these patients' HBV

DNA PCR did not reflect a high viral load, and there was no sign of a hepatitis flare, which was defined per AASLD guidelines as an ALT increase ≥ 3 times baseline and > 100 U/L.⁸ Additionally, no patient who experienced our primary outcome developed sequelae such as graft loss or death. However, one patient who did not receive antiviral prophylaxis was diagnosed with Stage F3 liver fibrosis on the Metavir histological index of grading fibrosis, indicating severe liver fibrosis. This patient developed HBV reactivation on post-operative day 108 with an HBV viral load of 22 mIU/ml, however, was not initiated on antiviral therapy immediately due to low-level viremia and normal liver function tests (aspartate aminotransferase (AST) 11 IU/L, ALT 8 IU/L, alkaline phosphatase 47 IU/L, and total bilirubin 0.3 mg/dl). The patient was referred to a hepatologist and a liver ultrasound (Fibroscan) was ordered, which revealed severe fibrosis. Antiviral treatment with entecavir was initiated for the patient 150 days after transplantation; however, entecavir was later switched to tenofovir alafenamide due to intolerance. With ongoing follow-up, the patient's liver disease has progressed to cirrhosis; however, it is well-compensated to date. It is the

TABLE 4 Logistic regression

Parameter	HBV reactivation (n = 6)	No HBV reactivation (n = 155)	Univariate p-value	Multivariate p-value
Age (years)	56.7 ± 14.1	59.7 ± 10.2	.48	.29
Asian	3 (50.0%)	54 (34.8%)	.67	–
HBV vaccine pre-transplant	1 (16.7%)	41 (26.5%)	> .99	–
Anti-HBs reactive pre-transplant	4 (66.7%)	124 (80.0%)	.60	–
Quantitative anti-HBs	44.8 [0.7-194.2]	96.9 [13.4-397.1]	.47	–
Delayed graft function	5 (83.3%)	53 (34.2%)	.02	.03
Induction IS				
Anti-thymocyte globulin	5 (83.3%)	117 (75.5%)	> .99	–
Basiliximab	1 (16.7%)	26 (16.8%)	> .99	–
Prednisone maintenance	6 (100.0%)	136 (87.7%)	> .99	–
HBV prophylaxis	1 (16.7%)	13 (8.4%)	.42	.36
Rejection of any type	1 (16.7%)	24 (15.5%)	> .99	–
Treatment for rejection				
High-dose corticosteroids				
Anti-thymocyte globulin	1 (16.7%)	17 (11.0%)	.51	–
Anti-thymocyte globulin	0	5 (3.2%)	> .99	–
IVIg	1 (16.7%)	3 (1.9%)	.14	> .99

Note: Data represented as n (%), median [interquartile range], or mean ± standard deviation.

Abbreviations: HBV, hepatitis B virus; IS, immunosuppression; IVIG, intravenous immune globulin.

authors' opinion that HBsAg-negative anti-HBc-positive kidney transplant recipients should receive routine follow-up with a hepatologist for close follow-up, routine monitoring of liver function tests, and treatment of HBV reactivation if needed. This may prevent delays in appropriate testing and minimize the risk for hepatic complications such as fibrosis or cirrhosis.

The authors of the study do acknowledge limitations of the study design including the retrospective nature and inability to control for confounding factors such as hepatitis B vaccination administration, tacrolimus trough concentrations, immunosuppression dosing, and inappropriate entecavir dosing. Our study population was robust with 161 patients; however, only 14 of these patients received antiviral prophylaxis which limited our ability to match the cohorts.

5 | CONCLUSION

In summary, our study found that the prevalence of HBV reactivation in HBsAg-negative anti-HBc-positive kidney transplant recipients is low, and there is a low incidence of significant clinical implications with

appropriate medical follow-up. Based on our results, monitoring of liver enzymes and viral load may be the best approach for both practitioners and patients rather than using antiviral prophylaxis targeted toward HBV. The authors of this study also recommend that HBsAg-negative anti-HBc-positive kidney transplant recipients should receive routine follow-up with a hepatologist. With already complicated medication regimens post transplant, this approach minimizes polypharmacy and cost-sharing of antiviral medications for kidney transplant recipients. Larger prospective studies with matched groups are warranted to evaluate the true impact hepatitis B antiviral prophylaxis has on this population of kidney transplant recipients.

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CONFLICT OF INTEREST

All authors declare no potential sources of conflict of interest.

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REFERENCES

- Smalls DJ, Kiger RE, Norris LB, et al. Hepatitis B virus reactivation: risk factors and current management strategies. *Pharmacotherapy*. 2019;39(12):1190-1203.
- Aroldi A, Lampertico P, Montagino G, et al. Natural history of hepatitis B and C in renal allograft recipients. *Transplantation*. 2005;79:1132-1136.
- Lok ASF. Hepatitis B virus: clinical manifestations and natural history. In: Post T, ed. *UpToDate*. Waltham, MA: UpToDate; 2016. Accessed March 24, 2021. <http://www.uptodate.com>.
- Pawlowska M, Flisiak R, Gil L, et al. Prophylaxis of hepatitis B virus (HBV) infection reactivation—recommendations of the working group for prevention of HBV reactivation. *Clin Exp Hepatol*. 2019;5(3):195-202.
- Marinaki S, Koluvou K, Sakellariou S, et al. Hepatitis B in renal transplant patients. *World J Hepatol*. 2017;9(25):1054-1063.
- Kim J, Chung SJ, Sinn DH, et al. Hepatitis B reactivation after kidney transplantation in hepatitis B surface antigen-negative, core antibody-positive recipients. *J Viral Hepat*. 2020;27(7):739-746.
- Terrault NA, Bzowej NH, Chang KM, et al. AASLD Guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;6(1):261-283.
- Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560-1590.
- Hoofnagle JH. Reactivation of hepatitis B. *Hepatology*. 2009;49:S156-S165.
- Querido S, Wiegert A, Adragao T, et al. Risk of hepatitis B reactivation in hepatitis B surface antigen seronegative and core antibody seropositive kidney transplant recipients. *Transpl Infect Dis*. 2019;21:e13009.
- Jeon JW, Kim SM, Cho H, et al. Presence of hepatitis B surface antibody in addition to hepatitis B core antibody confers protection against hepatitis B virus infection in hepatitis B surface antigen-negative patients undergoing kidney transplantation. *Transplantation*. 2018;102(10):1717-1723.
- Mei T, Noguchi H, Hisadome Y, et al. Hepatitis B virus reactivation in kidney transplant patients with resolved hepatitis B virus infection: risk factors and the safety and efficacy of preemptive therapy. *Transpl Infect Dis*. 2020;22:e13234.
- Chen GD, Gu JL, Qiu J, Chen LZ. Outcomes and risk factors for hepatitis B (HBV) reactivation after kidney transplantation in occult HBV carriers. *Transpl Infect Dis*. 2013;15:300-305.
- Te H, Doucette K. Viral hepatitis: guidelines by the American society of transplantation infectious disease community of practice. *Clin Transplant*. 2019;33(9):e13514.
- Sasadeusz J, Grigg A, Hughes PD, et al. Screening and prophylaxis to prevent hepatitis B reactivation. *Clin Liver Dis*. 2019:493-509.
- MacLachlan JH, Cowie BC. Hepatitis B virus epidemiology. *Cold Spring Harb Perspect Med*. 2015;5(5):a021410.
- Jeon JW, Kim SM, Cho H, et al. Presence of hepatitis B surface antibody in addition to hepatitis B core antibody confers protection against hepatitis B virus infection in hepatitis B surface antigen-negative patients undergoing kidney transplantation. *Transplantation*. 2018;102(10):1717-1723.
- Edey M, Barraclough K, Johnson DW. Review article: hepatitis B and dialysis. *Nephrology*. 2010;15(2):137-145.
- Damme PV, Ward JW, Shouval D, Zanetti A. 25-Hepatitis B vaccines. In: Plotkin SA, Orenstein WA, Offit PA, Edwards KA (eds.). *Plotkin's Vaccines*. Elsevier; 2018:342-374.

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