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HBsAg (−)/HBsAb (−)/HBeAg (−)/HBeAb (+)/HBcAb (+) predicts a high risk of hepatitis B reactivation in patients with B-cell lymphoma receiving rituximab based immunochemotherapy

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Abstract

Patterns of hepatitis B virus reactivation (HBV-R) in HBsAg (−)/HBcAb (+) patients with B-cell non-Hodgkin lymphoma (NHL) receiving rituximab based immunochemotherapy have not been well described. The retrospective study included 222 HBsAg (−)/HBcAb (+) NHL patients as training cohort and 127 cases as validation cohort. The incidence of HBV-R in HBsAg (−)/HBcAb (+) B-cell NHL patients was 6.3% (14/222), of which that in HBsAg (−)/HBsAb (−)/HBeAg (−)/HBeAb (+)/HBcAb (+) population was 23.7% (9/38). Multivariate analysis showed that HBsAg (-)/HBsAb (−)/HBeAg (−)/HBeAb (+)/HBcAb (+) correlated with a high risk of HBV-R in B-cell lymphoma patients (training phase hazard ratio [HR], 10.123; 95% confidence interval [CI], 3.389–30.239; $p < 0.001$; validation phase HR, 18.619; 95% CI, 1.684–205.906; $p = 0.017$; combined HR, 12.264; 95% CI, 4.529–33.207; $p < 0.001$). In the training cohort, the mortality rate of HBsAg (−)/HBcAb (+) B-cell NHL caused by HBV-R was 14.3% (2/14) while that for HBV reactivated HBsAg (-)/HBsAb (−)/HBeAg (−)/HBeAb (+)/HBcAb (+) population was up to 44.4% (4/9). As a high incidence of HBV-R and high mortality after HBV-R was found in HBsAg (−)/HBsAb (−)/HBcAb (+)/HBeAg (−)/HBeAb (+) patients with B-cell NHL receiving rituximab based immunochemotherapy, prophylactic antiviral therapy is recommended for these patients.

KEYWORDS

B-cell lymphoma, HBcAb, HBsAg, hepatitis B virus reactivation, rituximab

1 | INTRODUCTION

As a double-stranded DNA virus, hepatitis B virus (HBV) infection has reached global epidemic, varying between 2% in Europe to above 10% in East Asia.[1] China has historically been regarded as a highly endemic region for chronic HBV infection, and it has a large number of population with resolved HBV infection accounting for about 1/3 of people infected with HBV worldwide.[2,3] HBV reactivation (HBV-R) is a serious complication in patients with chronic HBV infection during or after cytotoxic chemotherapy or immunosuppressive

Li-Ping Shui and Yan Zhu contributed equally to this study.

treatment, with variable clinical outcomes, from asymptomatic to acute liver failure and death. HBV-R in those patients may correlate with a high mortality rate (up to 50%) even if anti-HBV therapy is initiated upon viral reactivation, and the interruption or premature discontinuation of chemotherapy may negatively influence patient survival.[4,5] The incidence of HBV-R in HBsAg(+) patients receiving therapy ranges from 20% to 65% and between 1.0% and 41.5% in those with HBsAg (−)/HBcAb (+), respectively,[5–14] which is likely due to the hepatotropic and lymphotropic nature of HBV assuring HBV replication in lymphoid tissue.[15,16] HBV-R has been most reported in patients with hematologic malignancies who received chemotherapy and underwent hematopoietic stem cell transplants.[17–19] A R-CHOP like regimen containing rituximab, anthracyclines, cyclophosphamide, vincristine, and prednisone is currently considered as standard first-line B-cell NHL therapy, attracting the attention to HBV reactivation in concerned patients.[5,20–24]

Considering the high risk of HBV-R in HBsAg (+) patients with lymphoma, there is a clinical consensus on the prophylactic use of antiviral drugs in these patients one week before chemotherapy.[25–27] HBsAg (−)/HBcAb (+) patients have a lower incidence of HBV-R compared to HBsAg (+) patients, but the prevalence of HBcAb (between 5% in Western and >50% in Far Eastern countries) is higher than that of HBsAg [28,29] with the proportion of HBsAg (−)/HBcAb (+) in NHL patients at 20%–44%.[5,30] Numerically many cases then experienced HBV exacerbations in HBsAg (−)/HBcAb (+) patients who receive immunosuppressive regimens.[27] Although prophylactic anti-HBV nucleos(t)ide analog therapy (NAT) remains one of the rational strategies for preventing HBV-R,[24,31–33] it would produce excessive budget pressure of public health care since more than 1/3 of the world's population is exposed to HBV, and the majority of these individuals reside in endemic areas, such as Southeast Asia, African Region, the Western Pacific regions, and Eastern Mediterranean Region. Therefore, seeking predictors for HBV-R and stratification of the risk of HBV-R among HBsAg (−)/HBcAb (+) patients are needed. Previous guidelines have recommended heterogeneously for the assessment of HBV-R in HBsAg (−)/HBcAb (+) patients with NHL after chemotherapy, particularly regarding patient selection for testing and choice of prophylactic antiviral therapy. Thus, studies are warranted to optimize clinical care paths for these patients and to establish a balance between clinical effectiveness and cost-effectiveness which will help to frame related public policy.

Although several guidelines recommend that HBsAg (−)/HBcAb (+) patients on drugs targeting B lymphocytes like rituximab be administered anti-HBV prophylaxis,[25,27,34] recent studies have shown that HBsAg (−)/HBcAb (+) patients after rituximab treatment had less HBV-R without prophylactic antiviral therapy.[35,36] It is essential to compare the efficacy and cost-effectiveness of different managing strategies (prophylactic anti-HBV therapy vs. regular HBV DNA monitoring). Antiviral prophylaxis or regular follow-up with HBV DNA testing and preemptive anti-HBV treatment can be an alternative for these patients,[31,37,38] but these strategies may bring about a heavy burden on HBV endemic area with limited health resources or may cause overexposure to antiviral therapy. Therefore, we conducted a retrospective study to identify risk factors and elucidate optimal prevention and treatment of HBV-R in HBsAg (−)/HBcAb (+) B-cell NHL patients treating with rituximab containing chemotherapy.

2 | PATIENTS AND METHODS

We performed a retrospective study of B-cell NHL patients at Department of Hematology of the First affiliated Hospital of Chongqing Medical University between October 1, 2014 and May 31, 2020. The inclusion criteria were as follows: patients initially with HBsAg (−)/HBcAb (+) and receiving at least three cycles of chemotherapy. HBsAg (−)/HBcAb (+) patients receiving rituximab; the exclusion criteria included HBsAg (−)/HBcAb (+) with detectable HBV DNA before chemotherapy; rare cases with HBeAg (+)/HBsAg (−)/HBcAb (+); prophylactic antiviral therapy in cases with HBsAg (−)/HBcAb (+); concomitant chronic liver disease due to chronic hepatitis C and D viral infection; Wilson's disease; autoimmune hepatitis; primary biliary cirrhosis; significant intake of alcohol (20 g per day for women, 30 g per day for men); history of cancer other than B-cell NHL and incomplete data. B-cell NHL patients from Department of Hematology, Southwest Hospital, Third Military Medical University (Army Medical University) during the same time period was used as validation cohort.

HBV vaccinations scheduled at 0, 1, and 6 months of age had been given to all patients in accordance with National immunization program in China. No patients were immunized with any extra HBV vaccinations before and after chemotherapy. The study was approved by the Research Ethics Commission at The First Affiliated Hospital of Chongqing Medical University, and written informed consent was waived due to a retrospective analysis of existing laboratory and clinical data by the Ethics Committees.

2.1 | Definition of HBV-R and hepatitis flare

Time to HBV-R was calculated as the time from the beginning day of chemotherapy to the day of HBV-R detection. For HBsAg (−)/HBcAb (+) patients, the following criteria are reasonable for HBV-R[26]: (i) HBV DNA is detectable or (ii) reverse HBsAg seroconversion occurs (reappearance of HBsAg). A hepatitis flare is reasonably defined as an alanine transaminase (ALT) increase to ≥3 times the baseline level and >100 U/L.[26]

2.2 | Laboratory measurements and preemptive antiviral therapy

The levels of HBsAg, HBsAb, HBeAg, HBeAb and HBcAb were evaluated using enzyme immunoassays via CMIA (Abbott Laboratories). A quantification of HBsAg <0.05 IU/mL and HBsAb <10.00 mIU/mL were defined as negativity. The upper limit of HBsAg and HBsAb detection was 25 000 and 1000 mIU/mL,

respectively. The HBeAg and HBcAb levels were qualitatively evaluated with minimum sensitivities of 1 S/CO. Qualitative detection of HBeAb by competitive two-step method, the S/CO ratios of HBeAb ≥1.00 were defined as negativity, HBeAb was positive when the titer is low (HBeAb <1.00).

HBV DNA was measured in serum using a quantitative, real-time polymerase chain reaction (PCR) assay (HBV nucleic acid quantitative detection kit, TaqMan HBV PCR assay) with the lower limit of quantitation of 1000 IU/mL since 2014. From March 2017, high-sensitivity HBV-DNA assay with a lower limit of 100 IU/mL was introduced. The former is to extract samples of nucleic acid by hand, while the latter is to extract nucleic acid by magnetic beads which would be more sensitive. These HBV-related markers of all enrolled patients were investigated monthly for 6–8months, every 3 months in the first year, and then every 3–6months later. Preemptive anti-HBV NAT was initiated immediately when HBV reactivation was diagnosed.

2.3 | Statistical analysis

The primary study endpoint of the analysis was to evaluate the HBV-R rate in HBsAg (−)/HBcAb (+) who receiving rituximab based immunochemotherapy. Secondary study endpoint was to assess factors related to HBV-R and survival of HBV-R B-cell NHL patients. All patients were followed up until May 31, 2021. Risk factors considered in the univariable analysis included age (≤60 vs. >60 years), sex (female/male), drinking history (yes/no), diagnosis (diffuse large B-cell lymphoma [DLBCL]/marginal zone lymphoma [MZL]/follicular lymphoma [FL]/others), response assessment at the end of follow-up (complete remission [CR]/partial remission [PR] vs. stable disease [SD]/progression disease [PD]) by the Lugano criteria,[39] B-cell lymphoma staging (stage I/II vs. III/IV), B symptoms (fever/weight loss/sweats, no), international prognostic index (IPI) score (0–2 vs. 3–5), types of chemotherapy regimens (corticosteroid vs. noncorticosteroid containing; cyclophosphamide vs. noncyclophosphamide containing; anthracycline vs. non anthracycline containing), autologous hematopoietic stem cell transplantation (auto-HSCT) (yes/no), radiotherapy (yes/no), baseline HBsAb status (positive vs. negative), baseline HBeAb status (positive vs. negative) and lactate dehydrogenase (LDH) (normal vs. high). The cumulative incidence of HBV-R was estimated by Kaplan–Meier (K–M) method. Univariate analyses and multivariable influences on the risk of HBV reactivation and clinical outcomes were determined using Cox regression analysis. All variables with p value below 0.2 from univariate models were then considered in the multivariate model (stepwise model). All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS®) ver.26.0 (SPSS Inc). A two-sided $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

A total of 1095 patients were screened between October 2014 and May 2020. After 873 patients were excluded, the retrospective study enrolled 222 HBsAg (−)/HBcAb (+) B-cell NHL patients for the present analysis (Figure 1). The median age of patients at diagnosis

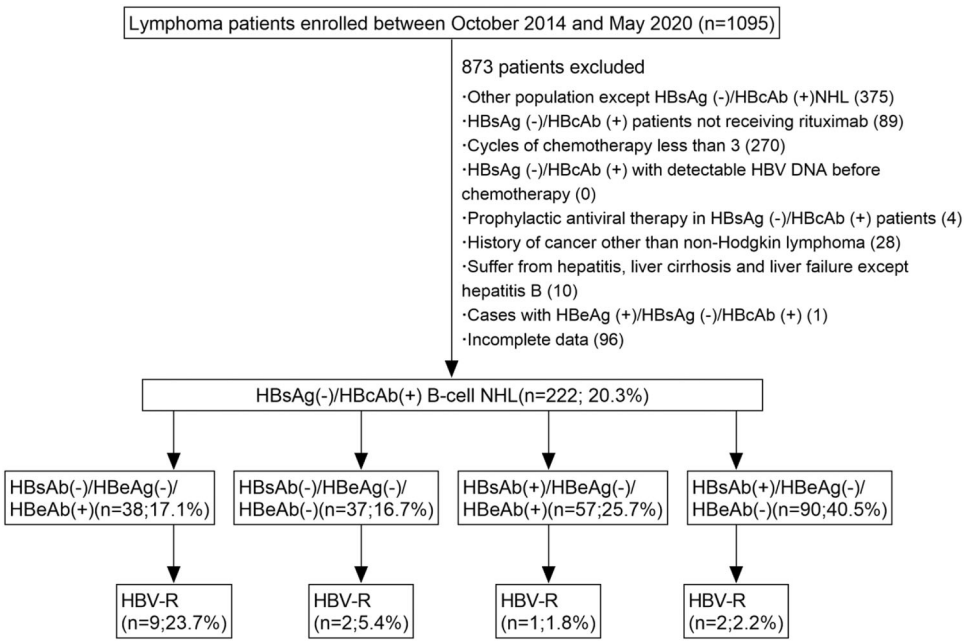

FIGURE 1 Flow chart of patient enrollment and follow-up in the training cohort. HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV-R, hepatitis B virus reactivation.

was 53 years old (range, 16–85 years) in the study. One hundred and fourteen (51.4%) patients were males. One hundred and seventy-four (78.4%) patients were diagnosed as diffuse large B-cell lymphoma (DLBCL) with 17 (7.7%) patients for follicular lymphoma (FL) and 16 (7.2%) patients for marginal zone lymphoma (MZL). The average cycles of chemotherapy were six (range, 3–22). One hundred and forty-seven of 222 (66.2%) HBsAg (−)/HBcAb (+) patients were HBsAb (+). Of the 222 HBsAg (−)/HBcAb (+) patients, one hundred and fifty-six had undetectable serum HBV-DNA ($<10^2$ or $<10^3$ IU/mL) at baseline and the left had no baseline values. Fourteen (6.3%) patients developed HBV-R and 36 (16.2%) of 222 patients died (Table 1) during the follow-up period. Table 1 presents the patient and disease characteristics, and HBsAb, HBeAg, and HBeAb status.

TABLE 1 Baseline characteristics of B-cell NHL patients.

Characteristic	All patients 349(%)	HBsAg (−)/HBcAb (+) Training *n* = 222(%)	Validation *n* = 127(%)
Gender (male)	188 (53.9)	114 (51.4)	74 (58.2)
Age (>60)	149 (42.7)	106 (47.7)	43 (33.8)
Drinking	93 (26.6)	58 (26.1)	35 (27.5)
Diagnosis			
DLBCL	264 (75.6)	174 (78.4)	90 (70.9)
FL	27 (7.7)	17 (7.7)	10 (7.8)
MZL	26 (7.4)	16 (7.2)	10 (7.8)
Others[a]	32 (9.2)	15 (6.8)	17 (13.5)
Primary disease (SD/PD)	159 (45.6)	98 (44.1)	61 (48.0)
Stage III to IV	228 (65.3)	156 (70.3)	72 (56.6)
B symptoms	104 (29.8)	66 (29.7)	38 (29.9)
IPI score (3-5)	122 (35.0)	84 (37.8)	38 (29.9)
Chemotherapeutic drugs			
Steroids containing	337 (96.6)	216 (97.3)	121 (95.2)
Anthracycline containing	333 (95.4)	215 (96.8)	118 (92.9)
Cyclophosphamide containing	340 (97.4)	218 (98.2)	122 (96.0)
Cycles of chemotherapy (>6)	184 (52.7)	122 (55.0)	62 (48.8)
Auto-HSCT	42 (12.0)	31 (14.0)	11 (8.6)
Radiotherapy	15 (4.3)	2 (0.9)	13 (10.2)
Elevated LDH	157 (45.0)	118 (53.2)	39 (30.7)
HBsAb (+)	243 (69.6)	147 (66.2)	96 (75.5)
HBeAg (+)	0 (0.0)	0 (0.0)	0 (0.0)
HBeAb (+)	149 (42.7)	95 (42.8)	54 (42.5)
HBsAb(−)/HBeAg(−)/HBeAb(+)	52 (14.9)	38 (17.1)	14 (11.0)
HBsAb(−)/HBeAg(−)/HBeAb(−)	54 (15.5)	37 (16.7)	17 (13.4)
HBsAb(+)/HBeAg(−)/HBeAb(+)	97 (27.8)	57 (25.7)	40 (31.5)
HBsAb(+)/HBeAg(−)/HBeAb(−)	146 (41.8)	90 (40.5)	56 (44.1)
HBV-R	17 (4.9)	14 (6.3)	3 (2.4)
Death toll	59 (16.9)	36 (16.2)	23 (18.1)

Abbreviations: Auto-HSCT, autologous hematopoietic stem cell transplantation; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HBV-R, hepatitis B virus reactivation; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; IPI, international prognostic index; LDH, lactate dehydrogenase; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PD, progression disease; SD, stable disease.

[a]Other lymphomas including mantle cell lymphoma, Burkitt lymphoma, and B-cell lymphoblastic lymphoma.

3.2 | Incidence of HBV-R

Of the 222 HBsAg (−)/HBcAb (+) patients, fourteen patients (6.3%) developed HBV-R at a median of 67 days (range, 20–378) after chemotherapy. Ten of these HBV-R patients were male, and 11 patients were HBsAb (−). Eleven patients with HBV-R were diagnosed as DLBCL. HBsAg reappearance (seroreversion) happened in 5 patients. HBV DNA elevation (>2 log10) occurred in 9 patients in HBsAg (−)/HBcAb (+) patients with a cumulative HBV-R rates at months 6, 12, and 18 after chemotherapy of 4.5%, 5.9%, and 6.3% without prophylaxis. Among these HBV-R patients, the median HBV-DNA level was 5.91×10^3 IU/mL (range, $<10^3$–5.06×10^8 IU/mL) with HBV-DNA levels higher than 1.0×10^6 IU/mL in five patients. Fourteen HBV-R patients were treated with entecavir, and six (26.7%) patients developed hepatitis flares, including two patients with liver failure. Two HBV-R patients achieved serologic clearance of HBV with persistent HBsAb(+) detected.

3.3 | Risk factors of HBV-R in HBsAg (−)/HBcAb (+) B-cell NHL patients

On univariate analysis, HBsAb (−) ($p = 0.002$), HBeAb (+) ($p = 0.033$) and HBsAb (−)/HBeAg (−)/HBeAb (+) ($p < 0.001$) (Figure 2) were associated with high incidence of HBV-R in HBsAg (−)/HBcAb (+) B-cell NHL patients (Table 2). In HBsAg (−)/HBcAb (+) B-cell NHL patients, after multivariate analysis, HBsAb (−)/HBeAg (−)/HBeAb (+) (hazard ratio [HR], 10.123; 95% confidence interval [CI], 3.389–30.239; $p < 0.001$) was associated with higher risk of HBV-R (Table 2). HBsAb (−)/HBeAg (−)/HBeAb (+) accounts for 17.1% (38/222) of HBsAg (−)/HBcAb (+) patients. Nine (23.7%) patients developed HBV-R in 38 HBsAb (−)/HBeAg (−)/HBeAb (+) B-cell NHL patients, and 4 of 9 patients had hepatitis flares. The mortality after HBV-R was 44.4% (4/9) in HBsAb (−)/HBeAg (−)/HBeAb (+) B-cell NHL patients.

3.4 | ROC curve analysis of baseline HBsAb/HBeAb/HBcAb levels predicting HBV-R in HBsAg (−)/HBcAb (+) B-cell NHL patients

Baseline HBsAb/HBeAb/HBcAb levels were measured in 222 patients with enough serum samples. The median levels of HBsAb, HBeAb and HBcAb were 29.54 mIU/mL (range: 0–1000), 1.225 S/CO (range: 0.01–99.75) and 5.415 S/CO (range: 1.01–543.52), respectively. The ROC analysis of baseline HBsAb/HBeAb/HBcAb levels implied that the optimal cutoff value to predict HBV-R in these patients were 14.33 mIU/mL for HBsAb, 0.025 S/CO for HBeAb and 8.455 S/CO for HBcAb. Low HBsAb (<14.33 mIU/mL), low HBeAb (<0.025 S/CO) (HBeAb was positive) and high HBcAb (≥8.455 S/CO) was associated with a significantly higher risk of HBV-R ($p < 0.001$) (Supporting Information: Table S1). The cumulative incidence of HBV-R at 450 days was 75.0% for the high-risk patients (HBsAb <14.33 mIU/mL, HBeAb <0.025 S/CO and HBcAb ≥8.455 S/CO) and 0.0–18.7% in other patients (Figure 3).

3.5 | Validation phase

We analyzed 127 patients of HBsAg (−)/HBcAb (+) B-cell NHL patients at Southwest Hospital, Third Military Medical University who received rituximab based immunochemotherapy without preventive antiviral therapy as validation cohort (Table 1). Three (2.4%) patients developed HBV-R at a median of 713 days (range, 85 to 910) after diagnosis. On univariate analysis, HBsAb (−)/HBeAg (−)/HBeAb (+) ($p = 0.017$) were associated with high incidence of HBV-R in HBsAg (−)/HBcAb (+) B-cell NHL patients (Supporting Information: Table S2). HBsAb (−)/HBeAg (−)/HBeAb (+) accounts for 11% (14/127) of HBsAg (−)/HBcAb (+) patients. Two (14.3%) developed HBV-R in 14 HBsAb (−)/HBeAg (−)/HBeAb (+) B-cell NHL patients. All variables with $p < 0.2$ (Anthracycline containing, HBsAb(−) and HBsAb (−)/HBeAg(−)/HBeAb(+) type) in the univariate model were included

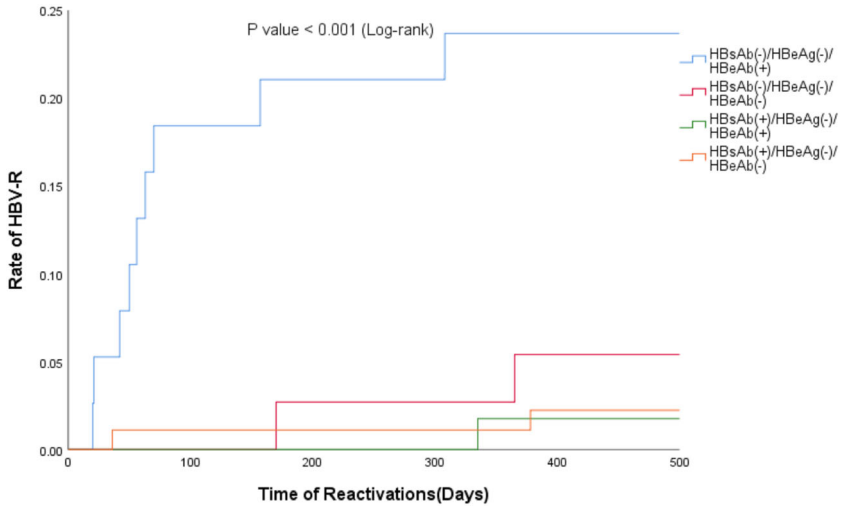

FIGURE 2 Kaplan–Meier HBV-R curve analysis of HBsAg (−)/HBcAb (+) B-cell non-Hodgkin lymphoma (NHL) patients in the training cohort. HBsAb (−)/HBeAg (−)/HBeAb (+) population were associated with a higher risk of HBV-R in HBsAg (−)/HBcAb (+) B-cell NHL patients. HBV-R, hepatitis B virus reactivation.

TABLE 2 Univariable and multivariable analyses of factors associated with HBV-R in the training cohort.

Variables	Univariable HR [95%CI]	*p* Value	Multivariable HR [95%CI]	*p* Value
Sex (male)	2.435 [0.763–7.763]	0.133		
Age (>60)	1.498 [0.520–4.318]	0.454		
Drinking	1.134 [0.356–3.617]	0.831		
Diagnosis				
DLBCL	ref	ref		
MZL	0.993 [0.128–7.688]	0.994		
FL	0.953 [0.123–7.379]	0.963		
Others[a]	1.082 [0.140–8.382]	0.940		
Primary disease (SD/PD)	1.051 [0.365–3.028]	0.927		
Stage (III/IV)	1.598 [0.446–5.730]	0.471		
B symptoms	1.771 [0.614–5.104]	0.29		
IPI score (3-5)	1.519 [0.4764–.844]	0.48		
Steroids containing	2.980 [0.389–22.799]	0.293		
Anthracycline containing	21.094 [0–12345915.220]	0.653		
Cyclophosphamide containing	4.778 [0.623–36.626]	0.132		
Cycles of chemotherapy (>6)	1.632 [0.566–4.704]	0.364		
Auto-HSCT	1.003 [0.224–4.482]	0.997		
Radiotherapy	20.370 [0–810949874339.696]	0.809		
Elevated LDH	1.613 [0.541–4.813]	0.391		
HBsAb(−)	7.731 [2.156–27.720]	0.002		
HBeAb(+)	3.521 [1.104–11.228]	0.033		
HBsAb(−)/HBeAg(−)/HBeAb(+) vs. others[b]				
	10.123 [3.389–30.239]	<0.001	10.123 [3.389–30.239]	<0.001

Abbreviations: Auto-HSCT, autologous hematopoietic stem cell transplantation; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, Follicular lymphoma; HBV-R, hepatitis B virus reactivation; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HR, hazard ratio; IPI, international prognostic index; LDH, lactate dehydrogenase; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PD, progression disease; SD, stable disease; ref, reference.

[a]Other lymphomas including mantle cell lymphoma, Burkitt lymphoma, and B-cell lymphoblastic lymphoma.

[b]Other combinations including HBsAb(−)/HBeAg(−)/HBeAb(−), HBsAb(+)/HBeAg(−)/HBeAb(+) and HBsAb(+)/HBeAg(−)/HBeAb(−).

in the multivariate model by stepwise regression method, and HBsAb (−)/HBeAg (−)/HBeAb (+) (18.619; 95% CI, 1.684–205.906; $p = 0.017$) was associated with higher risk of HBV-R (Supporting Information: Table S2).

Of the 349 HBsAg (−)/HBcAb (+) combined cohort (training and validation patients), 17 patients (4.9%) developed HBV-R. On univariate analysis, HBsAb (−) (< 0.001), HBeAb (+) ($p = 0.022$) and HBsAb (−)/HBeAg (−)/HBeAb (+) ($p < 0.001$) were associated with high incidence of HBV-R. After multivariate analysis, HBsAb (−)/HBeAg (−)/HBeAb (+) (HR, 12.264; 95% CI, 4.529–33.207; $p < 0.001$) was associated with higher risk of HBV-R (Supporting Information: Table S3).

3.6 | Hepatitis flare and clinical outcomes of HBsAg (−)/HBcAb (+) B-cell NHL patients

HBV-R occurred in 14 HBsAg (−)/HBcAb (+) B-cell lymphoma patients in the training cohort (Table 3). HBV-R was immediately treated with the anti-HBV drug in 14 patients, but six (42.9%) patients still had hepatitis flares, of which two died of liver failure. Seven of these 14 patients died, the other seven patients remained alive without lymphoma, with a median survival of 760 days (range, 410–1370 days). The mortality after HBV-R was 50.0% (7/14) (primary disease progression, $n = 3$; liver failure, $n = 2$; severe pneumonia, $n = 1$; multiple organ failure, $n = 1$). On univariate analysis, age (>60) ($p = 0.015$), primary disease (SD/PD)

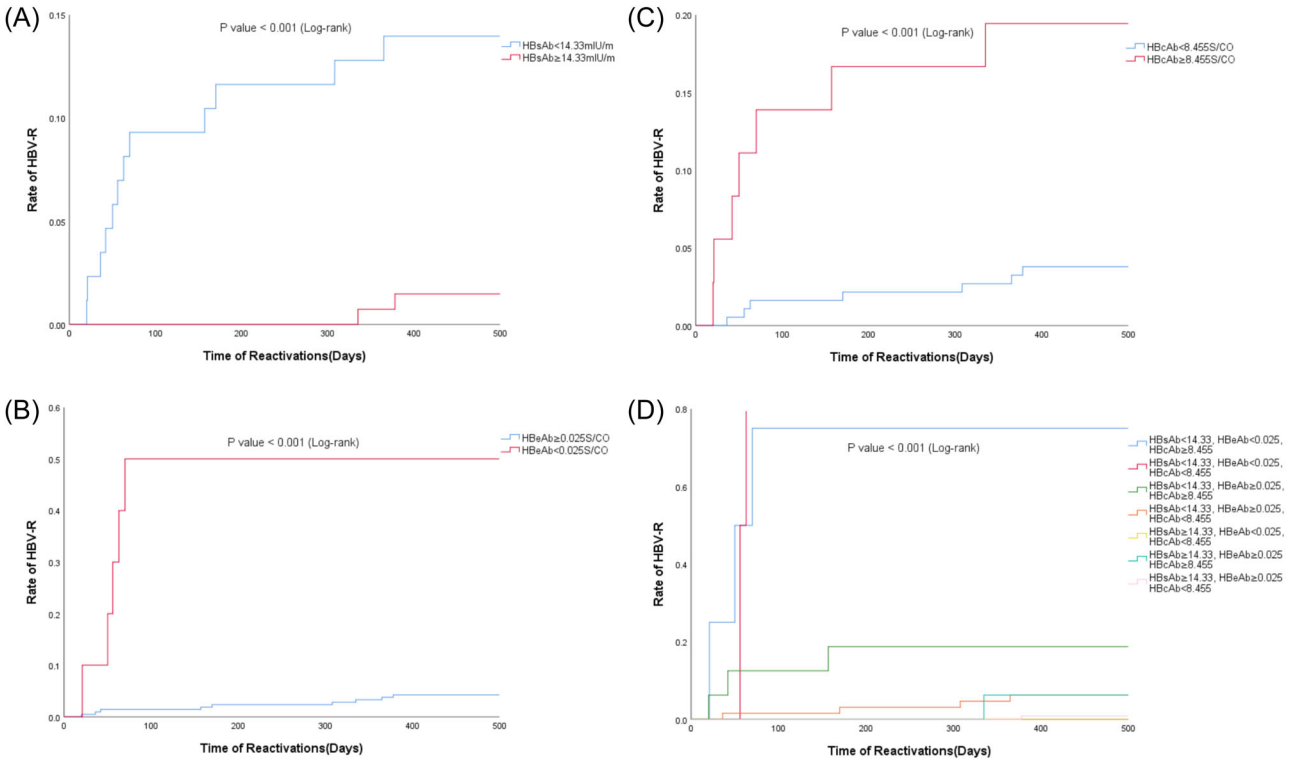

FIGURE 3 Kaplan–Meier curves for time to HBV-R of HBsAg (−)/HBcAb (+) NHL patients in the training cohort, stratified by baseline HBsAb, HBeAb, and HBcAb levels. (A) High (≥14.33 mIU/mL) versus low (<14.33 mIU/mL) HBsAb levels. (B) High (≥0.025 S/CO) versus low (<0.025 S/CO) HBeAb levels (HBeAb was positive when low HBeAb levels). (C) High (≥7.195 S/CO) versus low (<7.195 S/CO) HBcAb levels. (D) Stratified into seven groups based on baseline HBsAb, HBeAb, and HBcAb levels. Group (HBsAb ≥14.33, HBeAb <0.025, and HBcAb ≥8.455), n = 0. HBV-R, hepatitis B virus reactivation.

(p = 0.014), disease stage (III/IV) (p = 0.028), B symptoms (p = 0.001), IPI score (3–5) (p < 0.001), HBsAb(+) (p = 0.027), HBsAb (−)/HBeAg (−)/HBeAb (+) (p = 0.036) and HBV-R (p < 0.001) (Supporting Information: Figure S1) were associated with worse overall survival. Multivariate cox regression analysis indicated that advanced primary disease (SD/PD) (p = 0.015), B symptoms (p = 0.034), and HBV-R (p = 0.005) predicted worse overall survival (Supporting Information: Table S4). After chemotherapy, 124 patients (55.9%) achieved CR/PR with 98 (44.1%) in SD/PD. Thirty-six (16.2%) HBsAg (−)/HBcAb (+) patients died (primary disease progression, n = 23; severe pneumonia, n = 6; septic shock, n = 1; intracranial hemorrhage, n = 1; liver failure, n = 2; multiple organ failure, n = 2; stroke, n = 1). The main cause of death for HBV-R patients and no HBV-R patients were the progression of lymphoma and there was difference between them (p <0.001). Of 127 HBsAg (−)/HBcAb(+) B cell lymphoma patients in the validation cohort, 66 patients (52%) achieved CR/PR with 61(48%) in SD/PD. Twentythree (18.1%) HBsAg (−)/HBcAb (+) patients died during follow-up (Table 3).

4 | DISCUSSION

The risk of HBV-R in patients with resolved HBV infection depends on virus features, primary disease and immunosuppressive regimens.[25,26] Virus features associated with HBV-R are reported to contain HBsAg positivity, HBeAg positivity, and elevated HBV DNA copies before immunosuppressive therapy, all of which stand for poor immune control of HBV pre-chemotherapy.[40,41] In the present study, the risk of HBV-R in HBsAg (−)/HBcAb (+) B-cell NHL patients receiving rituximab was 6.3% in the training cohort. HBsAg (−)/HBsAb (−)/HBeAg (−)/HBeAb (+)/HBcAb (+) was associated with higher risk of HBV-R, and the incidence of HBV-R in this population was 23.7% with the mortality after HBV-R up to 44.4%. By using quantification of baseline HBcAb, HBeAb, and HBsAb levels, we have identified a high-risk subgroup of patients with B-cell NHL and resolved HBV infection that had a cumulative incidence of HBV-R of 75.0%, and 50.0% of these high-risk patients had severe HBV-related hepatitis flare.

There are many inconsistencies within the recommendations for preventing HBV-R in HBsAg (−)/HBcAb (+) patients with NHL receiving anti-CD20 antibody therapy. The APASL clinical practice guideline,[34] the American Association for the Study of Liver Disease,[26] the European Association for the Study of the Liver,[25] and the American Gastroenterological Association [27] recommend prophylactic NAT for HBsAg (−)/HBcAb (+) patients with a high risk of HBV reactivation, including patients undergoing anti-CD20 antibody therapy, although HBsAg (−)/HBcAb (+) patients with inflammatory bowel disease or rheumatological disease receiving biological agents have been successfully monitored without prophylaxis.[42–44]

TABLE 3 Details and outcomes of 17 HBsAg (−)/HBcAb (+) B-cell NHL patients With HBV-R.

		Baseline						Reactivation				
Group	Patient	Sex	Age (years)	Diagnosis	Chemotherapy	HBV-DNA (IU/mL)	HBsAg (IU/mL)	Days to HBV-R	Anti-HBV Drug	HBV-DNA (IU/mL)	HBsAg (IU/mL)	Outcome
Training	1	M	69	FL	R-ECHOP	$<10^3$	0.01	21	Entecavir	$<10^3$	10.91	Alive
	2	M	79	DLBCL	R-CHOP	$<10^2$	0	56	Entecavir	5.67×10^4	0.77	Died (multiple organ failure)
	3	M	65	MZL	RE-CHOP + MTX	$<10^3$	0	63	Entecavir	1.29×10^6	665.84	Died (primary disease progression)
	4	M	58	DLBCL	R-TPMD	$<10^2$	0.03	70	Entecavir	4.82×10^6	43.2	Alive
	5	F	66	DLBCL	R-ECHOP	$<10^3$	0.04	20	Entecavir	$<10^3$	0.12	Alive
	6	F	53	DLBCL	R-CHOP	$<10^3$	0	730	Entecavir	$<10^3$	5.11	Alive
	7	M	59	DLBCL	R-CHOP	$<10^3$	0	335	Entecavir	4.75×10^8	>25 000	Died (liver failure)
	8	M	68	DLBCL	R-CHOP	$<10^3$	0	378	Entecavir	6.23×10^4	0	Died (liver failure)
	9	F	51	DLBCL	R-ECHOP	$<10^3$	0	170	Entecavir	1.06×10^3	0.27	Died (primary disease progression)
	10	M	47	DLBCL	R-ECHOP	$<10^3$	0	308	Entecavir	1.22×10^7	21.05	Died (primary disease progression)
	11	M	55	MZL	R-Hyper-CVAD-A/B	$<10^3$	0.02	36	Entecavir	$<10^3$	1.63	Alive
	12	M	76	DLBCL	R-CHOP	$<10^3$	0	157	Entecavir	5.06×10^8	>25 000	Died (severe pneumonia)
	13	M	64	DLBCL	R-CHOP	$<10^3$	0	42	Entecavir	2.44×10^3	0	Alive
	14	F	70	DLBCL	R-CHOP	$<10^3$	0	50	Entecavir	$<10^3$	0.35	Alive
Validation	1	F	31	FL	R-CHOP	0	0	85	No	0	0.09	loss to follow-up
	2	F	57	FL	RFCD	0	0	713	Entecavir	2.43×10^2	155.52	Alive
	3	M	63	MCL	R-ECHOP	0	0	910	Entecavir	0	2.01	Alive

Abbreviations: DLBCL, diffuse large B- cell lymphoma; FL, follicular lymphoma; HBV-R, hepatitis B virus reactivation; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; RE-CHOP + MTX, etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab, and methotrexate; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab; R-ECHOP, etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab; R-Hyper-CVAD-A/B, dexamethasone, cyclophosphamide, vindesine, adriamycin, methotrexate, cytarabine, and rituximab; RFCD, rituximab, fludarabine, cyclophosphamide and prednisone; R-TPMD, liposome doxorubicin, temozolomide, methotrexate, dexamethasone, and rituximab.

However, the American Society of Clinical Oncology recommends either prophylactic NAT or careful HBV DNA follow-up for patients in high-risk HBV-R.[45] Emerging studies, particularly in Southeast Asia, investigated the cost-effectiveness of different ways to preventing HBV reactivation in HBsAg (−)/HBcAb (+) patients receiving chemotherapy and/or immunosuppressive therapy for lymphoma in Taiwan,[46] mainland China,[47] Japan,[48,49] Korean,[32] and Singapore.[50] It implies that for these patients with resolved HBV infection, meticulously monitoring levels of ALT and HBV DNA and promptly initiating anti-HBV therapy upon viral reactivation is a practical strategy.

The natural course of HBV is determined by the balance between viral reactivation and the host immunity. The frequency of HBsAg to HBsAb seroconversion increased overtime, but less than 25% of patients still had no HBsAb seroconversion more than 10 years after HBsAg seroclearance. In the present study, HBsAg (−)/HBsAb (−)/HBcAb (+)/HBeAg (−)/HBeAb (+) population at baseline just represents another high-risk group for HBV-R in NHL patients after HBsAg seroclearance. After cessation of therapy, HBsAg clearance was usually safe and durable during long-term follow-up, but HBsAg clearance does not imply complete elimination of the virus due to the presence of cccDNA.[51] Immunosuppressive or hormone treatment and drug resistance during NAT thearapy before HBsAg seroclearance provided possible explanations for reactivation of HBV.[52–54] An intracellular retention of HBsAg proteins may develop in patients carrying S region mutations.[55] These factors increase the incidence of HBV-R in patients with HBsAg seroclearance, even in individuals who are HBcAb (+) and/or HBsAb (+), and require regular follow-up.

The quantification of HBcAb levels has recently been recognized as a novel label of chronic HBV infection, although HBcAb (+) was previously regarded as a marker of past HBV infections. During the natural history of HBV infection, patients in HBeAg (−) hepatitis phases and the immune clearance have higher levels of HBcAb than those in the inactive carrier phases or the immune tolerant.[56–58] Higher levels of HBcAb in patients with resolved HBV infection was observed in those with detectable HBV DNA than those without detectable HBV DNA,[59] implying that HBcAb levels in this context may reflect the residual HBV replication. In clinical guidelines, HBcAb (+) patients are likewise considered to be a high-risk population (>10%) when undergoing rituximab treatment or HSCT, and the anti-HBV prophylaxis was recommended for this group.[25,26] In our analysis, the incidence of HBV-R (5.4%) was detected in patients with isolated HBcAb (2/37), and high HBcAb (≥8.455 S/CO) was associated with a significantly higher risk of HBV-R.

On the contrary, HBsAb (+) has been suggested to be protective against HBV-R, although it remains unclear whether the specific titer has any effect.[32,36,60,61] Low levels or absence of baseline HBsAb was the well-recognized risk factor of HBV-R in lymphoma patients with resolved HBV infection.[13,14,32,33,36,48,60–62] The risk of HBV-R in hematological malignancy patients with serological evidence of previous HBV infection is higher in those are HBsAb (−) before chemotherapy than HBsAb (+) cases.[14,32] A cut-off HBsAb titer above 100 IU/mL correlated with 0% rate of HBV-R in patients with lymphoma while a lower level of HBsAb titer was significantly correlated with HBV-R.[62] Additionally, the HBV infection rates were remarkably different between HBcAb (+)/HBsAb (+) patients and HBcAb (+)/HBsAb (−) patients (1.2% vs. 5.6%; $p < 0.001$) in 1959 patients undergoing renal transplantation.[32,63] The best threshold of HBsAb at baseline to predict HBV-R was 79.2 IU/L in the present study, which was lower than the values mentioned in the lymphoma patients receiving rituximab.[32,36,62] In this setting, monitoring HBsAb level can early warn of HBV-R risk. Our data confirmed the protective activity of HBsAbs in HBsAg (−)/HBcAb (+) NHL patients.

Few studies have reported the effect of HBeAb in HBsAg (−)/HBcAb (+) B-cell NHL patients and the detrimental role of HBeAb in HBsAg (−) patients remains controversial, as HBeAb is not typically regarded as a marker of resolved or occult HBV infection.[64,65] Since the proportion of HBeAb (+) in resolved HBV infection was pretty high (95/222, 42.8%), we were interested in the potential task of HBeAb in predicting HBV-R. HBeAb (+) is a prerequisite to quantify HBsAb and HBcAb to warn HBV-R implying the interaction among the anti-HBV immune responses, although the reason why the HBeAb status can influence the predictive value of HBsAb and HBcAb quantifications needs to be further explored. Here we state for the first time that the presence of HBeAb vulnerable to HBV-R in B-cell NHL patients, growing evidence of HBeAb' detrimental role which will be helpful to modify future antiviral prophylaxis in HBsAg (−)/HBcAb (+)/HBeAb (+)/HBeAg (−) B-cell NHL patients.

The clinical presentation of HBV reactivation rang from asymptomatic to acute liver failure and death. Higher mortality has been described in HBsAg (−)/HBcAb (+) patients compared to HBsAg (+) patients because of underestimated risk for HBV reactivation and the delayed diagnosis.[66] Thus, a prompt diagnosis to initialize early treatment is key to the effective management of those patients not under prophylactic anti-HBV therapy. Several studies in the past had shown that patients who received prophylactic NAT with a lower risk of HBV-R in HBsAg (−)/HBcAb (+) NHL patients, than patients who do not receive prophylactic NAT.[24,31,67] This result suggested that prophylactic antiviral therapy was also effective and may be necessary for high-risk HBsAg (−)/HBcAb (+) patients. Consistent with previous data,[68] three patients (21.4%) of our study had HBV-R more than 6 months after completion of lymphoma treatment in HBsAg (−)/HBcAb (+) patients, indicating that HBV DNA monitoring is essential for at least 1 year after the end of B-cell lymphoma treatment.[69]

Our study is limited by small number of patients with HBV-R and this retrospective observational study, but we have validated this by cases from another center. Future clinical application is needed to validate the threshold of HBcAb/HBeAb/HBsAb levels and define the high-risk populations. In addition, it is challenging to compare the rate of HBV-R in the present analysis with other studies owing to the multitude of assays measuring HBV-R and heterogeneous definitions of HBV-R. Notably, the presence of HBV viremia correlated negatively with HBsAb seroconversion, but HBV viremia still can be detected in approximately 5%–10% of patients with HBsAb seroconversion.[9,70] Nevertheless, in our study more than half of

HBsAg (−)/HBcAb (+) patients ($n = 156$) were quantified HBV DNA copies, and the incidence of positive HBV-DNA (>100 or >1000 UI/mL) at baseline of this population was 0%. Further studies are warranted to investigate the potential interplay among antiviral/antitumor immunity and their impact on clinical outcomes.

In conclusion, the incidence of HBV-R of HBsAg (−)/HBcAb (+) B-cell NHL patients receiving rituximab was 6.3%, but that of HBsAg (−)/HBsAb (−)/HBeAg (−)/HBeAb (+)/HBcAb (+) population was 23.7%, indicating the protective role of HBsAb, the detrimental role of HBcAb (+) and HBeAb (+) in HBV-resolved B-cell NHL patients. We found that it is a small subgroup of B-cell NHL patients, patients with high HBcAb, high HBeAb, and low HBsAb at baseline, were more likely to have frequent and severe hepatitis flare, suggesting anti-HBV prophylaxis most benefits this population in long-term clinical outcome. The result will help optimize a preventive strategy, especially in hepatitis B virus endemic regions with limited healthcare resources. Our findings favor the implementation of prophylactic antiviral therapy in HBsAg (−)/HBsAb (−)/HBeAg (−)/HBeAb (+)/HBcAb (+) patients with B-cell NHL, but not HBsAg (−)/HBcAb (+) population, receiving rituximab based immunochemotherapy in avoiding HBV-related complications at least for 1 year. Its efficacy and cost-effectiveness should be validated in more prospective, high quality RCTs with larger sample sizes and meta-analyses.

AUTHOR CONTRIBUTIONS

Li-Ping Shui analyzed, interpreted the data, wrote the first draft of the manuscript, conducted the literature search, reviewed the abstracts, and contributed to the final draft. Yan Zhu contributed to revising the manuscript and provided scientific input. Xiao-Qin Duan, Yu-Ting Chen, Li Yang, Xiao-Qiong Tang, Hong-Bing Zhang, Qing Xiao, Li Wang, and Lin Liu revised the manuscript. Xiao-Hua Luo initiated, designed, and supervised the study, revised, and wrote the final draft, and contributed to the analysis. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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