

## Hepatitis B virus infection status is not associated with poor prognosis in classical Hodgkin lymphoma patients

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Few studies focused on the relationship between hepatitis B virus (HBV) infection and classical Hodgkin lymphoma (cHL). This study was to evaluate the impact of HBV infection on the treatment outcome and survival of cHL patients. Clinical data of 352 cHL patients treated with ABVD regimen (doxorubicin, bleomycin, vincristine and dacarbazine) between January 2002 and January 2018 were retrospectively collected. According to HBV infection status, the patients were divided into three groups: with HBV infection [hepatitis B surface antigen (HBsAg)-positive], with past HBV infection [HBsAg-negative but anti-hepatitis B core antigen (anti-HBc)-positive], and without HBV infection (HBsAg-negative and anti-HBc-negative). The incidence of HBV infection and past HBV infection in cHL patients were 7.4% (26/352) and 16.5% (58/352), respectively. The median age of patients without HBV infection was lower than those in other two groups ( $p < 0.001$ ). The complete remission rates after first-line therapy were different among 3 groups (65.4% for the group with HBV infection, 87.9% for the group with past HBV infection, and 76.1% for the group without HBV infection, respectively,  $p = 0.049$ ). After a median follow-up of 34.6 months, the 3-year progression-free survival rates for the three groups were 69%, 74% and 80%, respectively ( $p = 0.566$ ) and the 3-year overall survival rates were 72%, 91% and 87%, respectively ( $p = 0.096$ ). No HBV reactivation was observed during chemotherapy among 3 groups, but 1 patient in the group with HBV infection experienced delayed HBV reactivation when prophylactic entecavir was discontinued 12 months after the last cycle of chemotherapy. HBV infection status did not affect the clinical outcome and prognosis of cHL patients, especially in the era of prophylactic antiviral therapy.

*Key words: Hodgkin disease, hepatitis B virus, therapeutics, prognosis*

Hepatitis B virus (HBV), a hepatotropic virus, can also infect peripheral blood mononuclear cells and lymph nodes [1]. HBV infection has been found to play a causative role in lymphomagenesis by either chronic antigenic stimulation model [2] or antigen-independent mechanism [3]. An epidemiological study involving 603,585 participants showed that hepatitis B surface antigen (HBsAg)-positive participants had an increased risk of non-Hodgkin lymphoma (NHL) overall compared with those who were HBsAg-negative (hazard ratio = 1.74). A meta-analysis [4] including 6 studies with a total of 38 Hodgkin lymphoma (HL) cases and 146,087

controls indicated a significantly increased risk of developing HL in HBV-infected individuals (odds ratio = 1.54).

HBV reactivation during antitumor therapy may lead to fulminant hepatitis, liver failure and death [5], which is related to poor survival. Additionally, HBV infection may confer resistance to chemotherapeutics in lymphoma [6]. Several studies have reported that HBV infection is associated with poor prognosis of patients with NHL, such as NK/T cell lymphoma [7] and diffuse large B-cell lymphoma (DLBCL) [8]. However, little is known about the association of HBV infection with classic HL (cHL) even in endemic

area. Importantly, the effect of HBV infection on clinical outcomes of cHL remains unknown.

## Patients and methods

**Patients.** We searched the database of cancer registries for cases registered from January 2002 to January 2018 with a diagnosis of cHL. To minimize the impact of different chemotherapy regimens, only those patients treated with ABVD regimen (doxorubicin, bleomycin, vincristine and dacarbazine) were included. All clinical information, including demographic findings, clinical presentations, physical examinations, histopathological reports, radiological features and laboratory results, were investigated. All patients in the study were followed up by medical record review until death or the last visit at our institute. The prevalence of HBsAg and hepatitis B core antibody (anti-HBc) in cHL patients was compared with those data from national hepatitis serosurvey conducted by China government [9]. To investigate the relationship between the HBV infection and the clinicopathological characteristics of cHL, we divided cHL patients into three groups according to HBV infection status: group with HBV infection (HBsAg-positive), group with past HBV infection (HBsAg-negative but anti-HBc-positive), and group without HBV infection (HBsAg-negative and anti-HBc-negative). This retrospective study was approved by the Ethics Committee at the Peking University Cancer Hospital and Institute and the institutional review boards of the participating centers, in accordance with the Declaration of Helsinki; and the requirement for informed consent was waived because of the anonymous nature of the data.

**HBV detection.** Enzyme-linked immunosorbent assay (ELISA) was used to determine the HBV infection status, including HBsAg, hepatitis B surface antibody (anti-HBs), hepatitis B e antigen (HBeAg), hepatitis B e antibody (anti-HBe) and anti-HBc. HBV DNA levels were quantitatively tested by real-time polymerase chain reaction with a low detection limit of 50 IU/ml. HBV DNA was detected at baseline and every 4 weeks, for at least one year after completion of chemotherapy.

**Definition of HBV reactivation.** Based on a previous study [10], HBV reactivation was defined as a marked increase in HBV replication ( $\geq 2 \log_{10}$  increase from baseline levels or a new appearance of HBV DNA to a level of  $\geq 100$  IU/ml) in a person with previously stable or undetectable levels. The reactivation of past HBV infection was defined as HBsAg reverse seroconversion (reappearance of HBsAg), or appearance of HBV DNA in serum in the absence of HBsAg.

**Follow up.** In the study, the follow-up period began at the date of cHL diagnosis and ended at the date of death or June 1st, 2018. Progression-free survival (PFS) was calculated from the time of diagnosis to progression, relapse, death or the end of the follow-up period; and overall survival (OS) was calculated from the time of diagnosis to death or the end of the follow-up period.

**Statistical analysis.** All statistical analyses were performed with the IBM SPSS Statistics for windows (Version 21.0; IBM Corp., New York, USA). Categorical variables were compared using Pearson  $\chi^2$  analysis or Fisher's exact test. Continuous variables were compared using the t-test. Kaplan-Meier curves were used to compare the differences in PFS and OS among the groups, and the log-rank Chi-square test was used to calculate the significance of the differences. Multivariate Cox proportional hazards analysis was performed to determine the effects of the variables on survival. All statistical tests were two-tailed, and  $p < 0.05$  was considered statistically significant.

## Results

**Baseline characteristics.** A total of 424 patients with cHL were reviewed, and 72 patients were excluded. Finally, 352 patients were analyzed in the study, including 207 males and 145 females. The median age of the patients at diagnosis of cHL was 32 years. Nodular sclerosis cHL was the most frequent pathological type, followed by mixed cellularity cHL, lymphocyte-rich cHL and lymphocyte-depleted cHL.

HBV infection was documented in 26 (7.4%) patients at diagnosis of cHL, and past HBV infection was in 58 (16.5%) patients. The prevalence of HBsAg in cHL patients was similar to that of general population (7.4% vs. 7.2%,  $p = 0.881$ ), but the prevalence of anti-HBc was significantly lower (23.9% vs. 34.1%,  $p < 0.001$ ). In addition, 43 (74.1%) patients had positive anti-HBs in the group with past HBV infection.

The group without HBV infection was younger than the other two groups. Higher proportion of absolute platelet count  $< 100 \times 10^9/L$  was observed in the group with HBV infection (Table 1). There was no other significant difference in clinicopathological characteristics among 3 groups. In the group with HBV infection, baseline HBV DNA was detectable in 15 patients with a median titer of  $5.58 \times 10^4$  (range,  $1.24 \times 10^2$ – $4.59 \times 10^8$ ) IU/mL. Only 1 patient had mildly elevated alanineaminotransferase (ALT) prior to chemotherapy. Prophylactic antiviral therapy was administered in all 26 patients, of which entecavir was used in 15 patients, lamivudine in 7, adefovir dipivoxil in 3 and telbivudine in 1. In the group with past HBV infection, all 58 patients had undetectable HBV DNA at baseline and only 3 patients received prophylactic antiviral therapy (2 with entecavir and 1 with lamivudine). Prophylactic antiviral therapy continued until at least 12 months after last chemotherapy in the group of HBV infection and 6 months after last chemotherapy in the group of past HBV infection.

**Response to antitumor therapy.** A total of 2,187 cycles of chemotherapy with ABVD regimen were administered (median, 6 cycles/patient; range, 2–8 cycles). After the first-line chemotherapy, 78 patients received radiotherapy, and 5 patients underwent autologous hematopoietic stem cell transplantation. The objective response rate (ORR) for all patients was 90.7% (319/352), with a complete remission (CR) rate of

**Table 1. Comparison of clinicopathological characteristics among patients according to HBV infection status.**

	All patients (n=352)	Group with HBV infection (n=26)	Group with past HBV infection (n=58)	Group without HBV infection (n=268)	p-value*
Age (mean ± SD, years)	36.0±15.5	43.6±15.4	44.3±14.3	33.5±14.9	<0.001
>60 years	27 (7.7%)	3 (11.5%)	7 (12.1%)	17 (6.3%)	0.247
Sex					0.125
Male	207 (58.8%)	19 (73.1%)	38 (65.5%)	150 (56.0%)	
Female	145 (41.2%)	7 (26.9%)	20 (34.5%)	118 (44.0%)	
Pathologic type					0.165
LR	20 (5.7%)	2 (7.7%)	3 (5.2%)	15 (5.6%)	
NS	207 (58.8%)	12 (46.2%)	28 (48.3%)	167 (62.3%)	
MC	111 (31.5%)	11 (42.3%)	25 (43.1%)	75 (28.0%)	
LD	2 (0.6%)	1 (3.8%)	0 (0)	1 (0.4%)	
unclassified	12 (3.4%)	0 (0)	2 (3.4%)	10 (3.7%)	
ECOG performance					0.246
Score 0-1	349 (99.1%)	25 (96.2%)	57 (98.3%)	267 (99.6%)	
Score 2-4	3 (0.9%)	1 (3.8%)	1 (1.7%)	1 (0.4%)	
Stage					0.127
1-2	211 (59.9%)	11 (42.3%)	33 (56.9%)	167 (62.3%)	
3-4	141 (40.1%)	15 (57.7%)	25 (43.1%)	101 (37.7%)	
B symptom	103 (29.3%)	8 (30.8%)	20 (34.5%)	75 (28.0%)	0.612
Extra-nodal involvement	88 (25.1%)	6 (23.1%)	15 (25.9%)	67 (25.1%)	0.963
WBC>10×10 <sup>9</sup> /L	101 (28.7%)	5 (19.2%)	15 (25.9%)	81 (30.2%)	0.413
ALC<1×10 <sup>9</sup> /L	76 (21.6%)	7 (26.9%)	15 (25.9%)	54 (20.1%)	0.510
Anemia	68 (19.3%)	5 (19.2%)	12 (20.7%)	51 (19.0%)	0.959
PLT<100×10 <sup>9</sup> /L	9 (2.6%)	3 (11.5%)	0 (0)	6 (2.2%)	0.021
ALB<35g/L	28 (8.0%)	4 (15.4%)	5 (8.6%)	19 (7.1%)	0.388
Elevated LDH	87 (24.7%)	9 (34.6%)	15 (25.9%)	63 (23.5%)	0.467

\*p-value refers to the difference among three groups; ALB, albumin; ALC, absolute lymphocyte count; ECOG, Eastern Cooperative Oncology Group; LD, lymphocyte-depleted classical Hodgkin lymphoma; LDH, lactate dehydrogenase; LR, lymphocyte-rich classical Hodgkin lymphoma; MC, mixed cellularity classical Hodgkin lymphoma; NS, nodular sclerosis classical Hodgkin lymphoma; PLT, platelet; SD, standard deviation; WBC, white blood cell

**Table 2. Comparison of treatment modality and effectiveness among patients according to HBV infection status.**

	All patients (n=352)	Group with HBV infection (n=26)	Group with past HBV infection (n=58)	Group without HBV infection (n=268)	p-value*
Median cycles of chemotherapy	6 (2-8)	6 (4-8)	6 (2-8)	6 (2-8)	0.603
Radiotherapy	78 (22.2%)	7 (26.9%)	7 (12.1%)	64 (23.9%)	0.121
AHSCT	5 (1.4%)	0 (0)	1 (1.7%)	4 (1.5%)	0.824
Response to antitumor therapy					0.212
CR	272 (77.3%)	17 (65.4%)	51 (87.9%)	204 (76.1%)	
PR	47 (13.4%)	5 (19.2%)	3 (5.2%)	39 (14.6%)	
SD	10 (2.8%)	1 (3.8%)	0 (0)	9 (3.4%)	
PD	23 (6.5%)	3 (11.5%)	4 (6.9%)	16 (6.0%)	

\*p-value refers to the difference among three groups; AHSCT, autologous hematopoietic stem cell transplantation; CR, Complete Remission; PD, progression disease; PR, partial remission; SD, stable disease

77.3% and a partial remission (PR) rate of 13.4% (Table 2). The ORR and CR rates were 84.6% and 65.4% for the group with HBV infection, 93.1% and 87.9% for the group with past HBV infection, 90.7% and 76.1% for the group without HBV infection, respectively. No disruption of chemotherapy due to adverse effects of antiviral therapy was observed.

**HBV reactivation in cHL patients.** In the group with HBV infection, no HBV reactivation was observed during

chemotherapy. However, one patient experienced delayed HBV reactivation after withdrawal of antiviral therapy. This 27-year-old male patient discontinued prophylactic entecavir 12 months after the last cycle of chemotherapy. Five months later, HBV reactivation was diagnosed because HBV DNA titer increased from undetectable levels to 1.28×10<sup>7</sup> IU/ml, and ALT increased from normal levels to 195 IU/ml. He recovered from HBV-related hepatitis after re-administration

of antiviral therapy with entecavir. The other 25 patients did not stop antiviral therapy until the end of follow-up period with a median duration of 34.2 (range, 14.1–86.1) months, and none experienced HBV reactivation.

While in the group with past HBV infection, only 3 patients received antiviral prophylaxis, and discontinued 6 months after the last cycle of chemotherapy. None of these 58 patients experienced HBV reactivation regardless of whether prophylactic antiviral therapy was administered or not.

**Survival rate and prognostic factors.** After a median follow-up period of 34.2 months, 56 patients had disease progression, 6 of which were in the group with HBV infection, 11 in the group with past HBV infection, and 39 in the group without HBV infection. The expected 3-year PFS rates

for the three groups were 69%, 80% and 74%, respectively ( $p=0.566$ , Figure 1).

Twenty-three patients died, 5 of which were in the group with HBV infection, 3 in the group with past HBV infection, and 15 in the group without HBV infection. The 3-year OS rates for the three groups were 72%, 91% and 87%, respectively ( $p=0.096$ , Figure 2).

In univariate analysis, age >60 years, B symptom, extra-nodal involvement, lower absolute lymphocyte count ( $<1 \times 10^9/l$ ), anemia, lower platelet count ( $<100 \times 10^9/l$ ), lower albumin level ( $<35$  g/l) and elevated lactate dehydrogenase were poor risk factors for OS (Table 3). Notably, HBV infection status was not a risk factor for OS in Cox analysis ( $p=0.506$ ). Multivariate analysis indicated that age > 60 years and anemia were independent poor predictors of OS.

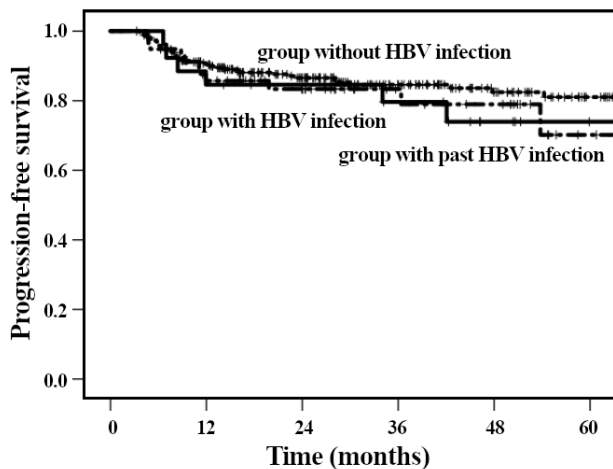


Figure 1. Comparison of progression-free survival according to HBV infection status ( $p=0.566$ )

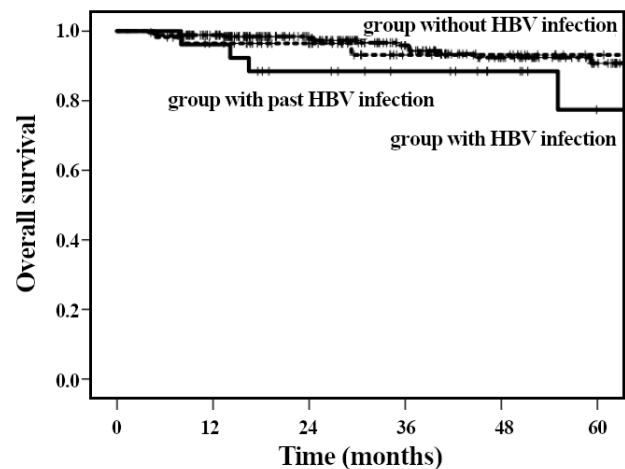


Figure 2. Comparison of overall survival according to HBV infection status ( $p=0.096$ )

Table 3. Analysis of risk factors for overall survival.

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Age >60 years	9.502	4.117–21.933	<0.001	8.613	3.694–20.085	<0.001
Sex	0.787	0.347–1.787	0.567			
Pathologic type	1.190	0.796–1.779	0.396			
ECOG performance	1.422	0.632–3.201	0.394			
Stage	1.859	0.817–4.227	0.139			
B symptom	2.878	1.268–6.530	0.011			
Extra-nodal involvement	3.025	1.319–6.941	0.009			
WBC $>10 \times 10^9/L$	0.370	0.110–1.245	0.108			
ALC $<1 \times 10^9/L$	3.196	1.366–7.477	0.007			
Anemia	3.709	1.572–8.748	0.003	3.032	1.287–7.144	0.011
PLT $<100 \times 10^9/L$	8.264	2.777–24.595	<0.001			
ALB $<35$ g/L	3.849	1.414–10.472	0.008			
Elevated LDH	2.648	1.158–6.054	0.021			
HBV infection status	1.192	0.711–1.998	0.506			

ALB, albumin; ALC, absolute lymphocyte count; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; LDH, lactate dehydrogenase; PLT, platelet; WBC, white blood cell

## Discussion

The prevalence of HBV infection is different between HL and NHL. A study [8] from an HBV endemic area demonstrated that HBsAg prevalence in DLBCL patients was significantly higher than that in general population (23.6% vs. 7.2%,  $p < 0.001$ ), which is consistent with the results of 405 NHL patients in our previous report [11]. A study [12] involving 120 HL patients indicated that HBsAg prevalence was similar between HL patients and general population. In our study, compared with general population, cHL patients had similar HBsAg prevalence and lower anti-HBc prevalence, which may be due to routine childhood immunization in China [13] and domination of younger people in HL patients [14]. These findings suggested HBV infection may be not a pathogenesis factor for cHL.

Prophylactic antiviral therapy has been recommended for HBsAg-positive patients to prevent HBV reactivation by clinical practice guidelines [15–18]. In our study, all 26 HBsAg-positive patients received prophylactic antiviral therapy, and none experienced HBV reactivation during chemotherapy. This finding is in agreement with the recommendations in clinical practice guidelines. Of note was that delayed HBV reactivation after withdrawal of prophylactic agents may be a problem. In our previous study [19], the incidence of delayed HBV reactivation and HBV-related hepatitis flares after withdrawal of prophylactic antiviral therapy in 46 HBsAg-positive patients with DLBCL was 21.7% and 10.9%, respectively. In the present study, one HBsAg-positive patient experienced delayed HBV reactivation after he discontinued the prophylactic agent even 12 months after the last cycle of chemotherapy. The median duration of prophylactic antiviral therapy in the other 15 HBsAg-positive patients was 34.2 months. Therefore, large prospective investigations need to be conducted to understand whether long-term use of antiviral therapy can be avoided for HBsAg-positive patients after the end of chemotherapy.

There is a concern about antiviral prophylaxis and HBV reactivation in patients with past HBV infection. A technical review [20] from American Gastroenterological Association Institute revealed that the mean frequency of HBV reactivation was 12.2% in 401 lymphoma patients with past HBV infection who were not given prophylactic antiviral therapy, and rituximab increased the risk of HBV reactivation. Those patients with past HBV infection receiving anthracycline-based regimens without rituximab were classified as the moderate-risk group with anticipated incidence of HBV reactivation of 1% to 10% [17]. In our study, 58 (16.5%) patients had past HBV infection, only 3 of whom received antiviral prophylaxis. None experienced HBV reactivation regardless of whether they received antiviral therapy. This finding suggested that no antiviral prophylaxis may be a reasonable choice for cHL patients treated with ABVD regimen when cost-effectiveness was considered.

Controversy remains concerning the effect of HBV infection on the outcomes of lymphoma patients. A study [8] involving 508 DLBCL patients showed that HBV infection had a negative effect on therapeutic outcomes with an odds ratio of 3.04, whereas another study [21] demonstrated that there was no significant difference in CR rate and OS between HBsAg-positive DLBCL group and HBsAg-negative DLBCL group. However, few study addressed this question in HL patients. Among the three groups in our study, the difference in response rates had no statistical significance. It is worth mentioning that there is no statistical difference in PFS and OS among three groups and HBV infection status was not a risk factor for OS in COX analysis. These results indicated that the status of HBV infection could not be a key factor influencing the prognosis of cHL patients after chemotherapy with ABVD regimen.

The interpretation of our study has several limitations. First, the small sample size in group with HBV infection due to the decreasing prevalence of HBV [9] and low burden of lymphoma in China [22, 23], should be taken into account when the clinical significance of statistic difference in response rates were evaluated. Second, the effect of HBV infection on prognosis may be weakened in HL patients because of good response to chemotherapy with ABVD regimen. Third, the follow-up period was variable due to death from lymphoma progression, which should also be considered. Finally, the correlation between HBV reactivation and salvage treatment was not evaluated due to the heterogeneity of regimens.

In conclusion, HBV infection and past HBV infection are not rare in cHL patients resided in HBV endemic areas. Prophylactic antiviral therapy should be administrated for those HBsAg-positive patients and may be an optional choice for those patients with past HBV infection. Both HBV infection and past HBV infection did not have negative effect on the prognosis of cHL, especially in the era of prophylactic antiviral therapy.

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