



Role of virological serum markers in patients with both hepatitis B virus infection and diffuse large B-cell lymphoma

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Abstract

Background: Causality between hepatitis B virus (HBV) infection and diffuse large B-cell lymphoma (DLBCL) was reported in various studies. However, the implication of different virological serum markers of HBV infection in patients with both HBV infection and DLBCL is not fully understood. The aim of this study was to investigate the impact of HBV markers on overall survival (OS) and progression-free survival (PFS) in patients with both HBV infection and DLBCL.

Methods: In this study, patients (n = 40) diagnosed with both HBV infection and DLBCL were identified between 2000 and 2017. Six patients with hepatitis C virus (HCV) and/or human immunodeficiency virus (HIV) co-infection were excluded from this study. We retrospectively analyzed patients' demographic characteristics, treatment, and the prognostic impact of different HBV markers at first diagnosis of DLBCL (HBsAg, anti-HBs, HBeAg, anti-HBe, and HBV-DNA) on OS and PFS.

Results: The majority of patients (n = 21, 62%) had advanced disease stage (III/IV) at diagnosis. In the first-line therapy, 24 patients (70%) were treated with R-CHOP regimen (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone). HBeAg positive patients had a trend toward inferior OS and PFS compared with HBeAg negative patients. Anti-HBe positive patients had a statistically significant better OS and PFS compared with anti-HBe negative group (both $P < .0001$). Viremia with HBV-DNA $\geq 2 \times 10^7$ IU/L had a significant negative impact on OS and PFS (both $P < .0001$).

Conclusion: High activity of viral replication is associated with a poor survival outcome of patients with both HBV infection and DLBCL.

KEYWORDS

diffuse large B-cell lymphoma, hepatitis B virus, prognosis



1 | INTRODUCTION

Hepatitis B virus (HBV) is not only a hepatotropic but also a lymphotropic and potentially oncogenic virus.¹ Several epidemiological studies suggested a notable association between HBV infection and non-Hodgkin lymphomas (NHLs), such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and primary central nervous system lymphoma (PCNSL).²⁻⁴ For instance, a large Italian study showed a positive association between HBV infection and NHL regardless of NHL subtypes.⁵ In a recent updated meta-analysis of 58 epidemiological studies, Li et al⁶ reported that DLBCL had the most significant association with HBV infection among NHL subtypes. Moreover, Ren et al observed an enhanced mutagenesis and a distinct set of mutation targets in genomes of patients with both DLBCL and HBV infection compared with DLBCL patients without HBV infection. This finding suggested that HBV might be a crucial driver in the pathogenesis of DLBCL by inducing genetic alterations.⁷ However, the biological mechanism of DLBCL development in patients with HBV infection remains not fully understood, and the clinical implication of HBV infection in patients with DLBCL is also a matter of debate. Various studies have demonstrated that HBV infection might impair overall survival (OS) and progression-free survival (PFS) of patients with DLBCL compared to HBV negative individuals.⁸⁻¹⁰ Within the patients with both DLBCL and chronic or resolved HBV infection with positive hepatitis B core antibody (anti-HBc), however, the impact of different virological serum markers of HBV infection such as hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B envelope antigen (HBeAg), hepatitis B envelope antibody (anti-HBe), and HBV-DNA on survival of patients are rarely reported and discussed. The implication of these virological markers in the clinical practice is still unclear. Therefore, a potential prognostic impact of these markers in patients with both HBV infection and DLBCL would provide additional information for clinical management.

The aim of the present study was to analyze the clinical characteristics and the impact of different baseline virological serum markers of HBV infection including HBsAg, anti-HBs, HBeAg, anti-HBe, and HBV-DNA on OS and PFS in patients diagnosed with both HBV infection and DLBCL.

2 | METHODS

2.1 | Collection of patients' data

We performed a retrospective single-center analysis of patients diagnosed with both DLBCL and HBV infection. Patients with hepatitis C virus (HCV) and/or human immunodeficiency virus (HIV) co-infection were excluded from this study. All diagnoses were encoded according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Searching the hospital database supported by the information technology department, we identified and collected the data of those patients with DLBCL (C83.3) and

acute or chronic hepatitis B (B16 or B18.0/1) who were treated or followed as in- or outpatient from January 2000 to June 2017 at our hospital. Patients' demographic characteristics, DLBCL-related data (diagnosis, stage, therapy, response to therapy, relapse, and relapse therapy), serological HBV markers at DLBCL diagnosis (HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe, and HBV-DNA), and antiviral prophylaxis/therapy-related data were collected and analyzed. Clinical data were evaluated with regard to the impact of virological markers of HBV infection on OS and PFS. Retrospective data analysis was approved by the Ethics Committee of the Medical Faculty, Heidelberg University.

2.2 | Assessment of the virological markers of HBV infection

The serological HBV markers including HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe, and HBV-DNA were assessed at diagnosis of DLBCL (baseline). Polymerase chain reaction (PCR) was used to quantify the HBV-DNA in serum at a sensitivity level of 10 IU/mL at the virology laboratory of our hospital. Enzyme immunoassay (EIA) was used for the determination of HBsAg, anti-HBs, anti-HBc, HBeAg, and anti-HBe in serum. In some cases, these tests were only performed as a qualitative detection.

2.3 | Statistical analysis

For descriptive statistics, we presented the data as absolute numbers and percentage, and if not otherwise stated as median, minimum, and maximum. To investigate the prognostic impact of different virological markers of HBV infection, we performed a survival analysis with Kaplan-Meier method. Since no patient was anti-HBc negative at baseline, it was not possible to evaluate the relationship between anti-HBc status and survival of patients. We used univariate log-rank tests to compare the survival curves in different groups. A *P*-value of less than .05 was considered to be statistically significant. The analysis was performed with GraphPad Prism 5.0 (GraphPad Software Inc). OS was defined as the period in months from diagnosis of DLBCL to death or the last follow-up. PFS was defined as the interval in months between diagnosis of DLBCL and relapse or progression or, if no relapse or progress occurred, as the time to the last follow-up at our institution.

3 | RESULTS

3.1 | Patients' characteristics, therapy, and response to first-line therapy

In total, we identified 40 patients diagnosed with both DLBCL and HBV infection. Of those, six patients (15%) were excluded from this study due to HCV and/or HIV co-infection. Data of a total of 34 patients were evaluated in the current analysis. The median age at diagnosis of DLBCL was 61 (range: 33-82 years) years. The percentage



of male patients was 71% (n = 24). Two patients (6%) had secondary transformed DLBCL from follicular lymphoma (FL) (n = 1, 3%) or chronic lymphocytic leukemia (CLL) (n = 1, 3%). The majority of patients (n = 21, 62%) had advanced disease stage (III/IV) at DLBCL diagnosis, and 15 patients (44%) had B-symptoms. In the first-line therapy, 24 patients (70%) were treated with R-CHOP regimen (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone), while five patients (15%) received only CHOP chemotherapy (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone). Among the patients without rituximab, rituximab was not given due to the risk of HBV reactivation in one

patient; the other four patients were treated before the rituximab era. 27 patients (79%) achieved complete remission (CR, n = 14, 41%) or partial remission (PR, n = 13, 38%) after first-line therapy. Relapse from CR or PR was observed in ten patients (29%). Median follow-up of patients was 53 (95% CI: 32-106) months. In four (12%) patients, HBV was diagnosed pre DLBCL; the median interval between HBV and DLBCL was 26 years (range: 5-34 years). HBV was diagnosed simultaneously with DLBCL in five (15%) patients. In 25 (73%) patients, the diagnosis of HBV infection was already registered before the diagnosis of DLBCL. However, the accurate time points of HBV

TABLE 1 Patients' characteristics and DLBCL-related data

Parameter	
Patients, n	34
Gender, n (%)	
Male	24 (71)
Female	10 (29)
DLBCL diagnosis	
Age at diagnosis, median years (min.-max.)	61 (33-82)
Histology, n (%)	
de novo DLBCL	32 (94)
Transformed DLBCL/FL	1 (3)
Transformed DLBCL/CLL	1 (3)
Stage, n (%)	
I/II	13 (38)
III/IV	21 (62)
B-symptoms, n (%)	
A	19 (56)
B	15 (44)
First-line therapy, n (%)	
R-CHOP-like	24 (70)
CHOP-like	5 (15)
GMALL-B-ALL/NHL	2 (6)
R-Benda	2 (6)
MATRix	1 (3)
Response to first-line therapy, n (%)	
CR	14 (41)
PR	13 (38)
SD	3 (9)
PD	3 (9)
NA	1 (3)

Abbreviations: CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone; CLL, chronic lymphocytic leukemia; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MATRix, methotrexate, cytarabine, thiotepa and rituximab; NA, not available; PD, progressive disease; PR, partial remission; R-Benda, rituximab, bendamustine; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone; SD, stable disease.

TABLE 2 HBV infection-related data

Virological serum parameter at diagnosis of DLBCL	
Anti-HBc, n (%)	
Positive	29 (85)
Negative	0 (0)
NA	5 (15)
HBsAg, n (%)	
Positive	15 (44)
Negative	15 (44)
NA	4 (12)
Anti-HBs, n (%)	
Positive	15 (44)
Negative	14 (41)
NA	5 (15)
HBeAg, n (%)	
Positive	3 (9)
Negative	18 (53)
NA	13 (38)
Anti-HBe, n (%)	
Positive	18 (53)
Negative	4 (12)
NA	12 (35)
HBV-DNA, n (%)	
$\geq 2 \times 10^7$ IU/L	2 (6)
$< 2 \times 10^7$ IU/L	18 (53)
NA	14 (41)
Primary antiviral prophylaxis, n (%)	
Lamivudine	13 (38)
Entecavir	7 (21)
Tenofovir	2 (6)
No antiviral prophylaxis registered	12 (35)
Reactivation, n (%)	
Yes	4 (12)
No	30 (88)

Abbreviations: Anti-HBc, hepatitis B core antibody; Anti-HBe, hepatitis B envelope antibody; Anti-HBs, hepatitis B surface antibody; DLBCL, diffuse large B-cell lymphoma; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not available.



diagnosis were not available in these 25 patients. Patients' characteristics, treatment, and response are summarized in Table 1.

3.2 | Serological HBV markers at first diagnosis of DLBCL

Anti-HBc status was not available in five patients (15%), and all remaining patients (n = 29, 85%) were anti-HBc positive. HBsAg was positive in 15 patients (44%) and negative in 15 patients (44%). Anti-HBs was positive in 15 patients (44%) and negative in 14 patients (41%). We observed three (9%) HBeAg positive, 18 (53%) HBeAg negative, 18 (53%) anti-HBe positive, and four (12%) anti-HBe negative patients, respectively. In 18 patients (53%), HBV-DNA was $< 2 \times 10^7$ IU/L in serum, while two patients (6%) had viremia with HBV-DNA $\geq 2 \times 10^7$ IU/L. In 14 cases (41%), the baseline HBV-DNA was not available. In the course of the disease, 13 patients (38%) received lamivudine as antiviral prophylaxis. Entecavir and tenofovir were given in seven (21%) and two (6%) patients, respectively. In 12 patients (35%), no antiviral treatment was registered. HBV reactivation was documented in four patients (12%), who were treated with entecavir (n = 2) or tenofovir (n = 2) and reached HBV-DNA negativity, respectively. One patient received an urgent liver transplant due

to HBV reactivation with fulminant hepatitis. HBV serum markers at first diagnosis of DLBCL are summarized in Table 2.

3.3 | Virological markers of HBV infection and survival of patients

We hypothesized that there might be a prognostic value of serological HBV markers at DLBCL first diagnosis and survival outcome.

No statistically significant difference in OS was observed between HBsAg positive and negative patients (Figure 1A). Compared with HBsAg negative patients, HBsAg positive patients had a shorter PFS. However, the difference in PFS was not statistically significant ($P = .24$, Figure 1B). Moreover, baseline anti-HBs status was not associated with changes in OS or PFS (Figure 2A,B). HBeAg positive patients did not have a significantly inferior OS and PFS compared with HBeAg negative patients ($P = .58$ and $P = .88$, respectively, Figure 3A,B). In contrast, anti-HBe positive patients showed a significantly longer OS and PFS compared with anti-HBe negative patients ($P < .0001$ and $P < .0001$, respectively, Figure 4A,B). In addition, viremia with HBV-DNA $\geq 2 \times 10^7$ IU/L was associated with significantly shorter OS ($P < .0001$, Figure 5A). Similarly, HBV-DNA $\geq 2 \times 10^7$ IU/L also indicated a significantly shorter PFS ($P < .0001$,

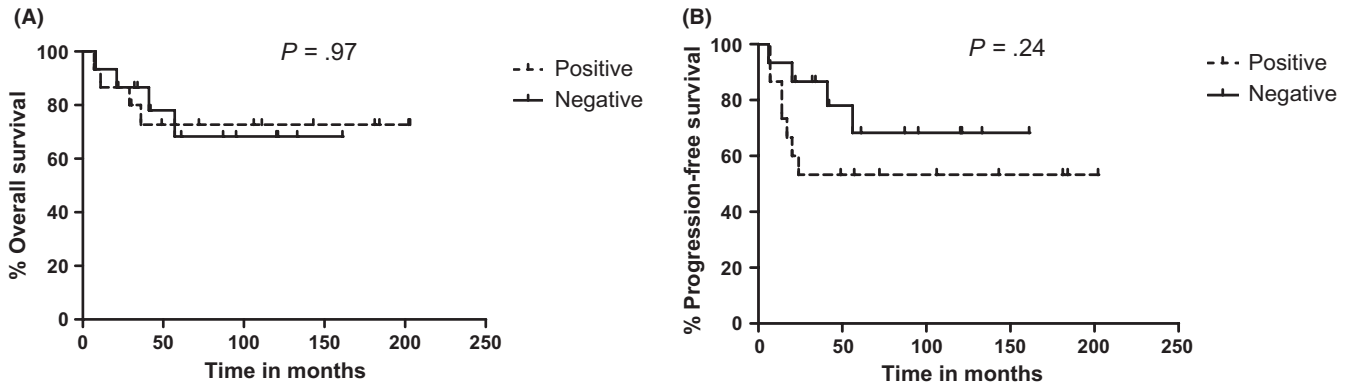


FIGURE 1 HBsAg and outcome. The figure shows OS (A) and PFS (B) survival curves with regard to HBsAg positivity (n = 15) and negativity (n = 15)

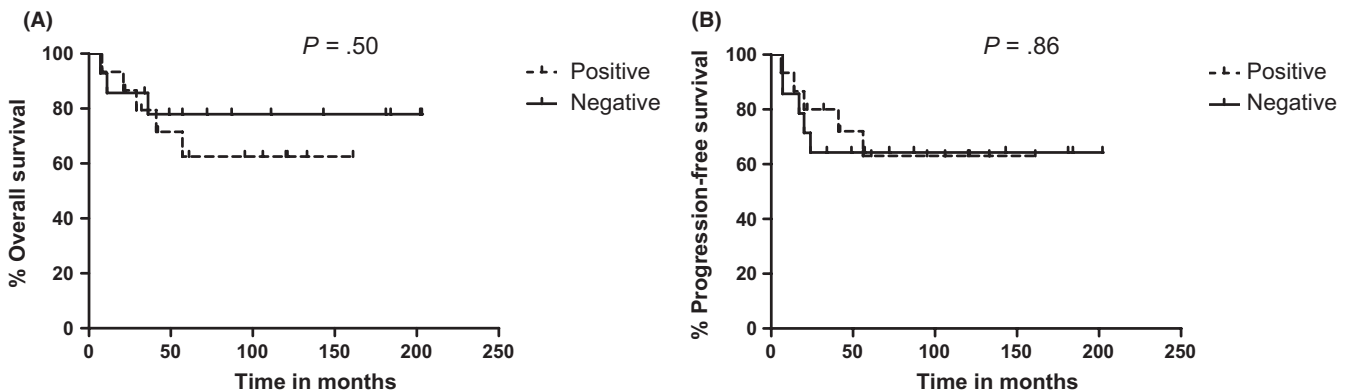


FIGURE 2 Anti-HBs and outcome. The figure shows OS (A) and PFS (B) survival curves with regard to anti-HBs positivity (n = 15) and negativity (n = 14)

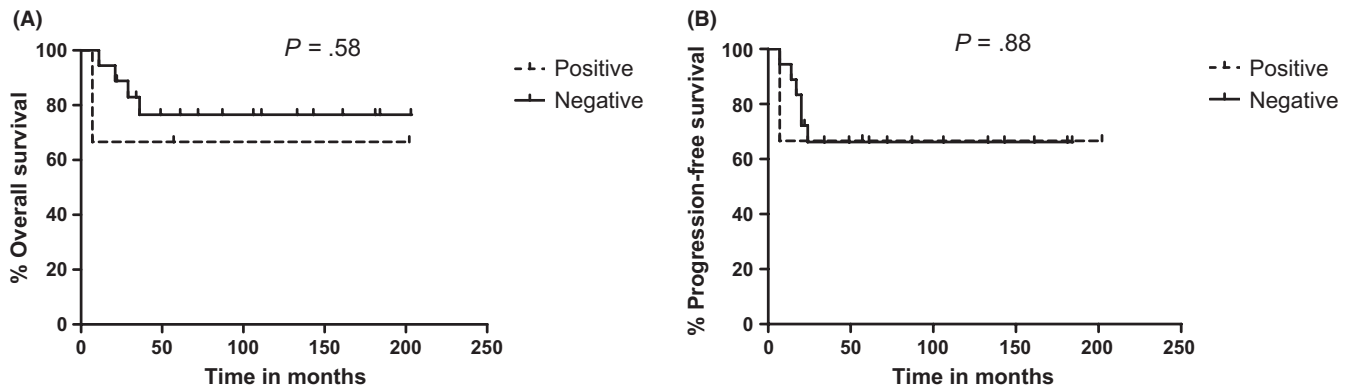


FIGURE 3 HBeAg and outcome. The figure shows OS (A) and PFS (B) survival curves with regard to HBeAg positivity ($n = 3$) and negativity ($n = 18$)

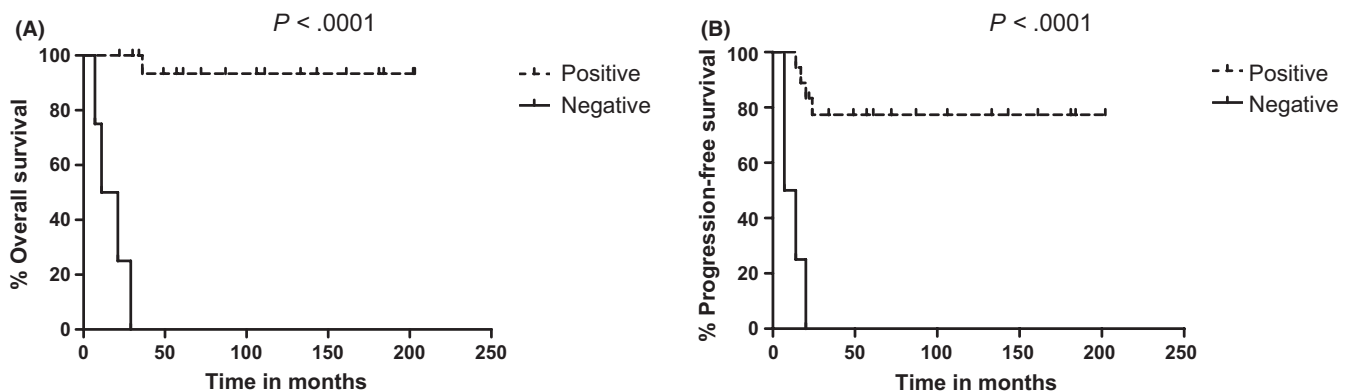


FIGURE 4 Anti-HBe and outcome. The figure shows OS (A) and PFS (B) survival curves with regard to HBeAg positivity ($n = 18$) and negativity ($n = 4$)

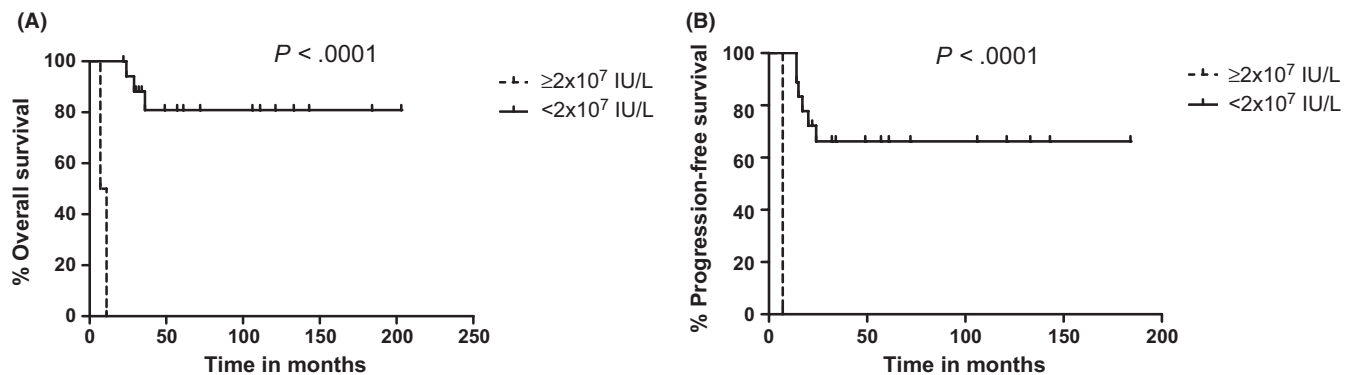


FIGURE 5 HBV-DNA and outcome. The figure shows the relationship between HBV-DNA level and OS (A) or PFS (B) ($n = 20$)

Figure 5B). Interestingly, we noticed that patients who received antiviral prophylaxis during chemotherapy cycles had a significantly inferior OS and PFS compared with those who did not obtain HBV-directed treatment ($P = .04$ and $P = .003$, respectively, Figure 6A,B).

Overall, nine patients (26%) died in the course of the disease. In two cases (6%), the reason of death was a septic complication during chemotherapy. The other seven patients (21%) died due to progression of DLBCL. The both patients who had HBV-DNA $\geq 2 \times 10^7$ IU/L were treated with R-CHOP-like regimen and simultaneous antiviral therapy with entecavir ($n = 1$) or lamivudine ($n = 1$),

respectively. One of the both patients reached CR after the first-line therapy. The cause of death was rapid progression of DLBCL in the both patients.

4 | DISCUSSION

We retrospectively analyzed demographic characteristics, therapy, baseline serological HBV markers, and their association with OS and PFS in patients diagnosed with both HBV infection and DLBCL.

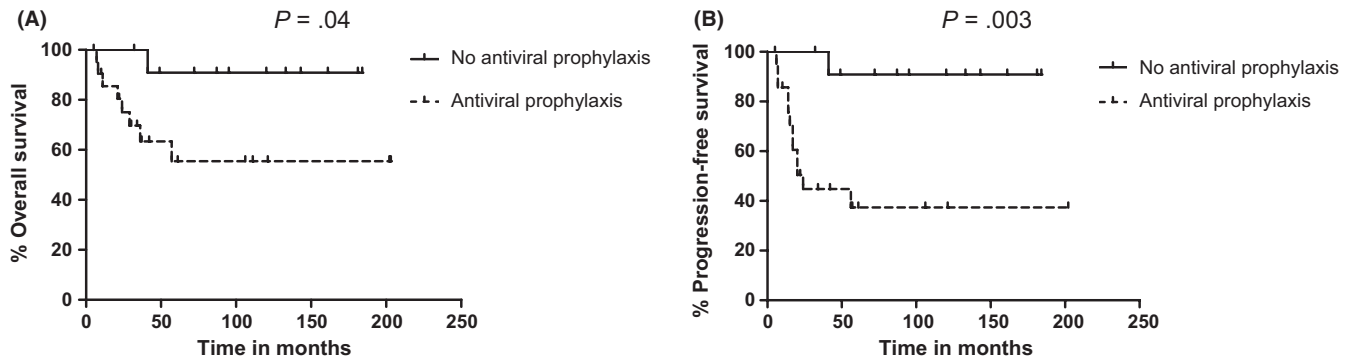


FIGURE 6 Antiviral prophylaxis and outcome. The figure shows the relationship between antiviral prophylaxis and OS (A) or PFS (B) ($n = 34$)

Positive HBsAg status indicates a current HBV infection, and the development of anti-HBs antibodies correlates generally with an immune response to HBV.¹¹ In the current study, we observed that baseline HBsAg status did not significantly affect OS and PFS of patients with both HBV infection and DLBCL. Comparably, a study of Wang et al showed no statistically significant difference in OS between HBsAg positive and negative DLBCL patients.¹² Moreover, Law et al¹³ reported that HBsAg positive DLBCL patients had a statistically not significant trend toward superior OS compared with HBsAg negative patients possibly due to the regular use of antiviral prophylaxis. By contrast, several other studies suggested that HBsAg positivity might indicate an inferior OS and/or PFS of patients with DLBCL.^{9,14-16} In these previous studies, the HBsAg negative group included also DLBCL without HBV infection. However, no anti-HBc negative cases could be detected in our cohort. Although the HBsAg negative group seemed to have a better PFS as compared with HBsAg positive patients, this difference was not statistically significant. At present, the relationship between anti-HBs status and survival of patients with both HBV infection and DLBCL was rarely reported. In our study, baseline anti-HBs status had no influence on OS and PFS in patients with HBV infection and DLBCL.

We observed that anti-HBe positive patients had a significantly superior OS and PFS compared with anti-HBe negative patients. Similarly, HBeAg positivity might indicate an inferior OS and PFS. However, the prognostic impact was not statistically significant. We could not identify any literature addressing the relationship between HBeAg and/or anti-HBe status and outcome of patients with both HBV infection and DLBCL. HBeAg is a serum marker that correlates with high HBV replication, and the presence of anti-HBe indicates a seroconversion with the loss of replicating virus—although reversion to HBeAg positivity can also occur.¹¹ Our results suggested that high activity of viral replication at baseline might be associated with poor outcome of patients with concurrent HBV infection and DLBCL. However, due to the limited number of cases and the missing data in our study, the results should be interpreted with caution and investigated in further studies.

Previous studies demonstrated that viremia with HBV-DNA $\geq 2 \times 10^7$ IU/L is correlated with a significantly inferior survival

outcome of patients with both HBV infection and DLBCL. For instance, Xie et al reported that HBV-DNA $>1 \times 10^3$ copies/mL at least at one time point during chemotherapy was associated with inferior OS of patients with both HBV infection and DLBCL.¹⁶ In the current guideline of the European Association for the Study of the Liver (EASL), HBV-DNA $\geq 2 \times 10^7$ IU/L is an indication for antiviral treatment in patients with HBV regardless of the degree of liver fibrosis.¹⁷ Our findings suggested that viremia with HBV-DNA $\geq 2 \times 10^7$ IU/L might also indicate an inferior survival of patients with both HBV infection and DLBCL. Of note, patients with high HBV activity did not suffer liver failure, but septic complication during chemotherapy or progression of DLBCL was the leading causes of death in the current study.

Interestingly, our results showed that patients who received antiviral prophylaxis during chemotherapy cycles had a significantly inferior OS and PFS compared with those who didn't obtain HBV-directed treatment. However, in patients without antiviral prophylaxis, eight patients (67%) were anti-HBe positive, while the rate of anti-HBe positivity was only 45% ($n = 10$) in the group of patients with antiviral prophylaxis. Moreover, no patient had a HBV-DNA $\geq 2 \times 10^7$ IU/L in the group without antiviral prophylaxis. As mentioned, HBV-DNA $< 2 \times 10^7$ IU/L and anti-HBe positivity were positive prognostic factors in patients with both HBV infection and DLBCL. Therefore, it is unsurprising to see the superior survival outcome of patients with antiviral prophylaxis compared with patients who received no antiviral prophylaxis. However, this finding might be a bias due to the more usual use of antiviral agents in patients with higher HBV activity. It was demonstrated in a recent study that HBV-DNA monitoring guided antiviral prophylaxis was effective in preventing HBV reactivation during CD20-antibody-containing immuno-chemotherapy in NHL patients with resolved HBV infection.¹⁸ In the current guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO), antiviral prophylaxis is recommended to prevent reactivation in patients with a history of HBV infection.¹⁹

There are several limitations of our current study. First, due to the small number of cases and the high proportion of missing data in our analysis, our results should be interpreted with caution and evaluated in larger studies. Second, in our cohort, not all virological



markers of HBV infection were regularly tested in the screening at diagnosis of DLBCL, and therefore, patients with occult HBV infection (ie, isolated positive HBV-DNA) could not be retrospectively identified. Third, HBV-DNA in serum may fluctuate in the course of disease. It has been shown that the status of the virological markers at baseline is dependent on different phases of HBV infection.^{17,20} These aspects are not reflected in the current analysis. Fourth, due to the limited number of cases, we didn't perform a multivariate analysis using cox regression model, which is more feasible for larger sample size. However, despite these limitations, our findings provided rationale for further investigations.

In summary, our findings suggested that high HBV activity with negative anti-HBe is associated with a less favorable survival outcome in patients with both HBV infection and DLBCL. Therefore, reducing the viral activity with early initiation of antiviral therapy could be relevant in these patients.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest relevant to the submitted manuscript.

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