Hepatology International (2019) 13:407–415
https://doi.org/10.1007/s12072-019-09966-z

REVIEW ARTICLE

Prediction and clinical implications of HBV reactivation in lymphoma patients with resolved HBV infection: focus on anti-HBs and anti-HBc antibody titers

Tsutomu Nishida[1] · Tokuhiro Matsubara[1] · Takayuki Yakushijin[2] · Masami Inada[1]

Received: 4 May 2019 / Accepted: 25 June 2019 / Published online: 9 July 2019

Abstract
Hepatitis B virus (HBV) reactivation (HBV-R) and hepatitis related to HBV-R are well-recognized complications that occur in patients who have undergone cytotoxic chemotherapy or immunosuppressive therapy. The degree of HBV-R in this population varies from self-limited or asymptomatic hepatitis to acute liver failure, which may lead to life-threatening events. However, no established treatment or standard surveillance method exists for monitoring patients to predict the development of HBV-R during or after chemotherapy or immunosuppressive therapy, particularly regarding resolved HBV infection. Prophylactic antiviral agents and regular monitoring of HBV-DNA levels are known to be useful methods for preventing HBV-R; however, these methods require considerable financial resources, and such resources are limited in the endemic areas of HBV infection. Most patients with resolved HBV infection do not develop a hepatitis flare or self-limited HBV-R with only an increase in HBV DNA. However, some patients may develop HBV-R even 1 year or more after the last chemotherapy treatment. Therefore, predicting the development of HBV-R and its timing is difficult, and exploring markers that could help predict whether or when HBV reactivation occurs is necessary. In this review, we address the predictive risk factors for HBV-R in patients with resolved HBV infection, focusing on the ability of anti-HBs and anti-HBc to predict HBV-R. We conclude that the combination of anti-HBc and anti-HBs titers may be a reliable and useful predictor for managing HBV-R.

Keywords HBV reactivation · Anti-HBs · Anti-HBc · Resolved HBV infection

Introduction

Hepatitis B virus (HBV) reactivation (HBV-R) is a well-recognized complication that occurs in patients who have undergone cytotoxic chemotherapy or immunosuppressive therapy [1]. In 1975, Wands et al. first reported that patients with HBsAg developed hepatitis with an increase in HBsAg titer during chemotherapy [2]. In 1994, Chazouilleres et al. reported that de novo hepatitis arising from a resolved HBV infection or "occult" HBV was commonly found in patients who had undergone liver transplantation [3]. Moreover, in 1999, Crespo et al. first reported the case of a patient with a resolved HBV infection who had acute liver failure after orthotopic liver transplantation [4]. However, currently, universal screening for HBV infection is not always performed in patients diagnosed with cancer [1]. The degree of HBV-R in this population varies from self-limited or asymptomatic hepatitis to acute liver failure, which may lead to life-threatening events [2, 5, 6]. The risk of HBV-R can be divided into 3 categories based on previous evidence: high (> 10%), moderate (1–10%), or low (< 1%) [7–9]. Generally, hepatitis B surface antigen (HBsAg)-negative, hepatitis B core antibody (anti-HBc)-positive patients with hepatitis that is considered resolved have a lower risk of HBV-R than do HBsAg-positive patients, especially if HBV-DNA levels are elevated [10–13]. However, patients with resolved HBV infection who were treated with rituximab, which most B cell lymphoma patients use, are included in the high-risk group. Retrospective studies conducted in lymphoma patients with resolved HBV infection who did not receive prophylaxis showed that HBV-R occurrence ranges from 2.7

✉ Tsutomu Nishida
tnishida.gastro@gmail.com

[1] Department of Gastroenterology, Toyonaka Municipal Hospital, 4-14-1 Shibahara, Toyonaka, Osaka 560-8565, Japan

[2] Department of Gastroenterology and Hepatology, Osaka General Medical Center, 3-1-56, Bandaihigashi, Sumiyoshi-ku, Osaka 558-0056, Japan

to 24% [14–19]. A prospective study by Seto et al. reported that the cumulative rates of HBV-R at 6 months, 1 year, and 2 years were 23%, 29%, and 45%, respectively [20]. The rates of HBV-R in the prospective study seem higher than those in a retrospective study, but the difference may depend on regular monitoring, the feasibility of regular monitoring or the clinical situation in the study, in addition to a difference in the definition of HBV-R.

In this review, we address the predictive risk factors for HBV-R in patients with resolved HBV infection, focusing on anti-HBs and anti-HBc. According to latest update of the American Association for the Study of Liver Diseases (AASLD) Guidelines in 2018, resolved HBV infection is defined by the sustained loss of HBsAg in a person who was previously HBsAg positive, with undetectable HBV-DNA levels and the absence of clinical or histological evidence of active viral infection [13]; in contrast, the previous AASLD Guidelines in 2016 defined a resolved HBV infection as the clearance of HBs and the acquisition of anti-HBsAg, with no mention of the HBV-DNA status [21]. Therefore, the definitions of resolved HBV infection used in the papers cited in this review differ subtly from this definition, e.g., HBsAg-negative and anti-HBc-positive without the mention of anti-HBs or HBsAg-negative and anti-HBs-positive and/or anti-HBc-positive with or without HBV-DNA-negative as a component.

Guidelines on screening, monitoring and antiviral prophylaxis for HBV-R

Several guidelines on the management of HBV infection have been published and updated for patients undergoing chemotherapy or immunosuppressive therapy [7, 9, 13, 21–26]. The 2007 AASLD guidelines recommend that patients with a high risk of HBV infection should undergo HBsAg screening, but no recommendation was made for HBsAg-negative, anti-HBc-positive patients [26]. Furthermore, the updated 2009 and 2016 AASLD guidelines did not provide an updated description of immunosuppressive or chemotherapy-induced HBV-R [21–27]. The updated 2018 AASLD guidelines recommend that both HBsAg and anti-HBc should be used for HBV screening but not anti-HBs. If a patient is HBsAg-negative but anti-HBc-positive, he or she should be carefully monitored; however, antiviral prophylaxis treatment is recommended for patients using drugs targeting B lymphocytes, such as rituximab, as well as those undergoing stem cell transplantation [13]. The 2012 European Association for the Study of the Liver (EASL) guidelines recommend testing for HBsAg and anti-HBc in all patients who are candidates for chemotherapy or immunosuppressive therapy [7, 27]. Recently, EASL guidelines updated in 2017 recommended starting oral antiviral prophylaxis when a patient was taking drugs targeting B lymphocytes such as rituximab and in high-risk HBV-R cases in addition to monitoring. [25]. The 2012 Asian Pacific Association for the Study of the Liver (APASL) guidelines recommend screening only for HBsAg and additional testing for anti-HBc in cases in which a patient uses biologics such as rituximab or anti-tumor necrosis factor-α [22]. Furthermore, the updated 2015 APASL guidelines recommended that HBsAg-negative, anti-HBc-positive patients with or without anti-HBs positivity should be closely monitored by the detection of HBV DNA during treatment and for at least 12 months after cessation. In particular, regarding patients using rituximab, monitoring should be more frequent, and antiviral prophylaxis should be started upon confirmation of HBV DNA presence [24]. The 2014 Japan Society of Hepatology (JSH) guidelines recommend testing for anti-HBs in addition to HBsAg and anti-HBc [23], although the role of anti-HBs screening prior to treatment has not yet been established [13]. If a patient is positive for HBsAg, prophylactic antiviral therapy is recommended; if a patient is HBsAg-negative but anti-HBc- or anti-HBs-positive, the JSH guidelines recommend testing for HBV DNA and providing antiviral prophylaxis if HBV DNA is detectable. If HBV DNA is not detected, close monitoring is recommended. Universal screening, monitoring and antiviral prophylaxis for HBV-R have not yet been established, particularly for patients with resolved HBV infection, because of the difference in the prevalence of occult HBV infection and the high costs associated with testing for HBV and the administration of prophylactic treatment. Antiviral prophylaxis has been shown to decrease the risk of HBV reactivation [28], and the recent updated guidelines also recommend starting antiviral prophylaxis when using rituximab, which targets B lymphocytes, rather than monitoring if the patient is at high risk of HBV-R, [13, 25], although HBsAg-negative, anti-HBc-positive patients with rheumatological disease [29, 30] or inflammatory bowel disease [31] receiving biological agents have been successfully monitored without prophylaxis. However, prophylactic antiviral agents or regular monitoring of HBV-DNA levels involves considerable financial resources; health care resources are limited because more than one-third of the world's population (an estimated 257 million carriers worldwide [32]) is exposed to HBV, and 75% of these individuals live in endemic areas, such as Japan, Southeast Asia and the Western Pacific regions [33, 34]. In such regions, universal HBV testing prior to immunosuppressive treatment or chemotherapy is recommended [23, 24]. Therefore, an exploration of predictive factors for HBV reactivation and stratification of the risk of HBV-R among patients with resolved HBV infection are needed.

Prediction of HBV-R by anti-HBs titers in patients with resolved HBV infection

Although only the JSH guidelines recommend testing for anti-HBs antibody prior to treatment, anti-HBs titers at baseline were known to predict the risk for developing HBV-R. Hsu et al. reported that in a group of lymphoma patients with resolved hepatitis B infection, patients with HBV-R were less likely to be positive for anti-HBs at baseline, but no other clinical predictive factors for HBV-R exist [35]. Seto et al. reported that negative anti-HBs (< 10 mIU/ml) at baseline was the only significant predictive factor for HBV-R in patients with resolved hepatitis B infection [20]. By using multivariate analysis, Kusumoto et al. also found that negative anti-HBs at baseline (adjusted hazard ratio [HR], 20.6; 95% confidential interval [CI] 3.9–106) and anti-HBs at 10–100 mIU/ml (adjusted HR, 5.2; 95% CI 1.0–26) were independent risk factors for HBV reactivation compared with higher titers of ≥ 100 mIU/ml [36]. Cho et al. reported that patients with resolved HBV infection and high baseline anti-HBs (100 mIU/ml) experienced a significantly lower risk of HBV reactivation than patients with low baseline anti-HBs (< 100 mIU/ml) among patients without antiviral prophylaxis [37]. The authors suggested that patients with higher anti-HBs (≥ 100 mIU/ml) at baseline could be carefully monitored for alanine aminotransferase (ALT) and HBV-DNA levels without antiviral prophylaxis [37].

A recent meta-analysis of 20 studies that included 1672 patients with resolved HBV who received chemotherapy for hematological malignancies also revealed that anti-HBs positivity was associated with a decreased risk of HBV-R and concluded that future studies should examine the effects of anti-HB titers [38]. We previously reported that anti-HB titer cutoff values of 28 mIU/ml using receiver operating characteristic (ROC) curve analysis can be used for predicting HBV-R (area under the curve (AUC), 0.725). Patients with lower anti-HBs titers (< 28 mIU/ml) experienced a significantly higher rate of HBV-R than patients with higher anti-HBs titers ($p = 0.031$) [19]. Based on these results, use of an optimal cutoff value of anti-HB titers to predict HBV-R may be useful. However, whether anti-HBs positivity protects against reactivation remains uncertain; Seto et al. did not identify the cutoff levels of anti-HBs to address this question [20]. Some studies showed a low risk of HBV-R in anti-HBc-positive, anti-HBs-negative patients [39, 40]. Moreover, some studies revealed that the anti-HBs titer decreased after chemotherapy or the administration of biologic agents [41–44]. We speculate that this variation in anti-HBs titers caused by treatment is the reason for the conflicting results. Therefore, anti-HBs-positive at the baseline may not be enough to suggest that the risk of HBV-R in patients in resolved HBV infection is relatively low (Table 1). Anti-HBs titers may actually indicate the underlying viral activity rather than acting as a protective factor. Individuals with inactive viral replication will have lower HBsAg levels and subsequently lower capacity to bind to anti-HBs to form complexes, leading to a higher detectable anti-HBs titer. Conversely, lower anti-HBs titers may reflect higher viral activity, with more HBsAg binding to anti-HBs, leading to a lower detectable anti-HBs titer.

Tables 1, 2, and 3 show the articles identified via a Medline search using the following terms: (HBV reactivation [ALL] AND lymphoma [ALL]) AND resolved hepatitis B [ALL]. Additional studies were located through manual searches of references. We excluded non-English publications, reviews, meta-analyses and publications not focusing on anti-HBs or anti-HBc titers.

Prediction of HBV-R using a combination of anti-HBc and anti-HBs titers in patients with resolved hepatitis B infection

Recently, we published a paper reporting that the combination of anti-HBc and anti-HBs levels is useful for predicting the development of HBV-R in lymphoma patients with resolved HBV infection [19]. Our results demonstrated that HBV-R occurred more often in lymphoma patients with higher anti-HBc titers at baseline than in patients with lower anti-HBc titers and suggested that anti-HBc was a significant predictive marker for HBV-R by univariate and multivariate analysis. Therefore, we set anti-HBc titer cutoff values that revealed 10 samples per cutoff (S/CO) using ROC curve analysis (AUC: 0.616). However, using a titer cutoff of 10 S/CO for anti-HBc did not have sufficient predictive value because of low accuracy [19]. Therefore, we grouped the patients by a combination of a high (C^{high}) or low anti-HBc titer (C^{low}) and high (S^{high}) or low (S^{low}) anti-HBs titer. The $C^{high}S^{high}$ and $C^{high}S^{low}$ groups were collectively analyzed as C^{high} because they had similarly high rates of HBV-R. Finally, we divided the patients into 3 groups according to HBV-R risk: C^{high}, $C^{low}S^{low}$ and $C^{low}S^{high}$. The HBV-R rates of the C^{high}, $C^{low}S^{low}$ and $C^{low}S^{high}$ groups were 35.7% (5/14), 21.7% (5/23) and 0% (0/40), respectively. This study was, however, a single-center, retrospective study and had several limitations due to the nature of the study. Recently, Yang et al. conducted a prospective study of HBV-R in lymphoma patients with resolved HBV infection, and the authors also reported that the combination of anti-HBs and anti-HBc levels may predict HBV-R [45]. According to the ROC analysis, the anti-HBs and anti-HBc titer cutoff values for predicting HBV-R were 56.48 mIU/ml and 6.41 IU/ml, respectively (Tables 2, 3), which suggests that anti-HBs

Table 1 HBV reactivation in lymphoma patients with resolved hepatitis B according to anti-HBs titers

	HBV reactivation (+)	HBV reactivation (−)	*p* value*
Hsu et al. 2014 [35]	Anti-HBs positive, *N* = 116		0.0107
N = 150	9, 7.8%	107, 92%	
	Anti-HBs negative, *N* = 34		
	8, 24%	26, 76%	
Seto et al. 2014 [20]	Anti-HBs positive, *N* = 49		0.0354
N = 63	11, 22%	38, 78%	
	Anti-HBs negative, *N* = 14		
	8, 57%	8, 57%	
Kusumoto et al. 2015 [36]	Anti-HBs positive, *N* = 220		0.0004
N = 220	12, 4.4%	208, 96%	
	Anti-HBs negative, *N* = 48		
	10, 21%	38, 79%	
Lu et al. 2015 [64]	Anti-HBs positive, *N* = 104		0.008
N = 150	0, 0%	104,100%	
	Anti-HBs negative, *N* = 46		
	4, 8.7%	42, 91%	
Cho et al. 2016 [37]	Anti-HBs titers ≥ 100 mIU/ml, *N* = 51		0.0050
N = 108	0, 0%	51, 100%	
	Anti-HBs titers < 100 mIU/ml, *N* = 57		
	8, 14%	48, 86%	
Matsubara et al. 2017 [19]	Anti-HBs titers ≥ 28 mIU/ml, *N* = 49		0.0178
N = 73	3, 6.1%	46, 94%	
	Anti-HBs titers < 28 mIU/ml, *N* = 28		
	7, 25%	21, 75%	
Yang et al. 2018 [45]	Anti-HBs titers ≥ 56.8 mIU/ml, *N* = 105		0.0001
N = 192	3, 2.9%	102, 97%	
	Anti-HBs titers < 28 mIU/ml, *N* = 87		
	18, 21%	69, 79%	
Guo et al. 2018 [65]	Anti-HBs titers ≥ 100 mIU/ml, *N* = 21		
N = 166	0, 0%	0, 0%	
	Anti-HBs titers 10–100 mIU/ml, *N* = 97		
	8, 8.3%	89, 92%	
	Anti-HBs negative, *N* = 48		
	9, 19%	9, 19%	

Anti-HBs levels with a lower limit of detection of 10 mIU/ml are defined as anti-HBs negative

*Chi-square test

may be a better predictive marker than anti-HBc as a single marker. Further evaluation of the optimal cutoff titers may be needed, although they may depend on the region or the results of anti-HBc measurement assays.

Quantification and measurement of anti-HBc

HBV has an inner nucleocapsid component of HBc antigen (HBc-Ag), which can usually be detected in the nucleus or cytoplasm of hepatocytes in the liver. HBV infection induces an immune response to HBc-Ag, producing an anti-HBc antibody [46] that may be the only serological marker for detecting chronic HBV infections and could potentially be a better marker than HBV DNA for HBV infection. HBV DNA is not detectable in most patients who are only anti-HBc positive [47], but low levels of HBV DNA cannot be excluded by a negative HBV DNA result. However, the standard of quantification of anti-HBc may not yet have been established. Recent immunoassays for anti-HBc are remarkably specific, but instrument failures and washing errors can occur, or serum sampling could be contaminated. Radioimmunoassay has been shown to be more specific than enzyme immunoassay for anti-HBc detection; however, radioimmunoassay is not currently available in clinical practice, and thus,

Table 2 HBV reactivation in lymphoma patients with resolved hepatitis B according to anti-HBc titers

	HBV reactivation (+)	HBV reactivation (−)	*p* value*
Chen et al. 2015 [66]	Anti-HBc positive, *N* = 55		0.001
N = 165	6, 11%	49, 89%	
	Anti-HBc negative, *N* = 110		
	0, 0%	110, 100%	
Matsubara et al. 2017 [19]	Anti-HBc titers > 10 mIU/ml, *N* = 14		0.0052
N = 77	5, 36%	9, 64%	
	Anti-HBs titers < 10 mIU/ml, *N* = 63		
	5, 7.9%	58, 92%	
Yang et al. 2018 [45]	Anti-HBc titers ≥ 6.41 mIU/ml, *N* = 69		0.0003
N = 197	15, 22%	54, 78%	
	Anti-HBc titers < 6.41 mIU/ml, *N* = 123		
	6, 5%	117, 95%	
Guo et al. 2018 [65]	Anti-HBc positive, *N* = 118		0.021
N = 166	8, 6.8%	110, 93%	
	Anti-HBc negative, *N* = 48		
	9, 19%	39, 81%	

*Chi-square test

Table 3 HBV reactivation in lymphoma patients with resolved hepatitis B according to combination anti-HBs and anti-HBc titers

	No. of patients	No. of HBV reactivation
Matsubara et al. 2017 [19]		
Cutoff titers: anti-HBc 10 S/CO, anti-HBs 28 mIU/ml		
$C^{high}S^{low}$	9	2, 22%
$C^{high}S^{high}$	5	3, 60%
$C^{low}S^{low}$	23	5, 22%
$C^{low}S^{high}$	40	0, 0%
Yang et al. 2018 [45]		
Cutoff titers: anti-HBc 6.41 IU/ml, anti-HBs 56.48 mIU/ml		
$C^{high}S^{low}$	36	14, 39%
$C^{high}S^{high}$	33	1, 3.0%
$C^{low}S^{low}$	51	4, 7.8%
$C^{low}S^{high}$	72	2, 2.8%

In Matsubara et al. [19], the authors collectively analyzed the $C^{high}S^{high}$ and $C^{high}S^{low}$ groups as one C^{high} group because they had similarly high rates of HBV-R. The HBV-R rates of the C^{high}, $C^{low}S^{low}$ and $C^{low}S^{high}$ groups were 35.7% (5/14), 21.7% (5/23) and 0% (0/40), respectively. The C^{high} and $C^{low}S^{low}$ groups experienced significantly higher rates of HBV-R than did the $C^{low}S^{high}$ group ($p \leq 0.0001$ and $p = 0.002$, according to the Kruskal–Wallis non-parametric test)

Yang et al. [45] showed that either C^{high} or S^{low} was significantly associated with a higher risk of HBV reactivation (HR: 4.52 and 8.48, $p = 0.0018$, $p = 0.00006$, respectively) using the Cox proportional hazards model

enzyme immunoassays are mainly used. Interestingly, however, 26% of patients who were positive only for anti-HBc by enzyme immunoassay were found to be negative for anti-HBc after retesting by radioimmunoassay [48]. Although WHO has a standard for anti-HBc to quantify concentrations of antibodies, no FDA-approved confirmatory assay for anti-HBc is available. The Architect chemiluminescent microparticle immunoassay (CMIA) and double-antigen sandwich enzyme-linked immunosorbent assay (ELISA) are available for measuring anti-HBc titers. Compared with those assays, sandwich ELISA has a two- to fourfold higher analytical sensitivity and a higher sensitivity and specificity than Abbott Architect CMIA (97.1% and 99.7% vs. 99.7% and 100%, respectively) [49]. The Japanese Red Cross blood centers have reported that blood donors with low anti-HBc titers between 1.0 and 11.9 S/CO could have low amounts of HBV DNA, suggesting occult HBV infection, and a higher anti-HBc titer above 12.0 S/CO is more likely to suggest past or present infection [50]. Recently, Caviglia et al. demonstrated that an anti-HBc titer above 4.4 on the CO index was independently associated with the detection of intrahepatic HBV cccDNA using an in-house droplet digital PCR assay [51]. Recently hepatitis B core-related antigen (HBcrAg) has also been identified as a significant risk factor for HBV reactivation in a prospective study [52]. However, based on the above evidence, a lower titer of anti-HBc may have a possibility of false-positive or false-negative results. Therefore, predicting HBV-R among patients with a lower anti-HBc titer may not be enough. Our proposed cutoff titer of approximately 10 S/CO for predicting HBV-R is a relatively high titer and seems to be within the error tolerance level. In addition, the combination of anti-HBc and anti-HBs titers may be a more reliable and useful predictor for managing HBV-R.

How often and for how long should we continue HBV DNA monitoring?

The timing of onset of HBV reactivation can vary greatly depending on the host status. Onset may occur at any time from within the first 2 weeks of initiation of chemotherapy to a year or more after the cessation of chemotherapy. Therefore, predicting the timing of HBV-R prior to therapy is difficult. Determining the duration of HBV DNA monitoring is a considerable problem with high medical costs. Recently, updated EASL guidelines indicated that high-risk HBV-R patients should receive antiviral prophylaxis for at least 12 months (18 months for rituximab use) after cessation of treatment and discontinue it if the disease is under remission [25]. Monitoring should also continue for at least 12 months after antiviral prophylaxis. Similarly, a recent AASLD guideline says that high-risk patients using rituximab should receive antiviral prophylaxis for at least 12 months after cessation of treatment, but the duration of monitoring was not addressed; however, patients without prophylaxis should be monitored for up to 12 months after the cessation of treatment [13]. For patients on immunosuppressive therapy, the JSH guidelines recommend that HBV-DNA levels should be monitored on a monthly basis for at least 6 months after commencement or alteration (including cessation) of treatment. After 6 months, the interval and duration should be tailored to the individual therapy regimen, but the guidelines do not describe the length of the monitoring period [23].

Generally, after chemotherapy or immunosuppressive therapy, most patients have been followed for approximately 1 year because most cases of HBV reactivation occurred within 1 year [53]. In clinical practice, the duration of HBV DNA monitoring depends on the individual physician in cases where patients achieve remission. Hui et al. reported that the median time to HBV-R in lymphoma patients with resolved HBV infection was 18.5 weeks after starting chemotherapy (range 12–28 weeks) [6]. Earlier reports tended to show that HBV-R occurred within 1 year after the completion of chemotherapy or immunosuppressive therapy. Cases of HBV-R occurring beyond 1 year after the completion of treatment are described as late onset. In particular, patients using rituximab should be monitored [54, 55]. A recent Japanese multicenter study revealed that 36% of patients with HBV-R were late-onset [56]. In a case report, Yamada et al. reported a late-onset flare hepatitis case in which a lymphoma patient with resolved HBV infection developed HBV-R 33 months after the completion of chemotherapy with rituximab. Therefore, late-onset HBV-R is not uncommon with increased awareness of HBV-R. This patient showed an anti-HBs titer of 52.9 mIU/ml and an anti-HBc titer of 9.9 (unit not described) at baseline. According to our criteria, he was classified into the $C^{low}S^{high}$ group with a very low risk of HBV-R, even though his anti-HBc titers were borderline for our cutoff of 10 S/CO [57]. Interestingly, in our cohort, the C^{high} group experienced a significantly shorter time to HBV-R than the $C^{low}S^{high}$ group ($p < 0.0001$), which did not completely reactivate.

The frequency of HBV DNA monitoring is important as is the monitoring duration. The updated 2018 ASLD guidelines and the JSH guidelines recommend monitoring HBV-DNA levels every 1-3 months [13, 23]. In addition, the JSH guidelines indicate that the interval of monitoring should be tailored to the individual therapy regimen [23].

In cases of liver transplantation, the maintenance of an anti-HBs titer > 100 IU/L by the administration of hepatitis B immunoglobulin (HBIG) is important for preventing HBV recurrence in HBV-DNA-negative patients before transplantation, as confirmed by multicenter studies in Europe and the United States [58–62]; however, maintaining anti-HBs titers of more than 100 mIU/ml/ml by passive HBIG is expensive and inconvenient, and it is probably more feasible to administer antiviral prophylaxis [63]. Similarly, anti-HBs titers of more than 100 mIU/ml at the baseline can confer a low risk of HBV-R, but the anti-HBs titer decreases due to chemotherapy or immunosuppressive therapy [41–44]. Therefore, a higher titer of anti-HBs when stopping close monitoring or tailored monitoring may be a predictive marker because anti-HBs is considered a neutralizing antibody.

Conclusions and implications

Predictive risk factors for HBV-R in patients with resolved HBV infection undergoing high-risk immunosuppressive therapy are not still established and pose a challenge to researchers. The combination of anti-HBc and anti-HBs titers may be a reliable and useful predictor for managing HBV-R because anti-HBs is considered a neutralizing antibody for HBV infection, and anti-HBc titers may reflect the residual HBV replication in HBV-DNA-negative patients with resolved HBV infection. However, it is known that antibody titers change significantly during chemotherapy, and the decrease in anti-HBs titers may be more important for predicting HBV-R. To clarify the importance of anti-HBs and anti-HBc antibody titers to the prediction of HBV-R, we need to assess the changes in titers over time and their associations with the outcomes in the future; furthermore, it is necessary to identify patients who will most benefit from prophylactic nucleoside analog treatment.

Author contributions TN wrote the initial draft of the manuscript. TY, TM and MI critically reviewed the manuscript.

Compliance with ethical standards

Conflict of interest Tsutomu Nishida, Tokuhiro Matsubara, Takayuki Yakushijin and Masami Inada declare no conflict of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Nishida T, Hiramatsu N, Mizuki M, Nagatomo I, Kida H, Tazumi K, et al. Managing hepatitis B virus carriers with systemic chemotherapy or biologic therapy in the outpatient clinic. Hepatol Res 2013;43(4):339–346. https://doi.org/10.1111/j.1872-034X.2012.01073.x **(Epub 2012/08/14)**
2. Wands JR, Chura CM, Roll FJ, Maddrey WC. Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. Gastroenterology 1975;68(1):105–112 **(Epub 1975/01/01)**
3. Chazouilleres O, Mamish D, Kim M, Carey K, Ferrell L, Roberts JP, et al. "Occult" hepatitis B virus as source of infection in liver transplant recipients. Lancet 1994;343(8890):142–146 **(Epub 1994/01/15)**
4. Crespo J, Fabrega E, Casafont F, Rivero M, Heras G, de la Pena J, et al. Severe clinical course of de novo hepatitis B infection after liver transplantation. Liver Transpl Surg 1999;5(3):175–183. https://doi.org/10.1002/lt.500050301 **(Epub 1999/05/05)**
5. Lau JY, Lai CL, Lin HJ, Lok AS, Liang RH, Wu PC, et al. Fatal reactivation of chronic hepatitis B virus infection following withdrawal of chemotherapy in lymphoma patients. Q J Med 1989;73(270):911–917 **(Epub 1989/10/01)**
6. Hui CK, Cheung WW, Zhang HY, Au WY, Yueng YH, Leung AY, et al. Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. Gastroenterology 2006;131(1):59–68. https://doi.org/10.1053/j.gastro.2006.04.015
7. European Association For The Study Of The L. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012;57(1):167–185. https://doi.org/10.1016/j.jhep.2012.02.010
8. Lampertico P, Maini M, Papatheodoridis G. Optimal management of hepatitis B virus infection—EASL Special Conference. J Hepatol 2015;63(5):1238–1253. https://doi.org/10.1016/j.jhep.2015.06.026 **(Epub 2015/07/08)**
9. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT, American Gastroenterological Association I. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148(1):215–219. https://doi.org/10.1053/j.gastro.2014.10.039 **(Epub 2014/12/03)**
10. Lau GK, Leung YH, Fong DY, Au WY, Kwong YL, Lie A, et al. High hepatitis B virus (HBV) DNA viral load as the most important risk factor for HBV reactivation in patients positive for HBV surface antigen undergoing autologous hematopoietic cell transplantation. Blood 2002;99(7):2324–2330 **(Epub 2002/03/16)**
11. Yeo W, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, et al. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. Br J Cancer 2004;90(7):1306–1311. https://doi.org/10.1038/sj.bjc.6601699 **(Epub 2004/04/01)**
12. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148(1):221–244. https://doi.org/10.1053/j.gastro.2014.10.038 **(Epub 2014/12/03)**
13. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67(4):1560–1599. https://doi.org/10.1002/hep.29800 **(Epub 2018/02/07)**
14. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 1991;100(1):182–188 **(Epub 1991/01/01)**
15. Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 2009;27(4):605–611. https://doi.org/10.1200/JCO.2008.18.0182
16. Matsue K, Kimura S, Takanashi Y, Iwama K, Fujiwara H, Yamakura M, et al. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. Cancer 2010;116(20):4769–4776. https://doi.org/10.1002/cncr.25253
17. Evens AM, Jovanovic BD, Su YC, Raisch DW, Ganger D, Belknap SM, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol 2011;22(5):1170–1180. https://doi.org/10.1093/annonc/mdq583 **(Epub 2010/12/01)**
18. Kim SJ, Hsu C, Song YQ, Tay K, Hong XN, Cao J, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. Eur J Cancer 2013;49(16):3486–3496. https://doi.org/10.1016/j.ejca.2013.07.006 **(Epub 2013/08/06)**
19. Matsubara T, Nishida T, Shimoda A, Shimakoshi H, Amano T, Sugimoto A, et al. The combination of anti-HBc and anti-HBs levels is a useful predictor of the development of chemotherapy-induced reactivation in lymphoma patients with resolved HBV infection. Oncol Lett 2017;14(6):6543–6552. https://doi.org/10.3892/ol.2017.7012
20. Seto WK, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, et al. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. J Clin Oncol 2014;32(33):3736–3743. https://doi.org/10.1200/JCO.2014.56.7081
21. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63(1):261–283. https://doi.org/10.1002/hep.28156 **(Epub 2015/11/14)**
22. Liaw YF, Kao JH, Piratvisuth T, Chan HL, Chien RN, Liu CJ, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int 2012;6(3):531–561. https://doi.org/10.1007/s12072-012-9365-4
23. Drafting Committee for Hepatitis Management G, the Japan Society of H. JSH Guidelines for the Management of Hepatitis B Virus Infection. Hepatology Research 2014;44(Suppl S1):1–58. https://doi.org/10.1111/hepr.12269
24. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10(1):1–98. https://doi.org/10.1007/s12072-015-9675-4
25. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370–398. https://doi.org/10.1016/j.jhep.2017.03.021 **(Epub 2017/04/22)**
26. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45(2):507–539. https://doi.org/10.1002/hep.21513

27. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50(3):661–62. https://doi.org/10.1002/hep.23190
28. Yeo W, Chan PK, Ho WM, Zee B, Lam KC, Lei KI, et al. Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. J Clin Oncol 2004;22(5):927–934. https://doi.org/10.1200/JCO.2004.05.161 **(Epub 2004/03/03)**
29. Barone M, Notarnicola A, Lopalco G, Viggiani MT, Sebastiani F, Covelli M, et al. Safety of long-term biologic therapy in rheumatologic patients with a previously resolved hepatitis B viral infection. Hepatology 2015;62(1):40–46. https://doi.org/10.1002/hep.27716 **(Epub 2015/01/24)**
30. Tamori A, Koike T, Goto H, Wakitani S, Tada M, Morikawa H, et al. Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. J Gastroenterol 2011;46(4):556–564. https://doi.org/10.1007/s00535-010-0367-5 **(Epub 2011/01/20)**
31. Papa A, Felice C, Marzo M, Andrisani G, Armuzzi A, Covino M, et al. Prevalence and natural history of hepatitis B and C infections in a large population of IBD patients treated with anti-tumor necrosis factor-alpha agents. J Crohns Colitis 2013;7(2):113–119. https://doi.org/10.1016/j.crohns.2012.03.001 **(Epub 2012/04/03)**
32. Organization WH. Hepatitis B. 2018. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Accessed 5 May 2019
33. Ganem D, Prince AM. Hepatitis B virus infection–natural history and clinical consequences. N Engl J Med 2004;350(11):1118–1129. https://doi.org/10.1056/NEJMra031087
34. Lok AS, Lai CL, Wu PC, Wong VC, Yeoh EK, Lin HJ. Hepatitis B virus infection in Chinese families in Hong Kong. Am J Epidemiol 1987;126(3):492–499
35. Hsu C, Tsou HH, Lin SJ, Wang MC, Yao M, Hwang WL, et al. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: a prospective study. Hepatology 2014;59(6):2092–2100. https://doi.org/10.1002/hep.26718
36. Kusumoto S, Tanaka Y, Suzuki R, Watanabe T, Nakata M, Takasaki H, et al. Monitoring of hepatitis B Virus (HBV) DNA and risk of HBV reactivation in B-cell lymphoma: a prospective observational study. Clin Infect Dis 2015;61(5):719–729. https://doi.org/10.1093/cid/civ344
37. Cho Y, Yu SJ, Cho EJ, Lee JH, Kim TM, Heo DS, et al. High titers of anti-HBs prevent rituximab-related viral reactivation in resolved hepatitis B patient with non-Hodgkin's lymphoma. J Med Virol 2016;88(6):1010–1017. https://doi.org/10.1002/jmv.24423
38. Paul S, Dickstein A, Saxena A, Terrin N, Viveiros K, Balk EM, et al. Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy: a meta-analysis. Hepatology 2017;66(2):379–388. https://doi.org/10.1002/hep.29082 **(Epub 2017/01/28)**
39. Koo YX, Tay M, Teh YE, Teng D, Tan DS, Tan IB, et al. Risk of hepatitis B virus (HBV) reactivation in hepatitis B surface antigen negative/hepatitis B core antibody positive patients receiving rituximab-containing combination chemotherapy without routine antiviral prophylaxis. Ann Hematol 2011;90(10):1219–1223. https://doi.org/10.1007/s00277-011-1241-0 **(Epub 2011/04/27)**
40. Targhetta C, Cabras MG, Mamusa AM, Mascia G, Angelucci E. Hepatitis B virus-related liver disease in isolated anti-hepatitis B-core positive lymphoma patients receiving chemo- or chemoimmune therapy. Haematologica 2008;93(6):951–952. https://doi.org/10.3324/haematol.12557 **(Epub 2008/06/03)**
41. Pei SN, Ma MC, Wang MC, Kuo CY, Rau KM, Su CY, et al. Analysis of hepatitis B surface antibody titers in B cell lymphoma patients after rituximab therapy. Ann Hematol 2012;91(7):1007–1012. https://doi.org/10.1007/s00277-012-1405-6 **(Epub 2012/01/26)**
42. Yilmaz B, Erdem D, Teker F, Goren I, Yildirim B, Kut E, et al. The effect of anticancer therapy on anti-hepatitis B antibody titres in patients with haematological malignancies and solid tumours. J Int Med Res 2016;44(3):627–638. https://doi.org/10.1177/0300060516638992 **(Epub 2016/04/07)**
43. Yagci M, Suyani E, Kizil Cakar M. The Impact of chemotherapy on hepatitis B antibody titer in patients with hematological malignancies. Turk J Haematol 2015;32(3):251–256. https://doi.org/10.4274/tjh.2013.0342 **(Epub 2015/09/18)**
44. Papalopoulos I, Fanouriakis A, Kougkas N, Flouri I, Sourvinos G, Bertsias G, et al. Liver safety of non-tumour necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: an observational, controlled, long-term study. Clin Exp Rheumatol 2018;36(1):102–109 **(Epub 2017/08/30)**
45. Yang HC, Tsou HH, Pei SN, Chang CS, Chen JH, Yao M, et al. Quantification of HBV core antibodies may help predict HBV reactivation in patients with lymphoma and resolved HBV infection. J Hepatol 2018;69(2):286–292. https://doi.org/10.1016/j.jhep.2018.02.033
46. Milich DR, McLachlan A. The nucleocapsid of hepatitis B virus is both a T-cell-independent and a T-cell-dependent antigen. Science 1986;234(4782):1398–1401
47. Raimondo G, Pollicino T, Cacciola I, Squadrito G. Occult hepatitis B virus infection. J Hepatol 2007;46(1):160–170. https://doi.org/10.1016/j.jhep.2006.10.007 **(Epub 2006/11/23)**
48. Silva AE, McMahon BJ, Parkinson AJ, Sjogren MH, Hoofnagle JH, Di Bisceglie AM. Hepatitis B virus DNA in persons with isolated antibody to hepatitis B core antigen who subsequently received hepatitis B vaccine. Clin Infect Dis 1998;26(4):895–897 **(Epub 1998/06/13)**
49. Li A, Yuan Q, Huang Z, Fan J, Guo R, Lou B, et al. Novel double-antigen sandwich immunoassay for human hepatitis B core antibody. Clin Vaccine Immunol 2010;17(3):464–469. https://doi.org/10.1128/CVI.00457-09 **(Epub 2010/01/29)**
50. Satake M, Taira R, Yugi H, Hino S, Kanemitsu K, Ikeda H, et al. Infectivity of blood components with low hepatitis B virus DNA levels identified in a lookback program. Transfusion 2007;47(7):1197–1205. https://doi.org/10.1111/j.1537-2995.2007.01276.x **(Epub 2007/06/22)**
51. Caviglia GP, Abate ML, Tandoi F, Ciancio A, Amoroso A, Salizzoni M, et al. Quantitation of HBV cccDNA in anti-HBc-positive liver donors by droplet digital PCR: a new tool to detect occult infection. J Hepatol 2018;69(2):301–307. https://doi.org/10.1016/j.jhep.2018.03.021 **(Epub 2018/04/06)**
52. Seto WK, Wong DK, Chan TS, Hwang YY, Fung J, Liu KS, et al. Association of hepatitis B core-related antigen with hepatitis B virus reactivation in occult viral carriers undergoing high-risk immunosuppressive therapy. Am J Gastroenterol 2016;111(12):1788–1795. https://doi.org/10.1038/ajg.2016.436 **(Epub 2016/09/21)**
53. Zoppoli G, Bruzzone B, Caligiuri P, Picciotto A, Balleari E, Bruzzone A, et al. From a medical mistake to a clinical warning: the case of HBV mutant virus reactivation in haematological patients. Br J Haematol 2009;144(6):969–970. https://doi.org/10.1111/j.1365-2141.2008.07539.x
54. Liu WP, Wang XP, Zheng W, Ping LY, Zhang C, Wang GQ, et al. Hepatitis B virus reactivation after withdrawal of prophylactic antiviral therapy in patients with diffuse large B cell lymphoma. Leuk Lymphoma 2016;57(6):1355–1362. https://doi.org/10.3109/10428194.2015.1116121 **(Epub 2016/01/05)**
55. Nakaya A, Fujita S, Satake A, Nakanishi T, Azuma Y, Tsubokura Y, et al. Delayed HBV reactivation in rituximab-containing chemotherapy: How long should we continue anti-virus prophylaxis or monitoring HBV-DNA? Leuk Res 2016;50:46–49. https://doi.org/10.1016/j.leukres.2016.09.014 **(Epub 2016/10/27)**

56. Takahashi H, Ikeda M, Kumada T, Osaki Y, Kondo S, Kusumoto S, et al. Multicenter cooperative case survey of hepatitis B virus reactivation by chemotherapeutic agents. Hepatol Res 2015. https://doi.org/10.1111/hepr.12496
57. Yamada T, Nannya Y, Suetsugu A, Shimizu S, Sugihara J, Shimizu M, et al. Late reactivation of hepatitis B virus after chemotherapies for hematological malignancies: a case report and review of the literature. Intern Med 2017;56(1):115–118. https://doi.org/10.2169/internalmedicine.56.7468
58. Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med 1993;329(25):1842–1847. https://doi.org/10.1056/NEJM199312163292503 **(Epub 1993/12/16)**
59. Muller R, Samuel D, Fassati LR, Benhamou JP, Bismuth H, Alexander GJ. 'EUROHEP' consensus report on the management of liver transplantation for hepatitis B virus infection. European Concerted Action on Viral Hepatitis. J Hepatol 1994;21(6):1140–1143 **(Epub 1994/12/01)**
60. Devlin J, Smith HM, O'Grady JG, Portmann B, Tan KC, Williams R. Impact of immunoprophylaxis and patient selection on outcome of transplantation for HBsAg-positive liver recipients. J Hepatol 1994;21(2):204–210 **(Epub 1994/08/01)**
61. Konig V, Hopf U, Neuhaus P, Bauditz J, Schmidt CA, Blumhardt G, et al. Long-term follow-up of hepatitis B virus-infected recipients after orthotopic liver transplantation. Transplantation 1994;58(5):553–559 **(Epub 1994/09/15)**
62. Polak WG, Gladysz A, Rotter K. Prevention of hepatitis B recurrence after liver transplantation. Ann Transplant 2005;10(3):11–16 **(Epub 2006/04/19)**
63. Wong TC, Fung JY, Cui TY, Lam AH, Dai JW, Chan AC, et al. Liver transplantation using hepatitis B core positive grafts with antiviral monotherapy prophylaxis. J Hepatol 2019. https://doi.org/10.1016/j.jhep.2019.03.003 **(Epub 2019/03/16)**
64. Lu S, Xu Y, Mu Q, Cao L, Chen J, Zhu Z, et al. The risk of hepatitis B virus reactivation and the role of antiviral prophylaxis in hepatitis B surface antigen negative/hepatitis B core antibody positive patients with diffuse large B-cell lymphoma receiving rituximab-based chemotherapy. Leuk Lymphoma 2015;56:1027–1032
65. Guo YF, Pan JX, Zhuang WH. Concurrent and reactivation of hepatitis B virus infection in diffuse large B-cell lymphoma: risk factors and survival outcome. Infect Agent Cancer 2018;13:40
66. Chen KL, Chen J, Rao HL, Guo Y, Huang HQ, Zhang L, et al. Hepatitis B virus reactivation and hepatitis in diffuse large B-cell lymphoma patients with resolved hepatitis B receiving rituximab-containing chemotherapy: risk factors and survival. Chin J Cancer 2015;34:225–234