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Role of Surface Antibody in Hepatitis B Reactivation in Patients with Resolved Infection and Hematologic Malignancy: A Meta-Analysis

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Abstract

Patients with resolved hepatitis B virus (HBV) infection who are treated for hematological malignancies remain at risk for HBV reactivation. Because of conflicting studies about whether the antibody to hepatitis B surface antigen (anti-HBs) protects against reactivation in patients with resolved infection (hepatitis B surface antigen negative) receiving chemotherapy for hematological malignancies, we conducted a meta-analysis to determine if anti-HBs reduces HBV reactivation risk. We sought English language studies through March 1, 2016 in Medline and other sources that examined reactivation in patients with resolved HBV infection receiving chemotherapy for hematologic malignancies. The absolute risks and odds ratio (OR) of reactivation with versus without anti-HBs were estimated in random-effects model meta-analyses. In 20 studies involving 1672 patients not receiving antiviral prophylaxis, the reactivation risk was 14% (95% CI 9.4 – 19%) in 388 patients who had antibodies to hepatitis B core antigen (anti-HBc) only versus 5.0% (95% CI 3.0 – 7.0%) in 1284 patients who also had anti-HBs. Anti-HBs reduced reactivation risk with a pooled OR of 0.21 (95% CI 0.14–0.32) versus patients with anti-HBc only. Similar results were found when limiting the analysis to rituximab chemotherapy (OR 0.19, 95% CI 0.11 – 0.32) and lymphoma (OR 0.18, 95% CI 0.11 – 0.28).

Conclusion: In patients with resolved HBV receiving chemotherapy for hematological malignancies without antiviral prophylaxis, anti-HBs-positivity is associated with a decreased risk of reactivation. HBV screening in this patient population should include the routine use of anti-HBs and those that are anti-HBs negative should receive antiviral prophylaxis. Future studies should examine the effect of anti-HBs serum titers, the potential role for booster vaccinations, and antiviral prophylaxis prior to chemotherapy in this patient population.

Keywords

lymphoma; cancer; oncology; chemotherapy; hepatitis b core antibody

Hepatitis B virus (HBV) reactivation in the setting of immunosuppressive therapy, and in particular chemotherapy, has garnered increasing attention (1–5) because reactivation can lead to hepatitis, liver failure, and death and also interrupt or delay treatment (6). The risk of reactivation depends on HBV serological status and the intensity of chemotherapy regimens (1, 2, 4, 7). Those with chronic HBV infection (positive hepatitis B surface antigen [HBsAg]) receiving rituximab-based chemotherapy or bone marrow transplantation have the highest risk of reactivation, ranging from 30 to 80% in the absence of antiviral prophylaxis (7).

Patients with resolved HBV infection (defined as negative HBsAg, positive anti-HBc, and positive anti-HBs) and past HBV infection (defined as negative HBsAg, positive anti-HBc, and negative or unknown HBsAb) remain at risk for reactivation, particularly when receiving rituximab-based chemotherapy with reactivation rates as high as 16% (8). However, whether a positive antibody to hepatitis B surface antigen (anti-HBs) protects against reactivation remains uncertain. Previous studies have suggested that decreased anti-HBs titer levels or absence of pre-treatment anti-HBs are risk factors for reactivation in hematological malignancies (9, 10). Conversely, other studies have shown a low risk of reactivation in those who are solely positive for anti-HBc but negative for anti-HBs (11, 12), leading to recent reviews questioning the protective effects of anti-HBs for HBV reactivation (1, 8).

Given the limited and conflicting data, we conducted a systematic review and meta-analysis to quantify the overall risk of HBV reactivation in patients with resolved or past HBV infection who receive chemotherapy for hematological malignancies and then quantify reactivation in those who are positive for anti-HBc with versus without anti-HBs. Of note, resolved and past HBV infection have been used interchangeably in studies and will be combined and reported as resolved HBV in the current meta-analysis.

Methods

Search Strategy

We searched MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials, and Scopus from 1965 to March 1, 2016 using 3 index search themes (hepatitis B virus, cancer chemotherapy, and virus reactivation; see eFigure 1). The search was restricted to published papers in English. Conference abstracts and proceedings, letters to the editor, and case reports were excluded. To identify other potential studies, we also examined reference

lists of review articles and previous meta-analyses and contacted authors of included studies with incomplete data. We adhered to systematic review and meta-analysis methodology consistent with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (13). We also developed and followed an unregistered protocol.

Study Selection

Two independent investigators (SP and AS) reviewed all citations for relevance, and discrepancies were settled through consultation with a third investigator (JW). We included published studies of patients with resolved HBV infection undergoing chemotherapy for any hematological malignancy, with or without concomitant HBV prophylaxis therapy. Resolved HBV infection was defined serologically (prior to chemotherapy initiation) as negative HBsAg and positive anti-HBc with or without anti-HBs. Studies had to report anti-HBs status to be included.

The primary outcome was HBV reactivation as defined by detectable or increase in HBV DNA levels from baseline or the re-emergence of HBsAg (or HBsAg seroconversion), as specified by authors. We included randomized controlled trials (RCTs) and observational comparative studies (retrospective or prospective). Studies had to include more than 5 patients and report a minimum of 1-month follow-up results. Studies with pediatric populations (age < 18 years), solid cancers, transplantation (including solid organ and bone marrow or hematopoietic stem cell), HIV, hepatitis C, or autoimmune conditions were excluded.

Data Extraction

Data were extracted by one researcher (SP) and verified by another independent researcher (AD). Pre-specified data extraction forms included study author, country, design, patient age and sex, HBV serology (including presence of HBsAg, anti-HBc, and anti-HBs), type of malignancy, chemotherapy received, antiviral prophylaxis (if any), and study follow-up period. If a study involved both solid and hematological malignancies, only the hematological malignancy data were extracted.

Quality Assessment

We used the Newcastle-Ottawa Scale (NOS) for observational studies (14) to assess study quality. A maximum of 9 points were awarded to each study: 4 points for patient selection, 2 points for comparability between study groups through design or analysis, and 3 points for outcome assessment and adequacy of follow up. Studies with zero points for at least 4 elements in the scale were considered low quality. Additionally, those studies not reporting demographic information (including patient age and sex) or total follow-up duration (all studies were followed for at least 1 month per inclusion criteria) were considered to be low quality.

Data Synthesis & Statistical Analysis

We estimated the absolute likelihood of HBV reactivation using pooled estimates of risk. Because of the low number of events, an arcsine transformation was applied to the risk estimates to stabilize the variance (15). Both the transformed risk estimates and the odds

ratios (OR) of HBV reactivation with versus without anti-HBs were meta-analyzed using a random-effects model (DerSimonian & Laird). For studies reporting zero events, we added a 0.5 correction factor to calculate the OR. The I^2 statistic was used to evaluate heterogeneity between studies with 0 to 40% considered to be low, 41 to 60% moderate, 61 to 80% substantial, and 81 to 100% considerable heterogeneity (16). A funnel plot and the Harbord test (17) assessed the relationship between study precision and treatment effect for the primary outcome. Statistical analyses were performed with OpenMetaAnalyst (18) and the metafor package in R, version 3.2.1 (R Foundation for Statistical Computing; (19). Pre-specified subgroup analyses explored differences in reactivation by rituximab-based chemotherapy, lymphoma malignancies, and geographic region. In addition, sensitivity analyses examined study design (retrospective versus prospective) and study quality.

Results

In the 2,248 citations identified through database searches, 20 original reports met eligibility criteria (Figure 1). Of the 19 observational studies, 11 were prospective (10, 20–29) and 8 were retrospective (9, 30–36). One RCT compared entecavir HBV prophylaxis (before chemotherapy) versus entecavir treatment for HBV reactivation (37).

Study and Patient Characteristics

Table 1 summarizes the baseline study characteristics. The 20 studies consisted of 1713 patients with complete serology data for analysis (range 8–234). Of these patients, only 41 patients in 1 study received antiviral prophylaxis (37). When reported, the median patient age across studies was 64 years (range 18–90) with 707 males and 552 females. Seventeen studies were from Asian countries and 3 from Italy. Fourteen studies examined only lymphoma while 3 included other hematological malignancies, e.g., leukemia and multiple myeloma. Chemotherapy regimens differed across studies with only rituximab used in 10 studies with complete HBV serologies.

The definition of HBV reactivation varied with 9 studies defining it as HBV DNA levels above a cutoff (7 studies used >10-fold increase versus previous nadir (23, 25, 28, 32, 34–36) and 2 studies used >10 IU/mL (21, 22)). Four studies simply defined reactivation as detectable HBV DNA (24, 27, 30, 37). Six studies used HBV detection with or without conversion from HBsAg negative to positive (9, 10, 20, 31, 33). One study used conversion to HBsAg positivity for reactivation (26). Only 3 studies provided information on serum titers of anti-HBs (22, 30, 31).

Quality Assessment

Based on the NOS quality scale items, all studies scored well on exposure ascertainment, outcome assessment, and absence of the outcome at study onset (eTable 1). However, because the primary purpose of these studies was to report reactivation in resolved HBV infection, demographic information was unavailable for the two cohorts with and without HBsAb, making it difficult to assess whether selection bias affected the cohort with anti-HBc alone. For RCTs, the Cochrane Collaboration's tool for assessing risk of bias is usually used to assess study quality. In the one RCT in this meta-analysis (37), patients were

randomized for treatment (to either entecavir or control) and not based on the presence of anti-HBs. As a result, the NOS scale was extrapolated to assess quality. In 7 low quality studies (Table 1, eTable1), 5 did not have both follow-up time and demographic information (26–28, 32, 35), 1 had incomplete demographic information (24), and one did not specify follow-up time (10).

HBV Reactivation in Patients without Antiviral Prophylaxis

In the 1672 patients in 20 studies with resolved HBV infection who did not receive antiviral prophylaxis, the overall risk of reactivation was 7.2% (95% CI 5.0 – 10%). In 800 patients from 10 studies (9, 20–23, 25, 33, 34, 36, 37) receiving rituximab chemotherapy, reactivation risk was 10% (95% CI 5.8–16%) versus a 4.0% risk (95% CI 2.2 – 6.3%) in 580 patients from 8 studies (20, 24, 30–32, 34–36) receiving non-rituximab chemotherapy. In 1142 lymphoma patients from 14 studies (10, 21–23, 25, 27, 28, 33–37), reactivation occurred in 8.0% (95% CI 4.0–11%).

In 388 patients who were only anti-HBc positive (anti-HBs negative) the risk of reactivation was 14% (95% CI 9.4 – 19%) compared to 5.0% (95% CI 3.0 – 7.0%) in 1284 patients who also had anti-HBs. Similar results with decreased reactivation risk in anti-HBs positive patients were seen when the data were analyzed by rituximab chemotherapy, lymphoma, and geographic region (Table 2).

A positive anti-HBs versus only anti-HBc reduced reactivation with a pooled OR of 0.21 (95% CI 0.14 – 0.32, Figure 2, (9, 10, 20–28, 30–37)). The regression test for funnel plot asymmetry was not significant ($p = 0.84$). In 800 patients from 10 studies (9, 20–23, 25, 33, 34, 36, 37) receiving only rituximab-based chemotherapies, anti-HBs versus only anti-HBc reduced reactivation with an OR 0.19 (95% CI 0.11 – 0.31, Figure 3). A similar trend was seen in 580 patients receiving non-rituximab based therapies but did not reach statistical significance (0.46, 95% CI 0.20 – 1.1). In 1142 lymphoma patients from 14 studies, (9, 10, 21–23, 25, 27, 28, 33–37), anti-HBs reduced reactivation with an OR 0.18 (95% CI 0.11 – 0.28, Figure 4) versus anti-HBc only. When analyzed by geographic region, the protective effect of anti-HBs was also significant (Asia OR 0.22, 95% CI 0.14–0.34; Italy OR 0.07, 95% CI 0.01–0.54).

No heterogeneity ($I^2 = 0\%$) was found in any of these analyses. When excluding the 7 low quality studies, the protective effect for positive anti-HBs versus only anti-HBc remained significant (OR 0.21, 95% CI 0.13 – 0.33 without heterogeneity). Anti-HBs significantly decreased HBV reactivation versus anti-HBc only in 12 prospective (including the RCT) and 8 retrospective studies (OR 0.19, 95% CI 0.12 – 0.32 and OR 0.25, 95% CI 0.11 – 0.47 respectively).

HBV Reactivation in Patients with Antiviral Prophylaxis

In the only study with complete serological data for patients receiving antiviral prophylaxis (37), 41 patients received prophylactic entecavir within 1 week before the first course of chemotherapy and continued until 3 months after chemotherapy cessation. Of the 33 patients who received entecavir and were anti-HBs positive, 1 reactivation event occurred (3.0%). No reactivation occurred in 8 patients who were anti-HBc positive alone.

Discussion

In patients with resolved HBV receiving chemotherapy for hematological malignancies, our analysis found that anti-HBs decreased HBV reactivation in the absence of antiviral prophylaxis, with an OR of 0.21 versus those with anti-HBc alone. Similar results were seen when the data were restricted to lymphoma patients or to those receiving only rituximab chemotherapy. Our results demonstrate very different reactivation risks in patients with and without anti-HBs and support the role of screening patients prior to chemotherapy with HBsAg, anti-HBc, and anti-HBs as currently recommended by the Centers for Disease Control and Prevention (38) and the American Association for the Study of Liver Diseases (5).

Two previous reviews have examined the role of anti-HBs in the risk of reactivation in patients with resolved HBV infection (2, 8). One meta-analysis that examined patients receiving rituximab chemotherapy only identified 3 studies involving 145 patients and found a non-significant reduction in reactivation risk in patients with measurable anti-HBs (OR 0.08, $p=0.151$, (8)). Similar to our results, the American Gastroenterology Association (AGA) review estimated a 4.3% risk of HBV reactivation in 6 studies involving 252 patients who had anti-HBs and resolved HBV (1). However, they concluded that this risk was only “slightly lower” than the overall HBV reactivation risk in all 401 patients with resolved infection (2). Given these results and the absence of serum anti-HBs titer information in most studies, the AGA currently does not recommend using anti-HBs status to guide antiviral prophylaxis in patients with resolved infection (1).

In contrast to the AGA review, our meta-analysis included 20 studies and 1672 patients. We found an overall 7.5% risk of HBV reactivation, a 10% risk with rituximab-based regimens, 4.0% risk with non-rituximab chemotherapy, and 8% risk in patients with lymphoma, similar to previous reports (2, 39–41). However, in the absence of anti-HBs, the risk of reactivation increased across all groups with the highest risk seen in rituximab chemotherapy (24%) and lymphoma (19%). This increased risk highlights 2 important points. First, routine screening for HBV in the setting of impending immunosuppression should include testing for anti-HBs (in conjunction with HBsAg and anti-HBc) because anti-HBs can help stratify reactivation risk. Second, patients without anti-HBs and resolved HBV infection have an increased risk of reactivation and should receive antiviral prophylaxis in this setting.

The presence of anti-HBs decreased reactivation risk among all groups but did not eliminate the risk. Those that received rituximab continued to have a reactivation risk of 5.6%. Given the increased risk of reactivation associated with rituximab-based therapy, we are in agreement with current guidelines (1) that recommend HBV antiviral prophylaxis in patients receiving rituximab-based regimens regardless of anti-HBs status.

However, management of patients with resolved HBV infection receiving non-rituximab based chemotherapy regimens remains uncertain. We did not find any studies examining the benefits of anti-viral prophylaxis versus vigilant monitoring of serum liver tests and HBV DNA levels. As currently suggested by the AGA, serum anti-HBs titers in those that are anti-HBs positive may help identify when to administer antiviral prophylaxis (1). In one study of

29 patients with lymphoma treated with rituximab, anti-HBs titers fell significantly lower after chemotherapy (42). None of the 10 patients with baseline anti-HBs titers > 100 mIU/mL experienced HBV reactivation, but 8 of 19 patients with baseline titers <100 mIU/mL developed HBV reactivation.

Although nearly all studies in the current meta-analysis did not report anti-HBs levels, we did identify 3 studies measuring baseline serum anti-HBs levels prior to chemotherapy (22, 30, 31). In 230 patients with multiple myeloma, anti-HBs negative status was the only statistically significant risk factor associated with HBV reactivation (31). In 24 patients with adult T-cell leukemia and lymphoma treated with mogamulizumab (an anti-CC chemokine receptor 4 monoclonal antibody), 2 of 13 patients with serum anti-HBs titers <100 mIU/mL developed reactivation, and 1 of 11 patients with higher titers developed reactivation (30). In patients with lymphoma undergoing rituximab-based chemotherapy, undetectable anti-HBs at baseline was the only factor statistically significantly associated with HBV reactivation with a hazard ratio of 3.51 (95% CI 1.37 to 8.98) (22). Given these findings, measuring serum titers of anti-HBs should be explored in future research as an additional reactivation risk predictor.

Given the important role of anti-HBs in HBV reactivation, 2 bone marrow transplantation studies suggest that augmenting the anti-HBs response with HBV vaccination may be beneficial (43, 44). In a cohort of 46 patients who received allogeneic bone marrow transplants, 21 received a standard 3-dose hepatitis B vaccine in the post-transplant period. Of the 25 non-vaccinated patients, 12 experienced HBV reactivation compared to none of the 21 vaccinated patients after a median follow up period of 60 months (43). Interestingly, even those patients who were vaccinated but remained anti-HBs negative averted HBV reactivation. Further vaccination investigations may be warranted for patients with hematological malignancies receiving chemotherapy, especially rituximab.

The current analysis is limited to hematological malignancies. A previous review examined the risk of HBV reactivation in those with resolved HBV infection and solid tumors (45). The reactivation risk ranged from 0.3 to 9.0% (median 3.0%) in 3 studies of 328 patients. Anti-HBs status was not reported in these studies to determine its role in HBV reactivation.

Our review has several limitations. First, the majority of the studies were observational, and some had missing demographic or clinical information and follow-up duration that influenced study quality. Study quality was difficult to assess with regards to selection bias and comparability between the two groups (with and without anti-HBs) and none of the studies had blinded outcome assessment. Notably, however, excluding poor quality studies did not appreciably affect the results. Second, no studies reported clinical meaningful endpoints such as delayed chemotherapy, liver failure, need for transplantation, tumor response, and cancer-related and all cause-mortality following HBV reactivation. Anti-HBs titer levels were also unavailable in the majority of the studies. Studies also used different HBV DNA assays with various sensitivities that could have potentially affected the results of the analysis. Additionally, a large proportion of the studies were from Asia potentially limiting the generalizability of the results to regions where the HBV prevalence is lower. Lastly, although the funnel plot asymmetry test was not significant, publication bias is still

possible as studies were limited to the publication in English language journals and excluded conference proceedings.

Conclusions

In patients with resolved HBV receiving chemotherapy for hematological malignancies, our results found the presence of anti-HBs decreased risk of HBV reactivation. This finding supports the inclusion of anti-HBs in screening protocols prior to chemotherapy for hematological malignancy with antiviral prophylaxis for those that are anti-HBs negative. Future studies should examine the effect of serum anti-HBs titers and the role of HBV vaccination on reactivation risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations.

HBV	Hepatitis B Virus
HBsAg	Hepatitis B surface antigen
Anti-HBc	Antibody to hepatitis B core antigen
Anti-HBs	Antibody to hepatitis B surface antigen
RCT	Randomized controlled trial

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Figure 1.
Flow diagram of study selection process

Figure 2.
Odds Ratio of HBV Reactivation With vs. Without anti-HBs in Patients with Resolved HBV and All Hematological Malignancies

Figure 3.

Odds Ratio of HBV Reactivation With vs. Without anti-HBs in Patients with Resolved HBV and Hematological Malignancies receiving Rituximab-based chemotherapy

Figure 4.
Odds Ratio of HBV Reactivation With vs. Without anti-HBs in Patients with Resolved HBV and Lymphoma

TABLE 1.

Study Characteristics Involving Hematologic Tumors and Past HBV Infection

Source	Country	Study Design	Disease	HBV+ Definition *	Total Patients	Rituximab Chemotherapy	Viral Ppx [†]	Male/ Female	Age, Years (Median, Range)	Follow-Up, Months (Median, Range)
Totani et al. ⁽³⁰⁾	Japan	R	T cell leukemia- lymphoma	A	24	N	N/A	12/12	62 (41–77)	7.9 (1.9–47.3)
Pompili et al. ⁽²⁰⁾	Italy	P	Leukemia, lymphoma, MM	B	12	Y (9)	N/A	7/5	60 (43–79)	35 (18–45)
Lee et al. ⁽³¹⁾	Korea	R	MM	B	230	N	N/A	147/83	151 patients <65 years 79 patients >65 years	28.8 (NR)
Kusumoto et al. ⁽²¹⁾	Japan	P	B-cell NHL	C	234	Y (234)	N/A	142/127	65 (IQR 59–70)	18.4 (IQR 18.1–19.1)
Chen et al. ⁽³²⁾	Taiwan	R	AML	D	149	N	N/A	NR	NR	NR
Chen et al. ⁽³³⁾	China	R	DLBCL	B	55	Y (55)	N/A	30/25	54 (18–83)	61 (1–93)
Seto et al. ⁽²²⁾	China	P	Lymphoma	C	63	Y (63)	N/A	25/38	70.9 (38.1–90.2)	16.3 (1.4–24.2)
Lu et al. ⁽²³⁾	China	P	DLBCL	D	147	Y (147)	N/A	90/57	57 (28–87)	28 (2–100)
Matsui et al. ⁽²⁴⁾	Japan	P	Lymphoma, MM	A	59	N	N/A	NR	NR	20.5 (1–58.5)
Huang et al. ⁽³⁷⁾	Taiwan	P	Lymphoma	A	80	Y (80)	41 (ENT) 28/11 Ppx: 26/15	No Ppx: 69.3 (11.3) Ppx: 68.2 (11.2)	No Ppx: 69.3 (11.3) Ppx: 68.2 (11.2)	18 (NR)
Hsu et al. ⁽²⁵⁾	Taiwan	P	B-cell NHL (DLBCL, follicular)	D	150	Y (150)	N/A	81/69	59.5 (27–84)	27.4 (1.1–45.7)
Cheung et al. ⁽³⁴⁾	Hong Kong	R	B-cell lymphoma (DLBCL)	D	9	Y (4)	N/A	6/3	68.5 (55–86)	17 (7–29)
Matsue et al. ⁽⁹⁾	Japan	R	CD20+ B-cell lymphoma	B	56	Y (56)	N/A	37/19	71 (43–90)	24 (NR)
Koo et al. ⁽³⁵⁾	Singapore	R	Lymphoma	D	67	N	L (7)	NR	NR	NR
Ji et al. ⁽³⁶⁾	China	R	CD20+ DLBCL	D	88	Y (43)	N/A	50/38	NR	22 (6–86)
Francisci et al. ⁽²⁶⁾	Italy	P	Liquid, not otherwise specified	E	56	N	N/A	NR	NR	NR
Yeo et al. ⁽¹⁰⁾	China	P	DLBCL	B	46	Y (21)	N/A	26/20	62.5 (40–88)	NR
Hui et al. ⁽²⁹⁾	China	P	Lymphoma	B	152	Y [‡]	N/A	NR	NR	12.4 (0.1–65.0)
Picardi et al. ⁽²⁷⁾	Italy	P	NHL	A	8	N	N/A	NR	NR	NR
Lok et al. ⁽²⁸⁾	Hong Kong	P	NHL	D	45	N	N/A	NR	NR	NR

* HBV reactivation definitions: A, detectable HBV DNA; B, HBV detection with or without conversion from HBsAg-negative to HBsAg-positive; C, HBV DNA > 10 IU/mL; D, HBV DNA > 10-fold increase versus previous nadir; E, conversion from HBsAg-negative to HBsAg-positive.

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[‡]Study included patients with prophylaxis but, given small numbers, was excluded from the analysis.

[‡]Some patients had rituximab, but we were unable to determine numbers with and without anti-HBs.

Abbreviations: AML, acute myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; ENT, entecavir; HBVr, HBV reactivation; IQR, interquartile range; L, lamivudine; MM, multiple myeloma; N/A, not applicable; NHL, non-Hodgkin lymphoma; NR, not reported; P, prospective cohort; Ppx, prophylaxis; R, retrospective cohort.

TABLE 2.

Absolute Risk of HBV Reactivation in All Patients With Resolved HBV and in Those With and Without anti-HBs in the Absence of Antiviral Prophylaxis

Group	Reactivation Risk, % (95% CI)		
	All Patients With Resolved HBV	Anti-HBs-Negative	Anti-HBs-Positive
Overall	7.2 (5.0–10)	14 (9.4–19)	5.0 (3.0–7.0)
Rituximab chemotherapy	10 (5.8–16)	24 (14–34)	5.6 (2.4–8.9)
Nonrituximab chemotherapy	4.0 (2.2–6.3)	4.6 (1.4–7.8)	2.9 (1.3–4.5)
Lymphoma patients	8.0 (4.0–11)	19 (12–27)	4.8 (2.4–7.9)