

## Original Article

# Hepatitis B virus reactivation in receiving prophylactic anti-viral therapy for Chinese HBsAg-positive patients of diffuse large B-cell lymphoma: a meta-analysis

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**Abstract:** Patients with hepatitis B virus (HBV) infection are associated with HBV reactivation without antiviral treatment undergoing conventional chemotherapy. Diffuse large B-cell lymphoma (DLBCL) patients with positive hepatitis B surface antigen (HBsAg) are also high risk. We aim to estimate the risk of HBV reactivation in HBsAg-positive patients receiving prophylactic anti-viral therapy (lamivudine/entecavir) for DLBCL by a systematic review of the English and Chinese language literature. In this study, we found that the rate of HBV reactivation in DLBCL patients with prophylactic anti-viral therapy was remarkably lower than those with no prophylaxis. Risk ratio [RR] was 0.32 (95% CI=0.19-0.54,  $I^2=45.0\%$ ,  $P<0.00001$ ). Pooled risks of HBV reactivation were also calculated. Data from 826 patients in 13 studies were included. Reactivation rate was estimated at 19.8% ( $I^2=44.5\%$ ,  $P<0.001$ ). Pooled risk of HBV reactivation in HBsAg+ patients receiving CHOP was 17.9% ( $I^2=47.6\%$ ,  $P=0.029$ ), and receiving R-CHOP was 20.7% ( $I^2=34.4\%$ ,  $P<0.001$ ). The HBsAg-positive DLBCL patients with anti-viral prophylaxis during chemotherapy is helpful to prevent HBV reactivation. Our meta-analysis confirms potentially critical risks of HBV reactivation in HBV-carrying DLBCL patients receiving an anti-viral therapy prior to CHOP/R-CHOP chemotherapy.

**Keywords:** Meta-analysis, HBV, hepatitis B reactivation, DLBCL, non-Hodgkin's lymphoma

## Introduction

Diffuse large B-cell lymphoma (DLBCL) constitutes the most common type of adult non-Hodgkin's lymphoma (NHL) that occurs in the world [1, 2], which is defined by the World Health Organization (WHO) classification as a heterogeneous group of clinically aggressive malignancy of B lymphocytes. The classical frontline treatment for DLBCL was CHOP regimen, which including cyclophosphamide, vincristine, doxorubicin, and prednisone. With the development of anti-CD20 monoclonal antibody, current treatment for DLBCL is rituximab plus CHOP (R-CHOP) regimen.

About 350 million people were affected by chronic hepatitis B infection (HBsAg-positive),

and many of them are unaware and asymptomatic that they are infected [3-5]. HBV reactivation has been previously reported in various kinds of cancers diagnosed with HBsAg-positive patients who were interfered with chemotherapy agents [6-8]. Therefore, the patients with lymphoma and chronic, HBsAg-positive-HBV have a high risk of HBV reactivation among conventional chemotherapy [9]. HBsAg-positive DLBCL patients are also at a higher risk with HBV reactivation when receiving cytotoxic chemotherapies, which may lead to inhibition of immune system. The reactivation rates range from 20 to 50% [10] and the rate of mortality range from 10 to 40% [11].

Proactive use of nucleoside analogues such as lamivudine, entecavir or tenofovir has been

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shown to largely reduce the risk for HBV reactivation in chronic HBV carriers [12-15]. Therefore, administration of prophylactic lamivudine or entecavir may be the critical path for preventing reactivation of HBV [16, 17]. However, whether a CHOP/RCHOP regimen combined with an anti-viral treatment bear a lower risk of HBV reactivation remains controversial. However, systematic evaluation of the relationship between prophylactic anti-viral therapy and the outcome of HBV-carrying DLBCL patients among chemotherapy is still has not been reported. Therefore, this study has clinical significance for the DLBCL treatment and prevention of HBV infection.

In this study, we completed a systematic review of the relevant literature to evaluate the impact of anti-viral prophylaxis on Chinese HBsAg-positive DLBCL patients during chemotherapy and estimate the pooled risks of HBV reactivation rates.

## Materials and methods

### Literature search strategy

PubMed, Web of science, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Chinese BioMedical Literature (CBM), Wanfang databases and Chinese Technological Journal of Database (VIP) were searched for eligible articles until June 2015 with English and Chinese language publication limitations. The medical subject headings (MeSH) were: diffuse large B-cell lymphoma and HBsAg.

### Quality assessment

The quality of included studies was assessed by three authors, independently (Li J, Zeng Q and Cao K). Ten items were taken from a well-validated checklist and modified (**Table 1**). The items were expressed as questions, and answers were graded as yes (1 point), no (0 points) or unable to determine (0 points). The study quality was assessed on a two-point scale as high ( $\geq 5$  points) or low ( $< 5$  points), only included studies with high grade.

### Inclusion and exclusion criteria

Inclusion criteria: previously diagnosed HBsAg-positive DLBCL patients receiving CHOP or R-CHOP chemotherapy for DLBCL. Lamivudine or entecavir was used prior to chemotherapy; HBV DNA levels and ALT were measured in patients

undergoing therapy; 4. including the data of HBV reactivation.

Exclusion criteria: patients with other primary liver diseases; coinfection with other type hepatitis virus such as hepatitis A, C, D and E virus; absent or inadequate information about study population, HBV status, HBV DNA levels, or lack sufficient information to calculate the 95% confidence intervals (CI); studies with sample size  $< 5$  subjects; reviews, case reports, clinical cases, or letters.

### Outcome measures

For this meta-analysis, the primary outcome of HBsAg-positive patients was the rate of HBV reactivation among chemotherapy for DLBCL. In this review, the definitions of HBV reactivation was defined as an absolute rise of serum HBV DNA exceeding  $> 10^5$  copies/mL, an increase in serum alanine transaminase (ALT) to greater than ten times the baseline levels, or serum HBV DNA turning from negative to positive.

### Statistical analysis

Review Manager 5.1 and Open MetaAnalyst was used for the Meta-analysis. A fixed model effects model was performed to estimate the probabilities of reactivation [18]. For all tests, a  $P$ -value of  $< 0.05$  was considered statistically significant, except for tests of heterogeneity.

### Assessment of heterogeneity

Statistical heterogeneity was calculated by the cochrane chi-square and  $I^2$  test. A  $P$  value  $< 0.05$  was considered statistical heterogeneity existed in the pooled estimates. The  $I^2$  statistic was evaluated as a measure of the degree of heterogeneity among eligible studies. According to the  $I^2$  values (25%, 50%, and 75%; respectively), degrees of heterogeneity were considered low, moderate and high.

## Results

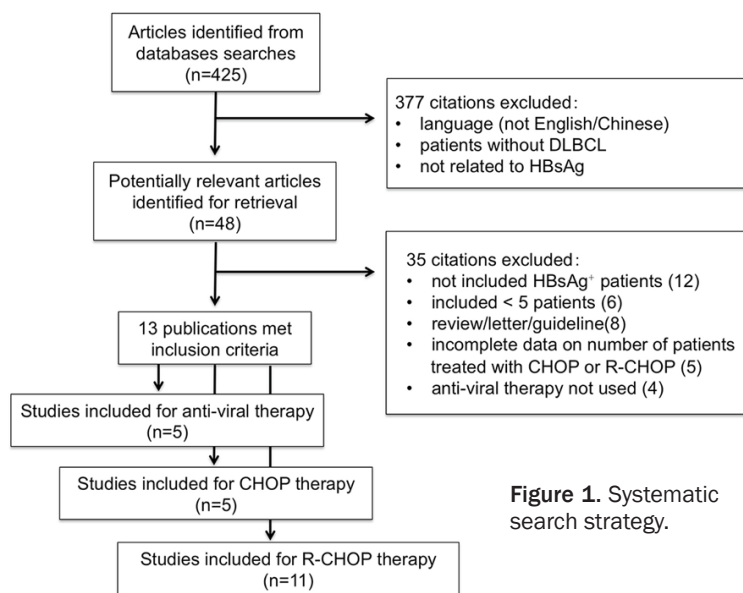
### Characteristics of included trials

As illustrated in **Figure 1**, 425 citations were identified using our search strategy. After title and abstract screening, 48 of those 425 were considered to have potential value. Based on the exclusion criteria and quality assessment (**Table 1**), thirteen studies were finally qualified for in the meta-analysis.

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**Table 1.** Checklist for the quality assessment of published studies

No.	Criteria	Item
1	Objective	Is the aim of study precisely described?
2	Study design	Are the study design and sampling method appropriate for the research question?
3	Study subjects	Are the study subjects pathologically confirmed patients with DLBCL?
4		Is the sample size adequate?
5	Exposure	Do the patients receive formal anti-viral therapy?
6		Do the patients receive formal chemotherapy (CHOP or R-CHOP)?
7	Control group	Is a control group included in the study?
8	Outcome	Is the definitions of HBV reactivation precisely described?
9	Analysis	Are the findings of the study clearly described?
10	Limitations	Were possible methodological limitations of the study discussed?



**Figure 1.** Systematic search strategy.

laxis and non-prophylaxis groups. The number of 159 patients were reported the HBV reactivation rates in the prophylactic anti-viral group, while 123 samples were reported in the control group. After applying the fixed effect model was assessed to analyze heterogeneity, the results of meta-analysis showed that DLBCL patients receiving prophylactic anti-viral had a remarkably reduction in risk of HBV reactivation when comparing non-prophylaxis patients (RR=0.32, 95% CI: 0.19-0.54,  $P < 0.00001$ ; **Figure 2A**).

The main features of studies are presented in **Table 2**. Twelve retrospective studies and one randomized controlled trials was included in eligible studies. In terms of geographic origin, all the studies were completed in Asia, which eleven from China [19-29], one from Hongkong [30], one from Taiwan [31]. After reading the full article and contacting the corresponding authors for detail data, thirteen of the selected studies were able to account the HBV reactivation rates.

### Comparison of HBV reactivation rate between the prophylaxis and non-prophylaxis groups

Five of the thirteen eligible studies accounted the performance of serum HBV-DNA and ALT for detecting HBV reactivation in the prophylaxis

Sensitivity analysis was performed to explore heterogeneity by excluding the study of Lu 2015 [22]. If Lu 2015 [22] was omitted, there was no statistically significant heterogeneity was identified, suggesting that the outcome was relatively stable ( $P=0.94$ ,  $I^2=0.0\%$ , **Figure 2B**). The overall risk estimates did not vary significantly (RR=0.22, 95% CI: 0.11-0.42,  $P < 0.00001$ , **Figure 2B**), indicating no significant variability among the eligible articles.

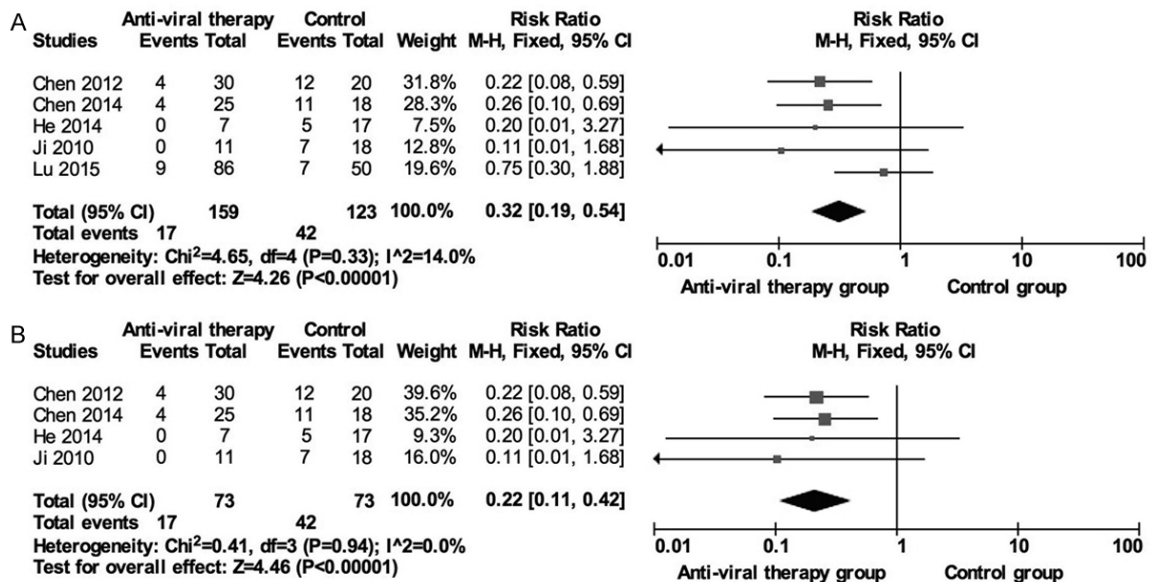
### Meta-analysis of HBV reactivation rate in DLBCL patients receiving prophylactic anti-viral therapy

In this analysis, the pooled standardized HBV reactivation rate among the thirteen selected studies was showed in **Figure 3A**. The results revealed that 165 reactivations of 826 DLBCL

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**Table 2.** Characteristics of 13 included studies

Year	First author	Design	Language	Country of origin	Total HBsAg+ patients	Chemotherapy	Anti-viral therapy	Reactivation rate
2013	Xie [19]	Retrospective	English	China	90	CHOP/R-CHOP	Lamivudine	31/90 (34.4%)
2012	Chen [20]	Retrospective	English	China	30	R-CHOP	Lamivudine	4/30 (13.3%)
2014	Huang [21]	Randomization	English	China	121	R-CHOP	Lamivudine/Entecavir	22/121 (18.2%)
2015	Lu [22]	Retrospective	English	China	136	CHOP/R-CHOP	Lamivudine	16/136 (11.8%)
2008	Wang [23]	Retrospective	English	China	81	CHOP	Lamivudine	38/81 (46.9%)
2015	Guo [24]	Retrospective	English	China	20	CHOP/R-CHOP	Lamivudine/Entecavir	6/20 (30.0%)
2014	Zhao [25]	Retrospective	Chineses	China	74	CHOP/R-CHOP	Lamivudine	9/74 (12.2%)
2014	Chen [26]	Retrospective	Chineses	China	25	R-CHOP	Lamivudine	4/25 (16.0%)
2010	Ji [27]	Retrospective	Chineses	China	11	R-CHOP	Lamivudine/Entecavir	0/11 (0)
2014	He [28]	Retrospective	Chineses	China	10	CHOP	Lamivudine	1/10 (10.0%)
2010	Li [29]	Retrospective	Chineses	China	14	R-CHOP	Lamivudine	4/14 (28.6%)
2015	Law [30]	Retrospective	English	Hong Kong	15	R-CHOP	Lamivudine	3/15 (20.0%)
2014	Wu [31]	Retrospective	English	Taiwan	199	R-CHOP	Entecavir	27/199 (13.6%)



**Figure 2.** Forest plot of HBV reactivation comparison: A: Prophylactic anti-viral therapy vs. no prophylactic anti-viral therapy outcome. B: Sensitivity analysis of the study design on HBV reactivation rate.

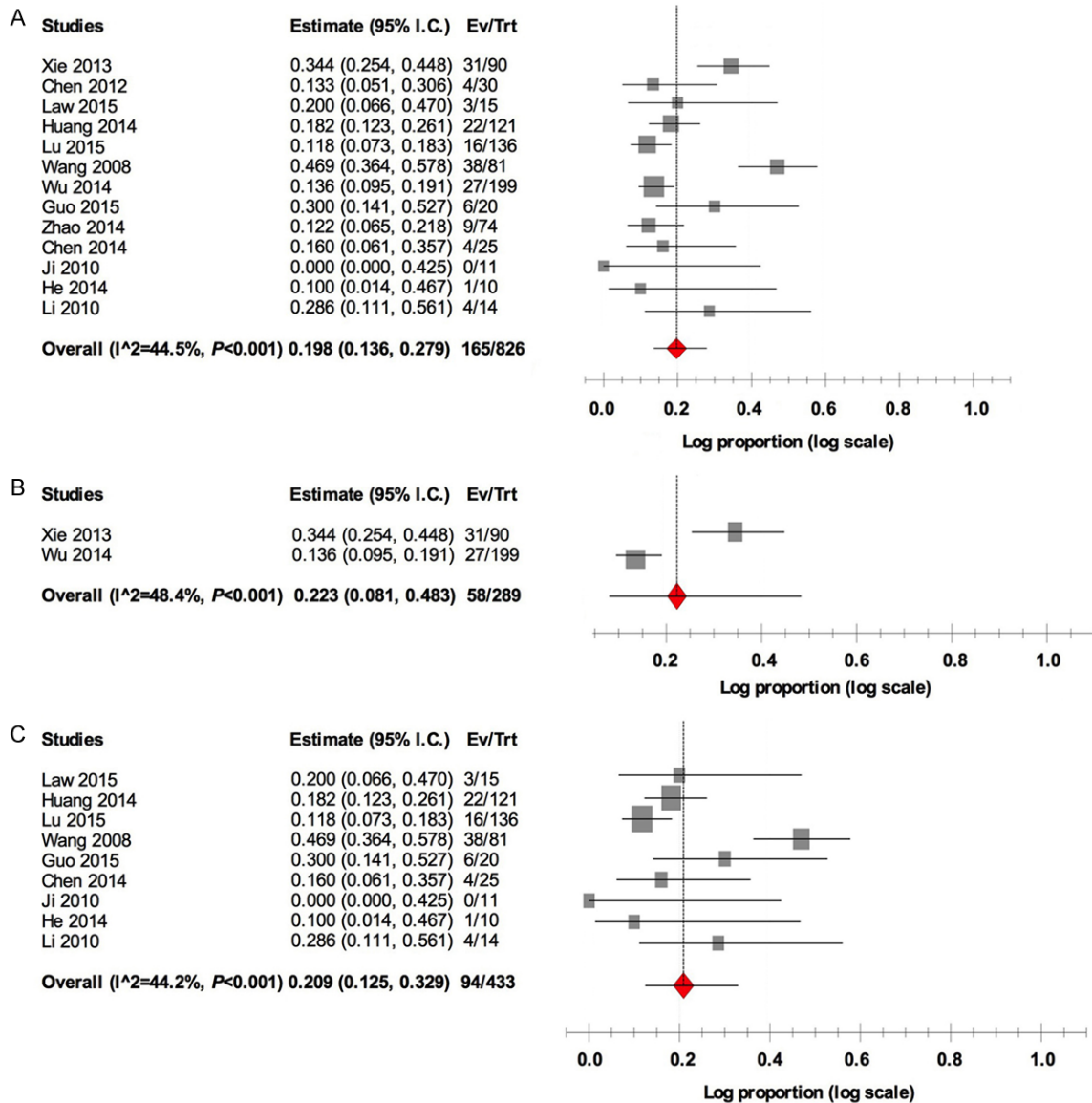
patients and pooled HBV reactivation rate was 19.8% with a moderate degree of statistical heterogeneity ( $I^2=44.5\%$ ,  $P<0.001$ ). Risk estimates for HBV reactivation ranged from 13.6% to 27.9%. To explore the various factors involving the HBV reactivation rate, subgroup analyses were applied to explore source of heterogeneity, including the aspects of definition of HBV reactivation and CHOP/R-CHOP regimen.

Statistical heterogeneity was investigated by analyzing the data according to the definitions of HBV reactivation from different studies. We further pooled HBV reactivation rate among

two studies with HBV reactivation was defined as HBV-DNA absolute rise exceeding  $>10^3$  copies/mL. Meta-analysis result showed that the pooled HBV reactivation rate is 22.3% (58 reactivations of 289 patients). The heterogeneity for this outcome was still moderate (**Figure 3B**;  $I^2=48.4\%$ ,  $P<0.001$ ).

HBV reactivation was further explored by using our standardized definition. Meta-analysis of the nine selected studies resulted in a pooled HBV reactivation rate of 20.9% (94 reactivations of 433 patients). The heterogeneity for this outcome was still moderate (**Figure 3C**;  $I^2=44.2\%$ ,  $P<0.001$ ).

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**Figure 3.** Pooled risk of HBV reactivation in HBsAg+ patients receiving prophylactic anti-viral therapy for DLBCL. A: Pooled overall risk of HBV reactivation in HBsAg+ patients. B: When the analysis was limited to studies reporting HBV-DNA absolute rise exceeding  $>10^3$  copies/mL was defined HBV reactivation, a pooled HBV reactivation rate of 22.3%. C: Pooled risk of HBV reactivation using our standardized definition.

The HBV reactivation rate in subgroup analyses that was mostly similar to the overall result. These results suggesting that variation is unlikely to be due to difference in definition of HBV reactivation alone.

### Meta-analysis of HBV reactivation rate in HBsAg+ DLBCL patients receiving prophylactic anti-viral therapy among CHOP regimen

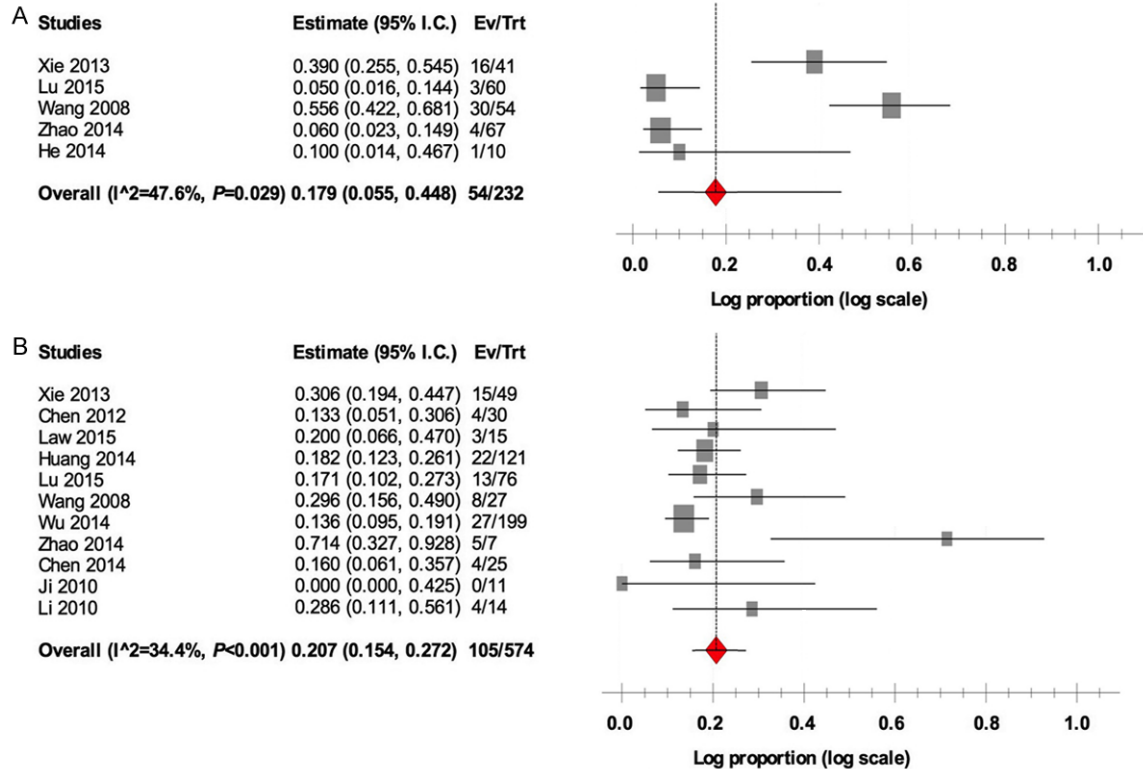
We further explored the statistical heterogeneity by analyzing the data by the chemotherapy regimen. The pooled HBV reactivation rate among the five eligible studies was presented

in **Figure 4A**. The meta-analysis result revealed that 54 reactivations of 232 DLBCL patients and pooled HBV reactivation rate was 17.9%. Risk estimates for HBV reactivation ranged from 5.5% to 44.8%. There was a moderate degree of statistical heterogeneity for this outcome ( $I^2=47.6\%$ ,  $P=0.029$ ).

### Meta-analysis of HBV reactivation rate in HBsAg+ DLBCL patients receiving prophylactic anti-viral therapy among R-CHOP regimen

The result of subgroup analysis was presented in **Figure 4B**, when the HBV reactivation

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**Figure 4.** Pooled risk of HBV reactivation in HBsAg+ patients receiving prophylactic anti-viral therapy for DLBCL among (A) CHOP regimen and (B) R-CHOP regimen.

rate is pooled among the eleven studies with R-CHOP regimen. The meta-analysis result revealed that 105 reactivations of 574 DLBCL patients and pooled HBV reactivation rate was 20.7%. 95% CI of HBV reactivation ranged from 15.4% to 27.2%. The heterogeneity for this outcome was moderate ( $I^2=34.4\%$ ,  $P<0.001$ ).

### Publication bias

The funnel plot ( $OR \times SE(\log[OR])$ ) was performed to assess publication bias for visual examination (**Figure 5A**), revealing no significant asymmetry in the included studies of this meta-analysis. However, this could be incidental account for the small number of studies included. Publication bias was assessed by MetaAnalyst, the funnel plot (**Figure 5B**) also revealed no significant asymmetry.

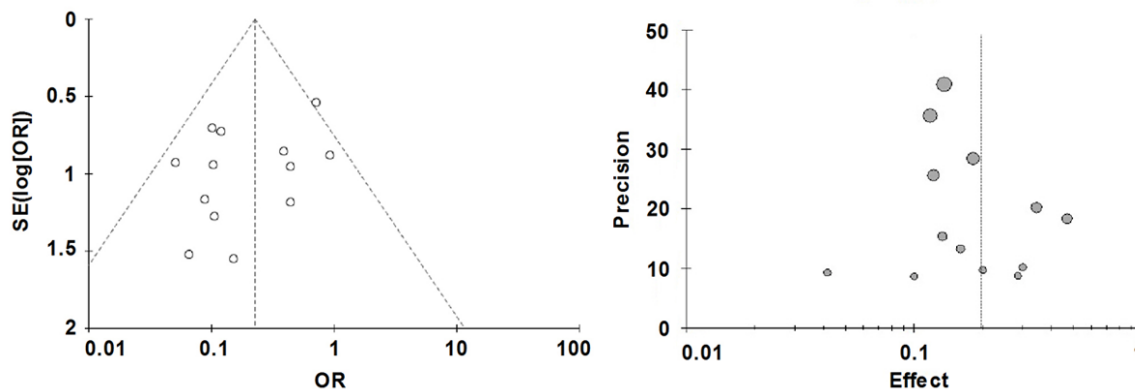
### Discussion

Hepatitis B virus (HBV) reactivation is a well-recognized serious complication in HBV-carrying NHL patients receiving antineoplastic chemotherapy, including DLBCL. CHOP regi-

men was once the conventional first-line treatment for DLBCL [32, 33]. CHOP plus rituximab may give additional risk of HBV reactivation comparing to classical CHOP chemotherapy. The role of lamivudine or entecavir prophylaxis for these patients remains to be elucidated. Owing to the heterogeneity in the study designs, such as characteristics of chemotherapy (CHOP or R-CHOP), characteristics of patients (HBV infection status or other hepatitis virus coinfection, ethnicity), and without uniform definition of HBV reactivation, there are still no efficient methods for precisely estimating the risk of HBV reactivation in patients with HBsAg+ who are receiving prophylactic anti-viral therapy. For this reason, this analysis focused on the relevant literature to evaluate the impact of anti-viral prophylaxis on Chinese HBsAg-positive DLBCL patients during chemotherapy, estimate the pooled risks of HBV reactivation rates and investigate heterogeneous results.

The strategy of anti-viral prophylaxis was applied in some researches. The risks of HBV reactivation rate from Asian region were not in accordance with western result of studies. And

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**Figure 5.** Funnel plot to detect publication bias. A: Funnel plot was performed to detect publication bias of 13 included studies. B: Publication bias was assessed by MetaAnalyst.

the outcomes of hepatitis and hepatic failure were also inconsistent in the anti-viral prophylaxis group when compared with the non-prophylaxis group [20, 22, 26-28, 34-36]. Despite all this, previous systematic assessment of the correlation between HBV-carrying DLBCL patients and the outcome of prophylactic anti-viral therapy is still limited. In this meta-analysis, we confirm that the use of lamivudine/entecavir prophylaxis may lower the risk of HBV reactivation for HBV-carrying DLBCL patients compared with that in no prophylaxis group. Data from 826 patients in thirteen studies were included. Risk ratio [RR] was 0.32 (95% CI=0.19-0.54,  $I^2=45.0%$ ,  $P<0.00001$ ), which meant the relative risk of HBV reactivation for HBV-carrying DLBCL patients receiving prophylactic anti-viral therapy is 0.32 (the risk of HBV reactivation for HBV-carrying DLBCL patients without anti-viral therapy and the prophylactic anti-viral therapy remarkably decreased the HBV reactivation rate. The results were similar to those obtained in similar studies in previous study [37]. We further our study of precisely estimating the risk of HBV reactivation in DLBCL patients with HBsAg+ who are receiving prophylactic anti-viral therapy. As a result, the pooled HBV reactivation rate was 19.8% (95% CI: 13.6%-27.9%) with a moderate degree of statistical heterogeneity ( $I^2=44.5%$ ,  $P<0.001$ ).

One challenge for this meta-analysis was that definitions of HBV reactivation varied with different studies. Different HBV reactivation rates have been observed by non-uniform definition of HBV reactivation. Statistical heterogeneity was investigated by analyzing the data according to the definitions of HBV reactivation from

different studies. We pooled HBV reactivation rate among two studies with HBV reactivation was defined as HBV-DNA absolute rise exceeding  $>10^3$  copies/mL. Meta-analysis result showed that the pooled HBV reactivation rate is 22.3% and the heterogeneity for this outcome was moderate ( $I^2=48.4%$ ,  $P<0.001$ ). We further explored the studies of HBV reactivation using our standardized definition. Meta-analysis of the 9 selected studies resulted in a pooled HBV reactivation rate of 20.9% and the heterogeneity for this outcome was still moderate ( $I^2=44.2%$ ,  $P<0.001$ ). Studies of HBV reactivation was defined as HBV-DNA absolute rise exceeding  $>10^3$  copies/mL tended to report little higher rates of HBV reactivation. However, these results suggesting that variation is unlikely to be due to difference in definition of HBV reactivation alone. The HBV reactivation rate in subgroup analyses was mostly similar to the overall result, which indicated that overall pooled HBV reactivation rate is trustworthy.

However, whether rituximab combined with CHOP treatment bear a higher risk of HBV reactivation remains controversial. We further explored the statistical heterogeneity by analyzing the data by the different chemotherapy regimen. The meta-analysis result revealed that the pooled HBV reactivation rate of CHOP treatment combined with prophylactic anti-viral therapy was 17.9%. Risk estimates for HBV reactivation ranged from 5.5% to 44.8%. There was a moderate degree of statistical heterogeneity for this outcome ( $I^2=47.6%$ ,  $P=0.029$ ). Whereas, the pooled HBV reactivation rate for R-CHOP was 20.7%. 95% CI of HBV reactivation ranged from 15.4% to 27.2%. The heterogene-

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ity for this outcome was moderate ( $I^2=34.4\%$ ,  $P<0.001$ ). Interestingly, in our present study, the strategy of R-CHOP was applied in HBsAg-positive DLBL patients during chemotherapy was no significant difference of the HBV reactivation rate compared with CHOP subgroup. In other words, CHOP plus rituximab was not significantly related with the reactivation of HBV. Ultimately, in this meta-analysis, we confirm that the application of CHOP or R-CHOP regimen for HBsAg+ DLBCL did not due to significant heterogeneity of the HBV reactivation rate.

Several limitations may affect the result of our meta-analysis study. First, the pooled HBV reactivation rate may be underestimate as a result of publication bias. In fact, smaller studies suggest a higher risk of HBV reactivation of R-CHOP regimen than CHOP regimen treatment and CHOP regimen bear a more beneficial effect are less likely to be published than the studies of R-CHOP regimen. Therefore, we may have missed a number of small studies. As well, another important issue is the frequency distribution of monitored patients for HBV reactivation is varied with different studies, which may have affected the HBV reactivation rates. A recent research showed that a risk of HBV reactivation persists for a number of months after 4-6 cycles chemotherapy [38], therefore researchers may be more likely to identify HBV reactivation with longer follow-up time.

However, the underlying mechanisms of lamivudine and entecavir prophylactic therapy are needed to elucidate. In the further studies, we aim to determine the long-term outcomes of the anti-viral prophylaxis for DLBCL patients during chemotherapy.

### Conclusions

Lamivudine or entecavir prophylaxis during chemotherapy may lower the risk of HBV reactivation for HBsAg-positive DLBL patients. Our meta-analysis confirms potentially critical risks of HBV reactivation in chronic HBV-carrying DLBCL patients with exposing to anti-viral therapy.

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### Disclosure of conflict of interest

None.

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