DOI: https://doi.org/10.53555/t0qwb657 Publication URL: https://nnpub.org/index.php/MHS/article/view/1902

RISK OF HBV REACTIVATION DURING THERAPIES FOR HCC: A SYSTEMATIC REVIEW

Aquarina Ashari sukahar*

*Faculty of Medicine, Gadjah Mada University, Indonesia

***Corresponding Author:**
aquakagome@gmail.com

Abstract

Background: *Hepatitis B virus (HBV) reactivation in the setting of immunosuppressive therapy, and in particular chemotherapy, has garnered increasing attention because reactivation can lead to hepatitis, liver failure, and death and also interrupt or delay treatment. The risk of reactivation depends on HBV serological status and the intensity of chemotherapy regimens. HBV reactivation can occur in hepatocellular carcinoma (HCC) treatment such as transarterial chemoemblization (TACE), resection, and radiofrequency ablation (RFA).*

The aim: *This study aims to explain the risk of HBV reactivation during therapies for HCC*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study can show that it meets all requirements. So, experts can ensure that the research is up to date. For this search approach, publications that came out between 2013 and 2023 are taken into account. Several different online reference sources were used to conduct this study. It was decided not to take into account cut reviews, works that have already been published, or works that are only half finished.*

Result: *On the PubMed database, our search results returned 49 articles, while our search results on Sage journal returned 105 articles. Search results conducted since 2013 yielded a total of 34 articles for PubMed and 80 articles for Sage journal. In the end, we compiled a total of 7 articles. We list five eligible studies.*

Conclusion: *HBV reactivation occurs after the curative resection of HBV-related HCC in patients with low hepatitis B viral loads. Postoperative HBV reactivation was related to the recurrence of HBV-related HCC. Use of antiviral therapy and close monitoring of viral loads may be helpful to reduce the recurrence of HBV-related HCC after resection.*

Keywords: *HBV reactivation, Hepatocellular carcinoma (HCC), Hepatitis B virus (HBV)*

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. It is the fifth most common cancer in the world and the third most common cause of cancer-related deaths. Viral hepatitis such as hepatitis B or C is the most common cause of hepatocellular carcinoma. Chronic infection with hepatitis B virus (HBV) results in the development of liver cirrhosis or HCC.[1,2]

Surgical resection is the treatment of choice for early stage HCC with favourable liver function. Overall survival was improved in patients with HCC treated with surgical resection. However, tumour recurrence is relatively high even after curative resection of HCC. The recurrence of HCC after resection is associated with tumour characteristics (i.e. tumour size and number), surgery-related factors (i.e. surgical margin) and underlying liver status (i.e. cirrhosis and hepatitis viral load). The incidence of HBV-related HCC is significantly higher in patients with high hepatitis B viral loads than in patients with low hepatitis B viral loads (HBV DNA level <2000 IU/ml).[1,3]

Reactivation of hepatitis B virus (HBV) is a well-known complication in chronic hepatitis B patients receiving immunosuppressive therapy. HBV reactivation can lead to asymptomatic increase of serum transaminase levels and acute hepatic failure. Thus, it is clinically important to prevent HBV reactivation in cancer patients. HBV reactivation in cancer patients receiving cytotoxic chemotherapy can lead to premature termination of chemotherapy or delay in treatment schedules.[4]

Immunotherapy has emerged as a popular therapeutic approach for cancer patients in recent years. However, the issue of hepatitis B virus reactivation (HBVr) has become a matter of increasing concern among some patients. Chronic hepatitis B represents a significant public health problem worldwide, with a high prevalence in East Asia. There are approximately 316 million hepatitis B surface antigen (HBsAg)-seropositive patients, and an estimated 1.5 million new infections annually, particularly in developing and impoverished countries. Given the large number of HBV carriers, many cancer patients also have concurrent hepatitis virus infection, which presents a considerable challenge.[5,6]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Egibility

For the purposes of this literature review, we compared and contrasted the the risk of HBV reactivation during therapies for HCC. This is done to provide an explanation and improve the handling of HBV reactivation during therapies for HCC. As the main purpose of this paper, to show the relevance of the difficulties that have been identified as a whole.

In order for investigators to take part in this study, they must meet the following requirements: 1) Papers must be written in English, and need to determine the best management of ileo-ileal intussusception after bowel resection. In order for a manuscript to be considered for publication, it must meet both of these requirements. 2) Papers studied include some papers published after 2013, but before the time period deemed relevant by this systematic review. Examples of research that are not allowed include editorials, submissions that do not have a DOI, reviews of articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " risk of HBV reactivation during therapies for HCC"; "risk of HBV" as keywords.The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("HBV"[MeSH Subheading] OR "HCC"[All Fields] OR "risk of HBV reactivation"[All Fields]) AND ("therapies of HCC"[All Fields] OR "HBV after HCC"[All Fields]) AND ("risk of HBV after HCC"[MeSH Terms] OR ("therapy of HCC"[All Fields]) OR ("complication of HCC"[All Fields]) AND "risk factor of HBV reactivation"[All Fields]) OR ("prevalence of HBV"[All Fields]) OR ("HBV mechanism"[All Fields]) OR ("mechanism of HBV"[All Fields]) AND "treatment of HBV "[All Fields])) AND ("treatment of HCC"[All Fields]) AND (clinicaltrial[Filter]))* used in searching the literature.

Data Retrieval

After reading the abstracts and titles of each study, the authors conducted an examination to determine whether the study met the inclusion criteria or not. The author then selects and chooses previous research that will be used as a source for the articles to be made. After looking at a number of different studies, all of which seemed to show the same trend, the following conclusions were drawn. All submissions must be written in English and cannot be viewed anywhere else.

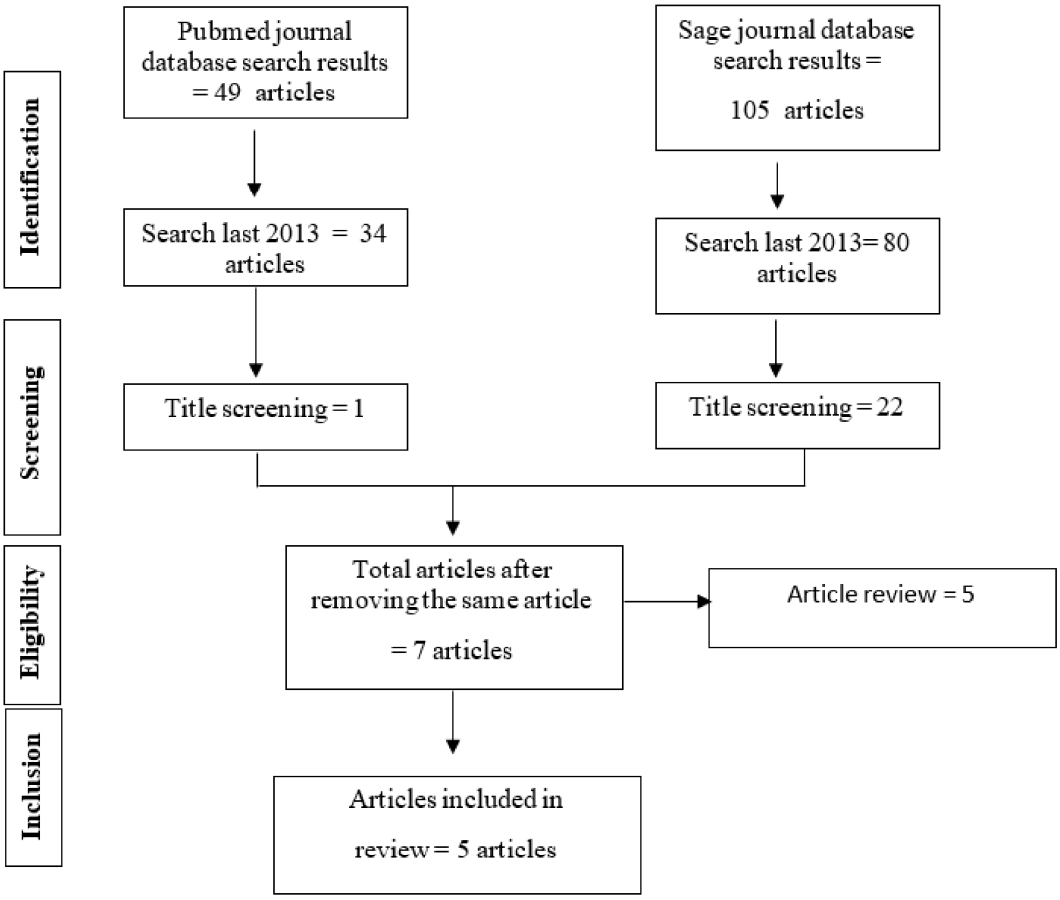

Figure 1. Article search flowchart

Quality Assessment and Data Synthesis

Each author conducts a study on the research included in the publication title and abstract before making a decision about which publication to explore further. The next step is to evaluate all the articles that are eligible for inclusion in the review and according to the criteria that have been set for the purpose that has been set. After that, the author will determine which articles will be included in the review and this depends on the findings we have found. These criteria are used in the process of selecting papers for further assessment in order to simplify the process as much as possible when selecting articles for evaluation. Which investigations were conducted previously, and what elements of those studies made them worthy of inclusion in the review, are discussed here.

RESULT

On the PubMed database, our search results returned 49 articles, while our search results on Sage journal returned 105 articles. Search results conducted since 2013 yielded a total of 34 articles for PubMed and 80 articles for Sage journal. In the end, we compiled a total of 7 articles. We list five eligible studies.

Jun, BG *et al* (2018)[4] showed that HBV reactivation could occur after RT. The incidence rate of HBV reactivation was 7.1% in the antiviral group and 31.0% in the non-antiviral group (P<0.001). We reported that mean duration of HBV reactivation after RT was 2.3 months. This result might be due to the fact that most patients underwent HBV DNA measurement within 2–3 months after RT.

Li, P *et al* (2021)[7] showed that the time to HBV reactivation often occurs up to 12 months after the last dose of anti-CD20-containing therapy, however, delayed HBV reactivation (>12 months) still remains a concern. Regarding CAR-T therapy specifically, so far, most of the published cases of HBV reactivation occurred within 6 months post CAR-T cell therapy. In this study, we observed a case of late reactivation occurring more than 1 year after CAR-T cell therapy. The rationale is that CAR-T cells as “a living drug” can persist in the blood for a prolonged period, which may cause long-lasting B-cell aplasia and a corresponding persistent reduction in immunoglobulin, thus prompting this late reactivation event. At HBV reactivation, the two patients had persistent blood CAR-T cells, absence of blood CD19+ B cells and hypoimmunoglobulinemia, which further support the viewpoint. These observations also imply that monitoring the persistence status of CAR-T cells in the blood in addition to blood CD19+ B cells and serum immunoglobulin levels may assist to determine the optimum interval and duration of HBV DNA monitoring.

Author	Origin	Method	Sample Size	Result
Jun, BG *et al.*, 2018[4]	South Korea	Retrospective study	133 patients	Factors related to HBV reactivation in HCC patients were evaluated. 17 (12.7%) of 133 patients developed HBV reactivation after RT. Patients in the antiviral group had significantly lower rates of HBV reactivation than those in the non-antiviral group (7.5% vs. 33.3%, p<0.001). HBV related hepatitis was also lower in the antiviral group (3.8% vs. 14.8%, p = 0.031). . In multivariate analysis, absence of antiviral treatment (OR: 8.339, 95% CI: 2.532– 27.470, p<0.001). and combined treatment of RT with transarterial chemoembolizatoin (TACE) (OR: 5.313, 95% CI: 1.548–18.232, p = 0.008) were risk factors for HBV reactivation. HBV reactivation can occur after radiotherapy. Combination treatment of RT with TACE and non-antiviral treatment are major risk factors for HBV reactivation during or after RT.
Li, P *et al.*, 2021[7]	China	A post-hoc analysis of a prospective clinical trial	30 patients	In this study, we investigated the risk of HBV reactivation after CART19 cell therapy in 30 consecutive patients with B-cell malignancies and resolved HBV infection without antiviral prophylaxis, in the Tongji Hospital of Tongji University. In this cohort, two patients developed HBV reactivation 2 months and 14 months after CAR-T cell infusion, respectively, the latter of whom developed severe hepatitis. These findings showed that the incidence of HBV reactivation was 6.67% (95% CI, 0.8–22.1). Specifically, none of the 21 patients who were HBsAb positive (0.0%) versus two of nine patients who were HBsAb negative (22.2%) experienced HBV reactivation (p = 0.03), suggesting HbsAb seronegativity at baseline is a possible risk factor in this population. Although use of tocilizumab or corticosteroids has been associated with increased risk of HBV reactivation, none of the patients who received these agents had HBV reactivation in this study.
Lin, H *et al.*, 2020[8]	China	Retrospective study	38 patients	27 patients received TACE with 3DCRT (TR group) and 11 received additional TACE following TACE and 3DCRT (sandwich group), respectively. The median intrahepatic progression-free survival (IPFS), progression-free survival (PFS), and overall survival (OS) in the TR group and sandwich group were 5.4 months vs. 17 months (P = 0.018), 5.4 months vs. 17 months (P = 0.008), and 13.5 months vs. 29.2 months (P = 0.011), respectively. Multivariate Cox regression demonstrated that TACE followed by radiotherapy alone had a shorter IPFS (HR: 2.516, 95% CI (1.136-5.570), P = 0.023) and PFS (HR: 2.637, 95% CI (1.182-5.880), P = 0.018) compared with the sandwich treatment. Hepatitis B virus reactivation occurred in 1 patient in the sandwich group. Myleosuppresion was considered a grade 3/4 adverse event.
Zhao, Q *et al.*, 2016[9]	China	Retrospective study	69 patients	The median follow up was 30 months (range, 4–68 months). The median survival time (MST), 1-year OS rate and 2-year OS rate of the whole group were 25 months, 51% and 39%, respectively. The average circulating lymphocyte counts declined during RT (1493.19 versus 503.48 cells/μl, p < 0.001). A lower Min ALC was associated with worse OS (p = 0.001), with a cut-off value of 450 cells/μl (sensitivity and specificity, 50% and 70.6%, respectively). The MSTs, 1-year OS rates and 2-year OS rates were 15 months versus 47 months, 27% versus 78% and 4% versus 71% for patients with relatively lower (⩽450 cells/μl) and higher Min ALCs (>450 cells/μl), respectively (p < 0.001). After adjusting for potential confounders, multivariate Cox regression analysis demonstrated that Min ALC independently predicted patients' OS (HR, 0.32; 95% CI, 0.15–0.69).
Spaan, M *et al.*, 2018[10]	United Kingdom	Cohort study	40 patients	The median follow up was 30 months (range, 4–68 months). The median survival time (MST), 1-year OS rate and 2-year OS rate of the whole group were 25 months, 51% and 39%, respectively. The average circulating lymphocyte counts declined during RT (1493.19 versus 503.48 cells/μl, p < 0.001). A lower Min ALC was associated with worse OS (p = 0.001), with a cut-off value of 450 cells/μl (sensitivity and specificity, 50% and 70.6%, respectively). The MSTs, 1-year OS rates and 2-year OS rates were 15 months versus 47 months, 27% versus 78% and 4% versus 71% for patients with relatively lower (⩽450 cells/μl) and higher Min ALCs (>450 cells/μl), respectively (p < 0.001). After adjusting for potential confounders, multivariate Cox regression analysis demonstrated that Min ALC independently predicted patients' OS (HR, 0.32; 95% CI, 0.15–0.69).

Lin, H *et al* (2020)[8] showed that The mean age of the patients was 58.2 years old. Most of the patients (86.8%, 33/38) were Hepatitis B virus-positive. Patients with cirrhosis accounted for 65.8% (25/38) and most of the patients (86.8%, 33/38) had a Child-Pugh score of 5. Approximately 65.8% (25/38) of the patients had 1 to 2 lesions, and half of them had a vascular invasion. T1-T2 stage (American Joint Committee on Cancer TNM system, Version 7) applied to up to 55.2% (21/38) of the patients, while BCLC stage (Barcelona clinical stage) applied to up to 63.2% (24/38). The serum AFP concentration was above the upper limit of normal (≥25ng/mL) in all patients, and 57.9% (22/38) had a serum AFP concentration of less than 200 ng/ml. There were no significant differences in the baseline characteristics among groups.
Zhao, Q *et al* (2016)[9] showed that At the end of the follow-up period, 22 (31.9%) patients were still alive. The median survival time (MST), 1-year OS rate and 2-year OS rate in the whole group were 25 months, 51%, and 39%, respectively. The MSTs of different subgroups and the results of univariate and multivariate analyses are detailed in Table 3. Survival was worse in patients with relatively lower Min ALCs (⩽450 cells/μl) than in those with higher Min ALCs (>450 cells/μl); the MSTs, 1-year OS rates and 2-year OS rates were 15 months versus 47 months, 27% versus 78% and 4% versus 71%, respectively, ($p < 0.001$) in the lower and higher Min ALC groups. No correlation of survival with age, gender, Karnofsky performance status (KPS), prognostic nutritional index (PNI), γ-glutamyl transferase (GGT), radiation dose or postradiotherapy treatment was found. The OS of patients with BCLC stage C, lower serum ALCs, higher serum neutrophil–lymphocyte ratio (NLR) and AFP levels before RT or lower serum Min ALCs during RT was significantly worse than that of patients with a BCLC stage of A/B, higher serum ALCs, lower serum NLR and AFP levels or higher serum Min ALCs (p values were <0.001, 0.018, 0.001, <0.001 and <0.001.
Spaan, M *et al* (2018)[10] showed that an incidence of 3,5% in the cohort, an alpha of 0.05 and power of 0.80, the calculated sample size was 37. Control patients were matched with reactivation cases according to genotype, treatment and fibrosis stage as much as possible.

DISCUSSION

Hepatitis B virus (HBV) infection is a major public health concern and the main cause of infection-related deaths worldwide. Globally, approximately 2 billion people have serologic evidence of resolved HBV infection, defined as undetectable serum HBV DNA and negative HB surface antigen (HBsAg) but positive antibody against HB core antigen (anti-HBc). In such population, HBV virions are cleared, while the HBV nucleocapsid is transported into the nucleus and generates closed circular (ccc) DNA. In solid organ transplant (SOT) recipients, immunosuppression can result in HBV reactivation with ccc DNA serving as the replication template, which may further cause progressive hepatitis, hepatic failure, and even death.[11]

HBV reactivation can occur in hepatocellular carcinoma (HCC) treatment such as transarterial chemoemblization (TACE), resection, and radiofrequency ablation (RFA). HBV reactivation after TACE in HCC treatment has been wellstudied. It has been reported that HBV reactivation can occur in 4%–40% of patients undergoing TACE treatment. HBV reactivation has also been observed in 15.5%–27.7% of patients after surgical resection of hepatocellular carcinoma. Previous study has suggested that RFA can reactivate HBV replication. However, the incidence of HBV reactivation after RFA is relatively lower (5.6%) than that after hepatic resection (14.0%). HBV reactivation during HCC treatment can affect liver function and survival. To reduce HBV reactivation and reserve liver function after TACE, resection, and RFA, antiviral therapy is very important. Radiotherapy (RT) was infrequently performed for HCC due to radiation induced liver disease (RILD). There is no effective treatment after the development of RILD. Recently, RT has been used to treat patients with HCC who are ineligible for locoregional therapy. With advances in radiation technology, RILD after RT treatment is tolerable. However, the risk of HBV reactivation after RT in HCC patients remains unclear.[4,12]

Recent studies have shown that HBVr may occur in chronic hepatitis B (HBsAg-positive) patients or even in patients with resolved HBV (HBsAg-negative/HBcAb-positive) infection during immunotherapy, which might cause a potentially fatal complication for cancer patients. Furthermore, HBVr could also cause interruption of antineoplastic therapy and impact overall survival. As the rate of HBVr and potential risk factors for HBVr in patients treated with ICI-based therapy remain undefined, there is a lack of consensus among various organizations regarding the optimal management strategies for this patient population.[5,13]

The reactivation of HBV(hepatitis B virus) replication in HBsAg-positive patients caused by chemotherapy has been observed for decades. The chemotherapy-induced liver damage is characterized by enhanced HBV replication and widespread infection of hepatocytes followed by rapid immune-mediated destruction. It is thought that viral replication precedes the clinical hepatitis flare-up by a few weeks. Upon the reactivation of HBV, the clinical consequences range from asymptomatic hepatitis to fatal hepatic failure. It may cause not only HBV-related mortality or morbidity but also interruption or early termination of planned chemotherapy, which might compromise a patient's prognosis.[14,15]

CONCLUSION

HBV reactivation can occur in hepatocellular carcinoma (HCC) treatment such as transarterial chemoemblization (TACE), resection, and radiofrequency ablation (RFA). HBV reactivation occurs after the curative resection of HBV-related HCC in patients with low hepatitis B viral loads. Postoperative HBV reactivation was related to the recurrence of HBV-related HCC. Use of antiviral therapy and close monitoring of viral loads may be helpful to reduce the recurrence of HBV-related HCC after resection.

REFERENCE

[1]. Sohn W, Paik YH, Cho JY, Ahn JM, Choi GS, Kim JM, et al. Influence of hepatitis B virus reactivation on the recurrence of HBV-related hepatocellular carcinoma after curative resection in patients with low viral load. J Viral Hepat. 2015;22(6):539–50.

[2]. Teng CF, Wu HC, Shyu WC, Jeng L Bin, Su IJ. Pre-s2 mutant-induced mammalian target of rapamycin signal pathways as potential therapeutic targets for hepatitis B virus-associated hepatocellular carcinoma. Cell Transplant. 2017;26(3):429–38.

[3]. Liao H, Liu Y, Li X, Wang J, Chen X, Zou J, et al. Monitoring of serum HBV RNA, HBcrAg, HBsAg and anti-HBc levels in patients during long-term nucleoside/nucleotide analogue therapy. Antivir Ther. 2019;24(2):105–15.

[4]. Jun BG, Kim YD, Kim SG, Kim YS, Jeong SW, Jang JY, et al. Hepatitis B virus reactivation after radiotherapy for hepatocellular carcinoma and efficacy of antiviral treatment: A multicenter study. PLoS One. 2018;13(7):1–10.

[5]. Xia Z, Zhang J, Chen W, Zhou H, Du D, Zhu K, et al. Hepatitis B reactivation in cancer patients receiving immune checkpoint inhibitors: a systematic review and meta-analysis. Infect Dis Poverty. 2023;12(1):1–20.

[6]. Hsu C, Rimassa L, Sun HC, Vogel A, Kaseb AO. Immunotherapy in hepatocellular carcinoma: evaluation and management of adverse events associated with atezolizumab plus bevacizumab. Ther Adv Med Oncol. 2021;13:1–20.

[7]. Li P, Zhou L, Ye S, Zhang W, Wang J, Tang X, et al. Risk of HBV Reactivation in Patients With Resolved HBV Infection Receiving Anti-CD19 Chimeric Antigen Receptor T Cell Therapy Without Antiviral Prophylaxis. Front Immunol. 2021;12(July):1–8.

[8]. Lin H, Wu H, Cong N, Liu B, Liu C, Han D. Transarterial Chemoembolization Followed by Radiotherapy Versus Sandwich Treatment for Unresectable or Ablative Hepatocellular Carcinoma. Technol Cancer Res Treat. 2020;19:1–6.

[9]. Zhao Q, Xu X, Yue J, Zhu K, Feng R, Jiang S, et al. Minimum absolute lymphocyte counts during radiation are associated with a worse prognosis in patients with unresectable hepatocellular carcinoma. Therap Adv Gastroenterol. 2017;10(2):231–41.

[10]. Spaan M, Bruce M, Agarwal K, Carey I. The role of anti-HBs in hepatitis B reactivation during direct-acting antiviral therapy for chronic hepatitis C. Antivir Ther. 2018;23:539–42.

[11]. Yin S, Zhang F, Wu J, Lin T, Wang X. Incidence, risk factors, and clinical outcomes of HBV reactivation in non-liver solid organ transplant recipients with resolved HBV infection: A systematic review and meta-analysis. PLoS Med [Internet]. 2023;20(3 March):1–20. Available from: http://dx.doi.org/10.1371/journal.pmed.1004196

[12]. Li Z, Dong Y, Fan M, Yin Y, Zhu J, Li B, et al. Analysis of Hepatitis B Virus Reactivation After Radiotherapy in Patients With Hepatocellular Carcinoma Using the Lyman NTCP Model. Technol Cancer Res Treat. 2019;18:1–9.

[13]. Kusumoto S, Arcaini L, Hong X, Jin J, Kim WS, Kwong YL, et al. Risk of HBV reactivation in patients with B-cell lymphomas receiving obinutuzumab or rituximab immunochemotherapy. Blood. 2019;133(2):137–46.

[14]. Tang W, Chen L, Zheng R, Pan L, Gao J, Ye X, et al. Prophylactic effect of lamivudine for chemotherapy-induced hepatitis B reactivation in breast cancer: A meta-analysis. PLoS One. 2015;10(6):1–12.

[15]. Jiang XW, Ye JZ, Li YT, Li LJ. Hepatitis B reactivation in patients receiving direct-acting antiviral therapy or interferon-based therapy for hepatitis C: A systematic review and meta-analysis. World J Gastroenterol. 2018;24(28):3181–91.