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Risk of hepatitis B virus reactivation during therapies for hepatocellular carcinoma: a systematic review

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LIST OF ABBREVIATIONS: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; TACE, transarterial chemoembolization; NA, nucleos(t)ide analogue; CI, confidence intervals; PD, programmed cell death

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ABSTRACT

Treatment for hepatocellular carcinoma (HCC) has evolved rapidly, but the risk of hepatitis B virus (HBV) reactivation to new therapies is unclear. We systematically reviewed data on HBV reactivation in patients receiving HCC therapy in relation to use of HBV antiviral prophylaxis. Literature search was performed to identify all published studies including HBsAg positive patients with HCC providing data on HBV

reactivation. Forty-one studies with 10,223 patients, all from Asia, were included. The pooled HBV reactivation rate was 5% in patients receiving no specific HCC therapy, and was higher in patients undergoing surgical resection (16%), transarterial chemoembolization (19%) or radiotherapy (14%) and intermediate in patients treated with local ablation therapy (7%) or systemic agents (7%). HBV reactivation rates were higher in those without compared to those with HBV prophylaxis (ablation: 9% vs. 0%, resection: 20% vs. 3%, chemoembolization: 23% vs. 1%, external radiotherapy alone: 18% vs. 0%, systemic therapy: 9% vs. 3%). HBV related biochemical reactivation rates varied between 6%-11% or 2% in patients receiving HCC therapies with high or intermediate HBV reactivation risk. Liver decompensation and death were rarely reported (0%-3%), and only in patients receiving HCC treatment with high HBV reactivation risk. In conclusion, HBsAg positive patients with HCC are at high or intermediate risk of HBV reactivation depending on the type of HCC therapy. Nucleos(t)ide analogue prophylaxis reduces the risk of HBV reactivation and practically eliminates the risk of hepatitis flare, and should be administered regardless of HCC treatment.

INTRODUCTION

Hepatocellular carcinoma (HCC) has a rising incidence and currently represents the fourth leading cause of cancer related death worldwide (1,2). Chronic infection with hepatitis B virus (HBV) accounts for >50% of all HCC cases globally (3,4). Antiviral treatment has been shown to decrease but not to eliminate the risk of HCC (5,6). Unfortunately, only 10% of patients with chronic HBV infection worldwide have been diagnosed and less than 25% of those diagnosed are receiving antiviral treatment (7). Thus, many patients with HBV-related HCC are not aware of their HBV infection prior to HCC diagnosis.

HCC treatment has been reported to be associated with a risk of HBV reactivation but the risk associated with each modality of HCC treatment is unclear (8,9). Many new treatment modalities with proven benefits have become available for patients with HCC in recent years (4,10). In particular, multiple systemic therapies including various kinase inhibitors and immune check-point inhibitors have been recently

approved for HCC treatment as monotherapy or in combination (4,10). Clinical trials of these therapies often excluded HBsAg positive patients or required use of nucleos(t)ide analogue (NA) therapy with virus suppression; thus, the risk of HBV reactivation associated with these new therapies is unclear. While antiviral therapy is recommended for all HBsAg positive patients with HCC, the lack of prior diagnosis of HBV infection means that many patients may not be receiving antiviral treatment at the time of HCC diagnosis or treatment. Development of HBV reactivation can negatively affect survival of patients with HCC, either by worsening of liver function or by hampering the continuation of potentially life-saving HCC therapies (8,9). Thus, awareness of the HBV reactivation risk and the benefits of NA prophylaxis is crucial to provide optimal management of patients with HCC.

We systematically reviewed data on HBV reactivation in patients with HCC in relation to the type of HCC therapy and the use of prophylactic HBV therapy.

METHODS

Search Strategy, Selection Criteria and Data Extraction

Medline/Pubmed and Embase from January 1995 to March 2021 were searched to identify all medical literature included under the following search text terms in titles/abstracts: (“hepatitis B”) AND (“exacerbation” OR “reactivation” OR “flare”) AND (“cancer” OR “carcinoma”) AND (“no treatment” OR “liver resection” OR “surgery” OR “alcohol injection” OR “ablation” OR “cryotherapy” OR “embolization” OR “radiation” OR “radiotherapy” OR “sorafenib” OR “regorafenib” OR “atezolizumab” OR “bevacizumab” OR “cabozantinib” OR “ramucirumab” OR “pembrolizumab” OR “lenvatinib” OR “nivolumab”). In addition, a full manual search of all relevant review articles and of the retrieved original studies was performed.

All studies published in English as full papers were included, if they fulfilled all of the following criteria: (1) observational studies (case-control, cross-sectional or cohort) or randomised trials, (2) included patients with HCC, (3) included patients who were HBsAg positive and/or anti-HBc positive, (4) provided data on HBV reactivation based on virological and/or biochemical definitions.

Literature search was performed by two independent reviewers (MP, MT), who determined which studies could be potentially included. Two lists of selected papers

were compared for concordance and discrepancies were discussed and arbitrated by a third reviewer (GP). Each study in the list of selected papers was evaluated by two independent reviewers (MP, MT) to determine whether it fulfilled all the inclusion criteria. These two reviewers extracted data from the selected papers according to a predefined form (**Supplementary Table 1**). The two data summary tables were compared for concordance and discrepancies were discussed and arbitrated by a third reviewer (GP). This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-P) (11).

Statistical analysis

The outcomes of interest were incidence of virological or biochemical reactivation. Results were analyzed according to HCC treatments (i.e. no specific treatment, radiofrequency ablation or ethanol injection, surgical resection, TACE, radiotherapy and systemic therapies) in patients with and without prophylactic NA therapy, whenever data were available.

Meta-analysis was performed using a generalized linear mixed model and Clopper-Pearson confidence intervals (exact binomial interval) for individual studies (12). Between studies variance was estimated using the maximum likelihood estimator. Heterogeneity was examined visually in the forest plots and its extent was described using the I^2 measure, as proposed by Higgins et al. (13). We used a test statistic based on a weighted linear regression of the treatment effect on the inverse of the total sample size using the variance of the average event rate as weights, as described by Peters (14). The pooled incidence rates and 95% confidence intervals (CI) are reported. Results from random-effects meta-analysis were chosen to be presented based on the assumption that the true effect varies across studies. Analysis was performed in R v3.6.0 (15) using the meta (16) and the metaphor packages (17).

RESULTS

Studies and Patient Characteristics

The literature search initially identified 661 studies (PubMed:144, Embase:517). Of these, 626 were excluded because they were duplicates (n=70) or did not fulfill the

inclusion criteria (n=556). Only one study included HBsAg negative, anti-HBc positive patients (18), which was excluded in order to have a homogeneous patient population of HBsAg positive patients. Thirty-four studies remained on the list (PubMed: 27, Embase: 7), another 7 studies were identified through the manual search. Thus, 41 studies were finally included in this systematic review (**Supplementary Figure 1**) (19–59).

The main characteristics of the included studies and patients are presented in **Table 1.** The 41 studies were all from Asia and included a total of 10,223 HBsAg positive patients. Ten studies were prospective (20,23,26,35,37,38,42–44,46), three were retrospective/prospective (28,51,55) and 28 were retrospective cohort studies (19,21,22,24,25,27,29–34,36,39–41,45,47,49–54,56–59). The median/mean patients' age ranged from 45 to 58 years old. Most studies included patients with variable serum HBV DNA levels, with seven studies included only patients with very low-undetectable (<100-200 IU/mL, n=4) (32,33,56,59) or low-undetectable (<500-2000 IU/mL, n=3) HBV DNA levels (26,38,47). Ten studies included patients with HCC receiving no prophylactic therapy with NA (19,20,29,30,36,37,41,42,44,45), 29 studies included mixed patient population regarding the use of NA therapy (21–28,31–35,38–40,43,46–49,51–54,56–59) and two studies did not clearly provide such information (50,55).

HBV reactivation was defined as an increase of serum HBV DNA >1 log or reappearance of HBV DNA in patients with undetectable HBV DNA at baseline in 33 studies (19–21,23–30,32–36,38–43,45–48,50–53,56–58), while this definition varied in 5 studies (31,44,49,55,59) and was not clearly provided in the remaining 3 studies (22,37,54). A definition of HBV-related biochemical reactivation was not provided in 18 studies (21–27,30,32–34,37–41,54,59), while it varied widely among the remaining 23 studies (19,20,28,29,31,35,36,42–53,55–58). Only increases in aminotransferase levels attributed to HBV reactivation by the authors were considered HBV-related biochemical reactivation. Pooled data regardless of the definitions of HBV-related virological and biochemical reactivations are provided in this review.

Risk of bias assessment

The risk of bias for each study was evaluated using the ROBIN-I tool by two independent authors (MP and MT). This tool includes 7 domains that classify the studies as low, moderate, serious or critically serious risk of bias. Of the 41 included studies, risk of bias was found to be serious in 20, moderate in another 20 and low in only one study (**Supplementary Table 2**).

HBV reactivation in patients who did not receive HCC treatment

There were 3 studies providing data for 83 patients who did not receive HCC treatment (19,20,31) (**Table 1**). HBV reactivation was diagnosed in 4 (4.8%) patients (random effects pooled estimate:5%, 95%CI:2-12%; heterogeneity, p=0.46) (**Figure 1**) none of whom received prophylactic NA therapy. Only one patient developed biochemical reactivation (19,20,31) and none of 40 patients developed liver decompensation or death in two studies though NAs were used after the diagnosis of HBV virological reactivation (19,20) (**Table 2**).

HBV reactivation after local ablation therapy for HCC

There were 3 studies providing data for 177 patients with HCC who underwent local ablation therapy (radiofrequency or alcohol injection) (19,42,53) (**Table 1**). HBV reactivation was diagnosed in 12 (6.8%) patients (pooled estimate:7%, 95%CI:4-12%; heterogeneity, p=0.43) (**Figure 2A**). The pooled HBV reactivation rate in 144 patients who received no prophylactic NA was 9% (95%CI:5-15%; heterogeneity, p=0.86) (**Figure 2B**). One study included 33 patients who received prophylactic NA and 92 who did not; HBV reactivation was diagnosed in none of those who received prophylactic NA therapy and in 7.6% of those who did not (53). Data on 52 patients who did not receive prophylactic NA showed only one (1.9%) developed HBV-related biochemical reactivation and none developed liver decompensation or death (19,42) (**Table 2**).

HBV reactivation after surgical resection for HCC

Twenty studies including 5,880 patients who underwent surgical resection for HCC provided data for HBV reactivation in 5587 patients (19,21–28,30,32–34,53–59) (**Tables 1-2**). HBV reactivation was diagnosed in 17.9% patients (pooled

estimate:16%, 95%CI:13-19%; heterogeneity, p<0.01) (**Figure 3A**). The pooled rates of HBV reactivation were higher in 3178 patients not receiving prophylactic NA (pooled estimate:20%, 95%CI:18-23%; heterogeneity, p<0.01) (**Figure 3B**) than 1340 patients who did (pooled estimate:3%, 95%CI:1-5%; heterogeneity, p<0.01) (**Figure 3C**) (21,22,33,34,53,54,57–59,23–28,30,32). The pooled rates of HBV reactivation were 16% (95%CI:13-20%; heterogeneity, p=0.06) in 8 studies with mean/median follow-up ≤6 months (22–27,30,59) and 16% (95%CI:10-26%; heterogeneity, p<0.01) in 7 studies with mean/median follow-up >6 months (19,21,28,32,55–57). Patients receiving entecavir prophylaxis had pooled HBV reactivation rate of 2% (95%CI:1-4%; heterogeneity, p=1.00) (22–27,32,33), compared to 4% (95%CI:1-22%; heterogeneity, p<0.01) for those receiving other NAs, most commonly lamivudine (28,34,57–59). Biochemical reactivation was reported in 11.0% (289/2629) of patients in 7 studies (19,28,55–59) (pooled estimate:6%, 95%CI:3-12%; heterogeneity, p<0.01) (**Figure 3D**), but data in relation to prophylactic NA use were not provided in most studies. In one study including a mix of patients who did and did not receive prophylactic NA (28), only 1.4% (1/69) of patients who did and 6.5% (33/505) of patients who did not receive prophylactic NA developed biochemical reactivation. In three studies reporting data in 564 patients receiving no prophylactic NA, the pooled estimate of biochemical reactivation was 9% (95%CI:4-19%; heterogeneity, p<0.01) (19,28,55). Among five studies that reported clinical outcomes, 6/217 (2.8%) patients were reported to have developed liver decompensation (19,28,56) and 53/2621 (2.6%) patients to have died due to HBV reactivation (19,34,56,57,59) (**Table 2**). In one study (34), HBV-related deaths were observed in 1.9% (10/538) of patients receiving NA prophylaxis and 6.2% (16/257) of patients who did not (p=0.001).

HBV reactivation after TACE for HCC

Twelve studies including 3474 patients who underwent TACE for HCC provided data for HBV reactivation, which was diagnosed in 517 (14.9%) patients (pooled estimate:19%, 95%CI:13-26%; heterogeneity, p<0.01) (**Table 1**) (**Figure 4A**) (19,20,35–43,58). The pooled rates of HBV reactivation were higher in 2296 patients who received no prophylactic NA (pooled estimate:23%, 95%CI:17-30%;

heterogeneity, p<0.01) (**Figure 4B**) (19,20,35–43,58) than in 1178 patients who did (pooled estimate:1%, 95%CI:0-10%; heterogeneity, p=0.13) (**Figure 4C**) (35,38–40,43,58). The pooled rates of HBV reactivation were 16% (95%CI:10-23%; heterogeneity, p<0.01) in 7 studies with mean/median follow-up ≤6 months (20,35,36,39,41,43,58) and 23% (95% CI: 11-42%, heterogeneity, p<0.01) in 3 studies with mean/median follow-up >6 months (19,40,42). Biochemical reactivation was reported in 144 (10.6%) of 1354 patients from 8 studies (pooled estimate:11%, 95%CI:6-20%; heterogeneity, p<0.01) (**Figure 4D**) (19,20,35–37,42,43,58). Biochemical reactivation was diagnosed in only 4/173 (2.3%) patients included in two studies who received prophylactic NA and in 15/70 (21.4%) patients included in the same studies who did not (35,43). Eight studies reported biochemical reactivation rates in a total of 795 patients receiving no prophylactic NA (pooled estimate:16%, 95%CI:10-25%; heterogeneity, p<0.01) (19,20,35–37,42,43,58). Five studies reported clinical outcomes including 16/488 (3.3%) patients with liver decompensation (19,35,42,43) and 7/716 (1.0%) patients with deaths due to HBV reactivation (19,35,36,42,43) (**Table 2).** In one study (35), HBV-related death was observed in 0/36 and 1/37 patients with and without NA prophylaxis.

HBV reactivation after radiotherapy for HCC

There were five studies which included 376 patients who underwent external radiotherapy for HCC providing data for HBV reactivation, which was diagnosed in 61 (16.2%) patients (pooled estimate:14%, 95%CI:8-24%; heterogeneity, p=0.21) (**Tables 1,2**) (**Figure 5A**) (29,31,44–46). HBV reactivation rates were higher in 254 patients from 5 studies receiving no prophylactic NA (pooled estimate:18%, 95%CI:9-33%; heterogeneity, p=0.83) (29,31,44–46) (**Figure 5B**) than 0% (0/16 patients treated with radiotherapy alone) and 7.5% (0/58 patients treated with radiotherapy alone and 8/48 patients treated with radiotherapy and TACE) in two studies of patients receiving prophylactic NA (31,46). Biochemical reactivation was reported in 45 (12.0%) of 376 patients (pooled estimate:9%, 95%CI:4-20%; heterogeneity, p<0.01) (**Figure 5C**). The pooled biochemical reactivation rate in 254 patients who received no prophylactic NA was 7% (95%CI:2-22%; heterogeneity, p<0.01) (31,44–47), while it was 0% and 4.7% in the two studies of patients receiving prophylactic NA (31,46).

Only two studies reported clinical outcomes with one study reporting no liver decompensation in 36 patients (44), and two studies reporting death due to HBV reactivation in 3/105 (2.9%) patients (44,45) (**Table 2**).

HBV reactivation after systemic therapy for HCC

There were six studies including 403 patients providing data for HBV reactivation in 366 patients treated with systemic therapy for HCC (47–52). Sorafenib was used in four studies (47–49,51) [combined with TACE in some patients in two studies (48,51)] and immune check-point inhibitors were used in the other two studies (50,52) [combined with anti-angiogenetic agents or locoregional therapy in some patients in one study (52)] (**Table 1**). HBV reactivation was diagnosed in 24/366 (6.6%) patients (pooled estimate:7%, 95%CI:4-10%; heterogeneity, p=0.81) (47–52) (**Figure 6A**) [17/276 (6.2%) patients treated with sorafenib and 7/90 (7.8%) patients treated with immune check-point inhibitors]. The overall pooled HBV reactivation rates were 9% (95%CI:4-19%; heterogeneity, p=0.92) in 66 patients who did not receive prophylactic NA (**Figure 6B**) (47,49,51,52) and 3% (95%CI:1-13%; heterogeneity, p=0.94) in 179 who did (**Figure 6C**) (47,49,51,52). Biochemical reactivation was reported in 6/321 (1.9%) patients (pooled estimate:2%, 95%CI:1-4%; heterogeneity, p=0.98) (48–52) (**Figure 6D**). In two studies (49,51), biochemical reactivation was reported in 3/44 (6.8%) patients not receiving prophylactic NA and 0/94 patients who did. None of 243 patients in four studies that reported clinical outcomes had liver decompensation or death due to HBV reactivation (48,50–52) (**Table 2**).

DISCUSSION

HBV reactivation occurs commonly in HBV-infected patients who become immunocompromised due to a disease and/or a therapeutic intervention (60,61). The severity of HBV reactivation varies from an asymptomatic increase in serum HBV DNA level with or without accompanying ALT increase to severe liver injury with jaundice, hepatic decompensation and even death (8,9,60,61). The risk of HBV reactivation depends on host, virus, and potency of immunosuppression; with higher risks in men, those with high baseline HBV DNA levels, and use of more potent

immunosuppressive therapy (8,9,60,61). Hematological malignancies such as lymphomas are associated with the highest risk, while HCC is thought to be associated with an intermediate risk for HBV reactivation (8,9). Whether these differences are related to the effect of the malignancy on immune response or the treatment used for the malignancy is unclear.

Our results support the classification of HCC itself at intermediate HBV reactivation risk, as the pooled virological reactivation rate was 5% in HBsAg positive patients with HCC who received no specific HCC treatment and no HBV prophylaxis, though the number of patients studied was small (n=83).

The risk of HBV reactivation in HBsAg positive patients with HCC is expected to be affected by the type of therapeutic intervention. According to our findings, the HBV reactivation risk was high (defined as >10%) in HBsAg positive patients undergoing surgical resection, TACE or external radiotherapy. Surgical resection is associated with stress responses, which may impair immune status particularly if complicated by infection or hepatic decompensation due to insufficient liver reserve (8,62). TACE is considered to have only local effects but systemic release of the chemotherapeutic agents through intrahepatic and/or intra-/peri-tumoral arterio-venous shunts may occur resulting in suppression of the host immune responses (63). Radiation therapy can suppress immune response even when radiation is delivered to only a small region of the liver as in the case of stereotactic external beam radiation or transarterial Y90 therapy (64). Our review found that prophylactic NA resulted in almost total elimination (0-3%) of HBV reactivation even though lamivudine, the only available at the time, was used in most of these studies.

The HBV reactivation risk was intermediate (7%) in HBsAg positive patients with HCC treated with local ablation or systemic therapies, and prophylactic NA was found to almost eliminate such risk. Local ablation therapies are not usually expected to increase the risk of HBV reactivation, but radiofrequency ablation has been suggested to potentially have an effect on the patients' immune status (65). HBV reactivation risk is high in HBsAg positive patients with HCC treated with traditional systemic chemotherapeutic agents (8). However, such agents are no longer used for HCC treatment. The risk of HBV reactivation with current systemic therapies appeared to be lower but requires confirmation. Of the current systemic HCC agents,

sorafenib was used in four of the six relevant studies. Sorafenib, a kinase inhibitor has been associated with some effects on patients' immune responses (66). The HBV reactivation risk in patients treated with sorafenib was approximately 6%, which cannot be attributed totally to this agent, since a proportion of patients in two of the four studies were also treated with TACE.

An increasing number of patients are treated with immunotherapeutic agents, which are expected to have an impact on the host immune system (67). There are limited data on the HBV reactivation risk in patients with HCC or other cancers who receive immunotherapeutic agents. The HBV reactivation risk was approximately 8% in 90 HBsAg positive patients with HCC receiving immunotherapeutic agents [anti-programmed cell death (PD)-1 or anti-PD ligand-1 in the vast majority of cases] in our review. In most clinical trials of immunotherapy for cancers other than HCC, patients with HBV infection were excluded, while all HBsAg positive patients in the trials for HCC were required to be receiving NA therapy and to have low or undetectable serum HBV DNA (<100 IU/L) before the onset of immunotherapy (68,69). In a retrospective cohort study including 114 HBsAg positive cancer patients (75% on NA prophylaxis) treated with anti-PD-1 or anti-PD ligand-1 therapy, HBV reactivation occurred in 6 (5.3%) patients at a median of 18 weeks after the onset of immunotherapy, in 5/29 (17%) patients without and 1/85 (1%) patients under anti-HBV prophylaxis (P=0.004). In that study, patients with HCC appeared to have a higher risk of ALT elevations compared to those with other cancers (P=0.038) (50). It should be noted that anti-PD-1 agents might have the potential to restore impaired immune response to HBV and have been evaluated as treatment of chronic hepatitis B, but results from a pilot clinical trial are inconclusive (70).

The pooled rates of biochemical reactivation were substantially lower (0%-11%) than the rates of virological reactivation for all HCC therapies regardless of the risk for HBV virological reactivation (high risk: 6%-11%, intermediate risk: 0%-4%). Liver decompensation and death were rare (0%-5%) and reported only in patients undergoing HCC treatment with high risk of HBV reactivation, though clinical outcomes were not reported in all studies and attribution of causation of these events to HBV reactivation versus underlying cirrhosis versus HCC progression can be challenging. Furthermore, administration of NA after the diagnosis of virological

reactivation might have prevented progression to biochemical reactivations, and liver decompensation and death (60,61).

HBV reactivation may occur not only in HBsAg positive but also in HBsAg negative, anti-HBc positive patients, receiving potent immunosuppressive therapy such as anti-CD20 (8,9). We were unable to study the risk of HBV reactivation in HBsAg-negative, anti-HBc positive patients receiving HCC treatment due to paucity of literature. In one such study of 43 patients treated with TACE, virological reactivation was observed in 9.3% of them (18).

The main limitation of this systematic review is related to the moderate or low quality of the available studies leading to moderate or serious risk of bias. In addition, variable definitions of HBV virological reactivation, and even more variable definition of biochemical reactivation were used in the studies. Moreover, differences in baseline characteristics such as HBV DNA levels may have affected outcomes. Interpretation of results is further compounded by the difficulty in ascertaining whether ALT increase or hepatic decompensation is caused by HBV reactivation, underlying cirrhosis or HCC progression. Our literature search identified studies that reported HBV virological reactivation but not all studies reported biochemical exacerbations, hepatic decompensations or deaths due to HBV reactivation. Due to the limited available information, subgroup analyses particularly use of prophylactic antiviral therapy could not be performed for all studies. Use of NA prophylaxis was not randomized in any of the studies,; thus the effect of NA prophylaxis cannot be directly estimated. However. patients with higher risk of HBV reactivation (e.g. high HBV DNA levels) were more likely to receive NA prophylaxis, which implies that its actual benefit was most probably under- and not over-estimated. Our search was meticulous, and involved two large databases plus manual searches, but we included only studies published in English and thus studies published in other languages may have been missed. All studies came from Asia where HBV-related HCC is common. Thus, our results may not be generalized to HBsAg positive patients receiving HCC treatment in other continents.

The strengths of our study include the entire spectrum of HCC treatment including recently approved immunotherapies and radiotherapy, and analyses of not only

virological reactivation but also biochemical reactivation and clinical outcomes, and relationship to use of prophylactic NA, whenever data were available.

Antiviral therapy has been recommended for HBsAg positive patients with HCC to reduce further liver damage and to prevent late recurrence. Our study provided additional evidence in support of NA use in all HBsAg-positive patients with HCC regardless of the type of HCC treatment they will receive. The risk of HBV reactivation is high in patients undergoing surgical resection, TACE or radiotherapy and intermediate in those undergoing local ablation and current systemic therapies including immunotherapy. Given the limited data for HCC treatments with intermediate HBV reactivation risk, additional studies could provide useful information in this setting. Despite the lack of data, prophylaxis with NA may also be considered in HBsAg negative, anti-HBc positive patients with HCC, especially when they receive HCC treatment with high risk of HBV reactivation.

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FIGURE LEGENDS

Figure 1. Rates of HBV reactivation in studies including HBsAg positive patients with hepatocellular carcinoma (HCC) who received no specific HCC treatment

Figure 2. Rates of HBV reactivation (A: all patients, B: patients without prophylactic HBV therapy) in studies including HBsAg positive patients with hepatocellular carcinoma (HCC) who were treated with ablation therapy for HCC.

Figure 3. Rates of HBV reactivation (A: all patients, B: patients without prophylactic HBV therapy, C: patients with prophylactic HBV therapy) and biochemical

exacerbation (D) in studies including HBsAg positive patients with hepatocellular carcinoma (HCC) who underwent surgical resection for HCC.

Figure 4. Rates of HBV reactivation (A: all patients, B: patients without prophylactic HBV therapy, C: patients with prophylactic HBV therapy) and biochemical exacerbation (D) in studies including HBsAg positive patients with hepatocellular carcinoma (HCC) who underwent transarterial chemoembolization for HCC.

Figure 5. Rates of HBV reactivation (A: all patients, B: patients without prophylactic HBV therapy) and biochemical exacerbation (C) in studies including HBsAg positive patients with hepatocellular carcinoma (HCC) who underwent external radiotherapy for HCC.

Figure 6. Rates of HBV reactivation (A: all patients, B: patients without prophylactic HBV therapy, C: patients with prophylactic HBV therapy) and biochemical exacerbation (D) in studies including HBsAg positive patients with hepatocellular carcinoma (HCC) who received systemic therapy for HCC.

Table 1. Main characteristics of studies providing data on HBV reactivation in HBsAg positive patients with HCC in relation to the type of HCC treatment.

1st author, year	Study design	Me(di)an age, yrs	Patients, n	HBV DNA levels	Prophylactic NA, n/Type	Follow-up^, mos	Definition of virological reactivation	Definition of biochemical reactivation
No specific HCC treatment								
Jang, 2004 (19)	R	n/a	20	Any	0	13	HBV DNA >1 log increase or reappearance	ALT >3-fold increase & >100 IU/L
Park, 2005[2] (20)	P	54	20	Positive: 15	0	2	HBV DNA reappearance	ALT ≥2-fold increase
Kim, 2007 (31)	R	53	43	Any	0	2	HBV DNA >2 log increase	ALT >2.5xULN
Radiofrequency ablation or ethanol injection								
Jang, 2004[1] (19)	R	n/a	9	Any	0	13	HBV DNA >1 log increase or reappearance	ALT >3-fold increase & >100 IU/L
Jang, 2011[3] (42)	P	55	43	Any	0	11	HBV DNA >1 log increase	ALT >3/2-fold increase if baseline ALT ≤/>ULN
Dan, 2013[4] (53)	R	55	125	Any	33/LAM, ADV, ETV	n/a	HBV DNA >1 log increase or reappearance	ALT >3-fold increase or >100 IU/L
Surgical resection								
Kubo, 2001 (55)	R/P	51	55 (25	≥7 Meq/mL:	n/a	36	HBV DNA ≥5-fold increase	ALT ≥2-fold increase

			followed)	12			within 3 mos	between 3 wks & 3 mos
Jang, 2004[1] (19)	R	n/a	34	Any	0	13	HBV DNA >1 log increase or reappearance	ALT ≥3-fold increase (ALT >100 IU/L)
Thia, 2007 (56)	R	58	77 (82 re-sections)	Undetectable: 10	14/LAM	20	Detectable HBV DNA without other causes	ALT >2-fold increase or >200 IU/L within 2-24 wks
Huang, 2013 (57)	R	n/a	1609	Any	150/LAM± ADV/ETV, ADV, ETV	12	HBV DNA >1 log increase or reappearance (>200 IU/mL)	Sustained ALT ≥3xULN
Lao, 2013[5] (58)	R	48	204	Any	83/LAM, ADV, TBV, ETV	n/a	HBV DNA >1 log increase or reappearance (>200 IU/mL)	ALT/Bilirubin >3/2-fold increase or ALT >100 IU/L
Dan, 2013[4] (53)	R	45	93	≥10^4 cp/mL: 55	35/LAM, ADV, ETV	n/a	HBV DNA >1 log increase or reappearance	ALT ≥3xULN or >100 IU/L
Lee, 2014 (59)	R	51	101	Undetectable: 33	53/LAM± ADV	3	HBV DNA >2 log increase within 3 mos	n/a
Sohn, 2015 (21)	R	53	130	Any	64/LAM±ADV, CLE, ETV	28	HBV DNA >1 log increase or reappearance	n/a
Zhang, 2015 (22)	R	n/a	112	Any	72/ETV	6	n/a	n/a

Xie, 2015 (23)	P	49	135	Any	45/ETV	1	HBV DNA >1 log increase or reappearance	n/a
Chen, 2016 (24)	R	n/a	74	Any	20/ETV	0.23	HBV-DNA >500 IU/mL	n/a
Xie, 2016 (25)	R	n/a	258	Any	33/ETV	1	HBV DNA >1 log increase or reappearance	n/a
Gong, 2017 (26)	P	50	174	<500 IU/mL	66/ETV	1	HBV DNA reappearance	n/a
Yuan, 2017 (27)	R	49	88	Any	44/ETV	6	HBV DNA >1 log increase	n/a
Huang, 2017 (28)	P/R	n/a	574 (+TACE: 110)	>2000 IU/mL: 296	69/LAM, ADV, ETV	53	HBV DNA >1 log increase or reappearance (>200 IU/mL) within 3 mos	Sustained ALT ≥3xULN
Li, 2019 (54)	R	n/a	857	>10^4 cp/mL: 376	329/LAM, ADV, ETV	n/a	n/a	n/a
Wang, 2019 (30)	R	n/a	209	Any	0	1	HBV DNA >1 log increase or reappearance within 1 mo	n/a
Xu, 2019 (32)	R	n/a	161	<100 IU/mL	73/ETV	36	HBV DNA >1 log increase	n/a
Li, 2020 (33)	R	49	140	<200 IU/mL	59/ETV	n/a	HBV DNA reappearance	n/a
Wang, 2020 (34)	R	n/a	795	>200 IU/mL:	538/LAM±	n/a	HBV DNA >1 log increase	n/a

			(+TACE: 337)	467	ADV, ETV, TBV		or reappearance (>200 IU/mL)	
Transarterial chemoembolization (TACE)								
Jang, 2004[1] (19)	R	54	83	Any	0	13	HBV DNA >1 log increase or reappearance	ALT >3-fold increase & >100 IU/L
Park, 2005[2] (20)	P	57	69	Positive: 46	0	2	HBV DNA reappearance	ALT ≥2-fold increase
Jang, 2006 (35)	P	53	73	$<10^7$ cp/mL	36/LAM	5.8	HBV DNA >1 log increase	ALT >3-fold increase & >100 IU/L
Jang, 2011[3] (42)	P	55	162	Any	0	11	HBV DNA >1 log increase	ALT >3/2-fold increase if baseline ALT ≤/>ULN
Lao, 2011 (36)	R	49	228 (sessions)	<6.1 logs IU/mL	0	1.7	HBV DNA >1 log increase or reappearance (>200 IU/mL)	ALT >3xULN or >100 IU/L
Yu, 2013 (37)	P	55	183	$>10^4$ cp/mL: 135	0	31	n/a	n/a
Lao, 2013[5] (58)	R	50	386	Any	66/LAM, ADV, TBV, ETV	3	HBV DNA >1 log increase or reappearance (>200 IU/mL)	ALT/Bilirubin >3/2-fold increase or ALT >100 IU/L
Shao, 2015 (38)	P	n/a	109	<2000 IU/mL	35/LAM, ADV, ETV	n/a	HBV DNA >1 log increase or reappearance	n/a

Li, 2017 (39)	R	51	356	Any	132/LAM, ETV	6	HBV DNA >1 log increase or reappearance (>200 IU/mL)	n/a
Jang, 2020 (40)	R	55	1547	Any	772/LAM, ADV, TBV, CLE, ETV, TDF	16.5	HBV DNA >1 log increase	n/a
Wang, 2021 (41)	R	59	108	>1000 cp/mL: 73	0	1	HBV DNA >1 log increase	n/a
Liu, 2021 (43)	P	51	170	Detectable: 126	137/LAM, ADV, TBV, ETV	3	HBV DNA >1 log increase or reappearance (>200 IU/mL)	ALT >3xULN
External radiotherapy								
Kim, 2007 (31)	R	53	48	Any	16/LAM	2	HBV DNA >2 log increase	ALT >2.5xULN
Choi, 2013 (44)	P	62	36	Positive: 23	0	3	HBV DNA >2 log increase	ALT >2.5xULN
Huang, 2014 (45)	R	n/a	69	Any	0	3.7	HBV DNA >1 log increase or reappearance	ALT >3xULN or >100 IU/L
Jun, 2018[6] (46)	P	n/a	133	>2000 IU/mL: 34	106/LAM, ADV, ETV, TDF	2.3	HBV DNA >1 log increase or reappearance (>200 IU/mL)	ALT >3xULN or >100 IU/L
Li, 2019 (29)	R	56	90	Any	0	3.7	HBV DNA >1 log increase or reappearance	ALT >3xULN or >100 IU/L

Systemic therapies								
Shim, 2009[7] (47)	R	n/a	45	<10^4 cp/mL	28/LAM, ADV, ETV, CLE	3	HBV DNA >1 log increase	ALT increase
Yang, 2015[8] (48)	R	46	130	>10^4 cp/mL: 35	64/LAM, ADV, ETV	n/a	HBV DNA ≥1 log increase or HBV DNA >10^5 cp/mL	ALT/AST ≥5xULN
Lim, 2015[7] (49)	R	56	78*	>2000 IU/mL: 40	40/ n/a	n/a	HBV DNA ≥2-fold increase	ALT/AST ≥2-fold increase
Zhang, 2019[9] (50)	R	n/a	28	Any	n/a	4.2	HBV DNA ≥1 log increase or ≥3-4 logs	ALT >3xULN or >100 IU/L
Lee, 2020[8] (51)	R/P	n/a	60	Any	54/ETV, TDF	10.4	HBV DNA >1 log increase or reappearance (>1000 IU/mL) or HBsAg reappearance	ALT >3xULN or >100 IU/L
Ng, 2020[10] (52)	R	n/a	62[#]	Any	57/ n/a	14	HBV DNA >1 log increase or reappearance or HBsAg reappearance	ALT >3-fold increase & >ULN

NA: nucleos(t)ide analogue, R: retrospective, P: prospective, yrs: years, n/a: not available, wks: weeks, mos: months, ULN: upper limit of normal, LAM: lamivudine, ADV: adefovir dipivoxil, TBV: telbivudine, ETV: entecavir, CLE: clevudine, TDF: tenofovir disoproxil fumarate.

[1]This study included HCC patients treated with no specific HCC therapy, ethanol injection, surgical resection or TACE; [2]This study included HCC patients treated with no specific HCC therapy or TACE; [3]This study included HCC patients treated with ablation therapy or TACE; [4]This study

included HCC patients treated with ablation therapy or surgical resection; [5]This study included HCC patients treated with surgical resection or TACE; [6]This study included HCC patients treated with radiotherapy ±TACE; [7]This study included HCC patients treated with sorafenib; [8]This study included HCC patients treated with sorafenib ±TACE; [9]This study included HCC patients treated with immune check-point inhibitors; [10]This study included HCC patients treated with immune check-point inhibitors ± anti-angiogenetic factors or locoregional therapy.

^Mean or median follow-up for the assessment of HBV virological reactivation; [*]72 HBsAg positive and 6 HBsAg negative & anti-HBc positive patients; [#]55 HBsAg positive and 7 HBsAg negative & anti-HBc positive patients.

Table 2. HBV reactivation in HBsAg positive patients with HCC in relation to the type of HCC treatment.

1st author, year	Patients with virological reactivation, n/N	Virological reactivation in relation to prophylactic NA, n/N		Patients with biochemical reactivation, n/N	Biochemical reactivation in relation to prophylactic NA, n/N		Liver decompensation, n/N	Death, n/N
		Yes	No		Yes	No		
No specific HCC treatment								
Jang, 2004 (19)	1/20	-	1/20	0/20	-	0/20	0/20	0/20
Park, 2005 (20)	2/20	-	2/20	0/20	-	0/20	0/20	0/20
Kim, 2007 (31)	1/43	-	1/43	1/43	-	1/43	n/a	n/a
Total	*4/83*	-	*4/83*	*1/83*	-	*1/83*	*0/40*	*0/40*
Radiofrequency ablation or ethanol injection								

Jang, 2004 (19)	0/9	-	0/9	0/9	-	0/9	0/9	0/9
Jang, 2011 (42)	5/43	-	5/43	1/43	-	1/43	0/43	0/43
Dan, 2013 (53)	7/125	0/33	7/92	n/a	n/a	n/a	n/a	n/a
Total	*12/177*	*0/33*	*12/144*	*1/52*	-	*1/52*	*0/52*	*0/52*
Surgical resection								
Kubo, 2001 (55)	7/25	-	7/25	6/25	-	6/25	n/a	n/a
Jang, 2004 (19)	1/34	-	1/34	1/34	-	1/34	0/34	0/34
Thia, 2007 (56)	7/82	n/a	n/a	7/82	n/a	n/a	6/82	3/82
Huang, 2013 (57)	308/1609	7/150	301/1459	236/1609	n/a	n/a	n/a	24/1609
Lao, 2013 (58)	19/204	0/83	19/121	2/204	n/a	n/a	n/a	n/a
Dan, 2013 (53)	13/93	1/35	12/58	n/a	n/a	n/a	n/a	n/a
Lee, 2014 (59)	18/101	1/53	17/48	3/101	n/a	n/a	0/101	0/101
Sohn, 2015 (21)	53/130	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Zhang, 2015 (22)	6/112	0/72	6/40	n/a	n/a	n/a	n/a	n/a
Xie, 2015 (23)	26/135	1/45	25/90	n/a	n/a	n/a	n/a	n/a
Chen, 2016 (24)	16/74	1/20	15/54	n/a	n/a	n/a	n/a	n/a
Xie, 2016 (25)	50/258	1/33	49/225	n/a	n/a	n/a	n/a	n/a
Gong, 2017 (26)	32/174	2/66	30/108	n/a	n/a	n/a	n/a	n/a

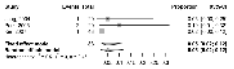
Yuan, 2017 (27)	12/88	1/44	11/44	n/a	n/a	n/a	n/a	n/a
Huang, 2017 (28)	87/574	4/69	83/505	34/574	1/69	33/505	n/a	n/a
Li, 2019 (54)	184/857	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Wang, 2019 (30)	31/209	-	31/209	n/a	n/a	n/a	n/a	n/a
Xu, 2019 (32)	22/161	2/73	20/88	n/a	n/a	n/a	n/a	n/a
Li, 2020 (33)	11/129	1/59	10/70	n/a	n/a	n/a	n/a	n/a
Wang, 2020 (34)*	99/538*	99/538*	n/a	n/a	n/a	n/a	n/a	26/795*
Total	*1002/5587*	*121/1340*	*637/3178*	*289/2629*	*1/69*	*70/564*	*6/217*	*53/2621*
Transarterial chemoembolization (TACE)								
Jang, 2004 (19)	28/83	-	28/83	18/83	-	18/83	3/83	3/83
Park, 2005 (20)	3/69	-	3/69	4/69	-	4/69	n/a	n/a
Jang, 2006 (35)	16/73	1/36	15/37	12/73	1/36	11/37	3/73	1/73
Jang, 2011 (42)	57/162	-	57/162	31/162	-	31/162	10/162	1/162
Lao, 2011 (36)	33/228	-	33/228	15/228	-	15/228	n/a	2/228
Yu, 2013 (37)	48/183	-	48/183	48/183	-	48/183	n/a	n/a
Lao, 2013 (58)	57/386	1/66	56/320	9/386	n/a	n/a	n/a	n/a
Shao, 2015 (38)	23/109	5/35	18/74	n/a	n/a	n/a	n/a	n/a
Li, 2017 (39)	42/356	6/132	36/224	n/a	n/a	n/a	n/a	n/a

Jang, 2020 (40)	143/1547	0/772	143/775	n/a	n/a	n/a	n/a	n/a
Wang, 2021 (41)	42/108	-	42/108	n/a	n/a	n/a	n/a	n/a
Liu, 2021 (43)	25/170	16/137	9/33	7/170	3/137	4/33	0/170	0/170
Total	*517/3474*	*29/1178*	*488/2296*	*144/1354*	*4/173*	*131/795*	*16/488*	*7/716*
External radiotherapy								
Kim, 2007 (31)	7/48	0/16	7/32	4/48	0/16	4/32	n/a	n/a
Choi, 2013 (44)	0/36	-	0/36	0/36	-	0/36	0/36	0/36
Huang, 2014 (45)	17/69	-	17/69	15/69	-	15/69	n/a	3/69
Jun, 2018[1] (46)	17/133 (5/75)[¶]	8/106 (0/58)[¶]	9/27 (5/17)[¶]	7/133	5/106	2/27	n/a	n/a
Li, 2019 (29)	20/90	-	20/90	19/90	-	19/90	n/a	n/a
Total	*61/376 (49/318)[¶]*	*8/122 (0/74)[¶]*	*53/254 (49/244)[¶]*	*45/376*	*5/122*	*40/254*	*0/36*	*3/105*
Systemic therapies								
Shim, 2009[2] (47)	0/45	0/28	0/17	n/a	n/a	n/a	n/a	n/a
Yang, 2015[3] (48)	9/93	n/a	n/a	0/93	n/a	n/a	0/93	0/93
Lim, 2015[2] (49)	4/78	0/40	4/38	2/78	0/40	2/38	n/a	n/a
Zhang, 2019[4] (50)	1/28	n/a	n/a	1/28	n/a	n/a	0/28	0/28
Lee, 2020[3] (51)	4/60	3/54	1/6	1/60	0/54	1/6	0/60	0/60
Ng, 2020[5] (52)	6/62	5/57	1/5	2/62	n/a	n/a	0/62	0/62

Total	*24/366*	*8/179*	*6/66*	*6/321*	*0/94*	*3/44*	*0/243*	*0/243*

NA: nucleos(t)ide analogue, n/a: not available. [1]Patients were treated with radiotherapy ±TACE ([¶]patients treated with radiotherapy alone without TACE); [2]Patients treated with sorafenib; [3]Patients treated with sorafenib ±TACE; [4]Patients treated with immune check-point inhibitors; [5]Patients treated with immune check-point inhibitors ±anti-angiogenetic factors or locoregional therapy.

*795 patients were included and assessed for HBV related survival, while HBV reactivation was assessed only in the 538 NA treated patients;



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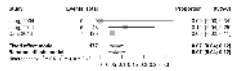

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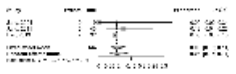

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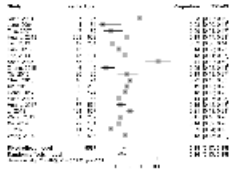

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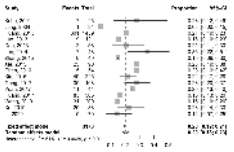

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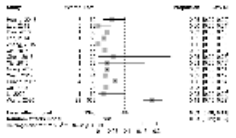

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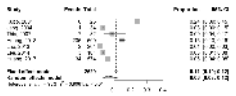

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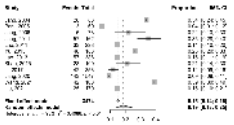

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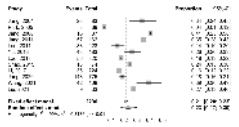

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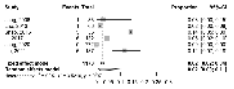

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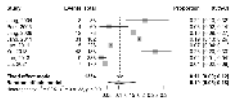

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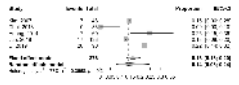

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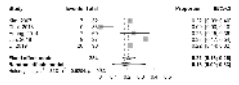

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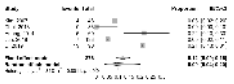

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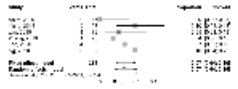

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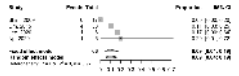

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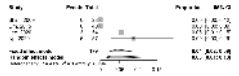

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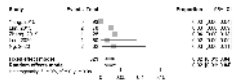

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