Received: 10 August 2021 | Revised: 5 November 2021 | Accepted: 9 November 2021

DOI: 10.1002/hep.32241

ORIGINAL ARTICLE

Risk of HBV reactivation during therapies for HCC: A systematic review

Margarita Papatheodoridi[1] | **Maria Tampaki**[2] | **Anna S. Lok**[3] | **George V. Papatheodoridis**[2]

[1]UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, UK

[2]Department of Gastroenterology and Liver Transplantation Unit, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens "Laiko", Athens, Greece

[3]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan, USA

Correspondence
Anna S. Lok, Division of Gastroenterology and Hepatology, University of Michigan, 1500 East Medical Center Drive, 3912 Taubman Center, SPC 5362, Ann Arbor, MI 48109, USA.
Email: aslok@med.umich.edu

George V. Papatheodoridis, Department of Gastroenterology and Liver Transplantation Unit, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens "Laiko," Athens, Greece.
Email: gepapath@med.uoa.gr

Abstract

Background and Aims: Treatment for HCC has evolved rapidly, but the risk of 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.

Approach and Results: A 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% versus 0%; resection, 20% versus 3%; chemoembolization, 23% versus 1%; external radiotherapy alone, 18% versus 0%; systemic therapy, 9% versus 3%). HBV-related biochemical reactivation rates varied between 6%–11% and 2% in patients receiving HCC therapies with high and intermediate HBV reactivation risk, respectively. Liver decompensation and death were rarely reported (0%–3%) and only in patients receiving HCC treatment with high HBV reactivation risk.

Conclusions: 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, practically eliminates the risk of hepatitis flare, and should be administered regardless of HCC treatment.

INTRODUCTION

HCC has a rising incidence and currently represents the fourth leading cause of cancer-related death worldwide.[1,2] Chronic infection with 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

SEE EDITORIAL ON PAGE 1075

Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; NA, nucleos(t)ide analogue; PD, programmed cell death; TACE, transarterial chemoembolization.

Margarita Papatheodoridi and Maria Tampaki contributed equally to this work.

chronic HBV infection worldwide have been diagnosed, and <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 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 checkpoint 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 randomized trials, (2) included patients with HCC, (3) included patients who were HBsAg-positive and/or positive for antibody to hepatitis B core antigen (anti-HBc), (4) provided data on HBV reactivation based on virological and/or biochemical definitions.

A literature search was performed by two independent reviewers (M. P., M. T.), 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 (G. V. P.). Each study in the list of selected papers was evaluated by two independent reviewers (M. P., M. T.) to determine whether it fulfilled all of the inclusion criteria. These two reviewers extracted data from the selected papers according to a predefined form (Supporting Table S1). The two data summary tables were compared for concordance, and discrepancies were discussed and arbitrated by a third reviewer (G. V. P.). This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis.[11]

Statistical analysis

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

A meta-analysis was performed using a generalized linear mixed model and Clopper-Pearson CIs (exact binomial interval) for individual studies.[12] Between-studies variance was estimated using the maximum likelihood estimator. Heterogeneity was examined visually in 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 et al.[14] The pooled incidence rates and 95% CIs 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, version 3.6.0,[15] using the meta[16] and the metaphor[17] packages.

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 population of HBsAg-positive patients. Thirty-four studies remained on the list (PubMed, 27; Embase, 7), and another seven studies were identified through the manual search. Thus, 41 studies were finally included in this systematic review (Supporting Figure S1).[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 patient age ranged from 45 to 58 years. Most studies included patients with variable serum HBV DNA levels, with seven studies including only patients with very low to undetectable (<100–200 IU/mL, $n = 4$)[32,33,56,59] or low to 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 populations 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 five studies[31,44,49,55,59] and was not clearly provided in the remaining three 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 (M. P. and M. T.). This tool includes seven 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 (Supporting Table S2).

HBV reactivation in patients who did not receive HCC treatment

There were three 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 three 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 that only 1 (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 5880 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 and 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 in 1340 patients who did (pooled estimate, 3%, 95% CI, 1%–5%; heterogeneity, $p < 0.01$) (Figure 3C).[21,22,23–28,30,32,33,34,53,54,57–59] The pooled rates of HBV reactivation were 16% (95% CI, 13%–20%; heterogeneity, $p = 0.06$) in eight studies with mean/median follow-up ≤6 months[22–27,30,59] and 16% (95% CI, 10%–26%; heterogeneity, $p < 0.01$) in seven studies with mean/median follow-up >6 months.[19,21,28,32,55–57] Patients receiving entecavir prophylaxis had a 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

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

Reference	Study design	Me(di)an age (years)	Patients (*n*)	HBV DNA levels	Prophylactic NA (*n*/type)	Follow-up[a] (months)	Definition of virological reactivation	Definition of biochemical reactivation
No specific HCC treatment								
Jang et al.[19]	R	n/a	20	Any	0	13	HBV DNA > 1 log increase or reappearance	ALT > 3-fold increase and >100 IU/L
Park et al.[20]b	P	54	20	Positive: 15	0	2	HBV DNA reappearance	ALT ≥ 2-fold increase
Kim et al.[31]	R	53	43	Any	0	2	HBV DNA > 2 log increase	ALT > 2.5 × ULN
Radiofrequency ablation or ethanol injection								
Jang et al.[19]c	R	n/a	9	Any	0	13	HBV DNA > 1 log increase or reappearance	ALT > 3-fold increase and >100 IU/L
Jang et al.[42]d	P	55	43	Any	0	11	HBV DNA > 1 log increase	ALT > 3/2-fold increase if baseline ALT ≤/> ULN
Dan et al.[53]e	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 et al.[55]	R/P	51	55 (25 followed)	≥7 MEq/mL: 12	n/a	36	HBV DNA ≥ 5-fold increase within 3 mos	ALT ≥ 2-fold increase between 3 weeks and 3 months
Jang et al.[19]c	R	n/a	34	Any	0	13	HBV DNA > 1 log increase or reappearance	ALT ≥ 3-fold increase (ALT > 100 IU/L)
Thia et al.[56]	R	58	77 (82 resections)	Undetectable: 10	14/LAM	20	Detectable HBV DNA without other causes	ALT > 2-fold increase or >200 IU/L within 2–24 weeks
Huang et al.[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 ≥ 3 × ULN
Lao et al.[58]f	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 et al.[53]e	R	45	93	≥10^4 cp/mL: 55	35/LAM, ADV, ETV	n/a	HBV DNA > 1 log increase or reappearance	ALT ≥ 3 × ULN or >100 IU/L
Lee et al.[59]	R	51	101	Undetectable: 33	53/LAM± ADV	3	HBV DNA > 2 log increase within 3 months	n/a
Sohn et al.[21]	R	53	130	Any	64/LAM ± ADV, CLE, ETV	28	HBV DNA > 1 log increase or reappearance	n/a
Zhang et al.[22]	R	n/a	112	Any	72/ETV	6	n/a	n/a
Xie et al.[23]	P	49	135	Any	45/ETV	1	HBV DNA > 1 log increase or reappearance	n/a
Chen et al.[24]	R	n/a	74	Any	20/ETV	0.23	HBV DNA > 500 IU/mL	n/a
Xie et al.[25]	R	n/a	258	Any	33/ETV	1	HBV DNA > 1 log increase or reappearance	n/a
Gong et al.[26]	P	50	174	<500 IU/mL	66/ETV	1	HBV DNA reappearance	n/a

TABLE 1 (Continued)

Reference	Study design	Me(di)an age (years)	Patients (*n*)	HBV DNA levels	Prophylactic NA (*n*/type)	Follow-up[a] (months)	Definition of virological reactivation	Definition of biochemical reactivation
Yuan et al.[27]	R	49	88	Any	44/ETV	6	HBV DNA > 1 log increase	n/a
Huang et al.[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 months	Sustained ALT ≥ 3 × ULN
Li et al.[54]	R	n/a	857	$>10^4$ cp/mL: 376	329/LAM, ADV, ETV	n/a	n/a	n/a
Wang et al.[30]	R	n/a	209	Any	0	1	HBV DNA > 1 log increase or reappearance within 1 month	n/a
Xu et al.[32]	R	n/a	161	<100 IU/mL	73/ETV	36	HBV DNA > 1 log increase	n/a
Li et al.[33]	R	49	140	<200 IU/mL	59/ETV	n/a	HBV DNA reappearance	n/a
Wang et al.[34]	R	n/a	795 (+TACE: 337)	>200 IU/mL: 467	538/LAM ± ADV, ETV, TBV	n/a	HBV DNA > 1 log increase or reappearance (>200 IU/mL)	n/a
TACE								
Jang et al.[19]c	R	54	83	Any	0	13	HBV DNA > 1 log increase or reappearance	ALT > 3-fold increase and >100 IU/L
Park et al.[20]b	P	57	69	Positive: 46	0	2	HBV DNA reappearance	ALT ≥ 2-fold increase
Jang et al.[35]	P	53	73	$<10^7$ cp/mL	36/LAM	5.8	HBV DNA > 1 log increase	ALT > 3-fold increase and >100 IU/L
Jang et al.[42]d	P	55	162	Any	0	11	HBV DNA > 1 log increase	ALT > 3/2-fold increase if baseline ALT ≤/> ULN
Lao et al.[36]	R	49	228 (sessions)	<6.1 logs IU/mL	0	1.7	HBV DNA > 1 log increase or reappearance (>200 IU/mL)	ALT > 3 × ULN or >100 IU/L
Yu et al.[37]	P	55	183	$>10^4$ cp/mL: 135	0	31	n/a	n/a
Lao et al.[58]f	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 et al.[38]	P	n/a	109	<2000 IU/mL	35/LAM, ADV, ETV	n/a	HBV DNA > 1 log increase or reappearance	n/a
Li et al.[39]	R	51	356	Any	132/LAM, ETV	6	HBV DNA > 1 log increase or reappearance (>200 IU/mL)	n/a
Jang et al.[40]	R	55	1547	Any	772/LAM, ADV, TBV, CLE, ETV, TDF	16.5	HBV DNA > 1 log increase	n/a
Wang et al.[41]	R	59	108	>1000 cp/mL: 73	0	1	HBV DNA > 1 log increase	n/a
Liu et al.[43]	P	51	170	Detectable: 126	137/LAM, ADV, TBV, ETV	3	HBV DNA > 1 log increase or reappearance (>200 IU/mL)	ALT > 3 × ULN

(Continues)

TABLE 1 (Continued)

Reference	Study design	Me(di)an age (years)	Patients (*n*)	HBV DNA levels	Prophylactic NA (*n*/ type)	Follow-up[a] (months)	Definition of virological reactivation	Definition of biochemical reactivation
External radiotherapy								
Kim et al.[31]	R	53	48	Any	16/LAM	2	HBV DNA > 2 log increase	ALT > 2.5 × ULN
Choi et al.[44]	P	62	36	Positive: 23	0	3	HBV DNA > 2 log increase	ALT > 2.5 × ULN
Huang et al.[45]	R	n/a	69	Any	0	3.7	HBV DNA > 1 log increase or reappearance	ALT > 3 × ULN or >100 IU/L
Jun et al.[46][g]	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 > 3 × ULN or >100 IU/L
Li et al.[29]	R	56	90	Any	0	3.7	HBV DNA > 1 log increase or reappearance	ALT > 3 × ULN or >100 IU/L
Systemic therapies								
Shim et al.[47][h]	R	n/a	45	$<10^4$ cp/mL	28/LAM, ADV, ETV, CLE	3	HBV DNA > 1 log increase	ALT increase
Yang et al.[48][i]	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 ≥ 5 × ULN
Lim et al.[49][h]	R	56	78[l]	>2000 IU/mL: 40	40/ n/a	n/a	HBV DNA ≥ 2-fold increase	ALT/AST ≥ 2-fold increase
Zhang et al.[50][j]	R	n/a	28	Any	n/a	4.2	HBV DNA ≥ 1 log increase or ≥3–4 logs	ALT > 3 × ULN or >100 IU/L
Lee et al.[51][j]	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 > 3 × ULN or >100 IU/L
Ng et al.[52][k]	R	n/a	62[m]	Any	57/ n/a	14	HBV DNA > 1 log increase or reappearance or HBsAg reappearance	ALT > 3-fold increase and >ULN

Abbreviations: ADV, adefovir dipivoxil; AST, aspartate aminotransferase; CLE, clevudine; ETV, entecavir; LAM, lamivudine; n/a, not available; P, prospective; R, retrospective; TBV, telbivudine; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

[a]Mean or median follow-up for the assessment of HBV virological reactivation.

[b]This study included patients with HCC treated with no specific HCC therapy or TACE.

[c]This study included patients with HCC treated with no specific HCC therapy, ethanol injection, surgical resection, or TACE.

[d]This study included patients with HCC treated with ablation therapy or TACE.

[e]This study included patients with HCC treated with ablation therapy or surgical resection.

[f]This study included patients with HCC treated with surgical resection or TACE.

[g]This study included patients with HCC treated with radiotherapy with or without TACE.

[h]This study included patients with HCC treated with sorafenib.

[i]This study included patients with HCC treated with sorafenib with or without TACE.

[j]This study included patients with HCC treated with immune checkpoint inhibitors.

[k]This study included patients with HCC treated with immune checkpoint inhibitors with or without antiangiogenetic factors or locoregional therapy.

[l]72 HBsAg-positive and 6 HBsAg-negative and anti-HBc-positive patients.

[m]55 HBsAg-positive and 7 HBsAg-negative and anti-HBc-positive patients.

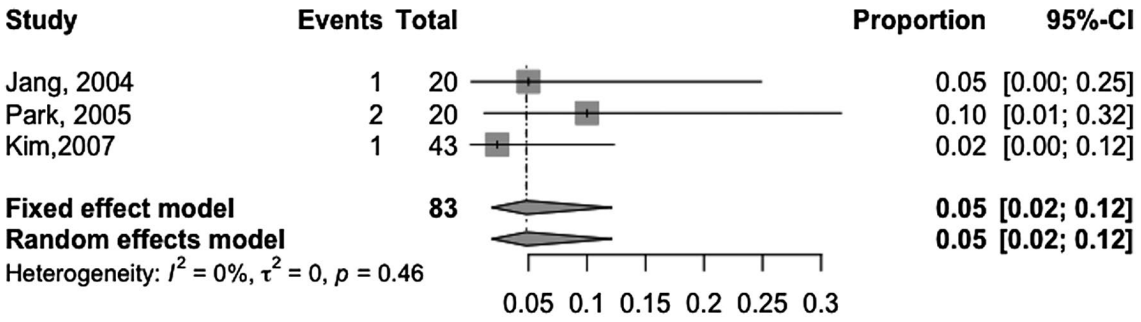

FIGURE 1 Rates of HBV reactivation in studies including HBsAg-positive patients with HCC who received no specific HCC treatment (Jang et al.,[19] Park et al.,[20] Kim et al.[31])

was reported in 11.0% (289/2629) of patients in seven 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 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 and 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 seven 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 three studies with mean/median follow-up >6 months.[19,40,42] Biochemical reactivation was reported in 144 (10.6%) of 1354 patients from eight 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, respectively.

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 and 2 and Figure 5A).[29,31,44–46] HBV reactivation rates were higher in 254 patients from five 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).

TABLE 2 HBV reactivation in HBsAg-positive patients with HCC in relation to the type of HCC treatment

Reference	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 et al.[19]	1/20	–	1/20	0/20	–	0/20	0/20	0/20
Park et al.[20]	2/20	–	2/20	0/20	–	0/20	0/20	0/20
Kim et al.[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 et al.[19]	0/9	–	0/9	0/9	–	0/9	0/9	0/9
Jang et al.[42]	5/43	–	5/43	1/43	–	1/43	0/43	0/43
Dan et al.[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 et al.[55]	7/25	–	7/25	6/25	–	6/25	n/a	n/a
Jang et al.[19]	1/34	–	1/34	1/34	–	1/34	0/34	0/34
Thia et al.[56]	7/82	n/a	n/a	7/82	n/a	n/a	6/82	3/82
Huang et al.[57]	308/1609	7/150	301/1459	236/1609	n/a	n/a	n/a	24/1609
Lao et al.[58]	19/204	0/83	19/121	2/204	n/a	n/a	n/a	n/a
Dan et al.[53]	13/93	1/35	12/58	n/a	n/a	n/a	n/a	n/a
Lee et al.[59]	18/101	1/53	17/48	3/101	n/a	n/a	0/101	0/101
Sohn et al.[21]	53/130	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Zhang et al.[22]	6/112	0/72	6/40	n/a	n/a	n/a	n/a	n/a
Xie et al.[23]	26/135	1/45	25/90	n/a	n/a	n/a	n/a	n/a
Chen et al.[24]	16/74	1/20	15/54	n/a	n/a	n/a	n/a	n/a
Xie et al.[25]	50/258	1/33	49/225	n/a	n/a	n/a	n/a	n/a
Gong et al.[26]	32/174	2/66	30/108	n/a	n/a	n/a	n/a	n/a
Yuan et al.[27]	12/88	1/44	11/44	n/a	n/a	n/a	n/a	n/a
Huang et al.[28]	87/574	4/69	83/505	34/574	1/69	33/505	n/a	n/a
Li et al.[54]	184/857	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Wang et al.[30]	31/209	–	31/209	n/a	n/a	n/a	n/a	n/a
Xu et al.[32]	22/161	2/73	20/88	n/a	n/a	n/a	n/a	n/a
Li et al.[33]	11/129	1/59	10/70	n/a	n/a	n/a	n/a	n/a

TABLE 2 (Continued)

Reference	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		
Wang et al.[34][a]	99/538[a]	99/538[a]	n/a	n/a	n/a	n/a	n/a	26/795[a]
Total	1002/5587	121/1340	637/3178	289/2629	1/69	70/564	6/217	53/2621
TACE								
Jang et al.[19]	28/83	–	28/83	18/83	–	18/83	3/83	3/83
Park et al.[20]	3/69	–	3/69	4/69	–	4/69	n/a	n/a
Jang et al.[35]	16/73	1/36	15/37	12/73	1/36	11/37	3/73	1/73
Jang et al.[42]	57/162	–	57/162	31/162	–	31/162	10/162	1/162
Lao et al.[36]	33/228	–	33/228	15/228	–	15/228	n/a	2/228
Yu et al.[37]	48/183	–	48/183	48/183	–	48/183	n/a	n/a
Lao et al.[58]	57/386	1/66	56/320	9/386	n/a	n/a	n/a	n/a
Shao et al.[38]	23/109	5/35	18/74	n/a	n/a	n/a	n/a	n/a
Li et al.[39]	42/356	6/132	36/224	n/a	n/a	n/a	n/a	n/a
Jang et al.[40]	143/1547	0/772	143/775	n/a	n/a	n/a	n/a	n/a
Wang et al.[41]	42/108	–	42/108	n/a	n/a	n/a	n/a	n/a
Liu et al.[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 et al.[31]	7/48	0/16	7/32	4/48	0/16	4/32	n/a	n/a
Choi et al.[44]	0/36	–	0/36	0/36	–	0/36	0/36	0/36
Huang et al.[45]	17/69	–	17/69	15/69	–	15/69	n/a	3/69
Jun et al.[46][c]	17/133 (5/75)[b]	8/106 (0/58)[b]	9/27 (5/17)[b]	7/133	5/106	2/27	n/a	n/a
Li et al.[29]	20/90	–	20/90	19/90	–	19/90	n/a	n/a
Total	61/376 (49/318)[b]	8/122 (0/74)[b]	53/254 (49/244)[b]	45/376	5/122	40/254	0/36	3/105
Systemic therapies								
Shim et al.[47][d]	0/45	0/28	0/17	n/a	n/a	n/a	n/a	n/a
Yang et al.[48][e]	9/93	n/a	n/a	0/93	n/a	n/a	0/93	0/93
Lim et al.[49][e]	4/78	0/40	4/38	2/78	0/40	2/38	n/a	n/a
Zhang et al.[50][f]	1/28	n/a	n/a	1/28	n/a	n/a	0/28	0/28
Lee et al.[51][e]	4/60	3/54	1/6	1/60	0/54	1/6	0/60	0/60

TABLE 2 (Continued)

Reference	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		
Ng et al.[52][g]	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

Abbreviation: n/a, not available.

[a]795 patients were included and assessed for HBV-related survival, while HBV reactivation was assessed only in the 538 NA-treated patients.

[b]Patients treated with radiotherapy alone without TACE.

[c]Patients were treated with radiotherapy with or without TACE.

[d]Patients treated with sorafenib.

[e]Patients treated with sorafenib with or without TACE.

[f]Patients treated with immune checkpoint inhibitors.

[g]Patients treated with immune checkpoint inhibitors with or without antiangiogenetic factors or locoregional therapy.

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 checkpoint inhibitors were used in the other two studies[50,52] (combined with antiangiogenetic 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 checkpoint 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 alanine aminotransferase (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 the 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).

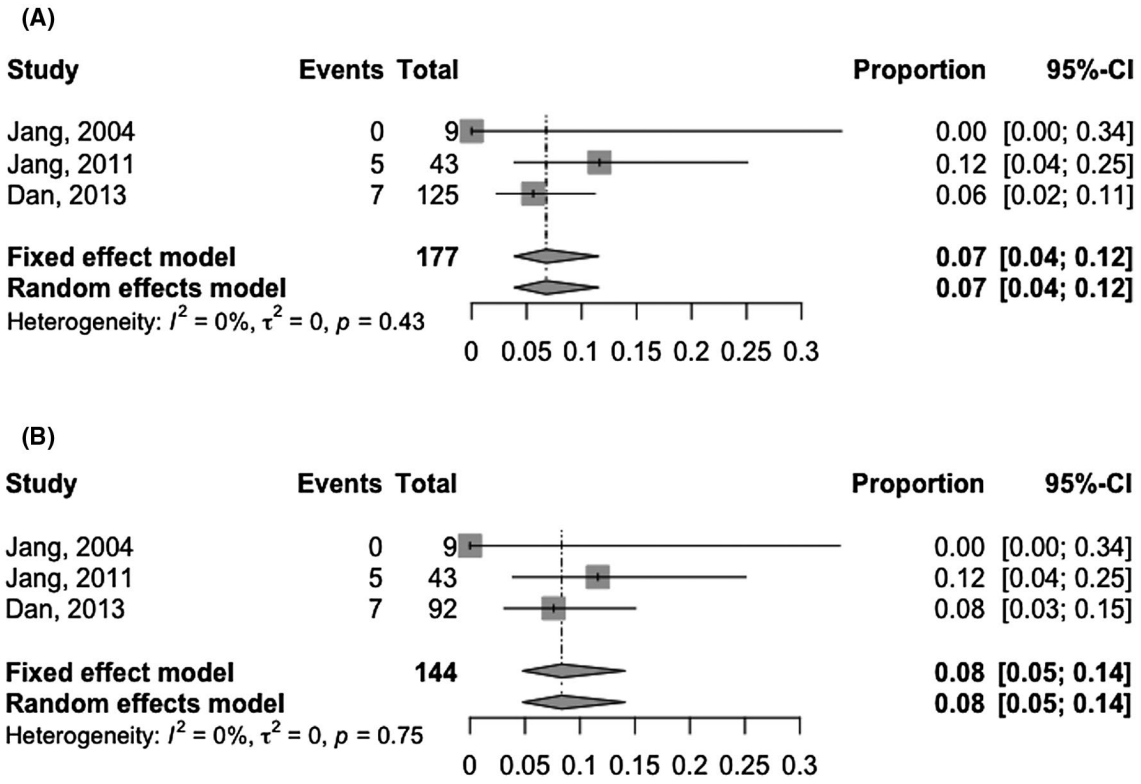

FIGURE 2 Rates of HBV reactivation (A, all patients; B, patients without prophylactic HBV therapy) in studies including HBsAg-positive patients with HCC who were treated with ablation therapy for HCC (Jang et al.,[19,42] Dan et al.[53])

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 intratumoral/peritumoral arteriovenous shunts may occur resulting in suppression of the host immune responses.[63] Radiation therapy can suppress the immune response even when 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 NA 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 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 because 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

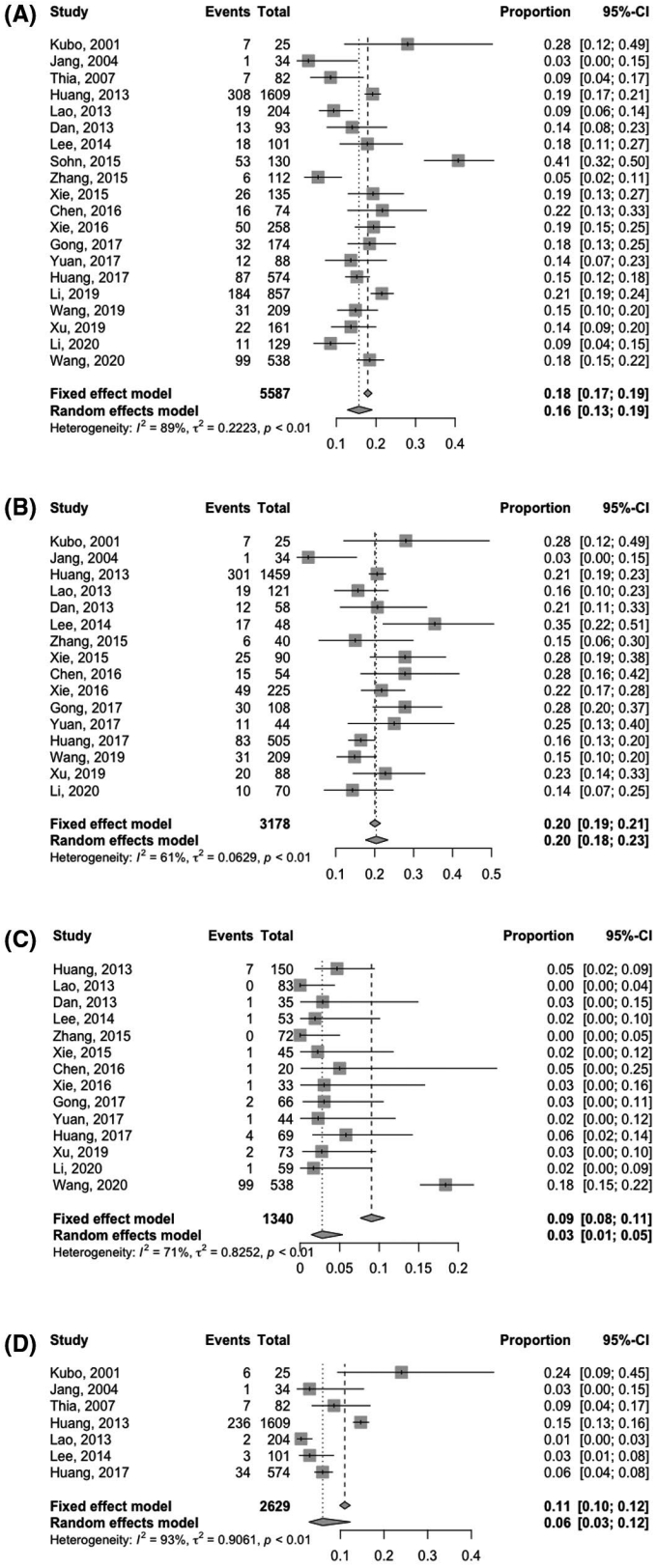

FIGURE 3 Rates of HBV reactivation (A, all patients; B, patients without prophylactic HBV therapy; C, patients with prophylactic HBV therapy) and biochemical exacerbation (D) in studies including HBsAg-positive patients with HCC who underwent surgical resection for HCC (Kubo et al.,[55] Jang et al.,[19] Thia et al.,[56] G. Huang et al.,[57] Lao et al.,[58] Dan et al.,[53] Lee et al.,[59] Sohn et al.,[21] Zhang et al.,[22] Xie et al.,[23,25] Chen et al.,[24] Gong et al.,[26] Yuan et al.,[27] S. Huang et al.,[28] Z. Li et al.,[29] X.-B. Wang et al.,[30] Xu et al.,[32] C. Li et al.,[33] Z.-Y. Wang et al.[34])

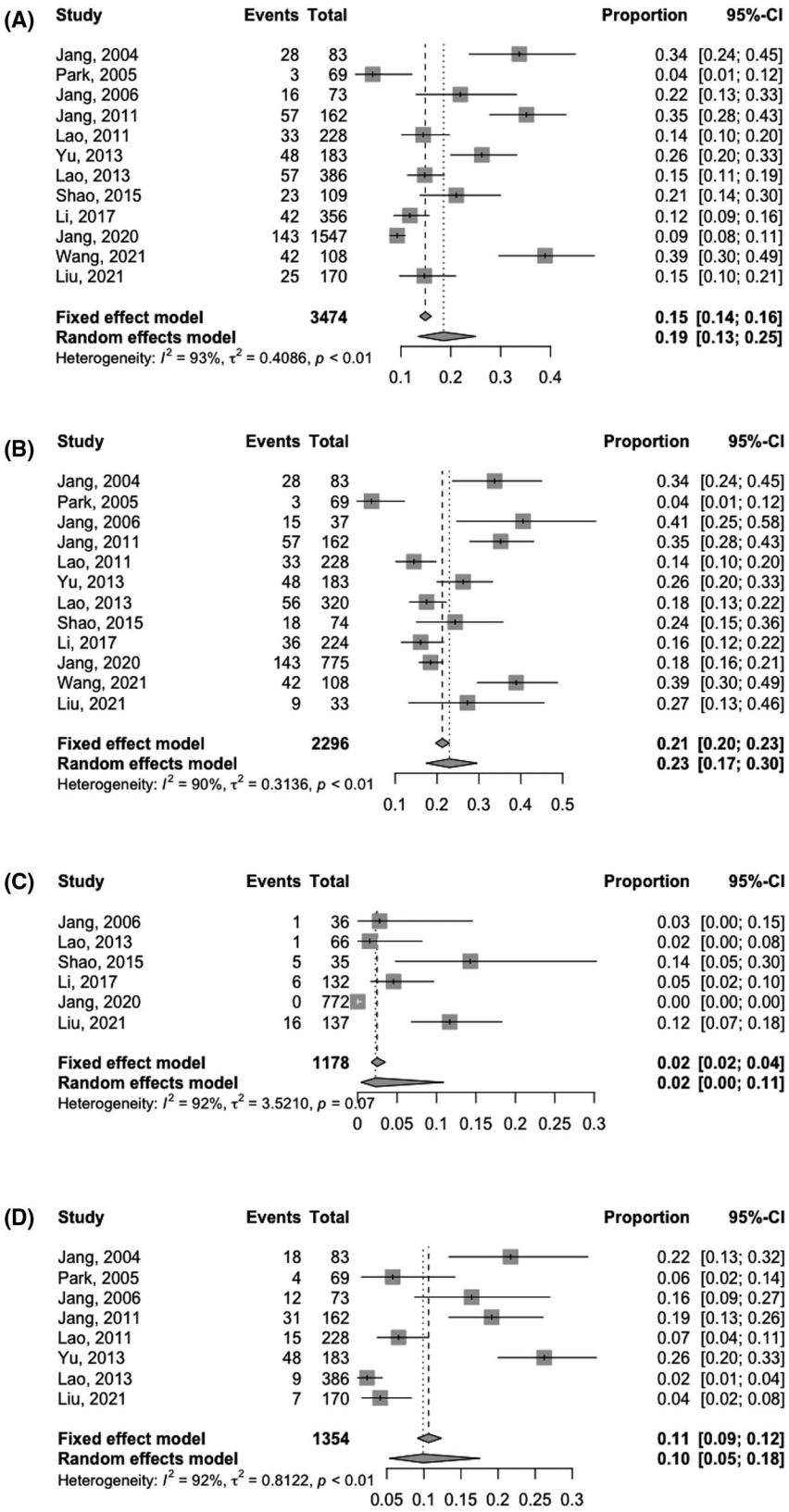

FIGURE 4 Rates of HBV reactivation (A, all patients; B, patients without prophylactic HBV therapy; C, patients with prophylactic HBV therapy) and biochemical exacerbation (D) in studies including HBsAg-positive patients with HCC who underwent TACE for HCC (Jang et al.,[19,35,40,42] Park et al.,[20] Lao et al.,[36,58] Yu et al.,[37] Shao et al.,[38] Li et al.,[39] X. Wang et al.,[41] Liu et al.,[43])

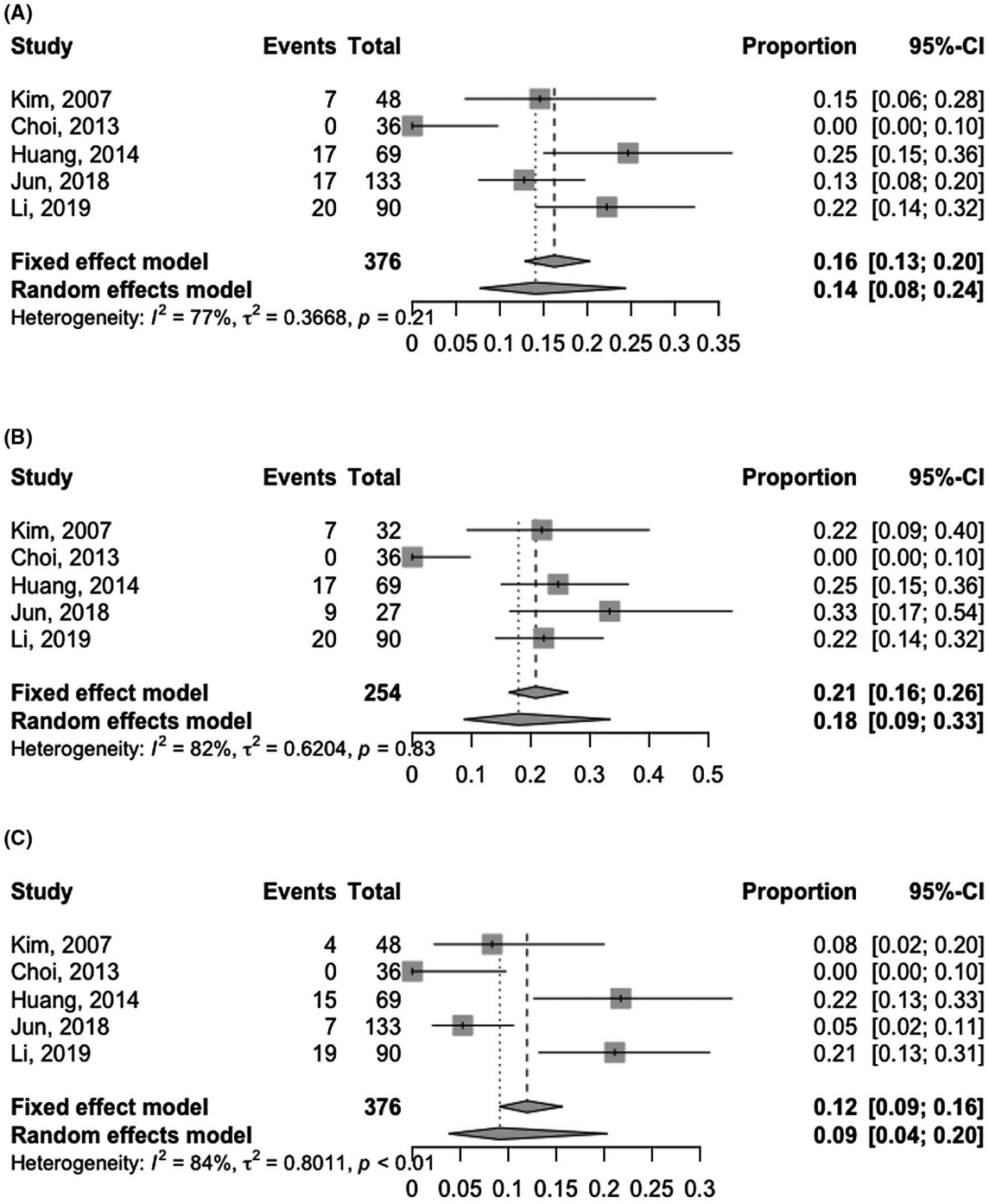

FIGURE 5 Rates of HBV reactivation (A, all patients; B, patients without prophylactic HBV therapy) and biochemical exacerbation (C) in studies including HBsAg-positive patients with HCC who underwent external radiotherapy for HCC (Kim et al.,[31] Choi et al.,[44] W. Huang et al.,[45] Jun et al.,[46] Z. Li et al.[29])

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 for 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

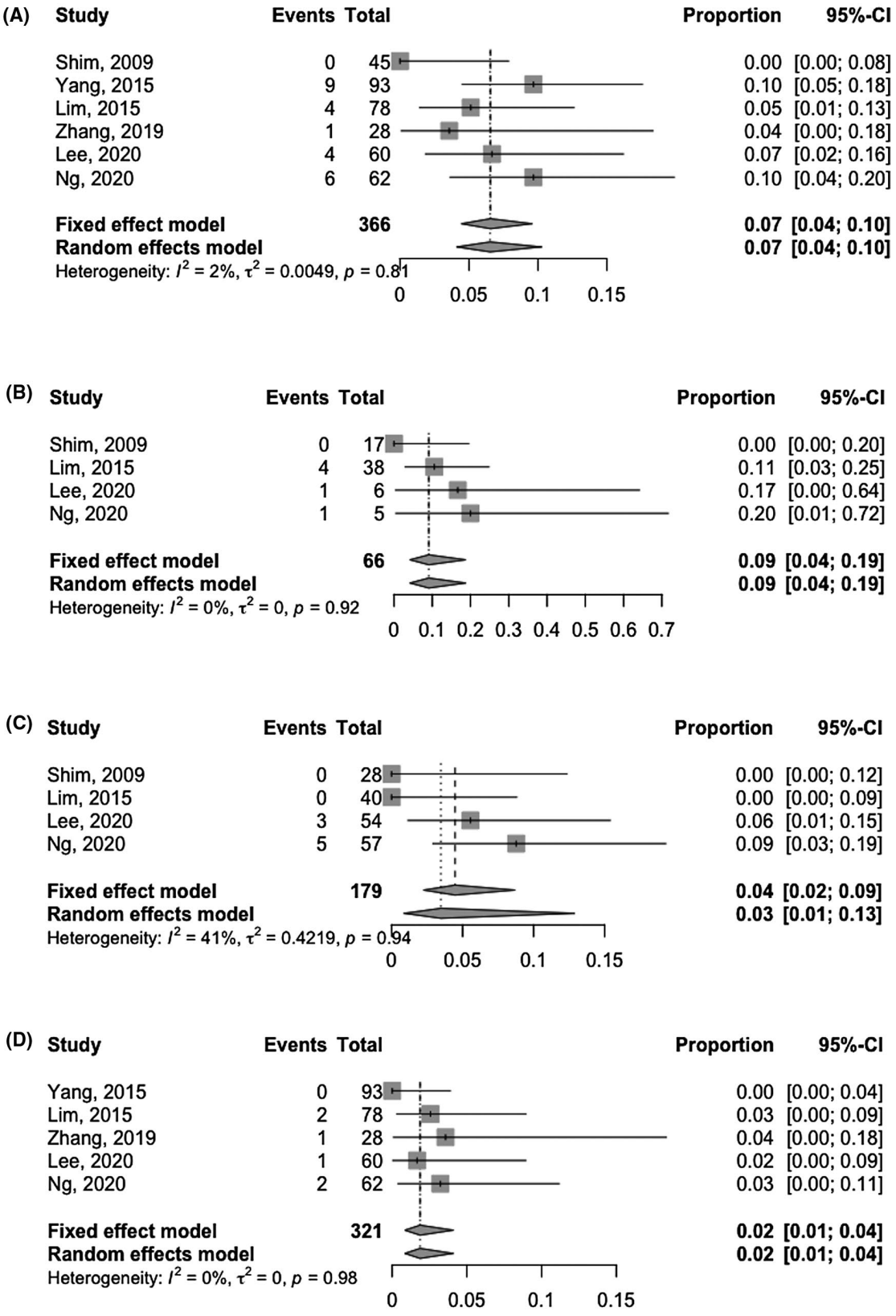

FIGURE 6 Rates of HBV reactivation (A, all patients; B, patients without prophylactic HBV therapy; C, patients with prophylactic HBV therapy) and biochemical exacerbation (D) in studies including HBsAg-positive patients with HCC who received systemic therapy for HCC (Shim et al.,[47] Yang et al.,[48] Lim et al.,[49] Zhang et al.,[50] Lee et al.,[51] Ng et al.[52])

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, 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–cluster of differentiation 20.[8,9] We were unable to study the risk of HBV reactivation in HBsAg-negative, anti-HBc-positive patients receiving HCC treatment due to a 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 definitions 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 was 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 underestimated and not overestimated. Our search was meticulous and involved two large databases plus manual searches, but we included only studies published in English; 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, clinical outcomes, and the 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.

CONFLICT OF INTEREST

Dr. Papatheodoridis advises, is on the speakers' bureau for, and received grants from AbbVie and Gilead. He advises and is on the speakers' bureau for Dicerna, GlaxoSmithKline, Ipsen, Janssen, MSD, Novo Nordisk, and Roche. Dr. Lok received grants from Bristol-Myers Squibb, Gilead, and TARGET.

AUTHOR CONTRIBUTIONS

Margarita Papatheodoridi: acquisition of data, analysis and interpretation of data, drafting the article, final approval; Maria Tampaki: acquisition of data, drafting the article, final approval. Anna S. Lok: contribution to conception and design, critical revision for important intellectual content, final approval; George V. Papatheodoridis: conception and design, analysis and interpretation of data, critical revision for important intellectual content, final approval.

ORCID

George V. Papatheodoridis https://orcid.org/0000-0002-3518-4060

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. Hepatology. 2021;73(Suppl 1):4–13.
3. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67:358–80.
4. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69:182–236.
5. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B

patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol. 2010;53:348–56.
6. Papatheodoridis GV, Sypsa V, Dalekos G, Yurdaydin C, van Boemmel F, Buti M, et al. Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. J Hepatol. 2018;68:1129–36.
7. World Health Organization. Hepatitis B. Geneva: World Health Organization; 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
8. Jang JW. Hepatitis B virus reactivation in patients with hepatocellular carcinoma undergoing anti-cancer therapy. World J Gastroenterol. 2014;20:7675.
9. Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology. 2006;43:209–20.
10. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68:723–50.
11. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
12. Stijnen T, Hamza TH, Özdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med. 2010;29:3046–67.
13. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
14. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. JAMA. 2006;295:676–80.
15. R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2019.
16. Schwarzer G. Meta: an r package for meta-analysis. R News. 2007;7:40–5.
17. Viechtbauer W. Conducting meta-analyses in R with the metaphor package. J Stat Softw. 2010;36:1–48.
18. Peng JW, Lin GN, Xiao JJ, Jiang XM. Hepatitis B virus reactivation in hepatocellular carcinoma patients undergoing transcatheter arterial chemoembolization therapy. Asia Pac J Clin Oncol. 2012;8:356–61.
19. Jang JW, Choi JY, Bae SH, Kim CW, Yoon SK, Cho SH, et al. Transarterial chemo-lipiodolization can reactivate hepatitis B virus replication in patients with hepatocellular carcinoma. J Hepatol. 2004;41:427–35.
20. Park J-W, Park KW, Cho SH, Park HS, Lee WJ, Lee DH, et al. Risk of hepatitis B exacerbation is low after transcatheter arterial chemoembolization therapy for patients with HBV-related hepatocellular carcinoma: report of a prospective study. Am J Gastroenterol. 2005;100:2194–200.
21. Sohn W, Paik Y-H, 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;22:539–50.
22. Zhang B, Xu D, Wang R, Zhu P, Mei B, Wei G, et al. Perioperative antiviral therapy improves safety in patients with hepatitis B related HCC following hepatectomy. Int J Surg. 2015;15:1–5.
23. Xie Z-B, Zhu S-L, Peng Y-C, Chen J, Wang X-B, Ma L, et al. Postoperative hepatitis B virus reactivation and surgery-induced immunosuppression in patients with hepatitis B–related hepatocellular carcinoma. J Surg Oncol. 2015;112:634–42.
24. Chen J, Bai T, Wang XB, Xie ZB, Liu JJ, Zhang Y, et al. Factors associated with postoperative HBV reactivation in HBV related hepatocellular carcinoma patients with HBV-DNA levels less than the minimum. Int J Clin Exp Med. 2016;9:4533–8.
25. Xie ZB, Wang XB, Fu DL, Zhong JH, Yang XW, Li LQ. Postoperative hepatitis B virus reactivation in hepatitis B virus–related hepatocellular carcinoma patients with hepatitis B virus DNA levels <500 copies/mL. Onco Targets Ther. 2016;9:4593–603.
26. Gong W-F, Zhong J-H, Lu S-D, Wang X-B, Zhang Q-M, Ma L, et al. Effects of antiviral therapy on post-hepatectomy HBV reactivation and liver function in HBV DNA-negative patients with HBV-related hepatocellular carcinoma. Oncotarget. 2017;8:15047–56.
27. Yuan B-H, Li R-H, Yuan W-P, Xiang B-D, Zheng M-H, Yang T, et al. Perioperative entecavir for patients with HBV-related hepatocellular carcinoma and low levels of viral DNA: analysis using propensity score matching. Oncotarget. 2017;8:51810–6.
28. Huang S, Xia Y, Lei Z, Zou Q, Li J, Yang T, et al. Antiviral therapy inhibits viral reactivation and improves survival after repeat hepatectomy for hepatitis B virus–related recurrent hepatocellular carcinoma. J Am Coll Surg. 2017;224:283–93.e4.
29. 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;18:1533033819875136.
30. Wang X-B, Chen J, Xiang B-D, Wu F-X, Li L-Q. High CONUT score predicts poor survival and postoperative HBV reactivation in HBV-related hepatocellular carcinoma patients with low HBV-DNA levels. Eur J Surg Oncol. 2019;45:782–7.
31. Kim JH, Park J-WW, Kim TH, Koh DW, Lee WJ, Kim C-MM. Hepatitis B virus reactivation after three-dimensional conformal radiotherapy in patients with hepatitis B virus–related hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2007;69:813–9.
32. Xu M, Zhou Z, Xu R, Zhang H, Lin N, Zhong Y. Antiviral therapy predicts the outcomes following resection of hepatocellular carcinoma in patients negative for HBV DNA: a propensity score matching analysis. World J Surg Oncol. 2019;17:45.
33. Li C, Li Z-C, Ma L, Li L-Q, Zhong J-H, Xiang B-D, et al. Perioperative antiviral therapy improves the prognosis of HBV DNA-negative patients with HBV-related hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol. 2020;14:749–56.
34. Wang Z-Y, Tao Q-F, Wang Z-H, Lin K-Y, Huang G, Yang Y, et al. Antiviral therapy improves post-operative survival outcomes in patients with HBV-related hepatocellular carcinoma of less than 3 cm—a retrospective cohort study. Am J Surg. 2020;219:717–25.
35. Jang JW, Choi JY, Bae SH, Yoon SK, Chang UI, Kim CW, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. Hepatology. 2006;43:233–40.
36. Lao X-M, Wang D, Shi M, Liu G, Li S, Guo R, et al. Changes in hepatitis B virus DNA levels and liver function after transcatheter arterial chemoembolization of hepatocellular carcinoma. Hepatol Res. 2011;41:553–63.
37. Yu SJ, Lee J-H, Jang ES, Cho EJ, Kwak M-S, Yoon J-H, et al. Hepatocellular carcinoma: high hepatitis B viral load and mortality in patients treated with transarterial chemoembolization. Radiology. 2013;267:638–47.
38. Shao W, Zhang F, Cong N, Li J, Song J. The hepatitis B virus reactivation after transarterial chemoembolization in Chinese hepatocellular carcinoma patients with low serum hepatitis B virus DNA level. Ther Clin Risk Manag. 2015;11:1367–70.
39. Li B, Chen A, Du X, Zhan J. Influence of antiviral therapy on survival of patients with hepatitis B–associated hepatocellular carcinoma undergoing transarterial chemoembolization. Trop J Pharm Res. 2017;16:1997–2005.
40. Jang JW, Yoo SH, Nam HC, Jang BH, Sung Sung PS, Lee W, et al. Association of prophylactic anti–hepatitis B virus therapy

with improved long-term survival in patients with hepatocellular carcinoma undergoing transarterial therapy. Clin Infect Dis. 2020;71:546–55.
41. Wang X, Yang X, Chen F, Wu S, Song Z, Fei J. Hepatitis B virus reactivation potential risk factors in hepatocellular carcinoma via transcatheter arterial chemoembolization: a retrospective research. Can J Gastroenterol Hepatol. 2021;2021:8864655.
42. Jang JW, Kwon JH, You CR, Kim JD, Woo HY, Bae SH, et al. Risk of HBV reactivation according to viral status and treatment intensity in patients with hepatocellular carcinoma. Antivir Ther. 2011;16:969–77.
43. Liu S, Lai J, Lyu N, Xie Q, Cao H, Chen D, et al. Effects of antiviral therapy on HBV reactivation and survival in hepatocellular carcinoma patients undergoing hepatic artery infusion chemotherapy. Front Oncol. 2021;10:582504.
44. Choi C, Lee F, Lam TC, Wong F, Wong VY, Lui C, et al. Impact of fractionated stereotactic body radiotherapy on liver function in patients with hepatitis B virus–related hepatocellular carcinoma: clinical and dosimetric analysis. Hong Kong J Radiol. 2013;16:94–9.
45. Huang W, Zhang W, Fan M, Lu Y, Zhang J, Li H, et al. Risk factors for hepatitis B virus reactivation after conformal radiotherapy in patients with hepatocellular carcinoma. Cancer Sci. 2014;105:697–703.
46. 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:e0201316.
47. Shim JH, Park J-W, Choi J-I, Park BJ, Kim C-M. Practical efficacy of sorafenib monotherapy for advanced hepatocellular carcinoma patients in a hepatitis B virus–endemic area. J Cancer Res Clin Oncol. 2009;135:617–25.
48. Yang YU, Wen F, Li J, Zhang P, Yan W, Hao P, et al. A high baseline HBV load and antiviral therapy affect the survival of patients with advanced HBV-related HCC treated with sorafenib. Liver Int. 2015;35:2147–54.
49. Lim S, Han J, Kim GM, Han K-H, Choi HJ. Hepatitis B viral load predicts survival in hepatocellular carcinoma patients treated with sorafenib. J Gastroenterol Hepatol. 2015;30:1024–31.
50. Zhang X, Zhou Y, Chen C, Fang W, Cai X, Zhang X, et al. Hepatitis B virus reactivation in cancer patients with positive Hepatitis B surface antigen undergoing PD-1 inhibition. J Immunother Cancer. 2019;7:322.
51. Lee P-C, Chao Y, Chen M-H, Lan K-H, Lee I-C, Hou M-C, et al. Risk of HBV reactivation in patients with immune checkpoint inhibitor–treated unresectable hepatocellular carcinoma. J Immunother Cancer. 2020;8:e001072.
52. Ng KYY, Wong LWJ, Ang AJS, Tan SH, Choo SP, Tai D-M, et al. Real-world efficacy and safety of immune checkpoint inhibitors in advanced hepatocellular carcinoma: experience of a tertiary Asian center. Asia Pac J Clin Oncol. 2021;17:e249–61.
53. Dan J-Q, Zhang Y-J, Huang J-T, Chen M-S, Gao H-J, Peng Z-W, et al. Hepatitis B virus reactivation after radiofrequency ablation or hepatic resection for HBV-related small hepatocellular carcinoma: a retrospective study. Eur J Surg Oncol. 2013;39:865–72.
54. Li Z-L, Yan W-T, Zhang J, Zhao Y-J, Lau WY, Mao X-H, et al. Identification of actual 10-year survival after hepatectomy of HBV-related hepatocellular carcinoma: a multicenter study. J Gastrointest Surg. 2019;23:288–96.
55. Kubo S, Nishiguchi S, Hamba H, Hirohashi K, Tanaka H, Shuto T, et al. Reactivation of viral replication after liver resection in patients infected with hepatitis B virus. Ann Surg. 2001;233:139–45.
56. Thia TJK, Lui HF, Ooi LL, Chung YF, Chow P-H, Cheow PC, et al. A study into the risk of exacerbation of chronic hepatitis B after liver resection for hepatocellular carcinoma. J Gastrointest Surg. 2007;11:612–8.
57. Huang G, Lai ECH, Lau WY, Zhou W-P, Shen F, Pan Z-Y, et al. Posthepatectomy HBV reactivation in hepatitis B–related hepatocellular carcinoma influences postoperative survival in patients with preoperative low HBV-DNA levels. Ann Surg. 2013;257:490–505.
58. Lao X-M, Luo G, Ye L-T, Luo C, Shi M, Wang D, et al. Effects of antiviral therapy on hepatitis B virus reactivation and liver function after resection or chemoembolization for hepatocellular carcinoma. Liver Int. 2013;33:595–604.
59. Lee JI, Kim JK, Chang HY, Lee J-W, Kim JM, Chung HJ, et al. Impact of postoperative hepatitis B virus reactivation in hepatocellular carcinoma patients who formerly had naturally suppressed virus. J Gastroenterol Hepatol. 2014;29:1019–27.
60. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148:221–44.e3.
61. Cholongitas E, Haidich AB, Apostolidou-Kiouti F, Chalevas PPG, Cholongitas E, Haidich A-B, et al. Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review. Ann Gastroenterol. 2018;31:480–90.
62. Burpee SE, Kurian M, Murakame Y, Benevides S, Gagner M. The metabolic and immune response to laparoscopic versus open liver resection. Surg Endosc. 2002;16:899–904.
63. Chang Y, Jeong SW, Jang JY, Jae KY. Recent updates of transarterial chemoembolization in hepatocellular carcinoma. Int J Mol Sci. 2020;21:8165.
64. Lee YH, Tai D, Yip C, Choo SP, Chew V. Combinational immunotherapy for hepatocellular carcinoma: radiotherapy, immune checkpoint blockade and beyond. Front Immunol. 2020;11:568759.
65. Fagnoni FF, Zerbini A, Pelosi G, Missale G. Combination of radiofrequency ablation and immunotherapy. Front Biosci. 2008;13:369–81.
66. Cabrera R, Ararat M, Xu Y, Brusko T, Wasserfall C, Atkinson MA, et al. Immune modulation of effector CD4+ and regulatory T cell function by sorafenib in patients with hepatocellular carcinoma. Cancer Immunol Immunother. 2013;62:737–46.
67. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2018;36:1714–68.
68. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389:2492–502.
69. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19:940–52.
70. Lake AC. Hepatitis B reactivation in a long-term nonprogressor due to nivolumab therapy. AIDS. 2017;31:2115–8.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Papatheodoridi M, Tampaki M, Lok AS, Papatheodoridis GV. Risk of HBV reactivation during therapies for HCC: A systematic review. Hepatology. 2022;75:1257–1274. https://doi.org/10.1002/hep.32241