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REVIEW

What is the benefit of prophylaxis to prevent HBV reactivation in HBsAg-negative anti-HBc-positive patients? Meta-analysis and decision curve analysis

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Abstract

Background and Aims: Patients with overt or occult hepatitis B virus (HBV) infection receiving immunosuppressive treatments have a wide risk of HBV reactivation (HBVr). We performed meta-analysis with decision curve analyses (DCA) to estimate the risk of HBVr in HBsAg-negative anti-HBc-positive patients naïve to nucleos(t)ide analogues (NAs) receiving immunosuppressive treatments.

Approach and Results: Studies were identified through literature search until October 2022. Pooled estimates were obtained using random-effects model. Subgroup analyses were performed according to underlying disease and immunosuppressive treatments. DCA was used to identify the threshold probability associated with the net benefit of antiviral prophylaxis in HBsAg-negative anti-HBc-positive patients. We selected 68 studies (40 retrospective and 28 prospective), including 8034 patients with HBsAg negative anti-HBc positive. HBVr was 4% (95% CI 3%–6%) in HBsAg-negative anti-HBc-positive patients, with a significantly high heterogeneity (I^2 69%; $p < .01$). The number-needed-to-treat (NNT) by DCA ranged from 8 to 24 for chemotherapy plus rituximab, from 12 to 24 for targeted therapies in cancer patients and from 13 to 39 for immune-mediated diseases. Net benefit was small for monoclonal antibodies.

Conclusions: Our DCA in HBsAg-negative anti-HBc-positive patients provided evidence that NA prophylaxis is strongly recommended in patients treated with

Abbreviations: anti-HBc, anti-hepatitis B core antigen; CI, confidence interval; DCA, decision curve analysis; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ICI, immune checkpoint inhibitors; NAs, nucleos(t)ide analogues; NNT, number-needed-to-treat.

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chemotherapy combined with rituximab and could be appropriate in patients with cancer treated with targeted therapies and in patients with immune-mediated diseases. Finally, in patients with cancer treated with monoclonal antibodies or with chemotherapy without rituximab, the net benefit is even lower.

KEYWORDS
chemotherapy, hepatology, meta-analysis, reactivation, systematic review

1 | INTRODUCTION

Patients with overt or occult hepatitis B virus (HBV) infection receiving immunosuppressive treatments for cancer and immune-mediated diseases have a wide range risk for HBV reactivation (HBVr).[1–4] HBVr represents a potentially life-threatening event, especially when virology screening is not appropriately interpreted before starting immunosuppressive treatment.[5–9] In the last years, there has been a large development of therapies targeting the immune system that could increase the risk for HBVr[10] and these drugs could interact with the host immune system involved in the regulation of HBV replication leading to the loss of the immune control.[11]

It is well known that the risk of HBVr is highly variable depending on patients and underlying disease characteristics and the class of immunosuppressive treatment,[4,12] making it difficult to assess the net benefit of antiviral prophylaxis. Previous meta-analyses[13–16] have not established what are the risk thresholds and the cost-benefit ratio for indicating prophylaxis with nucleos(t)ide analogues (NAs) in patients with different diseases and virological status. Moreover, concerns remain about the quantitative assessment of the pooled risk of HBVr,[17] given the issues related to quality of data and methodology used. Finally, the clinical and methodological complexity in this setting is increased because a worldwide accepted, robust and conclusive estimate of the risk stratification of HBVr at individual patient level is lacking, being guideline recommendations mainly based on expert opinion.[15] In the era of personalized medicine, the identification of risk thresholds for HBVr to guide physician decisions to administering NA prophylaxis or monitor in clinical practice represents an unmet medical need, especially in the setting of HBsAg-negative anti-HBc-positive patients. In order to overcome all these limitations, we performed aggregate data meta-analysis followed by decision curve analysis (DCA) of studies evaluating the risk for HBVr in HBsAg-negative anti-HBc-positive patients without cirrhosis receiving immunosuppressive treatments to identify the HBVr thresholds associated with the best net benefit, when comparing the strategy of administer or not administer NA prophylaxis.

Key points

We analysed the risk of hepatitis B virus (HBV) reactivation in patients with prior HBV infection (HBsAg negative, anti-HBc positive) who are undergoing immunosuppressive treatments. For the first time, to the best of our knowledge, we estimated the benefit of antiviral prophylaxis in terms of how many patients should receive antiviral prophylaxis in order to effectively prevent HBV reactivation. We found that while the overall risk of reactivation is relatively low, certain treatments, especially chemotherapy combined with rituximab, significantly increase this risk, while the risk is too low to recommend universal prophylaxis in patients with cancer treated with monoclonal antibodies or with chemotherapy alone.

2 | METHODS

2.1 | Data source and searches

We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[18] Studies were identified through literature search, using PubMed, MEDLINE, Embase and Cochrane library. A string including "HBV reactivation" or "hepatitis B reactivation" and the name of different immunosuppressive drugs potentially increasing the risk for HBVr was employed. The full search string is reported in Supplementary Materials. The search involved 12 physicians of different specialties, including Gastroenterology, Dermatology, Rheumatology, Neurology, Haematology and Oncology who analysed studies published until October 2022. The systematic search included reviews, meta-analyses, clinical trials and observational studies. To identify additional studies, the computer search was supplemented with manual searches of the reference lists of reviews and studies retrieved. When the results of the same cohort were analysed in more than one publication, only the most recent and complete data were included in the meta-analysis. Finally, hand

cross-reference check from the retrieved studies was performed to identify duplicated reports. Two authors (G.E.M.R. and Ci.C.) assessed the eligibility of the studies, and the discordances in eligibility assessment of individual studies were solved by discussion.

2.2 | Data study selection

Studies were included in the meta-analysis if they met the following criteria: (1) they included patients with negative HBsAg and positive anti-HBc treated with immunosuppressive drugs for oncologic or immune-mediated diseases; (2) they reported data on HBVr in patients who did not receive antiviral prophylaxis during immunosuppressive treatment; (3) they reported data on the number of patients developing HBVr during follow-up; and (4) they were available as full-text publication in English language. Studies were excluded if (1) they included only patients with cirrhosis, because this group of patients have a high risk of decompensation in case of HBVr and therefore the indication for prophylaxis depends mainly on the underlying liver disease (for studies including both patients with and without cirrhosis, only data on patients without cirrhosis were extracted, when available); (2) they included patients affected by other immunosuppressive states (i.e. coinfection with human immunodeficiency virus); (3) they included patients with solid organ transplantation or haematopoietic stem cell transplantation; and (4) they were case reports or case series (these latter defined as studies including and describing only patients with HBVr in the absence of a subgroup of patients without HBVr).

Study- and patient-level variables were extracted from all eligible studies and entered into a structured database. Study-level variables included the name of the first author, publication year, region where the study was conducted, study design, number of centres (single vs multicentre) and the definition of HBVr. We classified the studies according to their definition of HBVr into three categories: (1) increasing in HBV-DNA from baseline (independently from X-log increase from baseline levels), (2) appearance of HBV-DNA or HBsAg seroreversion and (3) other indirect definitions (as when defined as newly prescribed NA during follow-up or not specified). Patient-level variables included underlying disease needing immunosuppressive treatment (solid or haematological cancer vs. immune-mediated diseases) and the type of treatment. In patients with cancer, treatments were classified as: conventional systemic chemotherapy (with and without rituximab), targeted therapies and monoclonal antibodies. In patients with immune-mediated diseases, treatments were classified as anti-tumour necrosis factor-alfa (anti-TNF-α), other monoclonal antibodies and immunosuppressive therapies (Table S1).

2.3 | Data extraction and quality assessment

All studies were assessed for study quality according to a checklist based on a modified version of the Newcastle-Ottawa quality assessment scale,[19] with discrepancies resolved by consensus among researchers. Studies were graded using the following parameters: (1) representativeness of the cohort, (2) ascertainment of exposure, (3) HBV status, (4) assessment of outcome and (5) adequacy of follow-up evaluation. Each parameter was given a numeric score from 0 to 2 (Table S2). Studies with scores of 8 or greater were classified as high quality, with scores between 7 and 5 were classified as moderate quality and with scores lower than 5 were classified as low quality.

2.4 | Data synthesis and analysis

The number of patients with HBVr was extracted as an outcome measure. Pooled estimates were obtained using a random-effects model with the generic inverse variance method. The method of moments estimator, proposed by DerSimonian and Laird, was used to assess between study variance.[20,21] Heterogeneity was assessed with the I^2 statistic. We considered a priori subgroups based on study-level (geographic area, study design, number of centres, definition of HBVr and study quality) and patient-level variables (underlying disease needing immunosuppressive treatment and the type of treatment). Univariate and multivariate logistic meta-regression analysis was used to examine associations between patient- or study-level covariates and the risk for HBVr. Variables with a p-value < .1 in univariate meta-regression analysis were included in multivariate meta-regression analysis. For all other analyses, a p value < .05 was considered statistically significant. Funnel plot was performed to evaluate asymmetry for potential publication bias.

2.5 | Decision curve analysis

We performed a DCA for identifying threshold probabilities at which use of different strategies of NA prophylaxis will translate into maximum net benefit of preventing HBVr.[22,23]

DCA evaluated different NA prophylaxis strategies according to the risk of HBVr observed in the meta-analysis in comparison with default strategies of performing NA prophylaxis in all patients or none, allowing an assessment of overall benefit of NA prophylaxis. Particularly, two different NA prophylaxis strategies were predefined: (1) NA prophylaxis in patients with HBVr ≥5% and (2) NA prophylaxis in patients with HBVr ≥10%. Subsequently, DCA was performed for each treatment class.

In this setting, the unit of net benefit (y-axis) is true positive, that is HBVr successfully prevented by NA prophylaxis. Threshold probability (x-axis) represents the unit of preference of administering (or not) NA prophylaxis, and the relationship between preference and threshold probability can be explained by using odds. For example, the risk of 10% is an odds of 1:9, meaning that we are willing to administer 9 unnecessary NA prophylaxis (i.e. overtreatment) to successfully prevent 1 HBVr. This can be also interpreted as the "number-needed-to-treat" (NNT), where 10% is a NNT of 10.

The approach proposed by Hozo et al.[24] was modified and extended to obtain DCA on meta-analytical data, as explained in

Supplementary Materials. R (The R foundation) was used to obtain all analyses and graphics.

3 | RESULTS

3.1 | Literature search results

Our primary search identified 818 articles. We excluded 353 studies because they were not consistent with our aim, including review, editorials and letters to the editor. In addition, duplicate articles were also removed. After identification and screening process, 116 of initial studies were reviewed for inclusion and exclusion criteria (Figure S1). Finally, 68 studies were selected for meta-analysis.

3.2 | Study characteristics

Table S3 shows the characteristics of 68 studies included in the meta-analysis.[25–92] Overall, 8034 patients treated with immunosuppressive drugs were included in the meta-analysis. The number of patients included varied greatly among studies, ranging from 6 to 1127. Fifty studies were performed in Asian countries, and 46 were single-centre studies. In 38 studies, HBVr was defined as increasing in HBV-DNA from baseline, whereas in 23 studies, it was defined as appearance of HBV-DNA or HBsAg seroreversion. Moreover, HBVr had other indirect definitions in 7 studies.

According to the underlying disease, 2075 (25.8%) patients were affected by hematologic cancer, 2034 (25.3%) were affected by solid cancer, and 3925 (48.8%) were affected by immune-mediated diseases.

According to treatment, 58 studies assessed treatments belonging to the same drug class, while 10 studies assessed treatments belonging to different drug classes. In two out of these 10 studies,[69,80] data on patients treated with different drug class were extracted and analysed separately, as follows: the study from Tokmak et al.[80] included 246 patients undergoing chemotherapy and 266 undergoing immunosuppressive treatments; the study from Papalopoulos et al.[69] included 64 patients undergoing immunosuppressive treatments and 84 patients undergoing anti-TNF. Among the remaining eight studies, seven assessed combination of anti-TNF plus immunosuppressive drugs and were attributed to anti-TNF subgroup, while the other study assessed combination of chemotherapy and immune checkpoint inhibitors and it was attributed to chemotherapy subgroup.

Finally, 2791 patients (34.7%) were treated with anti-TNF-α, 1309 (16.3%) were treated with monoclonal antibodies for cancer, 1184 (14.7%) were treated with chemotherapy alone, 837 (10.4%) were treated with targeted therapies for cancer, 779 (9.7%) were treated with chemotherapy plus rituximab, and 659 (8.2%) and 475 (5.9%) were treated with immunosuppressive therapy and monoclonal antibodies, respectively, for immune-mediated diseases.

3.3 | Rate of HBVr

Overall, the pooled estimate of HBVr rate was 4% (95% CI, 3%–6%) (Figure 1). Heterogeneity was high ($I^2 = 69\%$) and statistically significant ($p < .01$).

Subgroup analyses were performed to identify potential source of heterogeneity among studies (Table 1). HBVr rate was significantly higher in studies conducted in Eastern countries (5.3%, 95% CI 3.8%–7.3%), compared with studies conducted in Western (2.3%, 95% CI 1.3%–4.1%) (p-value for subgroup comparison .013). HBVr rate was similar between retrospective (4.1%, 95% CI 2.9%–5.8%) and prospective studies (4.9%, 95% CI 3.0%–8.1%) (p-value for subgroup comparison .524) and between single-centre (4.5%, 95% CI 3.1%–6.7%) and multicentre studies (4.6%, 95% CI 3.1%–6.9%) (p-value for subgroup comparison .949). HBVr rate was 6.2% (95% CI 3.8%–9.8%) when HBVr was defined as appearance of HBV-DNA or HBsAg, 3.8% (95% CI 2.5%–5.6%) in studies that defined HBVr as increase in HBV-DNA from baseline and 2.7% (95% CI 1.0%–6.3%) in studies with indirect definitions of reactivation (p-value for subgroup comparison .145).

The HBVr rate was 3.2% (95% CI 1.7%–6.1%) in studies classified as high quality, 5.6% (95% CI 3.6%–8.4%) in studies classified as low quality and 3.7% (95% CI 2.5%–5.6%) in studies with very low quality (p-value for subgroup comparison .265).

Heterogeneity maintained significantly high in all the subgroup analyses according to study-level variables, except in the subgroup of Western studies ($I^2 = 0\%$, $p = .560$), indirect definition of reactivation ($I^2 = 0\%$, $p = .750$) and high-quality studies ($I^2 = 0\%$, $p = .470$).

HBVr rate was significantly higher in studies including hematologic tumours (10.3%, 95% CI 7.7%–13.7%), compared with studies including immune-mediated diseases (3.1%, 95% CI 2.1–4.5%) and with studies including solid tumours (1.6%, 95% CI .5%–5.5%) (p-value for subgroup comparison <.001). Patients with cancer had a risk for HBVr of 11% (95% CI 7%–17%) when treated with chemotherapy plus rituximab, 1% (95% CI 0%–23%) when treated with chemotherapy without rituximab, 7% (95% CI 2%–24%) when treated with targeted therapies and 4% (95% CI 2%–9%) when treated with monoclonal antibodies. Patients with immune-mediated diseases had HBVr rate of 4% (95% CI 2%–8%) when treated with other monoclonal antibodies, 3% (95% CI 2%–4%) with anti-TNF-α and 3% (95% CI 1%–9%) with immunosuppressive therapy (p-value for subgroup comparison .182) (Figure 2).

3.4 | Meta-regression

Univariate and multivariate logistic meta-regression analyses are shown in Table 2. Studies conducted in Eastern countries, haematological tumours, chemotherapy plus rituximab and targeted therapies were significantly associated with higher risk of HBVr by univariate analysis. Multivariate analysis showed that only chemotherapy plus rituximab was independently associated with higher risk of HBVr.

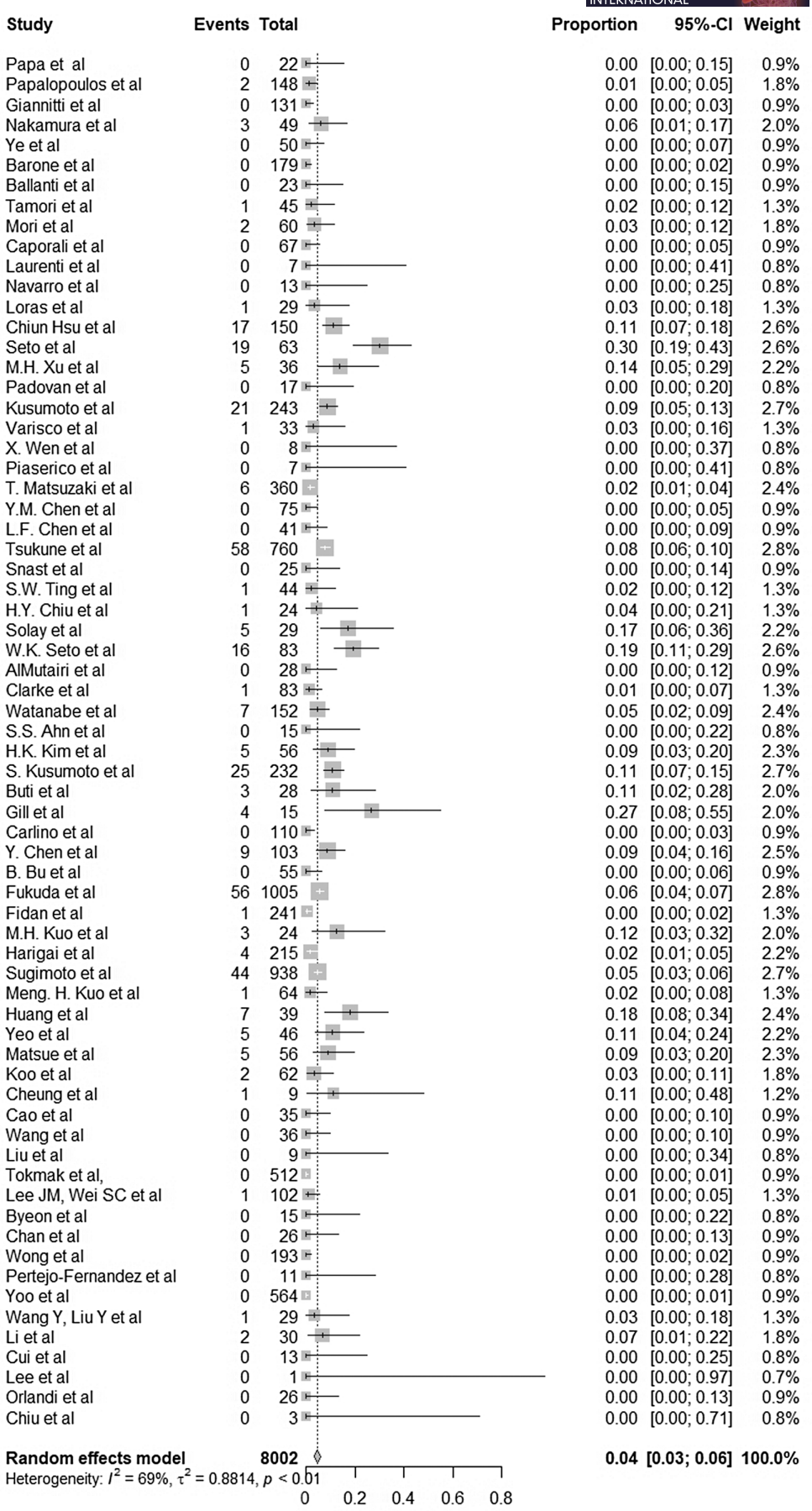

FIGURE 1 HBVr rate in the 68 studies included in the meta-analysis. HBVr, hepatitis B virus reactivation.

TABLE 1 Rates of HBV reactivation according to study- and patient-level variables.

Subgroups	Number of studies	Number of anti-HBc patients	Number of patients with rHBV	Pooled of rate of rHBV (95% CI)	I^2 (*p*-value)	*p*-value for subgroup comparison
Study-level variables						
Geographical area						
Western	18	979	9	.0233 [.0131; .0410]	0% (.56)	.013
Eastern	50	7055	337	.0532 [.0385; .0732]	73.5% (<.01)	
Study design						
Retrospective	40	4209	198	.0409 [.0286; .0582]	53.6% (<.01)	.524
Prospective	28	3825	215	.0499 [.0303; .0811]	77.5% (<.01)	
Number of centres						
Single centre	46	4408	148	.0454 [.0307; .0668]	73.2% (<.01)	.949
Multicentre	22	3626	198	.0463 [.0306; .0694]	58.1% (<.01)	
rHBV definition						
Definition 1*	38	3050	77	.0378 [.0255; .0558]	58.2% (<.01)	.145
Definition 2**	23	4713	267	.0616 [.0383; .0976]	81.0% (<.01)	
Definition 3***	7	271	2	.0257 [.0102; .0632]	0% (.75)	
Quality						
High	8	431	7	.0322 [.0168; .0609]	0% (.47)	.265
Low	38	2795	131	.0556 [.0364; .0839]	67.0% (<.01)	
Very Low	22	4808	208	.0373 [.0245; .0564]	62.4% (<.01)	
Patient-level variables						
Underlying disease						
Immune-mediated diseases	37	3925	111	.0313 [.0215; .0454]	47.8% (<.01)	<.001
Hematologic tumours	22	2075	191	.1030 [.0767; .1371]	63.9% (<.01)	
Solid tumours	9	2034	44	.0164 [.0048; .0551]	62.6% (<.01)	

*increasing in HBV-DNA from baseline (independently from X-log increase from baseline levels); **appearance of HBV-DNA or HBsAg (seroreversion); ***other indirect definitions (newly prescribed NA during follow up, or not specified).

3.5 | Publication bias

The results of the funnel plot for publication bias of overall HBVr rate are shown in Figure S2.

3.6 | Quality assessment

Methodologic quality scores (scale, 0–9) ranged from 4 to 9, and it is provided in Table S4. All of the studies had cohorts that were appropriately representative. Exposure ascertainment varied among the studies. Overall, eight studies showed high quality, while 22 were considered of very low quality and the remaining 38 showed a low quality.

3.7 | Decision curve analysis

DCA is shown in Figure 3. At threshold probabilities lower than 2% (meaning that we are willing to administer a number of unnecessary NA prophylaxis higher than 49), the net benefit of prophylaxis strategies based on risk of HBVr was not better than that of strategy to administer NA prophylaxis in all patients. At threshold probabilities between 2% and 7% (meaning that we are willing to prevent one HBVr at the cost of a number of unnecessary NA prophylaxis between 49 and 13, respectively), the strategy of administering NA prophylaxis only in patients with HBVr ≥5% showed the best net benefit. At threshold probabilities between 7% and 14% (meaning that we are willing to prevent one HBVr at the cost of a number of unnecessary NA prophylaxis between 13 and 6, respectively), the strategy of administering NA prophylaxis only in patients with HBVr ≥10% showed the best net benefit.

When evaluating the net benefit of NA prophylaxis according to treatment in patients with cancer, patients treated with chemotherapy plus rituximab showed the best net benefit at the cost of unnecessary treatments ranging from 8 to 24 (Figure 4B). In patients treated with chemotherapy without rituximab, only a small benefit was observed (Figure 4A). In patients treated with targeted therapies, benefit was associated with a number of unnecessary treatments ranging from 12 to 24 (Figure 4C), while in patients treated

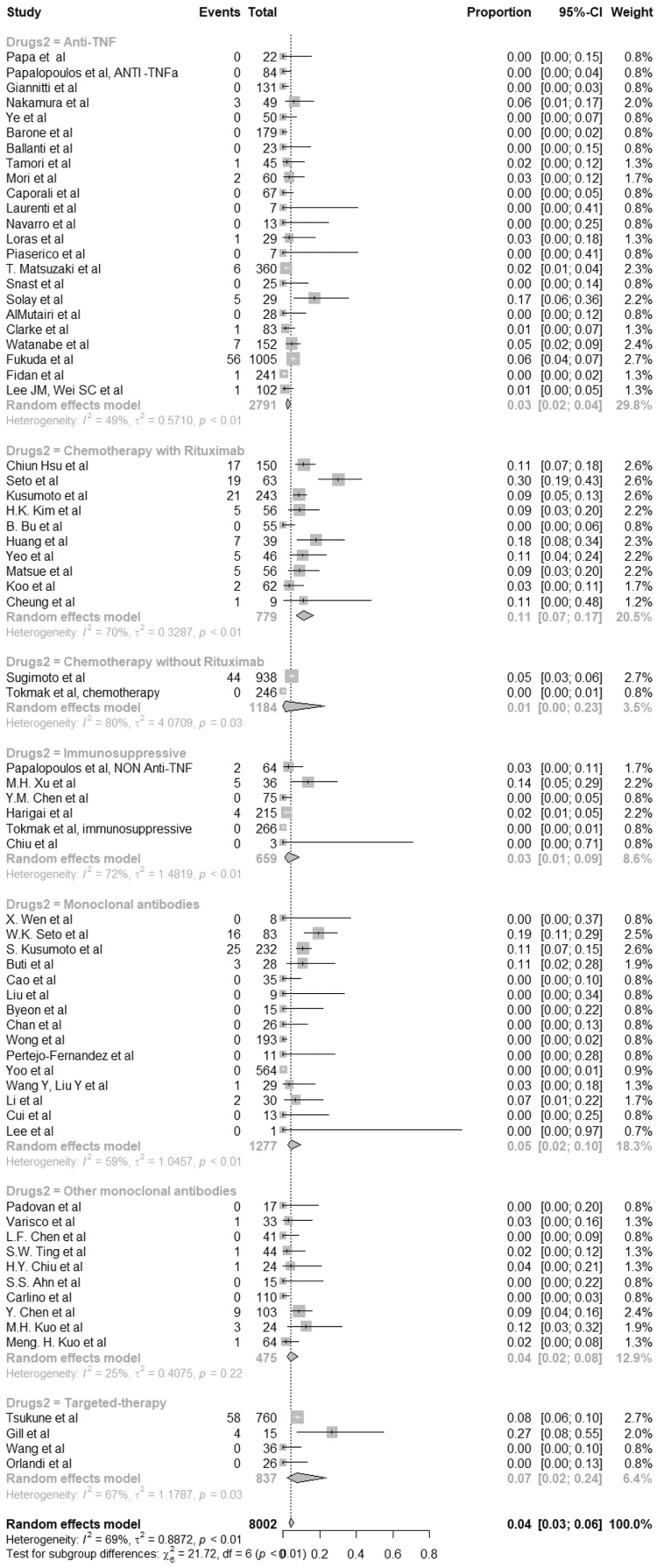

FIGURE 2 HBVr rates according to the underlying disease and treatment. HBVr, hepatitis B virus reactivation.

TABLE 2 Univariate and multivariate meta-regression analysis of predictors of HBV reactivation.

	Univariate analysis			Multivariate analysis		
Covariate	Beta	95% confidence interval	*p*-value	Beta	95% confidence interval	*p*-value
Geographical area						
Eastern	.946	.193; 1.699	.056	1.165	−.222; 1.298	.166
Western	REF	-	-	REF		
Study design						
Retrospective	−.344	−.960; .271	.272			
Prospective	REF		-			
Number of centres						
Multicentre	−.163	−.820; .494	.494			
Single centre	REF		-			
Definition of HBVr						
Definition 1	.165	−.334; .663	.517			
Definition 2+3	REF		-			
Study quality						
High	−.260	−1.341; .820	.637			
Low	.563	−.075; 1.202	.118			
Very low	REF		-			
Underlying disease						
Haematological tumours	1.183	.643; 1.724	<.001*			
Solid tumours	−.450	−1.398; .497	.351			
Immune-mediated diseases	REF					
Drug class						
Chemotherapy plus rituximab (cancer)	1.479	.681; 2.278	<.001	1.286	.462; 2.109	.002
Targeted therapies (cancer)	1.213	−.0004; 2.426	.050	1.083	−.0113; 2.280	.076
Monoclonal antibodies (cancer)	.762	−.080; 1.604	.076	.663	−.177; 1.502	.121
Other monoclonal antibodies (immune-mediated diseases)	.389	−.561; 1.340	.422	.317	−.621; 1.256	.507
Immunosuppressive therapies (immune-mediated diseases)	.206	−.889; 1.302	.711	.126	−.952; 1.205	.818
Chemotherapy without rituximab (cancer)	−.405	−1.581; 1.500	.959	−.213	−1.733; 1.306	.783
Anti-TNF-alfa	REF		-	REF		-

*Underlying disease was not entered into the multivariate model together with drug class to avoid collinearity.

with monoclonal antibodies, only a small benefit was observed (Figure 4D). Finally, in patients with immune-mediated diseases, the benefit of NA prophylaxis was associated with a number of unnecessary treatments ranging from 13 to 39 (Figure 5).

4 | DISCUSSION

This meta-analysis including more than 8000 HBsAg-negative anti-HBc-positive patients without cirrhosis with cancer or immune-mediated disease naïve to antiviral prophylaxis receiving immunosuppressive treatment showed a pooled HBVr rate of 4%. The highest net benefit associated to NA prophylaxis was observed in patients with cancer treated with chemotherapy with rituximab and targeted therapies, an intermediate net benefit was observed in patients with immune-mediated diseases, while the lowest net benefit was observed in patients with cancer treated with monoclonal antibodies or with chemotherapy without rituximab.

All the previously published meta-analyses, as well as ours, showed a wide range of HBVr risk,[14,93] with a high heterogeneity, depending on the underlying disease needing immunosuppressive treatment, the class of administered drug and finally the host HBV status. Moreover, this clinical heterogeneity combined with the lack of worldwide accepted consensus on the definition, methods and reporting of HBVr and biases in the selection of patients with different characteristics led to the provisional recommendations mainly

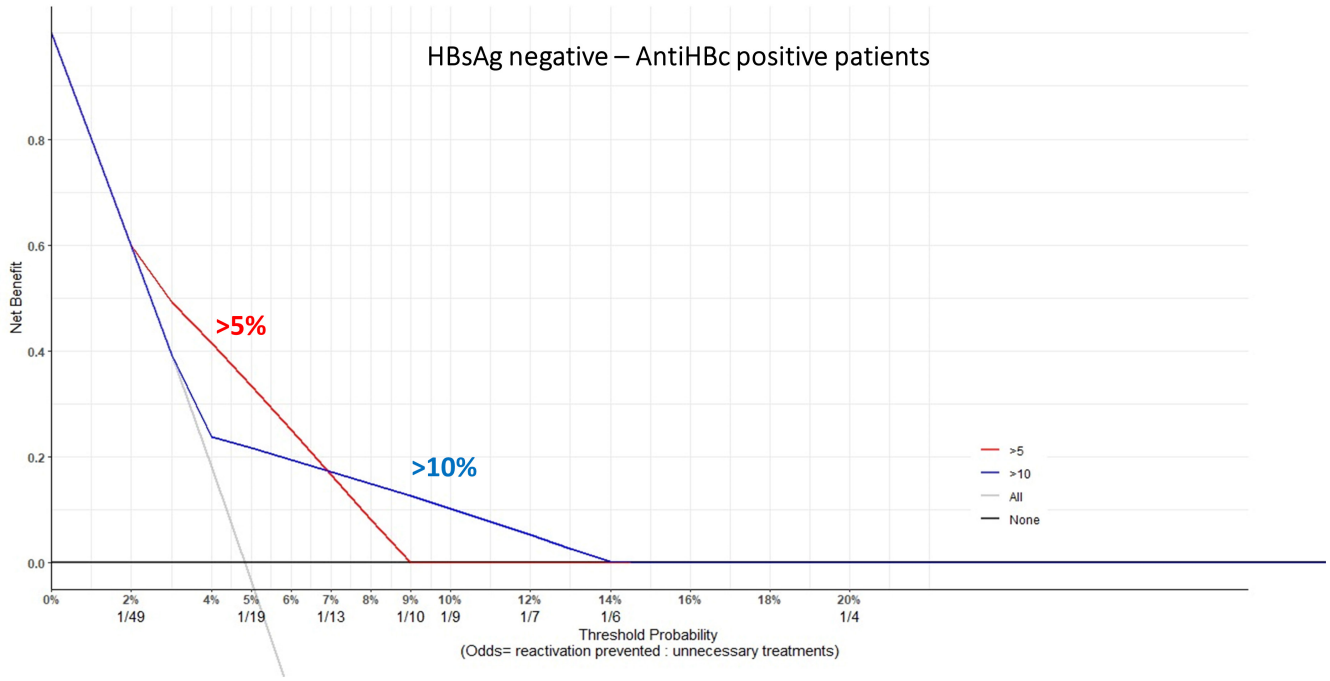

FIGURE 3 Decision curve analysis comparing the net benefit of strategies of administering NA prophylaxis when HBVr is >5% or 10% with the strategies of treating all or none at different threshold probabilities in HBsAg-negative anti-HBc-positive patients. anti-HBc, anti-hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBVr, hepatitis B virus reactivation; NAs, nucleos(t)ide analogues.

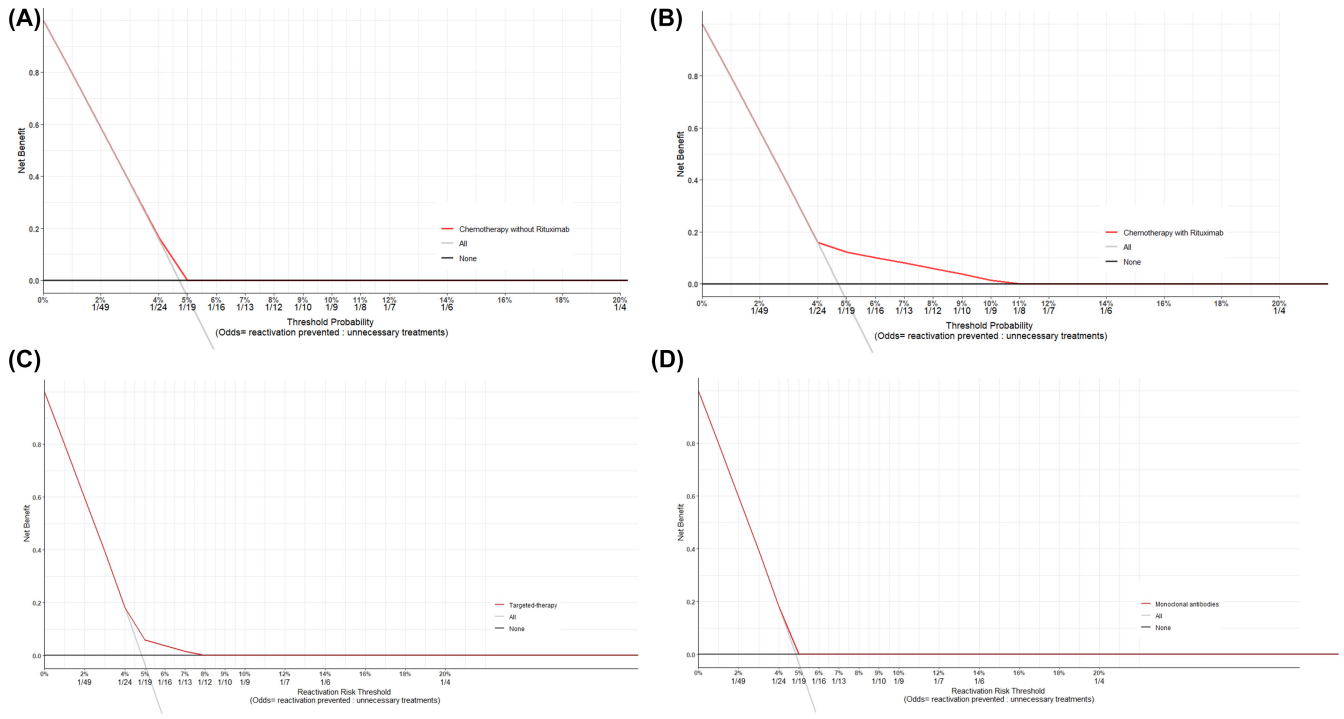

FIGURE 4 Decision curve analysis evaluating the net benefit of NA prophylaxis in HBsAg-negative anti-HBc-positive patients with cancer receiving: (A) chemotherapy without rituximab; (B) chemotherapy plus rituximab; (C) targeted therapies; and (D) monoclonal antibodies. anti-HBc, anti-hepatitis B core antigen; HBsAg, hepatitis B surface antigen; NAs, nucleos(t)ide analogues.

based on expert opinion in the last published meta-analysis.[15,17] Similarly to all the six previously published meta-analyses,[13,14,94–97] also our study is affected by the low quality of included studies, the significantly higher heterogeneity and the lack of a worldwide accepted definition of HBVr. Indeed, it is not surprising that heterogeneity remained high even in the subgroup analysis according

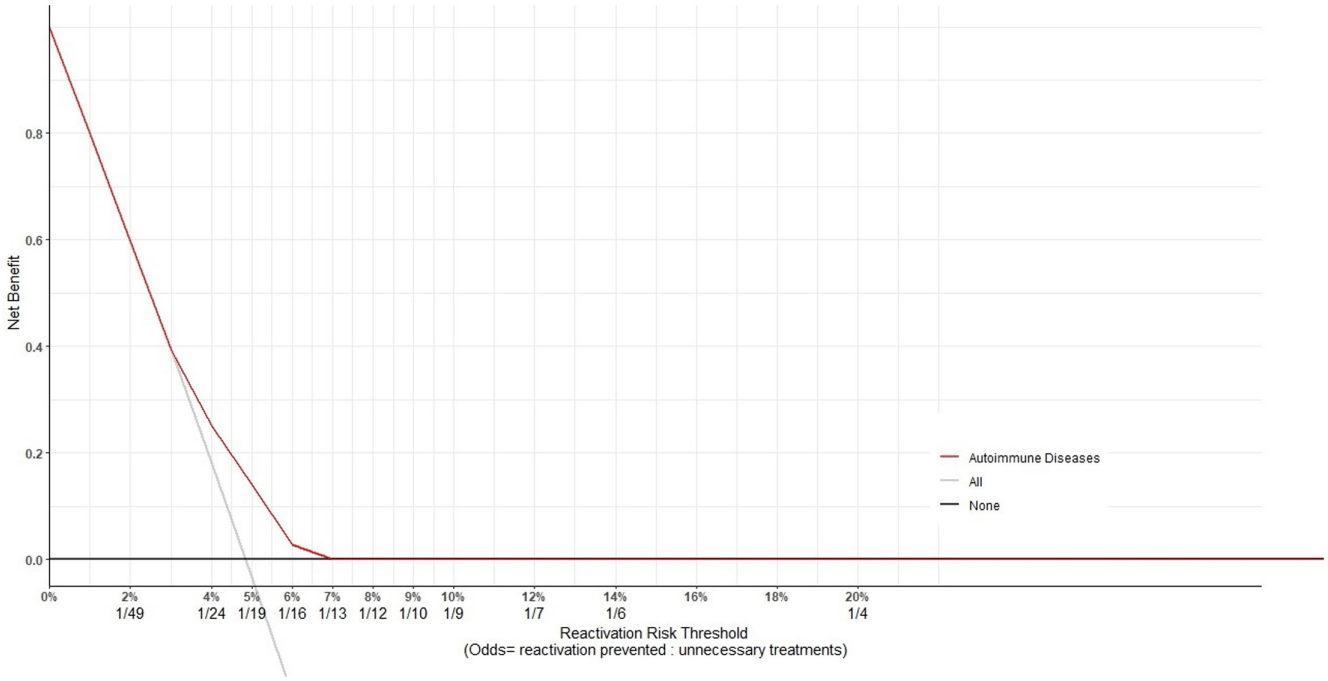

FIGURE 5 Decision curve analysis evaluating the net benefit of NA prophylaxis in HBsAg-negative anti-HBc-positive patients with immune-mediated diseases. anti-HBc, anti-hepatitis B core antigen; HBsAg, hepatitis B surface antigen; NAs, nucleos(t)ide analogues.

to different definitions of HBVr. Therefore, aggregate data meta-analyses are not suitable tools to generate practical clinical recommendations in this setting. Waiting for individual patient-data meta-analysis, randomized controlled trials or carefully designed prospective studies, DCA could be a useful quantitative methodological tool to support clinical decision making.

Taking into account all the previously published evidence, although universal NA prophylaxis should be recommended in HBsAg-positive patients, in HBsAg-negative anti-HBc-positive patients the comparison between the strategies of treating all patients versus monitoring is challenging. In order to support physician decision making in anti-HBc-positive patients, we evaluated the net benefit of NA prophylaxis for preventing HBVr in clinically meaningful subgroups with an alternative methodology, represented by DCA. This tool allows the physician to balance between over- and under-treatment, where overtreatment means that all patients will receive NA prophylaxis, while undertreatment means not to treat a patient who will develop HBVr. We assessed the net benefit, defined as a measure of true positive (i.e. to effectively administer NA prophylaxis in patients who will develop HBVr), by comparing two different strategies, according to HBVr probability. The first one consists in treating patients when HBVr is >5%, while the second one consists in treating only patients with HBVr >10%. We found that treating patients with HBVr >5% was associated with a higher net benefit when physicians are willing to successfully prevent one HBVr at the cost of 49 to 13 unnecessary treatments (so-called the number-needed-to-treat [NNT]). Otherwise, the strategy of treating only patients with HBVr higher than 10% was favoured when physicians are willing to successfully prevent one HBVr at the cost of unnecessary treatments ranging from 13 to 6.

Since the estimate of the risk of HBVr remains highly variable, we calculated DCA in four different clinical scenarios, according to class of drug and underlying disease. In patients with cancer treated with chemotherapy plus rituximab, the NNT by DCA ranged from 8 to 24, suggesting that an aggressive strategy of treating all these patients with NA prophylaxis could be optimal, similarly to HBsAg-positive patients. In patients with cancer treated with targeted therapies, the NNT ranged from 12 to 24, suggesting that either NA prophylaxis or close monitoring and on-demand NAs can be considered. In patients with immune-mediated diseases, NNT ranged from 13 to 39, suggesting that in these patients a conservative strategy of monitoring and on-demand NA prophylaxis could be the best strategy. Finally, in patients with cancer treated with monoclonal antibodies (including immune checkpoint inhibitors [ICIs]), DCA showed only a small benefit, suggesting that only monitoring could be useful. Despite this evidence from DCA, most of studies evaluating the risk of HBVr during ICI treatment were conducted in patients receiving antiviral prophylaxis,[90,98] due to the physicians' perception that the risk of HBVr is high in these patients. Although even in the DCA, a considerable overlap was observed between the different treatment classes in the ranges of NNT, it should be noted that when interpreting DCA results, the strategy with the highest expected utility should be chosen, irrespective of the size or statistical significance of the benefit and, theoretically, any improvement in net benefit is therefore worth having.[23]

This study suffers from several limitations. First, due to the lack of individual patient data, we were not able to perform meaningful subgroup analyses on treatment characteristics that could have a

relevant impact on the risk of HBVr, such as the use of single versus combination treatments.

Second, our results cannot be applied to patients with cirrhosis, because studies including only cirrhotic patients have been excluded from our analysis. However, the threshold to start antiviral prophylaxis in these patients should be lower, given the high risk of death, hepatic decompensation and liver failure associated with HBVr.[99]

In conclusion, this DCA in HBsAg-negative anti-HBc-positive patients without cirrhosis with cancer or immune-mediated disease naïve to antiviral prophylaxis receiving immunosuppressive treatment provided evidence that:

(i) NA prophylaxis is clearly recommended in patients with cancer undergoing chemotherapy combined with rituximab.
(ii) Either monitoring or NA prophylaxis could be appropriate in patients with cancer treated with targeted therapies and in patients with immune-mediated diseases.
(iii) Monitoring and on-demand NAs could be recommended in patients with cancer treated with monoclonal antibodies or with chemotherapy without rituximab.

AUTHOR CONTRIBUTIONS

G.E.M.R. and Ci.C assessed the eligibility of the studies, organized the statistical analysis and interpretation of data and wrote the manuscript; G.R., P.G. and G.F. selected the studies; G.D. and M.V. performed the statistical analysis and interpretation of data; M.E. performed the statistical analysis, validated the results and the interpretation of the data; and S. P., G.C., M.E., V.C., C.C. and V.D.M. participated in the review of the data, the critical analysis of the results and the writing of the paper.

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CONFLICT OF INTEREST STATEMENT

Vincenza Calvaruso: speaking for AbbVie and Advanz Pharma; Ciro Celsa: speaking for Eisai and Ipsen. Salvatore Petta advises and/or is on the speakers' bureau for AbbVie, Echosens, Gilead, Intercept, MSD, Novo Nordisk, Pfizer and Resalis. Giuseppe Cabibbo has served as a consultant or on advisory boards for Bayer, Eisai, Ipsen, MSD, AstraZeneca and Roche. Calogero Cammà: speaking for Eisai, Ipsen and Roche; Vito Di Marco: research support from AbbVie, Gilead, Advanz Pharma and Novo Nordisk and speaking for Gilead and AbbVie. The other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data used in this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval was not required because this study retrieved and synthesized results from other already published studies.

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REFERENCES

1. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67(2):370-398.
2. Ramsey SD, Unger JM, Baker LH, et al. Prevalence of hepatitis B virus, hepatitis C virus, and HIV infection among patients with newly diagnosed cancer from academic and community oncology practices. *JAMA Oncol*. 2019;5(4):497-505.
3. Ziogas DC, Kostantinou F, Cholongitas E, et al. Reconsidering the management of patients with cancer with viral hepatitis in the era of immunotherapy. *J Immunother Cancer*. 2020;8(2):e000943.
4. Raimondo G, Locarnini S, Pollicino T, et al. Update of the statements on biology and clinical impact of occult hepatitis B virus infection. *J Hepatol*. 2019;71(2):397-408.
5. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT, American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148(1):215-219.
6. 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(1):221-244.e3.
7. Voican CS, Mir O, Loulergue P, et al. Hepatitis B virus reactivation in patients with solid tumors receiving systemic anticancer treatment. *Ann Oncol*. 2016;27(12):2172-2184.
8. Hwang JP, Huang D, Vierling JM, et al. Cost-effectiveness analysis of hepatitis B virus screening and management in patients with hematologic or solid malignancies anticipating immunosuppressive cancer therapy. *JCO Clin Cancer Inform*. 2019;3:1-12.
9. Hwang JP, Somerfield MR, Alston-Johnson DE, et al. Hepatitis B virus screening for patients with cancer before therapy: American Society of Clinical Oncology provisional clinical opinion update. *J Clin Oncol*. 2015;33(19):2212-2220.
10. *LiverTox: Clinical and Research Information on Drug Induced Liver Injury*. National Institute of Diabetes and Digestive and Kidney Diseases; 2021.
11. Guo L, Wang D, Ouyang X, et al. Recent advances in HBV reactivation research. *Biomed Res Int*. 2018;2018:2931402.

12. Yardeni D, Chang KM, Ghany MG. Current best practice in hepatitis B management and understanding long-term prospects for cure. *Gastroenterology*. 2023;164(1):42-60.e6.
13. Loomba R, Rowley A, Wesley R, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med*. 2008;148(7):519-528.
14. Paul S, Saxena A, Terrin N, Viveiros K, Balk EM, Wong JB. Hepatitis B virus reactivation and prophylaxis during solid tumor chemotherapy: a systematic review and meta-analysis. *Ann Intern Med*. 2016;164(1):30-40.
15. Papatheodoridis GV, Lekakis V, Voulgaris T, et al. Hepatitis B virus reactivation associated with new classes of immunosuppressants and immunomodulators: a systematic review, meta-analysis, and expert opinion. *J Hepatol*. 2022;77(6):1670-1689.
16. Su YC, Lin PC, Yu HC, Wu CC. Antiviral prophylaxis during chemotherapy or immunosuppressive drug therapy to prevent HBV reactivation in patients with resolved HBV infection: a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2018;74(9):1111-1119.
17. Camma C, Enea M, Celsa C. Expert opinion vs. meta-analysis: to be or not to be? *J Hepatol*. 2023;78(3):e104-e105.
18. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160.
19. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. 2009.
20. Earle CC, Pham B, Wells GA. An assessment of methods to combine published survival curves. *Med Decis Mak*. 2000;20(1):104-111.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
22. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Mak*. 2006;26(6):565-574.
23. Vickers AJ, van Calster B, Steyerberg EW. A simple, step-by-step guide to interpreting decision curve analysis. *Diagn Progn Res*. 2019;3:18.
24. Hozo I, Tsalatsanis A, Djulbegovic B. Monte Carlo decision curve analysis using aggregate data. *Eur J Clin Investig*. 2017;47(2):176-183.
25. Ming-Xu H, Chen M, Cai Y, Yan-Jia H. Clinical outcomes of low-dose leflunomide for rheumatoid arthritis complicated with hepatitis B virus carriage and safety observation. *Pak J Med Sci*. 2015;31(2):320-324.
26. Ting SW, Chen YC, Huang YH. Risk of hepatitis B reactivation in patients with psoriasis on Ustekinumab. *Clin Drug Investig*. 2018;38(9):873-880.
27. Chiu HY, Hui RC, Huang YH, et al. Safety pro fi le of Secukinumab in treatment of patients with psoriasis and concurrent hepatitis B or C: a multicentric prospective cohort study. *Acta Derm Venereol*. 2018;98(9):829-834.
28. Solay AH, Acar A, Eser F, et al. Reactivation rates in patients using biological agents, with resolved HBV infection or isolated anti-HBc IgG positivity. *Turk J Gastroenterol*. 2018;29(5):561-565.
29. Fidan S, Capkın E, Arıca DA, Durak S, Okatan IE. Risk of hepatitis B reactivation in patients receiving anti-tumor necrosis factor-alpha therapy. *Int J Rheum Dis*. 2021;24(2):254-259.
30. Kuo MH, Tseng CW, Lu MC, et al. Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing Tocilizumab-containing treatment. *Dig Dis Sci*. 2021;66(11):4026-4034.
31. Piaserico S, Dapavo P, Conti A, Gisondi P, Russo FP. Adalimumab is a safe option for psoriasis patients with concomitant hepatitis B or C infection: a multicentre cohort study of 37 patients and review of the literature. *J Eur Acad Dermatol Venereol*. 2017;31(11):1853-1859.
32. Seto WK, Chan TSY, Hwang YY, et al. Monitoring and treatment of patients undergoing immunotherapy with anti-CD20 who are exposed to HBV. *Clin Gastroenterol Hepatol*. 2019;17(7):1410-1412.
33. AlMutairi N, Abouzaid HA. Safety of biologic agents for psoriasis in patients with viral hepatitis. *J Dermatolog Treat*. 2018;29(6):553-556.
34. Navarro R, Concha-Garzón MJ, Castaño C, Casal C, Guiu A, Daudén E. Outcome of patients with serology suggestive of past hepatitis B virus infection during antitumor necrosis factor therapy for psoriasis. *Int J Dermatol*. 2014;53(7):909-911.
35. Clarke WT, Amin SS, Papamichael K, Feuerstein JD, Cheifetz AS. Patients with core antibody positive and surface antigen negative hepatitis B (anti-HBc+, HBsAg-) on anti-TNF therapy have a low rate of reactivation. *Clin Immunol*. 2018;191:59-62.
36. Loras C, Gisbert JP, Saro MC, et al. Impact of surveillance of hepatitis b and hepatitis c in patients with inflammatory bowel disease under anti-TNF therapies: multicenter prospective observational study (REPENTINA 3). *J Crohns Colitis*. 2014;8(11):1529-1538.
37. Watanabe T, Fukae J, Fukaya S, et al. Incidence and risk factors for reactivation from resolved hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. *Int J Rheum Dis*. 2019;22(4):574-582.
38. Carlino G, Fornaro M, Santo L, et al. Occult HBV infection may negatively impact on drug survival in patients with rheumatoid arthritis on treatment with a first biologic drug. An appraisal from the biologic Apulian registry (BIOPURE). *Reumatismo*. 2019;71(1):24-30.
39. Matsuzaki T, Eguchi K, Nagao N, et al. Hepatitis B virus reactivation in patients with rheumatoid arthritis: a single-center study. *Mod Rheumatol*. 2018;28(5):808-813.
40. Laurenti R, Giovannangeli F, Gubinelli E, et al. Long-term safety of anti-TNF adalimumab in HBc antibody-positive psoriatic arthritis patients: a retrospective case series of 8 patients. *Clin Dev Immunol*. 2013;2013:410521.
41. Padovan M, Filippini M, Tincani A, et al. Safety of Abatacept in rheumatoid arthritis with serologic evidence of past or present hepatitis B virus infection. *Arthritis Care Res*. 2016;68(6):738-743.
42. Kuo MH, Tseng CW, Lee CH, Tung CH, Tseng KC, Lai NS. Moderate risk of hepatitis B virus reactivation in HBsAg(–)/HBcAb(+) carriers receiving rituximab for rheumatoid arthritis. *Sci Rep*. 2020;10(1):2456.
43. Chen YM, Chen HH, Huang WN, et al. Reactivation of hepatitis B virus infection following rituximab treatment in HBsAg-negative, HBcAb-positive rheumatoid arthritis patients: a long-term, real-world observation. *Int J Rheum Dis*. 2019;22(6):1145-1151.
44. Varisco V, Viganò M, Batticciotto A, et al. Low risk of hepatitis B virus reactivation in HBsAg-negative/anti-HBc-positive carriers receiving rituximab for rheumatoid arthritis: a retrospective multicenter Italian study. *J Rheumatol*. 2016;43(5):869-874.
45. Chen YM, Huang WN, Wu YD, et al. Reactivation of hepatitis B virus infection in patients with rheumatoid arthritis receiving tofacitinib: a real-world study. *Ann Rheum Dis*. 2018;77(5):780-782.
46. Harigai M, Winthrop K, Takeuchi T, et al. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. *RMD Open*. 2020;6(1):e001095.
47. Ahn SS, Jung SM, Song JJ, Park YB, Park JY, Lee SW. Safety of Tocilizumab in rheumatoid arthritis patients with resolved hepatitis B virus infection: data from real-world experience. *Yonsei Med J*. 2018;59(3):452-456.
48. Chen LF, Mo YQ, Jing J, Ma JD, Zheng DH, Dai L. Short-course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation. *Int J Rheum Dis*. 2017;20(7):859-869.
49. Tsukune Y, Sasaki M, Odajima T, et al. Incidence and risk factors of hepatitis B virus reactivation in patients with multiple myeloma in an era with novel agents: a nationwide retrospective study in Japan. *Blood Cancer J*. 2017;7(12):631.
50. Kim HK, Kang W, Sinn DH, Lee JH, Kim WS, Kim SJ. Real world data on follicular lymphoma patients treated by rituximab-containing

immunochemotherapy and rituximab maintenance. *Korean J Intern Med*. 2020;35(1):194-204.
51. Kusumoto S, Arcaini L, Hong X, et al. Risk of HBV reactivation in patients with B-cell lymphomas receiving obinutuzumab or rituximab immunochemotherapy. *Blood*. 2019;133(2):137-146.
52. Buti M, Manzano ML, Morillas RM, et al. Correction: randomized prospective study evaluating tenofovir disoproxil fumarate prophylaxis against hepatitis B virus reactivation in anti-HBc-positive patients with rituximab-based regimens to treat hematologic malignancies: the Preblin study. *PLoS One*. 2018;13(6):e0199926.
53. Gill H, Leung GMK, Seto WK, Kwong YL. Risk of viral reactivation in patients with occult hepatitis B virus infection during ruxolitinib treatment. *Ann Hematol*. 2019;98(1):215-218.
54. Wen X, Wang Y, Ding Y, et al. Safety of immune checkpoint inhibitors in Chinese patients with melanoma. *Melanoma Res*. 2016;26(3):284-289.
55. Bu B, Yi K, Wang H, et al. Hepatitis B virus infection status is not associated with poor prognosis in classical Hodgkin lymphoma patients. *Neoplasma*. 2020;67(1):203-208.
56. Fukuda W, Hanyu T, Katayama M, et al. Risk stratification and clinical course of hepatitis B virus reactivation in rheumatoid arthritis patients with resolved infection: final report of a multicenter prospective observational study at Japanese red cross hospital. *Arthritis Res Ther*. 2019;21(1):255.
57. Nakamura J, Nagashima T, Nagatani K, Yoshio T, Iwamoto M, Minota S. Reactivation of hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. *Int J Rheum Dis*. 2016;19(5):470-475.
58. Snast I, Atzmony L, Braun M, Hodak E, Pavlovsky L. Risk for hepatitis B and C virus reactivation in patients with psoriasis on biologic therapies: a retrospective cohort study and systematic review of the literature. *J Am Acad Dermatol*. 2017;77(1):88-97 e5.
59. Hsu C, Tsou HH, Lin SJ, et al. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: a prospective study. *Hepatology*. 2014;59(6):2092-2100.
60. Seto WK, Chan TSY, Hwang YY, et al. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. *J Clin Oncol*. 2014;32(33):3736-3743.
61. Kusumoto S, Tanaka Y, Suzuki R, et al. Monitoring of hepatitis B virus (HBV) DNA and risk of HBV reactivation in B-cell lymphoma: a prospective observational study. *Clin Infect Dis*. 2015;61(5):719-729.
62. Sugimoto R, Furukawa M, Senju T, et al. Risk factors for de novo hepatitis B during solid cancer treatment. *World J Clin Cases*. 2020;8(24):6264-6273.
63. Huang YH, Hsiao LT, Hong YC, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol*. 2013;31(22):2765-2772.
64. Yeo W, Chan TC, Leung NWY, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol*. 2009;27(4):605-611.
65. Matsue K, Kimura SI, Takanashi Y, et al. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. *Cancer*. 2010;116(20):4769-4776.
66. Koo YX, Tay M, Teh YE, et al. Risk of hepatitis B virus (HBV) reactivation in hepatitis B surface antigen negative/hepatitis B core antibody positive patients receiving rituximab-containing combination chemotherapy without routine antiviral prophylaxis. *Ann Hematol*. 2011;90(10):1219-1223.
67. Cheung WI, Lin SY, Leung VK, et al. Prospective evaluation of seropositive occult hepatitis B viral infection in lymphoma patients receiving chemotherapy. *Hong Kong Med J*. 2011;17(5):376-380.
68. Papa A, Felice C, Marzo M, et al. Prevalence and natural history of hepatitis B and C infections in a large population of IBD patients treated with anti-tumor necrosis factor-alpha agents. *J Crohns Colitis*. 2013;7(2):113-119.
69. Papalopoulos I, Fanouriakis A, Kougkas N, et al. Liver safety of non-tumour necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: an observational, controlled, long-term study. *Clin Exp Rheumatol*. 2018;36(1):102-109.
70. Giannitti C, Lopalco G, Vitale A, et al. Long-term safety of anti-TNF agents on the liver of patients with spondyloarthritis and potential occult hepatitis B viral infection: an observational multicentre study. *Clin Exp Rheumatol*. 2017;35(1):93-97.
71. Ye H, Zhang XW, Mu R, et al. Anti-TNF therapy in patients with HBV infection—analysis of 87 patients with inflammatory arthritis. *Clin Rheumatol*. 2014;33(1):119-123.
72. Barone M, Notarnicola A, Lopalco G, et al. Safety of long-term biologic therapy in rheumatologic patients with a previously resolved hepatitis B viral infection. *Hepatology*. 2015;62(1):40-46.
73. Ballanti E, Conigliaro P, Chimenti MS, et al. Use of anti-tumor necrosis factor alpha therapy in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: a retrospective analysis of 32 patients. *Drug Dev Res*. 2014;75(Suppl 1):S42-S45.
74. Tamori A, Koike T, Goto H, et al. Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. *J Gastroenterol*. 2011;46(4):556-564.
75. Mori S. Past hepatitis B virus infection in rheumatoid arthritis patients receiving biological and/or nonbiological disease-modifying antirheumatic drugs. *Mod Rheumatol*. 2011;21(6):621-627.
76. Caporali R, Bobbio-Pallavicini F, Atzeni F, et al. Safety of tumor necrosis factor alpha blockers in hepatitis B virus occult carriers (hepatitis B surface antigen negative/anti-hepatitis B core antigen positive) with rheumatic diseases. *Arthritis Care Res*. 2010;62(6):749-754.
77. Cao W, Wei J, Wang N, et al. Entecavir prophylaxis for hepatitis B virus reactivation in patients with CAR T-cell therapy. *Blood*. 2020;136(4):516-519.
78. Wang YH, Liang JD, Sheng WH, Tien FM, Chen CY, Tien HF. Hepatitis B reactivation during treatment of tyrosine kinase inhibitors-experience in 142 adult patients with chronic myeloid leukemia. *Leuk Res*. 2019;81:95-97.
79. Liu W, Huang W, Wang M, et al. Risk of hepatitis B reactivation is controllable in patients with B-cell lymphoma receiving anti-CD19 CAR T cell therapy. *Br J Haematol*. 2020;191(1):126-129.
80. Tokmak S, Gümürdülü Y, A Taş D, O Kara İ, B Güzel A. What is the risk of reactivation in patients with resolved and past HBV infection during immunosuppressive therapy if HBV-DNA negative before treatment? *Turk J Gastroenterol*. 2021;32(3):294-301.
81. Lee JM, Wei SC, Lee KM, et al. Clinical course of hepatitis B viral infection in patients undergoing anti-tumor necrosis factor alpha therapy for inflammatory bowel disease. *Gut Liver*. 2022;16(3):396-403.
82. Byeon S, Cho JH, Jung HA, et al. PD-1 inhibitors for non-small cell lung cancer patients with special issues: real-world evidence. *Cancer Med*. 2020;9(7):2352-2362.
83. Chan GH, Gwee YX, Low JL, et al. Immune checkpoint inhibition for non-small cell lung cancer in patients with pulmonary tuberculosis or hepatitis B: experience from a single Asian centre. *Lung Cancer*. 2020;146:145-153.
84. Wong GL, Wong VW, Hui VW, et al. Hepatitis flare during immunotherapy in patients with current or past hepatitis B virus infection. *Am J Gastroenterol*. 2021;116(6):1274-1283.
85. Pertejo-Fernandez A, Ricciuti B, Hammond SP, et al. Safety and efficacy of immune checkpoint inhibitors in patients with non-small cell lung cancer and hepatitis B or hepatitis C infection. *Lung Cancer*. 2020;145:181-185.
86. Yoo S, Lee D, Shim JH, et al. Risk of hepatitis B virus reactivation in patients treated with immunotherapy for anti-cancer treatment. *Clin Gastroenterol Hepatol*. 2022;20(4):898-907.

87. Wang Y, Liu Y, Tan X, et al. Safety and efficacy of chimeric antigen receptor (CAR)-T-cell therapy in persons with advanced B-cell cancers and hepatitis B virus-infection. *Leukemia*. 2020;34(10):2704-2707.
88. Li P, Zhou L, Ye S, et al. Risk of HBV reactivation in patients with resolved HBV infection receiving anti-CD19 chimeric antigen receptor T cell therapy without antiviral prophylaxis. *Front Immunol*. 2021;12:638678.
89. Cui R, Lyu C, Li Q, et al. Humanized anti-CD19 chimeric antigen receptor-T cell therapy is safe and effective in lymphoma and leukemia patients with chronic and resolved hepatitis B virus infection. *Hematol Oncol*. 2021;39(1):75-86.
90. Lee PC, Chao Y, Chen MH, et al. Risk of HBV reactivation in patients with immune checkpoint inhibitor-treated unresectable hepatocellular carcinoma. *J Immunother Cancer*. 2020;8(2):e001072.
91. Orlandi EM, Elena C, Bono E. Risk of hepatitis B reactivation under treatment with tyrosine-kinase inhibitors for chronic myeloid leukemia. *Leuk Lymphoma*. 2017;58(7):1764-1766.
92. Chiu HY, Chen CH, Wu MS, Cheng YP, Tsai TF. The safety profile of ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B or C. *Br J Dermatol*. 2013;169(6):1295-1303.
93. Paul S, Dickstein A, Saxena A, et al. Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy: a meta-analysis. *Hepatology*. 2017;66(2):379-388.
94. Lin TC, Yoshida K, Tedeschi SK, de Abreu MM, Hashemi N, Solomon DH. Risk of hepatitis B virus reactivation in patients with inflammatory arthritis receiving disease-modifying Antirheumatic drugs: a systematic review and meta-analysis. *Arthritis Care Res*. 2018;70(5):724-731.
95. Su J, Long L, Zou K. Antiviral prophylaxis for preventing reactivation of hepatitis B virus in rheumatic patients: a systematic review and meta-analysis. *Clin Rheumatol*. 2018;37(12):3201-3214.
96. Tang Z, Li X, Wu S, et al. Risk of hepatitis B reactivation in HBsAg-negative/HBcAb-positive patients with undetectable serum HBV DNA after treatment with rituximab for lymphoma: a meta-analysis. *Hepatol Int*. 2017;11(5):429-433.
97. Wu YT, Li X, Liu ZL, et al. Hepatitis B virus reactivation and antiviral prophylaxis during lung cancer chemotherapy: a systematic review and meta-analysis. *PLoS One*. 2017;12(6):e0179680.
98. Zhang X, Zhou Y, Chen C, et al. Hepatitis B virus reactivation in cancer patients with positive hepatitis B surface antigen undergoing PD-1 inhibition. *J Immunother Cancer*. 2019;7(1):322.
99. Lau G, Yu ML, Wong G, et al. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. *Hepatol Int*. 2021;15(5):1031-1048.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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