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Efficacy, HBV Reactivation, and the Association of Baseline Viral Load with Treatment Response in HBV-Related Unresectable Hepatocellular Carcinoma Receiving Immune Checkpoint Inhibitors Plus Antiangiogenic Therapy: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION**Support** - This study is funded by the Scientific and technological innovation project of China Academy of Chinese Medical Sciences (CI2026A01705) to Ke chen.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100103**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 October 2026 and was last updated on 26 October 2026.**INTRODUCTION**

Review question / Objective (1) Should a high baseline HBV DNA titer preclude patients from receiving first-line ICI plus antiangiogenic therapy? (2) What is the true incidence of HBV reactivation under current real-world antiviral prophylaxis practices, and is it clinically manageable? (3) Can we translate the available low-to-very-low certainty evidence into a bedside-ready, risk-stratified safety monitoring algorithm that explicitly integrates baseline viral load, prophylactic antiviral strategy, and graded response to HBV reactivation, thereby bridging the gap between pooled real-world data and daily oncologic practice?

Condition being studied Immune checkpoint inhibitor (ICI) combined with antiangiogenic therapy has become a key systemic treatment strategy for advanced hepatocellular carcinoma (HCC). However, patients with hepatitis B virus

(HBV)-related HCC are underrepresented in pivotal trials, and although recent meta-analyses have addressed overall ICI safety, none have specifically quantified baseline HBV DNA as a treatment effect modifier within the ICI-antiangiogenic combination framework, nor have they translated the pooled estimates into a practical clinical algorithm. We therefore evaluated tumor efficacy, HBV reactivation, and the modifier effect of baseline viral load to guide patient selection and monitoring.

METHODS

Participant or population Population (P), adults with HBV-related advanced, unresectable, or metastatic HCC; Intervention.

Intervention Intervention (I), ICI combined with antiangiogenic agents.

Comparator Comparator (C), low baseline HBV DNA, alternative therapies, or no comparator depending on study design.

Study designs to be included Study design (S), randomized trials, prospective or retrospective cohorts, and single-arm studies with extractable clinical outcomes. Outcomes (O), tumor efficacy, survival endpoints, and HBV-related safety.

Eligibility criteria We included adult patients with HBV-related advanced, unresectable, or metastatic HCC. HBV association was met if the study explicitly reported HBsAg positivity or chronic HBV infection, provided a subgroup of HBV-related HCC, or allowed separation of HBV-specific patients and outcomes from the overall cohort. The intervention was ICI combined with antiangiogenic therapy. ICIs included anti-PD-1, anti-PD-L1, or anti-CTLA-4 agents; antiangiogenic agents included bevacizumab, lenvatinib, apatinib, sorafenib, regorafenib, cabozantinib, ramucirumab, anlotinib, or other VEGF/VEGFR inhibitors. Single-arm studies were used to estimate ORR, DCR, or HBV reactivation rates. For studies with a comparator, we extracted hazard ratios (HRs) or risk ratios (RRs) where available.

Information sources We searched PubMed, Embase, Scopus, Web of Science, and the Cochrane Library from database inception to 31 July 2026.

Main outcome(s) A standardized data extraction form was used to collect the following information: first author and year of publication, country or region, study design, study period, sample size, HCC stage or unresectable status, HBV definition, baseline HBV DNA stratification, HBeAg or cirrhosis information, ICI and antiangiogenic regimen, line of therapy, antiviral agents and timing of prophylaxis, follow-up duration, response criteria, ORR, DCR, PFS, OS, HBV reactivation, HBV-related hepatitis, and treatment discontinuation. For comparative studies, we additionally extracted the comparator definition, direction of effect, HR or RR with 95% confidence intervals (CIs). For safety studies, we extracted event counts, total population, reactivation definition, whether HBV flare was reported, and monitoring strategies.

Quality assessment / Risk of bias analysis Risk of bias was assessed independently by two reviewers, Ningning Sun and Jing Li. Each reviewer applied the prespecified tool to every included study or report and recorded domain-level and overall judgments; disagreements were resolved

by discussion, and Ke Chen adjudicated when consensus could not be reached. Assessments were performed manually, and no automation tool was used for risk-of-bias assessment. For non-randomized interventional studies, the ROBINS-I tool was used to assess bias across seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selective reporting. For post hoc HBV safety subgroup analyses derived from randomized trials, the RoB 2 tool was used to evaluate bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selective reporting. The unit of assessment was the reported result rather than the clinical cohort, to avoid double counting reports from the same cohort.

Strategy of data synthesis Potential overlap among eligible cohorts was evaluated at the report and outcome levels. Reports were compared according to recruitment institutions, geographic locations, enrollment periods, patient eligibility criteria, treatment regimens, sample sizes, and reported outcomes. Studies originating from the same institution or involving overlapping recruitment periods were not automatically considered independent. Where cohort independence could not be established, the possibility of shared participants was recorded as unresolved. Reports contributing distinct outcomes were considered separately from reports contributing to the same quantitative synthesis to avoid conflating complementary reporting with independent patient populations. The available information and unresolved overlap concerns were summarized in a study-overlap matrix. Sensitivity analyses excluding potentially overlapping cohorts were considered to assess their influence on pooled estimates.

Clinical and methodological heterogeneity was further characterized by extracting study-level information on HBV reactivation criteria, virological monitoring intervals, antiviral drug regimens, prophylaxis timing and adherence, HBeAg status, cirrhosis, Child–Pugh classification, treatment line, previous anticancer therapy, and radiological response criteria. Variables not explicitly reported in the source studies were recorded as not reported rather than inferred from general study characteristics or treatment protocols. These factors were considered potential sources of confounding or effect modification. Their distribution and completeness of reporting were summarized descriptively, and the feasibility of quantitative subgroup or sensitivity analyses was

assessed according to the number of contributing studies and the consistency of available definitions.

Subgroup analysis RoB 2 assessment for Hsu 2022, a post hoc HBV safety subgroup analysis of a randomized trial.

Sensitivity analysis Leave-one-study-out and overlap-restricted sensitivity analyses were considered but were not undertaken quantitatively, because the small number of contributing studies and inconsistent definitions would have yielded unstable estimates. Changes in pooled estimates, confidence intervals, and heterogeneity statistics were therefore not examined in formal sensitivity analyses.

Country(ies) involved China.

Keywords hepatocellular carcinoma; hepatitis B virus; immune checkpoint inhibitors; antiangiogenic therapy; HBV reactivation; viral load; systematic review; meta-analysis.

Contributions of each author

Author 1 - Ningning Sun.

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