The role of hepatitis B core-related antigen in predicting the occurrence and recurrence of hepatocellular carcinoma in patients with chronic hepatitis B: a systemic review and meta-analysis

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Abstract

Background

The purpose of the current study was to investigate the predictive value of hepatitis B core-related antigen (HBcrAg) on the occurrence and recurrence of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB).

Methods

Based on PubMed, Embase, Scopus, and Web of Science, we conducted a systematic review and meta-analysis of original clinical literature. The primary outcomes were the occurrence and recurrence of HCC assessed by the hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI).

Results

A total of 18 publications with 9039 CHB patients were included in the preliminary analysis. The pooled results suggest that HBcrAg positivity (adjusted HR = 3.10, 95%CI: 2.07–4.64, P < 0.001, I^2 = 62.4%, P = 0.021; OR = 5.65, 95%CI: 3.44–5.82, P < 0.001, I^2 = 0.00%, P = 0.42) was an independent risk factor for the occurrence of HCC. Further subgroup analysis revealed that 4.0 logU/ml may be the optimal cut-off value for HBcrAg to predict the occurrence of HCC. Our meta-analysis also suggests that HBcrAg is a predictor of HCC recurrence during antiviral therapy (adjusted HR = 1.71, 95%CI: 1.26–2.32; I^2 = 78.6%, P = 0.031) and is closely related to recurrence-free survival (RFS) after curative treatment of HCC (P = 0.001).

Conclusion

For patients with CHB, serum HBcrAg level is closely associated with the occurrence of HCC, regardless of whether nucleoside/nucleotide analogues (NAs) are administered, may also serve as a novel prognostic biomarker of recurrence in HCC. Confirmation of these findings requires more research.

1. Introduction

Hepatocellular carcinoma (HCC), which accounts for more than 80% of primary liver cancer worldwide, has become the fourth most common cause of cancer-related death worldwide[1, 2]. There was a 4.6% increase in mortality from liver cancer between 2005 and 2015, second only to lung cancer in terms of years of life lost[3]. The risk factors for HCC are diverse and include chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), alcoholism, non-alcoholic fatty liver disease (NAFLD), aflatoxin and aristolochic acid A, and other risk factors for cirrhosis[4]. Among these risk factors, chronic hepatitis B (CHB) is the leading cause of HCC worldwide. HCC caused by persistent chronic HBV infection usually occurs after cirrhosis and chronic liver disease[5]. In addition, some HBV-related HCC did not show significant cirrhosis, suggesting that HBV may be involved in the progression of HCC through direct or indirect mechanisms of interaction with the body[6]. Specifically, HBV DNA integration into the host cell genome can directly induce gene instability and multiple oncogene insertion mutations, as well as long-term expression of viral products such as HBx and large HBV surface proteins containing pre S1, pre S2 and S domains and epigenetic disorders of tumor suppressor genes. These pathways are involved in the progression of HCC[7].

Currently, HBV cannot be completely eradicated by current NAs therapies due to the presence of covalently closed circular DNA (cccDNA) in the nucleus of infected liver[8, 9]. Therefore, the inhibition of virus replication in hepatocytes is particularly important. Hepatic biopsy is the most accurate method for monitoring viral replication activity and viral reservoir, but it has some limitations in clinical application, because it is often difficult to collect liver specimens and obtain patient consent. Therefore, it is necessary to find a biomarker with small trauma, high accuracy and good repeatability to reflect the transcriptional activity of HBV cccDNA. Serological monitoring is of greater application value. Serum HBV DNA level and serum hepatitis B surface antigen (HBsAg) titer are widely used in clinical practice among serological indicators that have been shown to predict the risk of cirrhosis and HCC[10–12]. But in some CHB patients with cirrhosis and liver cancer, these levels are not significantly abnormal[13]. This makes it urgent to develop new biomarkers to improve the risk management of patients with CHB. A recent study by Liu et al. reported that patients with very low HBV titers also have a significantly greater risk of HCC occurrence[14]. Thus, it is imperative to develop a biomarker that can distinguish high-risk from low-risk CHB patients, as well as predict HCC recurrence.

Serum HBcrAg has been reported as a novel serum marker that could estimate intrahepatic HBV cccDNA. It is composed of several antigens encoded by the HBV pre-C/C region genes, including hepatitis B core antigen (HBcAg), hepatitis B e antigen (HBeAg) and a truncated 22kDa precore protein (p22Cr)[15]. Studies have shown that serum HBcrAg level can reflect the content and transcriptional activity of cccDNA in hepatocytes of patients with CHB and may also reflect the transcriptional activity of integrated HBV DNA[16, 17]. It also shows great potential in predicting the occurrence and recurrence of HCC[18]. However, contrary studies also exist which have shown that serum HBcrAg is not associated with the survival and recurrence risk of HCC patients[19]. In this paper, we conducted a systematic review and meta-analysis on the association between HBcrAg and the occurrence and recurrence of HCC in patients with CHB, in order to confirm the application value of HBcrAg and guide clinical practice.

2. Methods

Systematic reviews and meta-analyses were performed according to the priority reporting items for systematic reviews and meta-analyses (PRISMA) to design, organize and report our meta-analysis results[20]. **Supplementary Table S1** provides PRISMA Checklist. The protocol for this this systematic review and

meta-analysis was registered in the PROSPERO prospective register of systematic reviews (ID: CRD42023422139).

2.1. Eligibility criteria

We included prospective cohort studies and retrospective case-control studies, and the specific inclusion criteria were developed after retrieval. The literature included in this meta-analysis should meet all the following criteria: (i) patients diagnosed with HBV infection, irrespective of whether they received NAs treatment. (ii) these articles must include the detection of serum HBcrAg levels. (iii) the original literature must directly or indirectly provide the OR or HR with 95% CI of HBcrAg and the occurrence and recurrence of HCC. Studies excluded in this systematic review met one of the following inclusion criteria: (i) review, meta-analysis, letter, conference and abstract. (ii) case report (n□5) (iii) non-English language articles. (iv) studies without control or comparison groups. (v) for the same article using the same cohort study, only the latest literature, relevant data, or the study with the largest sample size can be collected.

2.2. Data sources and search methods

We searched PubMed, Embase, Scopus and Web of Science from database inception to 6 April 2023. **Supplementary Table S2** provide a detailed search strategy. Each database was appropriately adjusted, and the publication date was not limited. The detailed search process and research selection are shown in Fig. 1.

2.3. Selection process and data extraction

Two authors (QHC and HL) independently screened literature that met the inclusion criteria using the online reference management system (Endnote 20.5). Firstly, Repeated articles were excluded through the Endnote 20 software and by reading the title and abstract, the non-conforming articles also were preliminarily excluded. Then full-text search and accurate screening of the included literature. When differences arise, they are resolved by seeking consensus or arbitration by a third author (LJY). Data extraction was performed independently by the same authors (QHC and HL) to form a standardized data table and resolve differences through discussion. We extracted basic characteristics including overall age, gender, and country. In addition, serum HBcrAg cut-off values, measurement methods of serum HBcrAg, number of patients, year of publication, study design, and outcomes (including risk measures HR or OR with 95% CI). When both univariate analysis and multivariate analysis data are available, we analyze the two separately to explore the impact of internal factors. In the spreadsheet, the research is divided into different types according to different research designs.

2.4. Quality assessment

We used the Newcastle-Ottawa Scale (NOS) tool to assess the risk of bias of the included studies[21]. NOS criteria were adopted to assess the quality of cohort study and case-control study. Cohort studies and case-control studies were scored on different scales. If the same study included both retrospective case-control and prospective cohort studies, both scales were used for evaluation. The assessment was scored on a scale of 0 to 9, with < 5 indicating low quality, 5 to 7 as moderate quality, and 8 to 9 as high quality. **Supplementary Table S3 and S4** provide a detailed.

2.5. Statistical analysis

Statistical heterogeneity was evaluated by using the Cochran Q and inconsistency index (I^2) statistic tests. I^2 < 50% or P > 0.1 indicated a lack of heterogeneity. P < 0.1 was considered statistically significant, and the random-effect model would be used. Meta-analysis was used to pool the estimates, using a random-effects model. The HCC occurrence rate was estimated by using HR or OR with 95% CI and the recurrence rate was evaluate by using HR with 95%CI. Funnel plots, Egger's, and Begg's tests were used to examine the potential publication bias[22]. Tests for publication bias are not correctly applied in small meta-analysis. We only examined the publication bias of article on the relationship between HBcrAg levels and HCC using HR values. Statistical analyses were performed using Stata 13.0 statistical software (Statacorp LP, College Station, TX USA).

3. Results

3.1. Study selection and characteristics

In total, 464 publications were identified after the preliminary search, and 222 were retained after 242 duplicated records were removed. After screening titles and abstracts, 128 studies were excluded due to comments, reviews, case reports. After browsing the full text of the remaining 94 articles, 76 articles were excluded due to lack of available data (HR or OR) or duplication of data. Ultimately, 18 cohort studies were included in the final meta-analysis. The details of the flow diagram in this meta-analysis were shown in Fig. 1.

By reading the full text, we summarized the characteristics of the 18 articles included in Table 1. 15 of the 18 articles described the relationship between HBcrAg level and HCC occurrence, including 11 cohort studies, 3 retrospective case-control studies and 1 cross-sectional study. There were 3 cohort studies discussing the relationship between HBcrAg level and recurrence of HBV-related HCC. To measure occurrence and recurrence of HCC in the cohort study, we extracted HR and 95%CI, and OR and 95%CI were used in the case-control study. Although the chemiluminescence enzyme immunoassay (CLEIA) method is used to measure the serum HBcrAg of patients in all literatures, the definition of high HBcrAg boundary value is different in different studies. Therefore, we did not define the specific HBcrAg value, and converts it into a binary variable, only collecting the HR or OR in these studies.

Table 1
Characteristics of studies included in the meta-analysis.

Author	Year	Country	Study type	Follow-up time (years)	Intervention	NO. of patients (F/M)	The average age (years)	Cut-off value	Outcomes	Meth meas
Atsunori Kusakabe	2011	Japan	prospective	12.7	Not mention	479 (259/220)	55.2 ± 8.5	qualitative analysis	HR	CLEI
Takashi Kumada	2012	Japan	prospective	13.0	With or not NAs treatment	234 (89/145)	52 (21–77)	HBcrAg > 2.9 logU/ml	HR	CLEI
Masao Honda	2015	Japan	prospective	6.5	NAs treatment	109(33/76)	52(30–79)	HBcrAg > 3.0 logU/mL	HR	CLEI
Toshifumi Tada	2016	Japan	prospective	10	Without NAs treatment	1031 (473/558)	49.0 (35.0–59.5)	HBcrAg > 2.9 logU/ml	HR	CLEI
Tetsuya Hosaka	2018	Japan	prospective	8.9	NAs treatment	1268 (339/929)	44 (34–57)	HBeAg + cohort: HBcrAg > 4.9 logU/ml HBeAg- cohort: HBcrAg > 4.30logU/ml	HR	CLEI
Yusuke Ando	2018	Japan	prospective	4.8	NAs treatment	133 (54/79)	51 (20–79)	HBcrAg > 3.4logU/ml	HR	CLEI
Wai-Pan To	2019	China Hong Kong	prospective	13.1	Without NAs treatment	207 (89/118)	40 (34–45)	HBcrAg > 5.12logU/ml	HR	CLEI
Shun Kaneko	2021	Japan	prospective	5.30	NAs treatment	245 (98/147)	48 (16–85)	HBcrAg > 4.1logU/ml	HR	CLEI
Tai-Chung Tseng	2022	China taiwan	prospective	15.88	Without NAs treatment	2150 (39.02/60.98)	42.4 ± 10.1	HBcrAg > 4.0logU/ml	HR	NA
Lilian Yan Liang	2020	China Hong Kong	prospective	3.75	NAs treatment	1400 (387/1013)	53.5 ± 11.8	HBcrAg > 2.9logU/ml	HR	CLEI
Tetsuya Hosaka	2022	Japan	prospective	11	NAs treatment	180 (69/111)	51 ± 9.90	iTACT-HBcrAg > 2.9logU/ml	HR	iTAC
Tetsuya Hosaka	2010	Japan	prospective	2.7	NAs treatment	55 (10/45)	51 (32–73)	HBcrAg > 4.8logU/ml	HR	CLEI
Shipeng Chen	2018	China	prospective	5	With or not NAs treatment	56	52.50 (30–87)	HBcrAg > 5.2logU/ml	HR	CLEI
Boris J. B. Beudeker	2021	Netherlands	prospective	1.8	With or not NAs treatment	119 (27/92)	55	HBcrAg ≤ 3.0 logU/ml; HBcrAg = 3.1-5.0 logU/ml. HBcrAg ≥ 5.1 logU/ml	P	CLEI
Ka-Shing Cheung	2017	China Hong Kong	retrospective	January 2007-November 2014	NAs treatment	228 (39/189)	HCC:61.3 (54.8–66.8) Non-HCC:60.7 (56.6–65.8)	HBcrAg ≥ 7.8 kU/ml	OR	CLEI
Fumitaka Suzuki	2021	Japan	retrospective	Until 2014(more than 4 years before)	With or not NAs treatment	17 (5/12)	80.25(44–70)	iTACT-HBcrAg > 2.7logU/ml	OR	iTAC
Yi-Chung Hsieh	2022	China Taiwan	retrospective	1991–2014	Not Mention	679 (245/404)	55 (49–60)	HBcrAg ≥ 1000 U/ml	OR	CLEI

Abbreviations: NAs, nucleoside/nucleotide analogues; CLEIA, chemiluminescent enzyme immunoassay; iTACT, immunoassay for total antigen including con pretreatment technology.

Author	Year	Country	Study type	Follow-up time (years)	Intervention	NO. of patients (F/M)	The average age (years)	Cut-off value	Outcomes	Meth meas
Yuichiro Suzuki	2019	Japan	Cross-ectional	NA	With or not NAs treatment	449 (296/153)	54.8	HBcrAg ≥ 3.0 logU/ml	OR	CLEI

Abbreviations: NAs, nucleoside/nucleotide analogues; CLEIA, chemiluminescent enzyme immunoassay; iTACT, immunoassay for total antigen including con pretreatment technology.

3.2. The relationship between HBcrAg level and the incidence of HBV-related HCC

A total of 15 studies involving 8890 patients were included. Among the 15 selected studies, there were 11 cohort studies[17, 23–32], 3 case-control studies[33–35] and 1 cross-sectional study[36]. To measure the cumulative prevalence rate for data merging, we extracted HR from the cohort study. The OR was used to measure the association between HBcrAg and HCC in the remaining four studies. The pooled unadjusted HR (95% CI) from 6 cohort studies was 3.10 (95% CI 2.07–4.64, P < 0.001), but with substantial heterogeneity (I^2 = 62.4%, P = 0.021; Fig. 2a). Sensitivity analysis showed stability of the results (**Figure S1a**). The pooled adjusted HR from 11 comparative studies was 2.95 (95%CI: 2.14–4.08, P < 0.001), but also with substantial heterogeneity (I^2 = 44.3%, P = 0.056; Fig. 2b). Sensitivity analysis showed stability of the results (**Figure S1b**). The pooled OR (95% CI) from 4 case-control study or cross-sectional study cohort studies was 5.65 (95% CI: 3.44–5.82, P < 0.001), and the data were homogeneous (I^2 = 0.00%, P = 0.42; Fig. 2c).

3.3. The relationship between HBcrAg and the recurrence of HCC in patients with CHB

At present, only 3 literatures have reported the relationship between HBcrAg level and the recurrence of HCC, among which two cohort study only provided HR with 95% CI and a retrospective cohort study provided only P-value. In multivariate analysis using fixed effect model, serum HBcrAg level was an independent risk factor for HCC recurrence (HR = 1.71, 95% CI: 1.26–2.32, I^2 = 78.6%, P = 0.031, Fig. 2d)[37, 38]. Another study showed that in univariate analysis, HBcrAg level was not associated with survival (HR = 1.082, 95% CI: 0.948–1.235, p = 0.243), but in multivariate analysis, higher HBcrAg level at the time of HCC diagnosis was independently associated with poorer OS (p = 0.01) and RFS (p = 0.001)[19].

3.4. Subgroup analyses of HBcrAg positivity and HCC occurrence rate.

Detailed results of subgroup analyses for HCC occurrence rate were summarized in Fig. 3 and Fig. 4. In order to further explore the source of heterogeneity, we conducted a subgroup analysis of univariate analysis HR and multivariate analysis HR with 95% CI for the study location, number of patients, follow-up time, treatment, and HBcrAg cut-off value. There was significant heterogeneity in subgroup analyses, and the I^2 value of most subgroup analyses was remaining greater than 50%.

A subgroup analysis of whether patients received NAs treatment led to our idea. The multivariate analysis HR (95% CI) of cumulative incidence of HCC was 2.68 (95% CI: 1.74–4.11) for patients receiving NAs treatment, and 3.39 (95% CI: 1.63–7.03) for patients not receiving NAs treatment. There was no significant difference between the two groups, suggesting that HBcrAg is an independent risk factor for predicting the occurrence of HCC, whether or not the patient is receiving NAs therapy.

Among the subgroups of HR without covariate adjustment, the significant association was found in groups that country is Japan (HR = 3.39, 95%CI: 1.97–5.83, p < 0.001), patients number more than 1000 (HR = 3.66, 95%CI: 2.56–5.23, p < 0.001), follow-up time < 10 years (HR = 5.31, 95%CI: 2.05–13.78, p = 0.001), HBcrAg cut-off value < 4.0logU/ml (HR = 3.48, 95%CI: 0.93–13.04, p = 0.065), and received NAs treatment (HR = 3.40, 95%CI: 1.98–5.83, p < 0.001). In the HR with covariate adjustment, significant association with occurrence was observed in groups that country is Japan (HR = 3.21, 95%CI: 2.12–4.85, p < 0.001), patients number more than 1000 (HR = 3.62, 95%CI: 2.44–5.37, p < 0.001), follow-up time < 10 years (HR = 3.12, 95%CI: 2.06–4.74, p < 0.001), HBcrAg cut-off value > 4.0logU/ml (HR = 3.18, 95%CI: 1.77–5.72, p < 0.001), and without NAs treatment (HR = 3.39, 95%CI: 1.63–7.03, p = 0.001).

3.5. Publication bias

The funnel plot was used to assess publication bias. In view of the limited number of included literatures, we only analyzed the publication bias of HR results in multivariate analysis (Fig. 5). Visual corresponding funnel plot symmetry is not general, so Egger 's and Begg 's tests were also used to evaluate publication bias. Although Begg 's Test showed no significant publication bias (p > 0.1), Egger 's test indicated potential publication bias. In order to further evaluate the symmetry of the funnel plot, we used the clipping method to analyze the included 11 articles (**Figure S2**). No significant publication bias was found.

4. Discussion

As an emerging monitoring indicator of CHB infection in recent years, HBcrAg has shown its broad potential in many fields. HBcrAg is a product of translation and transcription that occurs in actively replicating CHB patients, and is a composite component of HBcAg, HBeAg, and p22cr. Although the contribution of these three components to the results has not been fully evaluated, HBeAg is dominant in HBeAg-positive patients[17, 39]. HBcrAg, which is an ELISA assay consisting of a mixture of the viral precore/core gene products, is strongly correlated with cccDNA, HBsAg transcriptional activity, HBV RNA and DNA, and serves as a reliable surrogate marker of viral replication[16, 40]. Studies have shown that HBcrAg level can be used to distinguish chronic infection from hepatitis. There was a significant difference in HBcrAg levels between HBeAg-negative inactive/quiescent carrier (ENQ) patients and HBeAg-negative hepatitis (ENH) patients in all four phases of HBV infection, and HBcrAg levels were more predictive than quantitative HBsAg of ENQ patients versus ENH patients[41]. With an AUROC of 0.70, HBcrAg > 9.25 logU/mL can also differentiate chronic infection from chronic hepatitis in HBeAg positive patients[42].

Additionally, HBcrAg has shown significant advantages in predicting clinical outcomes, such as HBeAg seroconversion, virological response to treatment with NAs and/or PEG-IFN, HBsAg loss, virological relapse and clinical relapse[43–45].

For patients with CHB infection, progression to cirrhosis and HCC is a common clinical outcome. In this process, it is particularly important to identify the high risk of HCC in patients as early as possible and give timely intervention. However, there is no consensus on the prognostic predictors of HCC in patients with CHB infection, although there are many predictive models, such as REAL-B and CAMD data models[46]. At present, the research on the clinical application of HBcrAg mainly focuses on four aspects: assisting clinical staging of CHB patients, predicting clinical outcomes, exploring the relationship with other biomarkers, and guiding clinical practice with other markers. First, in all CHB stages, serum HBcrAg level correlates with serum HBV DNA. HBcrAg can still be used as a dominant indicator to detect HBV reactivation, cirrhosis and HCC in patients who achieve “functional cure” without detection of serum HBV DNA and HBsAg. For the foreseeable future, improving the prognosis of CHB patients by comparing long-term outcomes of HBcrAg-positive and HBcrAg-negative patients may be the main research focus. Additionally, due to the development of potential therapeutic agents that eliminate intrahepatic cccDNA, monitoring HBcrAg might be an appropriate way of evaluating therapeutic effects and clinical outcomes[47]. Therefore, this meta-analysis is devoted to exploring the predictive value of serum HBcrAg in predicting the occurrence and recurrence of HCC in patients with CHB, to broaden the application of HBcrAg.

According to our meta-analysis, a significant correlation was observed between HBcrAg and the occurrence of HCC in CHB patients. However, clinical studies use different cutoff values for HBcrAg, which makes it difficult to unify them. Therefore, we took the 4.0 logU/ml of each included literature as the cut-off value for the subgroup analysis. The results showed that the cut-off value > 4.0 logU/ml was more significant for the occurrence of HCC. There is evidence that higher expression levels of HBcrAg increase the risk of HCC. Multiple factors need to be considered in future clinical studies in order to establish a value.

As mentioned above, the test results of serum HBcrAg containing three components in HBeAg-positive patients are dominated by HBeAg. Therefore, the current research on HBcrAg focuses on its predictive value in HBeAg-negative patients. At present, studies have confirmed that with HBcrAg, patients with HBeAg-negative CHB can be identified accurately single-point, regardless of HBV genotype, with high diagnostic performance[48]. Several cohorts in the included literatures have concluded that HBcrAg is an excellent biomarker in predicting the risk of HCC in HBeAg-negative patients, and it is independent of NAs treatment. Regardless of whether patients with high HBcrAg levels achieved a negative HBV DNA status during NA treatment, NA treatment did not prevent the occurrence of HCC[24, 27, 29]. We also included two studies using a more sensitive serum HBcrAg detection method (iTACT-HBcrAg). The lower limit of serum HBcrAg detected by the traditional HBcrAg analysis method is 2.8 logU/ml, and this highly sensitive method can extend it to 2.1 logU/ml[49]. According to Suzuki F.’s research, iTACT-HBcrAg assay is an ultra-highly sensitive assay useful for monitoring, because it is less affected by coexisting antibodies in the patients[34]. The majority of research on HBcrAg is concentrated in East Asia, and further studies, especially in Europe and North America, are recommended to verify whether HBcrAg is a reliable predictor of HCC occurrence and recurrence in CHB.

Our meta-analysis provides a more comprehensive overview based on current data on the predictive value of serum HBcrAg in the pathogenesis of HCC in patients with CHB. These data point the way to future development of therapeutic strategies to improve clinical outcomes of patients with CHB. However, our research still has limitations. First, there are too few research exploring the association between the recurrence of HCC and HBcrAg to carry out a systematic meta-analysis, so more studies are needed to confirm these findings. Second, although we conducted a subgroup analysis, significant heterogeneity still existed in some subgroups. In the discussion section, we attributed it to the bias of patient selection in different studies. Third, because we only selected English literature and excluded other language literature, this inevitably leads to some publication bias. Fourth, the original research on the definition of HBcrAg threshold cannot reach a unified consensus, which is also the difficulty of the research. Further clinical trials are needed to formulate reasonable norms for clinical application.

5. Conclusion

In summary, serum HBcrAg level is an independent biological indicator for predicting the occurrence of HCC in CHB patients. Additionally, HBcrAg also is a potential serum biomarker for predicting the recurrence of HCC after curative resection or percutaneous ablation. NAs treatment does not affect this predictive effect, which allows clinicians to identify high-risk patients and intervene earlier.

Abbreviations

HbcrAg, hepatitis B core-related antigen; HCC, hepatocellular carcinoma; HR, hazard ratio; OR, odds ratio; CI, confidence intervalsh; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; CHB, chronic hepatitis B; NAs, nucleoside/nucleotide analogues; cccDNA, covalently closed circular DNA. HBsAg, hepatitis B surface antigen; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; NOS, Newcastle-Ottawa Scale; CLEIA, chemiluminescence enzyme immunoassay; OS, overall survival; RFS, recurrence-free survival. ENQ, HBeAg-negative inactive/quiescent carrier; ENH, HBeAg-negative hepatitis.

Declarations

Ethics approval and consent to participate: Not applicable.

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Authors' contributions: QHC, HL and TL designed the study. QHC and HL performed the systematic search. QHC, HL, LJY, ZND, LSY, GQP, YCY, and DXW selected eligible articles and conducted the quality assessment. QHC, HL and LJY analyzed, interpreted the data, and drafted the manuscript. TL revised the manuscript. All authors have read and approved the final version of the manuscript.

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Figures

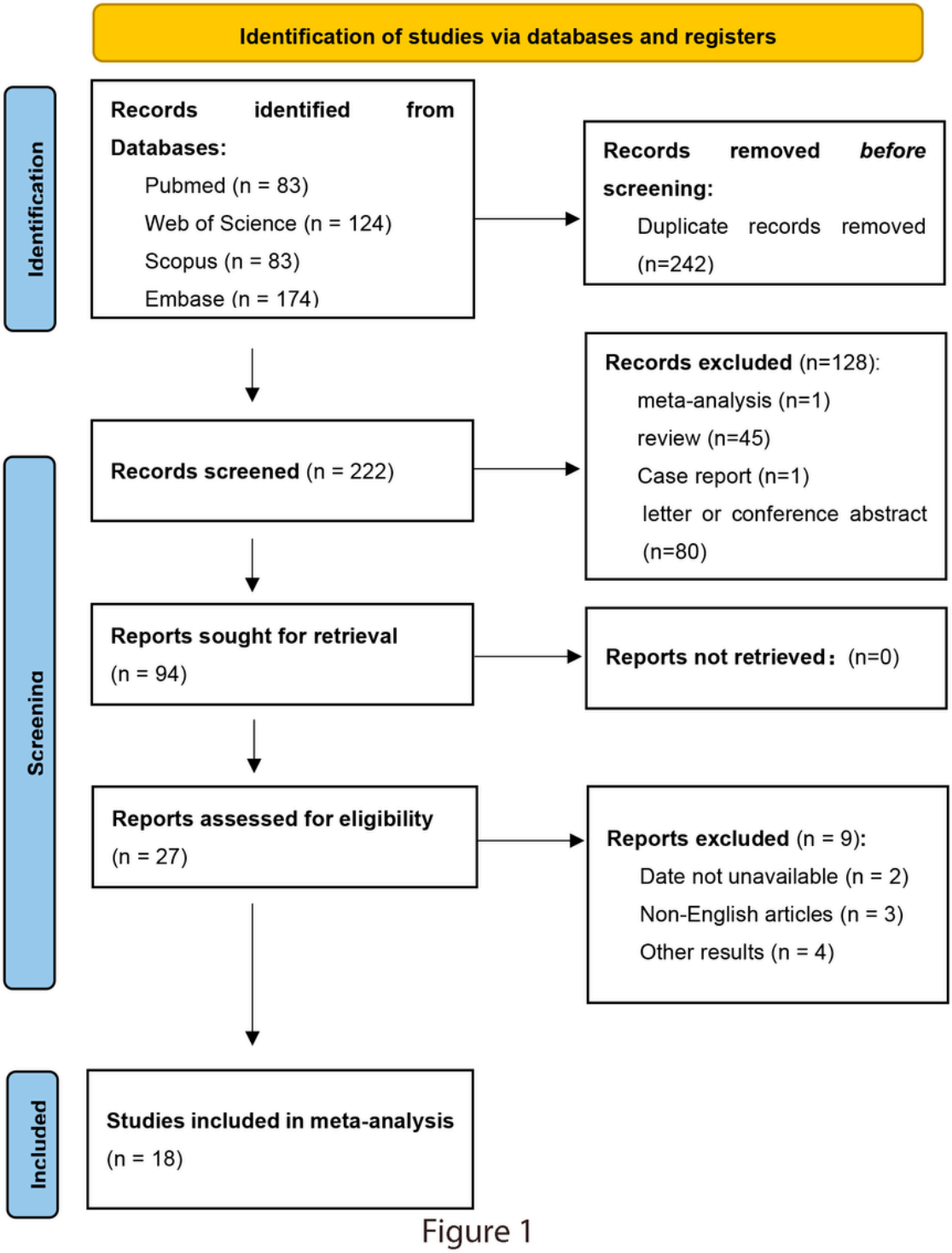

Figure 1

PRISMA flow chart of the study selection process.

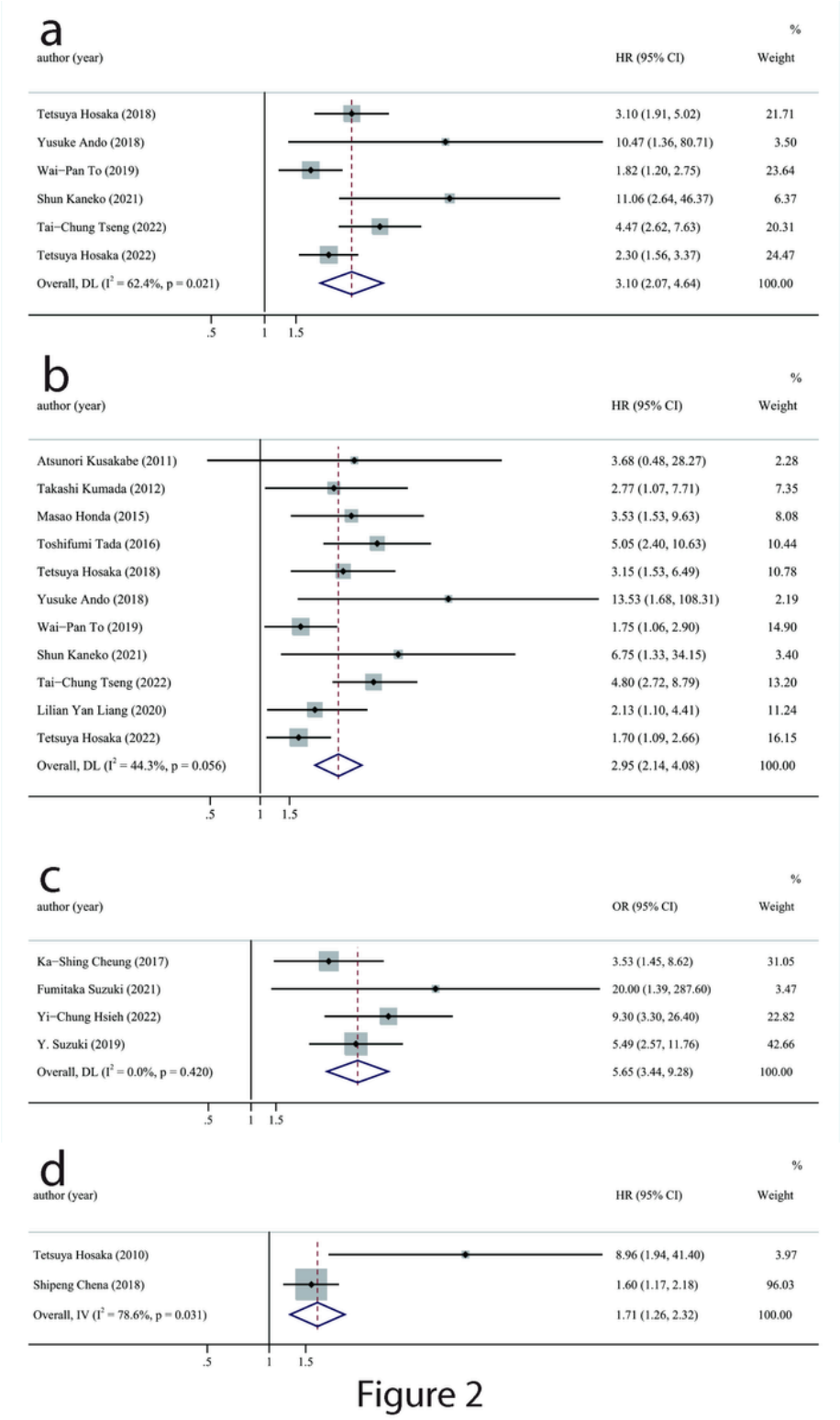

Figure 2

Forest plots of effect between HCC occurrence or recurrence in CHB patients and HBcrAg positive. (a) HR of occurrence rate without covariate adjustment; (b) HR of occurrence rate with covariate adjustment; (c) OR of occurrence rate; (d) HR of recurrence rate with covariate adjustment.

Subgroup factor	Divided standard	Numbers of studies	Unadjusted HR [95%CI]	P	Heterogeneity I^2	Heterogeneity P	Effects model
Country	Japan	4	3.39 (1.97,5.83)	<0.001	52.40%	0.098	REM
	China	2	2.81 (1.16,6.76)	0.022	85.20%	0.009	REM
Number of patients	≥ 1000	2	3.66 (2.56,5.23)	<0.001	0.00%	0.319	REM
	< 1000	4	2.83 (1.58,5.06)	<0.001	62.20%	0.047	REM
Follow-up time	≥ 10 years	3	2.58 (1.61,4.14)	<0.001	71.20%	0.031	REM
	< 10 years	3	5.31 (2.05,13.78)	0.001	46.70%	0.153	REM
HBcrAg cut-off value	≥ 4.0 logU/ml	4	3.34 (1.91,5.83)	<0.001	72.10%	0.013	REM
	< 4.0 logU/ml	2	3.48 (0.93,13.04)	0.065	51.10%	0.153	REM
Treatment	NAs	4	3.40 (1.98,5.83)	<0.001	52.40%	0.098	REM
	not NAs	2	2.81 (1.16,6.77)	0.022	85.20%	0.009	REM

Figure 3

Figure 3

Subgroup analyses of cumulative prevalence rate in high HBcrAg with univariate analysis.

Subgroup factor	Divided standard	Numbers of studies	Adjusted HR [95%CI]	P	Heterogeneity I^2	Heterogeneity P	Effects model
Country	Japan	8	3.21 (2.12, 4.85)	<0.001	36.10%	0.141	REM
	China	3	2.61 (1.38, 4.90)	0.003	70.90%	0.032	REM
Number of patients	≥1000	4	3.62 (2.44, 5.37)	<0.001	25.80%	0.257	REM
	< 1000	7	2.38 (1.61, 2.66)	<0.001	27.20%	0.221	REM
Follow-up time	≥10years	6	2.80 (1.76, 4.45)	<0.001	62.00%	0.022	REM
	< 10years	5	3.12 (2.06, 4.74)	<0.001	0.20%	0.405	REM
HBcrAg cut-off value	qualitative analysis	1	3.68 (0.48, 28.24)	0.21	-	-	REM
	≥4.0LogU/ml	4	3.18 (1.77, 5.72)	<0.001	61.50%	0.05	REM
	<4.0LogU/ml	6	2.85 (1.80,4.51)	<0.001	48.00%	0.087	REM
	not distinguish	2	2.92 (1.20, 7.11)	0.018	0.00%	0.806	REM
Treatment	NAs	6	2.68 (1.74, 4.11)	<0.001	36.10%	0.166	REM
	not NAs	3	3.39 (1.63, 7.03)	0.001	77.10%	0.013	REM

Figure 4

Figure 4

Subgroup analyses of cumulative prevalence rate in high HBcrAg with multivariate analysis.

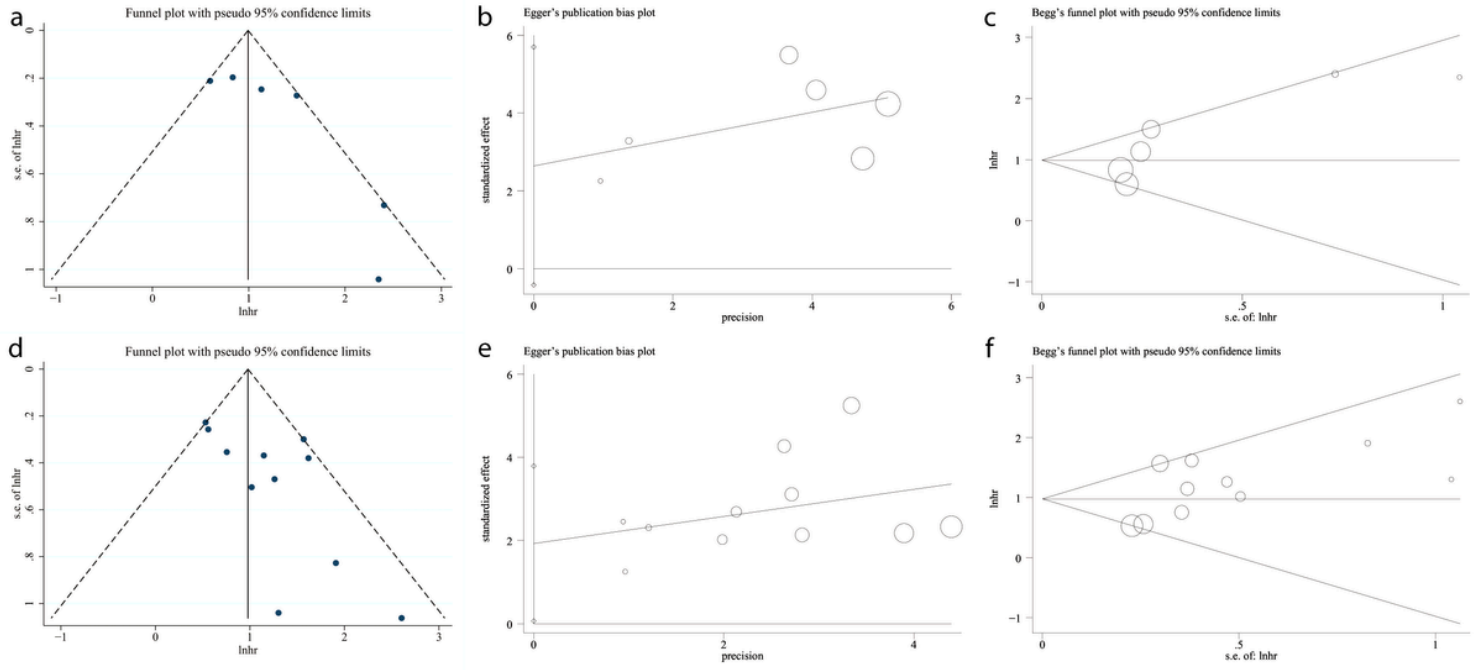

Figure 5

Figure 5

Publication bias. (a) funnel plot of the pooled unadjusted HR; (b) Egger's funnel plot of the pooled unadjusted HR; (c) Begg's funnel plot of the pooled unadjusted HR; (d) funnel plot of the pooled adjusted HR; (e) Egger's funnel plot of the pooled adjusted HR; (f) Begg's funnel plot of the pooled adjusted HR.

Supplementary Files

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