

Global Reappraisal of HBV and HCV Attribution in Hepatocellular Carcinoma: a systematic review and meta-analysis of 878,083 patients reveals a recent resurgence

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Abstract

Background and Aims

The contribution of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection to hepatocellular carcinoma (HCC) has changed with advances in vaccination and antiviral therapy. We aimed to quantify their global contribution and evaluate geographic and temporal variations.

Methods

We performed a systematic review and meta-analysis of observational studies reporting HBV or HCV infection among HCC patients. PubMed, Embase, Web of Science, and Cochrane databases were searched from inception to February 19, 2026. Random-effects models were used to estimate pooled proportions. Global estimates were generated by weighting country-specific estimates according to HCC incidence from GLOBOCAN 2022. Temporal trends were assessed using nonlinear meta-regression with restricted cubic splines.

Results

A total of 344 studies including 878,083 HCC patients were included. HBV infection was identified in 50.4% of patients and HCV infection in 25.8%. HBV was the predominant viral etiology in East Asia, Southeast Asia, and sub-Saharan Africa, whereas HCV contribution was highest in North Africa and the Middle East, Central Asia, and high-income North America. Temporal analyses showed a decline in HBV-associated HCC during earlier decades followed by an increase after approximately 2010. HCV-associated HCC demonstrated a nonlinear pattern, increasing in earlier decades and declining after a peak around 2005. HBV&HCV co-infection accounted for 4.4% of HCC cases globally.

Conclusions

The viral etiology of HCC is changing worldwide despite advances in hepatitis prevention and treatment. Continued identification and surveillance of individuals with chronic HBV or HCV infection remain essential for reducing the global burden of HCC.

Introduction

Since the 1970s, the incidence of primary liver cancer (PLC) has been rising, making it the sixth most commonly diagnosed cancer and the third leading cause of cancer deaths worldwide in 2020.¹ It is estimated that the number of new PLC cases will exceed 1 million worldwide in 2025, of which approximately 830,000 will die from the disease.² Hepatocellular carcinoma (HCC) is the predominant histopathologic type of PLC, accounting for approximately 75%-85% of cases.³ The main risk factors for HCC include viral hepatitis, aflatoxin-contaminated food, heavy alcohol consumption, and being overweight.⁴ Among these, viral hepatitis, particularly hepatitis B virus (HBV) and hepatitis C virus (HCV), is the core etiological factor in the development of HCC.⁵ Together, they account for nearly 75% of HCC cases, but there are significant differences between regions: in Asia and sub-Saharan Africa, HBV is the dominant factor (accounting for 60% of HCC cases), whereas in North America, Europe, and Japan, HCV is more prominent.⁶

In May 2016, the World Health Organization (WHO) adopted a Global Hepatitis Strategy, which sets targets to reduce new cases of chronic hepatitis B by 90% and mortality from hepatitis B and C by 65%.⁷ Achieving these goals will ultimately reduce the incidence of HCC and its associated mortality. Prior to this, understanding the patterns of HBV and HCV infection in HCC across different countries and regions can help inform the implementation of targeted strategies. However, current data on HBV and HCV positivity rates in HCC are scattered across regional studies and lack systematic comparative analysis. Additionally, with the widespread adoption of hepatitis B vaccination (recommended by the WHO for inclusion in routine immunisation programmes since 1992) and the introduction of highly effective antiviral drugs for hepatitis C (such as direct-acting antivirals), the seroprevalence of hepatitis viruses may have undergone significant changes.⁸ Currently, there is a lack of large-scale, cross-sectional data to assess this trend, and understanding of viral evolution patterns remains limited, particularly in low- and middle-income countries (LMICs).

In this study, we conducted a systematic review of the seroprevalence rates of HBV and HCV infection (either alone or in combination) in published case series of HCC, and, where possible, determined the general temporal trends in seroprevalence rates. This study will provide a baseline reference for the WHO goal of 'eliminating viral hepatitis by 2030', provide scientific evidence for the development of regionally tailored prevention and treatment strategies, and contribute to the precise prevention and control of the global disease burden of HCC.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines⁹ (Supplementary Table S1). We searched MEDLINE (PubMed), Web of Science, Cochrane, and Embase for relevant studies published from the inception of the databases to February 19, 2026, with no language restrictions. Search terms included, but were not limited to, "liver neoplasms", "(Hepatocellular Carcinoma)", "hepatitis B", "HBV", "hepatitis C" and "HCV" in the title and abstracts (see Supplemental Table S2 for detailed search strategy). References to key publications were also screened.

Studies were eligible only if they reported the prevalence of HBV and/or HCV infection in at least 20 cases of HCC. For study design, only original observational articles were included, including cross-sectional studies, case-control studies, cohort studies, and descriptive studies. Studies were excluded if patients were selected on the basis of etiology or on the basis of specific populations (e.g., human immunodeficiency virus-infected patients, populations in

specific age groups, patient groups with specific comorbidities, or liver transplant recipients). We also excluded studies that used first-generation HCV assays; where information on HCV serologic testing was not available, we retained studies published after 1994 or studies that included cases tested after 1992. Full inclusion and exclusion criteria are detailed in Appendix Table S3. The study protocol is registered with PROSPERO (CRD42024578626).

Many studies did not report cases of HBV and HCV co-infection. For such studies, we assume that the reported numbers of HBV infection and/or HCV infection cases include patients with HBV and HCV co-infection. For studies that reported cases of HBV and HCV co-infection, we included co-infection cases in our calculations of HBV infection and HCV infection.

Data extraction

Three independent reviewers (WBJ and WH) screened the identified citations for potentially relevant articles after deletion of duplicate records and reviewed the full text of all relevant publications according to predefined inclusion and exclusion criteria. Any disagreements about the selected studies were resolved through discussion or by requesting the assistance of another author. If multiple articles reported on the same study population, only the article with the most complete or recent data was included. Four authors (DZ, WNJ, CSB and QHH) extracted and imported the following data from the included articles into a Microsoft Excel spreadsheet: first author, year of publication, study period, country or territory, region, socio-demographic index (SDI) of the country, median year, sample size, number of events, participant characteristics (i.e., mean age, gender), study quality, and study design (Supplementary Table S4). In multinational studies, data are presented separately by country whenever possible. Median year was determined based on the midpoint of the sample collection period (in years) or, if no study period was available, was defined as the first 2 years of the year of publication. If mean age was not available, we used the formula proposed by Wan and colleagues¹⁰ to estimate it.

Data analysis

Quality assessment of the included studies was performed using a modified version of the Joanna Briggs Institute (JBI) Prevalence Critical Appraisal Tool (Supplementary Table S5). Studies with a quality score of less than 6 were classified as low-quality studies. The primary outcomes of interest was the seroprevalence of HBV and/or HCV (both including HBV and HCV co-infection) in HCC, and the secondary study outcome was the prevalence of HBV and HCV co-infection in HCC. Outcome prevalence was calculated using a DerSimonian-Laird random effects model after stabilizing proportional variance by Freeman-Tukey double arcsine transformation (PFT). Subsequently, we estimated the global prevalence by weighting the country-specific prevalence (obtained by random effects model) with the number of new HCC cases in each country in 2022 (based on GLOBOCAN estimates). Heterogeneity was quantified by the I^2 statistic and Cochran's Q test, with an $I^2 > 50\%$ or a P value less than 0.05 implying high heterogeneity.

To explore the temporal variation in the prevalence of outcomes, we used the median year as a time variable and performed random-effects meta-regression (linear mixed effects) analysis using the inverse variance method. Linear regression was used to show the trend in seropositivity rates over time.

To explore potential non-linear temporal trends in seropositivity, we performed random-effects meta-regression within a single-proportion framework, modeling the median year with restricted cubic splines. Median year was centered at its overall mean to reduce collinearity. Three knots were placed at the 10th, 50th, and 90th percentiles of the year distribution. Between-study variance (τ^2) was estimated using restricted maximum likelihood. The presence of a non-linear association was tested by comparing the spline model with a nested linear-year-only model via a likelihood ratio test. For visualization, we plotted the predicted positivity rate (with its 95% confidence band) over the median years, superimposed with the observed study-level estimates.

To further explore the sources of heterogeneity, we conducted subgroup analyses of pre-specified factors, including country or territory, region, age, study quality, SDI, and study period. Of these, study period were stratified according to median year. Sensitivity analyses were conducted to assess the robustness of pooled prevalence by excluding each study individually and excluding low-quality studies. Publication bias was detected by funnel plots and Egger's test, and when the P value was less than 0.05, we considered that there was evidence of publication bias, and then the estimates were corrected using the cut-off method. All analyses were performed using the "meta", "metafor", "splines" and "ggplot2" packages in the R software (version 4.4.3).

Results

The literature search generated 32101 citations, and after removing duplicates and irrelevant records by screening titles and abstracts, we conducted a full-text review of the remaining records as well as eight articles searched from references in major publications. Ultimately, 344 studies from 60 countries were included in the meta-analysis (Fig. 1).

Table 1 summarizes 344 studies conducted from January 1958 to February 2026, involving 353 cohorts with a total of 878,083 HCC patients. Sex ratio data were available for 869,343 patients from 335 cohorts, showing an overall male proportion of 75.1%, with only three cohorts having a male ratio below 50%. Mean age was reported as 58.1 years from 290 cohorts encompassing 753,226 patients. In terms of quality, most studies were rated moderate (260/353) or high (81/353), while only 12 were considered low quality. Geographically, East Asia (mainly China) and high-income North America (primarily the United States) contributed the most cohorts, with 63 and 55 respectively, and China reported the highest number of HCC cases. The majority of cohorts were from high SDI (178/353) and high-middle SDI (101/353) countries and regions, with just 3 cohorts originating from low SDI areas. Detailed extracted data are provided in the appendix on page 11.

Table 1
Basic characteristics of HCC patient cohorts by country or territory.

Central Asia	Number of cohorts	Study years (calendar year)	Age* (mean)	Men* (%)	Number of patients (n)	Quality score (mean)
Mongolia	6	2000–2023	59.9	55.1	1967	7
Georgia	1	2015–2019	–	75.0	496	6
Central Europe						
Poland	1	2012–2019	64.3	75	104	7
Romania	2	2001–2010	57.6	69.3	648	7
Serbia	1	1999–2008	55	73.3	1500	8
East Asia						
China, Taiwan	20	1985–2023	52.9	63.6	30982	7.4
Mainland China	43	1958–2024	55.0	74.7	430511	6.9
Eastern Europe						
Moldova	1	2014–2017	59.2	66.9	139	7
Russia	1	2000–2008	71.1	58.8	311	7
High-income Asia Pacific						
Japan	31	1970–2023	67.1	73.3	28965	7.1
Korea	19	1989–2023	59.0	77.7	111043	7.2
Singapore	4	1980–2018	62.3	78	5903	7.8
High-income Australasia						
Australia	11	1975–2021	64.5	79.3	16893	7.4
New Zealand	2	1987–2008	58.7	79.1	382	7
High-income North America						
Canada	1	2008–2018	66.2	80.3	274	7
United States	55	1969–2022	63.9	75.0	159344	7.2
Latin America						
Argentina	1	2007	58.3	71.7	587	7
Brazil	5	1993–2022	54.9	78.1	2215	7
Mexico	1	2008–2014	63.9	66.2	148	7
North Africa and Middle East						
Egypt	9	1993–2023	58.6	77.9	11329	7.4
Iran	2	2006–2017	62.3	77.7	287	7
Iraq	2	2000–2024	–	69.5	95	5.5
Lebanon	1	1998–2003	60.5	84.8	92	7
Oman	1	2008–2015	61.0	67.6	284	7
Qatar	1	2004–2010	58.8	76	150	7
Saudi Arabia	9	1983–2022	62.8	77.8	1348	6.7
Sudan	1	1996–1998	–	58.7	150	6
Tunisia	1	2019	63	53.4	73	6
Turkey	7	1994–2023	60.8	79.3	2174	7.3
Studies were included if they reported the seroprevalence of HBV and HCV among HCC patients. Empty cells indicate that this information was not available. *Many studies did not report the age and gender ratios of the HCC cohorts. For studies that did, we excluded them when calculating the average age and male proportion. HBV=hepatitis B virus, HCC=hepatocellular carcinoma, HCV=hepatitis C virus.						

Central Asia	Number of cohorts	Study years (calendar year)	Age* (mean)	Men* (%)	Number of patients (n)	Quality score (mean)
Yemen	1	2008–2010	61.2	36.4	88	7
South Asia						
India	7	1988–2020	59.2	87.6	2923	7.4
Pakistan	6	1989–2024	60.4	71.9	1067	6.7
Southeast Asia						
Cambodia	2	2003–2015	54.7	73.1	792	7
Indonesia	3	1984–2015	53.0	73.7	186	6
Malaysia	1	1987–2008	55	78.6	210	7
Philippines	2	1979–2014	55.8	83.8	284	7
Thailand	3	1993–2010	56.4	84	305	6.3
Vietnam	3	2010–2023	61.0	81.8	25276	7.3
Sub-Saharan Africa						
Central African Republic	1	2006–2009	47	56.6	175	7
Ethiopia	1	1992–1994	49	75	68	7
Gambia	2	1997–2001	48.5	80	409	7
Ghana	2	2015–2021	44.5	66.3	270	7
Malawi	1	2017–2019	41.7	61.5	78	6
Mozambique	1	2011–2013	48.3	70.4	206	7
Nigeria	2	1996–2008	50.6	68.4	174	6.5
Senegal	1	1972–1974	41.4	77	165	7
South Africa	7	1971–2012	43.5	89.2	1375	7
Tanzania	1	2009–2013	45.3	69	142	7
Zimbabwe	2	1995–2000	47.1	68.3	123	7
Western Europe						
Austria	1	1991–1998	63.3	76.3	245	7
Belgium	1	1994–2012	58.3	77.3	181	7
Denmark	1	2008–2014	69.5	89.6	67	7
France	5	1982–2023	66.5	85.1	2075	6.8
Germany	10	1986–2020	68.0	76.9	7389	7.3
Greece	6	1976–2019	61.5	85.8	1497	6.3
Italy	15	1975–2019	65.5	75.9	5802	7.1
Netherlands	1	2010–2019	–	70.8	240	7
Spain	5	1986–2022	64.7	79.2	1312	7
Sweden	2	2003–2018	68.5	75.0	5739	8
Switzerland	1	1975–1982	68.4	85.3	75	7
United Kingdom	2	1978–1994	58.9	87.1	419	7
Multinational	14	1990–2021	59.9	71.7	10332	7.1
World	353	1958–2024	58.1	75.1	878083	7.1
Studies were included if they reported the seroprevalence of HBV and HCV among HCC patients. Empty cells indicate that this information was not available. *Many studies did not report the age and gender ratios of the HCC cohorts. For studies that did, we excluded them when calculating the average age and male proportion. HBV=hepatitis B virus, HCC=hepatocellular carcinoma, HCV=hepatitis C virus.						

A total of 339 studies, comprising 348 HCC cohorts with 869,946 HCC patients, reported a pooled HBV prevalence of 36.29% (95% CI: 33.40 – 39.23) (Table 2). The weighted global HBV prevalence rate was calculated as 50.45%. At the regional level, the highest prevalence of HBV infection among HCC patients was observed in East Asia (68.72%; 64.12–73.15), particularly in mainland China (73.50%; 68.41–78.30), followed by Southeast Asia (55.91%; 48.58–63.11) and sub-Saharan Africa (53.18%; 46.58–59.74). Among countries categorized by SDI, high-middle SDI countries exhibited the highest HBV prevalence (60.10%; 55.70 – 64.43), while high SDI countries had the lowest prevalence (23.70%; 20.79 – 26.74) (Fig. 2 and Supplementary Figure S3). The prevalence of HBV infection was highest at 56.39% (95% CI: 47.09–65.47) in HCC patients with an average age of 50–55 years, showing a decreasing trend with increasing age groups. Temporally, the highest prevalence occurred between 1991 and 1995 (45.28%; 36.82 – 53.89). A linear model fitted based on the median year indicated that the prevalence of HBV infection did not change significantly over time ($P = 0.1789$) (Supplementary Figure S1). In contrast, the non-linear model showed that the prevalence of HBV infection followed a downward trend prior to 2010, after which it showed signs of rebounding ($P = 0.018$) (Fig. 4).

Table 2

Pooled prevalence of HBV infection, HCV infection and HBV&HCV co-infection among patients with HCC, stratified by country or territory, region, period, SDI and age.

	HBV infection*			HCV infection*			HBV&HCV co-infection			Viral	HBV/HCV*
	Number of cohorts	prevalence	(95% CI), %	Number of cohorts	prevalence	(95% CI), %	Number of cohorts	prevalence	(95% CI), %	prevalence	ratio
Central Asia	6	48.23%	(35.67–60.90)	7	43.85%	(33.73–54.22)	5	11.35%	(5.20–19.42)	80.73%	1.1
Mongolia	6	48.23%	(35.67–60.90)	6	42.22%	(30.93–53.94)	5	11.35%	(5.20–19.42)	79.10%	1.14
Georgia	0	--	--	1	53.23	(48.82–57.61)	0	--	--	--	--
Central Europe	4	39.47%	(12.72–70.20)	4	23.98%	(7.36–46.25)	3	4.20%	(0.78–9.94)	59.25%	1.65
Poland	1	24.04%	(16.27–32.76)	1	34.62%	(25.74–44.06)	1	0.96%	(0.00–4.08)	57.70%	0.69
Romania	2	58.40%	(9.55–97.98)	2	25.09%	(0.00–74.49)	1	9.65%	(6.95–12.74)	73.84%	2.33
Serbia	1	20.00%	(18.01–22.06)	1	13.33%	(11.66–15.10)	1	3.33%	(2.48–4.31)	30.00%	1.5
East Asia	63	68.72%	(64.12–73.15)	44	15.91%	(12.05–20.20)	24	4.99%	(3.58–6.60)	79.64%	4.32
China	43	73.50%	(68.41–78.30)	26	8.20%	(5.79–10.98)	11	4.30%	(2.50–6.53)	77.40%	8.96
China, Taiwan	20	57.82%	(50.30–65.16)	18	29.94%	(24.59–35.58)	13	5.60%	(3.54–8.07)	82.16%	1.93
Eastern Europe	2	41.00%	(32.39–49.89)	2	38.09%	(10.23–71.15)	1	13.67%	(8.41–19.93)	65.42%	1.08
Moldova	1	35.97%	(28.17–44.15)	1	55.40%	(47.05–63.59)	1	13.67%	(8.41–19.93)	77.70%	0.65
Russia	1	45.02%	(39.52–50.58)	1	22.51%	(18.03–27.33)	0	--	--	--	2
High-income Asia Pacific	54	36.17%	(29.87–42.71)	44	32.73%	(24.38–41.67)	25	2.56%	(1.25–4.28)	66.34%	1.11
Japan	31	19.35%	(16.44–22.42)	23	60.49%	(55.37–65.51)	14	3.41%	(0.97–7.15)	76.43%	0.32
Korea	19	61.61%	(55.78–67.29)	19	9.10%	(7.63–10.69)	10	1.57%	(0.88–2.45)	69.14%	6.77
Singapore	4	55.82%	(34.83–75.78)	2	7.68%	(6.91–8.48)	1	3.93%	(2.97–5.01)	59.57%	7.27
High-income Australasia	13	28.14%	(19.64–37.50)	12	27.36%	(18.05–37.79)	6	2.92%	(0.33–7.85)	52.58%	1.03
Australia	11	25.43%	(17.69–34.03)	10	32.92%	(24.76–41.63)	6	2.92%	(0.33–7.85)	55.43%	0.77
New Zealand	2	44.35%	(10.07–82.10)	2	5.59%	(0.21–16.60)	0	--	--	--	7.93
High-income North America	55	16.72%	(12.59–21.30)	53	41.21%	(35.95–46.56)	25	5.58%	(3.40–8.23)	52.14%	0.39
Canada	1	20.07%	(15.53–25.04)	49	27.37%	(22.24–32.82)	0	--	--	--	0.73
United States	54	16.67%	(12.47–21.33)	52	41.48%	(36.15–46.92)	25	5.58%	(3.40–8.23)	52.35%	0.38
Latin America	10	15.89%	(10.84–21.67)	10	38.39%	(29.10–48.12)	7	0.87%	(0.35–1.55)	52.11%	0.4

*The prevalence rates of HBV infection and HCV infection both include the prevalence rate of HBV&HCV co-infection. †The global prevalence rate was estimated by weighting the country-specific prevalence rates with the number of new HCC cases in each country in 2022 (based on GLOBOCAN estimates). HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; SDI=socio-demographic index.

	HBV infection*			HCV infection*			HBV&HCV co-infection			Viral	HBV/HCV*
	Number of cohorts	prevalence	(95% CI), %	Number of cohorts	prevalence	(95% CI), %	Number of cohorts	prevalence	(95% CI), %	prevalence	ratio
Central Asia	6	48.23%	(35.67–60.90)	7	43.85%	(33.73–54.22)	5	11.35%	(5.20–19.42)	80.73%	1.1
Argentina	1	12.61%	(10.04–15.42)	1	37.99%	(34.10–41.96)	1	1.19%	(0.45–2.26)	49.41%	0.33
Brazil	5	21.45%	(11.94–32.78)	5	44.19%	(26.22–62.98)	3	3.41%	(0.00–15.49)	57.62%	0.46
Mexico	1	6.08%	(2.71–10.58)	1	25.68%	(18.93–33.05)	1	0.68%	(0.00–2.88)	31.08%	0.24
Multinational	3	13.58%	(12.08–15.16)	3	35.26%	(20.38–51.76)	2	0.76%	(0.36–1.28)	48.08%	0.39
North Africa and Middle East	34	34.07%	(25.99–42.67)	32	45.64%	(33.31–58.24)	21	3.66%	(1.93–5.85)	74.82%	0.75
Egypt	9	7.42%	(2.89–13.69)	9	90.69%	(86.40–94.26)	7	2.91%	(0.46–7.04)	95.20%	0.08
Iran	2	51.92%	(41.57–62.19)	1	40.53%	(34.22–47.00)	1	7.93%	(4.73–11.84)	84.52%	1.28
Iraq	1	53.33%	(35.22–71.03)	2	28.28%	(19.50–37.93)	0	--	--	--	1.89
Lebanon	1	75.00%	(65.59–83.37)	1	27.17%	(18.52–36.77)	1	7.61%	(2.93–14.05)	94.56%	2.76
Oman	1	32.39%	(27.07–37.96)	1	34.86%	(29.42–40.51)	0	--	--	--	0.93
Qatar	1	26.67%	(19.87–34.06)	1	45.33%	(37.42–53.37)	0	--	--	--	0.59
Saudi Arabia	9	40.27%	(29.55–51.47)	7	26.04%	(13.85–40.44)	4	2.26%	(1.31–3.43)	61.38%	1.52
Sudan	1	32.67%	(25.37–40.40)	1	8.67%	(4.63–13.76)	1	0.67%	(0.00–2.84)	40.67%	3.77
Tunisia	1	53.42%	(41.88–64.79)	1	64.38%	(53.00–75.02)	1	30.14%	(20.09–41.22)	87.66%	0.83
Turkey	7	55.49%	(49.82–61.09)	7	17.90%	(13.09–23.26)	5	2.46%	(0.82–4.79)	70.93%	3.1
Yemen	1	29.55%	(20.42–39.55)	1	28.41%	(19.42–38.33)	1	3.41%	(0.43–8.46)	54.55%	1.04
South Asia	13	25.64%	(15.50–37.29)	12	37.72%	(18.86–58.73)	8	4.14%	(1.73–7.45)	59.22%	0.68
India	7	29.77%	(17.19–44.12)	6	11.05%	(6.33–16.86)	4	2.79%	(0.33–7.28)	38.03%	2.69
Pakistan	6	21.09%	(6.39–41.16)	6	69.62%	(52.77–84.15)	4	5.96%	(2.44–10.78)	84.75%	0.3
Southeast Asia	13	55.91%	(48.58–63.11)	12	19.17%	(10.84–29.15)	9	2.92%	(2.06–3.91)	72.16%	2.92
Cambodia	2	42.78%	(38.79–46.82)	2	32.09%	(13.34–54.46)	2	4.56%	(2.98–6.45)	70.31%	1.33
Indonesia	2	53.59%	(41.40–65.58)	2	34.14%	(0.00–88.67)	0	--	--	--	1.57
Malaysia	1	57.62%	(50.86–64.24)	1	2.38%	(0.67–4.97)	0	--	--	--	24.21
Philippines	2	54.02%	(23.07–83.36)	1	8.89%	(5.12–13.53)	1	1.11%	(0.02–3.32)	61.80%	6.08

*The prevalence rates of HBV infection and HCV infection both include the prevalence rate of HBV&HCV co-infection. †The global prevalence rate was estimated by weighting the country-specific prevalence rates with the number of new HCC cases in each country in 2022 (based on GLOBOCAN estimates). HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; SDI=socio-demographic index.

	HBV infection*			HCV infection*			HBV&HCV co-infection			Viral	HBV/HCV*
	Number of cohorts	prevalence	(95% CI), %	Number of cohorts	prevalence	(95% CI), %	Number of cohorts	prevalence	(95% CI), %	prevalence	ratio
Central Asia	6	48.23%	(35.67–60.90)	7	43.85%	(33.73–54.22)	5	11.35%	(5.20–19.42)	80.73%	1.1
Thailand	3	59.59%	(51.01–67.88)	3	15.05%	(11.20–19.34)	3	3.79%	(1.82–6.35)	70.85%	3.96
Vietnam	3	63.43%	(41.96–82.42)	3	19.58%	(5.99–38.47)	3	2.52%	(2.16–2.91)	80.49%	3.24
Sub-Saharan Africa	22	53.18%	(46.58–59.74)	15	14.15%	(8.98–20.23)	7	3.52%	(1.67–5.91)	63.81%	3.76
Central African Republic	1	39.43%	(32.30–46.79)	1	1.71%	(0.21–4.30)	0	--	--	--	23.06
Ethiopia	1	19.12%	(10.54–29.42)	1	47.06%	(35.26–59.02)	1	1.47%	(0.00–6.21)	64.71%	0.41
Gambia	2	48.24%	(26.50–70.33)	2	13.41%	(7.86–20.14)	1	1.04%	(0.02–3.10)	60.61%	3.6
Ghana	2	58.27%	(52.01–64.40)	2	4.67%	(2.37–7.62)	0	--	--	--	12.48
Malawi	1	74.36%	(64.03–83.50)	1	6.41%	(1.85–13.12)	0	--	--	--	11.6
Mozambique	1	55.34%	(48.50–62.08)	1	8.74%	(5.22–13.02)	1	1.94%	(0.42–4.37)	62.14%	6.33
Nigeria	2	64.01%	(14.31–99.25)	1	8.33%	(2.43–16.89)	1	5.00%	(0.64–12.29)	67.34%	7.68
Senegal	1	61.21%	(53.64–68.52)	0	--	--	0	--	--	--	--
South Africa	7	49.86%	(43.22–56.51)	2	19.34%	(7.39–35.10)	1	6.76%	(3.19–11.44)	62.44%	2.58
Tanzania	1	66.20%	(58.19–73.77)	1	16.90%	(11.15–23.55)	1	4.93%	(1.88–9.20)	78.17%	3.92
Zimbabwe	2	44.70%	(35.94–53.63)	2	21.92%	(14.94–29.77)	1	8.33%	(2.43–16.89)	58.29%	2.04
Multinational	1	70.00%	(62.65–76.87)	1	27.50%	(20.83–34.70)	0	--	--	--	2.55
Western Europe	52	18.34%	(14.63–22.35)	38	31.62%	(25.87–37.61)	22	3.15%	(1.91–4.65)	46.71%	0.56
Austria	1	11.43%	(7.72–5.74)	1	36.73%	(30.80–42.88)	1	1.63%	(0.35–3.68)	46.53%	0.31
Belgium	1	18.23%	(12.92–24.22)	1	40.88%	(33.81–48.15)	0	--	--	--	0.45
Denmark	1	7.46%	(2.17–15.19)	1	14.93%	(7.26–24.58)	1	1.49%	(0.00–6.30)	20.90%	0.5
France	5	13.63%	(4.61–26.15)	4	20.33%	(9.92–33.19)	4	6.37%	(0.67–16.42)	27.59%	0.67
Germany	10	13.19%	(7.42–20.28)	9	21.09%	(16.23–26.39)	5	1.36%	(0.48–2.63)	32.92%	0.63
Greece	6	51.35%	(44.53–58.15)	4	19.25%	(14.10–24.97)	3	2.34%	(0.59–4.99)	68.26%	2.67
Italy	14	17.53%	(13.12–22.42)	8	59.30%	(47.23–70.82)	6	3.77%	(2.88–4.77)	69.95%	0.29
Netherlands	1	26.25%	(20.86–30.02)	1	35.83%	(29.87–42.02)	0	--	--	--	0.73

*The prevalence rates of HBV infection and HCV infection both include the prevalence rate of HBV&HCV co-infection. †The global prevalence rate was estimated by weighting the country-specific prevalence rates with the number of new HCC cases in each country in 2022 (based on GLOBOCAN estimates). HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; SDI=socio-demographic index.

	HBV infection*			HCV infection*			HBV&HCV co-infection			Viral	HBV/HCV*
	Number of	prevalence	(95% CI), %	Number of	prevalence	(95% CI), %	Number of	prevalence	(95% CI), %	prevalence	ratio
	cohorts			cohorts			cohorts				
Central Asia	6	48.23%	(35.67–60.90)	7	43.85%	(33.73–54.22)	5	11.35%	(5.20–19.42)	80.73%	1.1
Spain	5	8.37%	(4.34–13.51)	3	43.96%	(28.09–60.48)	1	10.00%	(5.00–16.39)	42.33%	0.19
Sweden	2	7.19%	(4.88–9.92)	2	25.72%	(24.59–26.86)	0	--	--	--	0.28
Switzerland	1	26.67%	(17.20–37.31)	0	--	--	0	--	--	--	--
United Kingdom	2	21.51%	(4.73–45.74)	1	21.05%	(14.01–29.06)	1	1.75%	(0.03–5.21)	40.81%	1.02
Multinational	3	18.89%	(11.35–27.79)	3	25.43%	(20.99–30.15)	0	--	--	--	0.74
Cross-regional	7	42.28%	(32.74–52.12)	7	37.10%	(26.56–48.30)	2	11.68%	(0.00–46.39)	67.70%	1.14
Period											
≤ 1990	53	36.95%	(31.03–43.07)	10	28.14%	(17.89–39.66)	7	5.74%	(1.41–12.45)	59.35%	1.31
1991 ~ 1995	34	45.28%	(36.82–53.89)	32	29.74%	(22.18–37.90)	23	6.02%	(3.47–9.19)	69.00%	1.52
1996 ~ 2000	49	39.46%	(31.45–47.77)	47	31.17%	(23.89–38.94)	32	4.81%	(3.25–6.63)	65.82%	1.27
2001 ~ 2005	47	33.31%	(25.91–41.15)	47	37.18%	(31.65–42.89)	28	4.39%	(2.69–6.47)	66.10%	0.9
2006 ~ 2010	66	31.46%	(25.74–37.48)	64	34.51%	(28.01–41.32)	35	2.95%	(1.97–4.09)	63.02%	0.91
2011 ~ 2015	56	32.70%	(24.72–41.22)	50	31.20%	(24.77–38.01)	24	2.86%	(2.02–3.84)	59.82%	0.98
2016 ~ 2020	36	40.78%	(31.29–50.63)	35	21.08%	(14.50–28.51)	15	3.12%	(1.27–5.71)	57.68%	1.78
2021 ~ 2025	7	40.72%	(12.29–73.00)	7	36.38%	(6.90–73.07)	1	0.00%	(0.00–4.25)	77.10%	1.12
SDI											
Low SDI	3	43.89%	(14.57–75.74)	3	13.79%	(0.00–46.75)	1	1.47%	(0.00–6.21)	56.21%	3.18
Low-Middle SDI	19	39.98%	(29.35–51.10)	17	34.81%	(21.40–49.55)	12	4.00%	(2.34–6.02)	70.79%	1.15
Middle SDI	35	35.42%	(26.75–44.59)	35	43.67%	(31.37–56.37)	18	6.80%	(3.71–10.69)	72.29%	0.81
High-Middle SDI	101	60.10%	(55.70–64.43)	74	18.82%	(15.57–22.30)	40	4.40%	(3.33–5.59)	74.15%	3.14
High SDI	176	23.70%	(20.79–26.74)	149	35.27%	(31.59–39.05)	73	3.64%	(2.66–4.76)	55.02%	0.66
Others	14	31.92%	(21.96–42.79)	14	33.24%	(26.88–39.92)	4	4.33%	(0.00–17.16)	60.83%	0.96
Age											
< 50	28	50.14%	(43.62–56.66)	17	14.00%	(8.65–20.35)	8	3.28%	(1.69–5.31)	60.86%	3.58
50 ~ 55	33	56.39%	(47.09–65.47)	29	24.63%	(15.80–34.68)	19	5.49%	(3.49–7.89)	75.53%	2.29
*The prevalence rates of HBV infection and HCV infection both include the prevalence rate of HBV&HCV co-infection. †The global prevalence rate was estimated by weighting the country-specific prevalence rates with the number of new HCC cases in each country in 2022 (based on GLOBOCAN estimates). HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; SDI=socio-demographic index.											

	HBV infection*			HCV infection*			HBV&HCV co-infection			Viral	HBV/HCV*
	Number of cohorts	prevalence	(95% CI), %	Number of cohorts	prevalence	(95% CI), %	Number of cohorts	prevalence	(95% CI), %	prevalence	ratio
Central Asia	6	48.23%	(35.67–60.90)	7	43.85%	(33.73–54.22)	5	11.35%	(5.20–19.42)	80.73%	1.1
55 ~ 60	72	40.29%	(33.44–47.35)	57	35.26%	(27.63–43.29)	31	4.01%	(2.58–5.72)	71.54%	1.14
60 ~ 65	101	29.28%	(25.19–33.54)	88	33.68%	(28.76–38.79)	56	3.57%	(2.67–4.60)	59.06%	0.85
65 ~ 70	44	16.25%	(13.26–19.49)	40	42.24%	(36.07–48.52)	21	3.16%	(1.79–4.88)	54.97%	0.38
≥ 70	9	11.21%	(4.87–19.69)	9	22.92%	(14.83–32.17)	1	0.09%	(0.04–0.15)	34.46%	0.53
Others	61	47.55%	(39.92–55.24)	52	27.21%	(21.52–33.29)	29	5.03%	(2.72–7.95)	69.18%	1.69
Overall	348	36.29%	(33.40–39.23)	292	31.43%	(28.61–34.32)	165	3.98%	(3.31–4.70)	63.36%	1.13
World[†]	–	50.45%	–	–	25.78%	–	–	4.38%	–	71.85%	1.96

*The prevalence rates of HBV infection and HCV infection both include the prevalence rate of HBV&HCV co-infection. [†]The global prevalence rate was estimated by weighting the country-specific prevalence rates with the number of new HCC cases in each country in 2022 (based on GLOBOCAN estimates). HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; SDI=socio-demographic index.

The pooled HCV prevalence reported by 284 studies comprising 292 HCC cohorts with 860,916 HCC cases was 31·43% (95% CI, 28.61–34.32), with no evidence of publication bias (Egger's test, $P = 0.12$) (Table 2). The weighted estimated prevalence of HCV in HCC worldwide is 25·78%. At the regional level, the region with the highest HCV rate was North Africa and Middle East (45·64%; 33·31–58·24); followed by Central Asia (43·85%; 33·73–54·22) (mainly Mongolia) and high-income North America (41·21%; 35·95–46·56) (Fig. 2 and S4). HCV prevalence was highest in Middle SDI countries (43·67%; 31·37–56·37) and lowest in Low SDI countries (13·79%; 0·00–46·75). Among HCC patients with an average age of 65–70 years, the prevalence of HCV was highest at 42·24% (95% CI, 36·07–48·52). Temporally, the highest HCV infection rate was in 2001–2005 (37·18%; 31·65–42·89), and the lowest was in 2016–2020 (21·08%; 14·50–28·51). A linear model, fitted using the median year as the temporal reference, indicated that the overall proportion of HCV infection did not exhibit a significant temporal trend ($P = 0.765$) (Supplementary Figure S1). In contrast, a non-linear model revealed that the prevalence of HCV infection generally followed a "W"-shaped pattern over time, with a peak occurring around 2005 ($P < 0.01$) (Fig. 4).

The pooled HBV and HCV co-infection rate, derived from 158 studies encompassing 165 HCC cohorts with a total of 207,873 HCC cases, was 3·98% (95% CI: 3·31–4·70) (Table 2). The weighted global HBV and HCV co-infection rate was estimated at 4·38%. At the regional level, the highest co-infection rates were observed in Eastern Europe (13·67%; 8·41–19·93) and Central Asia (11·35%; 5·20–19·42), the latter primarily driven by data from Mongolia (Fig. 2 and Supplementary Figure S5). Consistent with the pattern for HCV infection, co-infection rates were highest in middle-SDI countries (6·80%; 3·71–10·69) and lowest in low-SDI countries (1·47%; 0·00–6·21). Mirroring the age distribution of HBV infection, co-infection rates peaked among HCC patients with a mean age of 50–55 years at 5·49% (95% CI: 3·49–7·89), exhibiting an overall declining trend across increasing age groups. Subgroup analysis stratified by study period indicated that the co-infection rate was highest between 1991 and 1995 (6·02%; 3·47–9·19). Both linear ($P = 0.006$) and non-linear models ($P = 0.042$) based on median year fitting indicate that the proportion of co-infections in HCC shows an overall downward trend (Fig. 4 and Supplementary Figure S1).

As shown in Fig. 3, the proportion of hepatitis is highest in Central Asia and lowest in Western Europe. The HBV:HCV ratio is highest in East Asia and lowest in High-income North America. At the national level, Egypt has the highest proportion of hepatitis in HCC at 95·2% and also has the lowest HBV/HCV ratio. Denmark had the lowest hepatitis prevalence at 20·9%, while Malaysia showed the highest HBV/HCV ratio. Furthermore, for the five countries or territories with the highest number of studies, we conducted subgroup analyses based on the study period, with results shown in Supplementary Figure S2. In our sensitivity analyses, there was little effect on the pooled HBV, HCV, and co-infection rate estimates after exclusion of low-quality studies or exclusion of any included studies. However, when grouped according to region, HBV prevalence declined by 3·2% in South Asia after excluding low-quality studies; meanwhile, HCV prevalence rose by 2·6% in high-income Asia-Pacific and declined by 3·3% in Southeast Asia (Supplementary Table S6). Egger's test showed significant publication bias for both HBV ($t = -4.98$, $P < 0.01$) and co-infection ($t = 5.42$, $P < 0.01$) estimates (Supplementary Figure S6-8). After correction using the cut-off method, the prevalence estimates were adjusted to 58.0% for HBV and 1.44% for co-infection.

Discussion

This systematic review and meta-analysis, encompassing 344 studies and 878,083 HCC patients across 60 countries, provides the most comprehensive and contemporary global landscape of HBV and HCV prevalence in HCC to date. Consistent with previous studies¹¹, our findings confirm that HBV and HCV remain the dominant etiological drivers, accounting for an estimated 50.4% and 25.8% of global HCC cases, respectively, when weighted against 2022 GLOBOCAN data. While these aggregated figures align with historical paradigms, the temporal trajectories uncovered by our restricted cubic spline models fundamentally challenge the conventional narrative of steady viral hepatitis decline and unveil a previously unrecognized epidemiological shift-specifically, a significant rebound in HBV proportion among HCC patients since 2010, and a complex "W"-shaped fluctuation for HCV.

The most striking and clinically consequential finding of our study is the non-linear temporal trend of HBV prevalence. The non-linear spline analysis rigorously demonstrated a clear downward trend from the 1990s to approximately 2010, followed by a significant resurgence. This is the first meta-analytical evidence documenting such a rebound. We postulate that this phenomenon is not attributable to a single cause but rather an intricate interplay of several factors: First, the relative denominator effect cannot be overlooked. The period after 2010 witnessed a dramatic decline in HCV-related HCC in many regions, largely driven by the widespread adoption of DAAs and improved blood screening¹². This sharper decline in HCV proportions may have mathematically inflated the relative proportion of HBV among the remaining HCC cases. Second, the cohort aging effect in highly endemic areas is critical. In countries like China and parts of Southeast Asia, the large birth cohorts that predate universal infant HBV vaccination (initiated in 1992 and scaled up post-2000) are now entering the age of peak HCC incidence (50–55 years)^{13, 14}. As this “vaccine-naïve” generation ages, the absolute burden of HBV-related HCC persists, counteracting the gains made in younger populations. Third, while infant vaccination coverage is high in many regions, adult catch-up vaccination and booster strategies have been largely neglected in most LMICs, leaving a susceptible adult reservoir¹⁵. Our finding serves as an urgent wake-up call: the global strategy focused primarily on infant immunization is insufficient to achieve the WHO's 2030 mortality reduction target; proactive case-finding and antiviral treatment scale-up among middle-aged adults are imperatively needed¹⁶.

Contrasting with HBV, the HCV prevalence among HCC patients exhibited a distinct “W”-shaped trajectory, peaking notably around 2005. This pattern plausibly reflects the legacy of unsafe medical practices and contaminated blood product transfusions prevalent in the 1980s and 1990s, which culminated in a surge of HCV-related cirrhosis and HCC approximately two decades later¹⁷. The subsequent decline observed after 2005 aligns with the global implementation of blood donor screening and, more recently, the DAA era¹⁸. However, the slight uptick in recent years warrants cautious surveillance, possibly linked to injection drug use resurgence in high-income North America and iatrogenic transmission in resource-limited settings¹⁹.

Critically, our age-stratified analysis unveils a stark clinical dichotomy: HBV-related HCC presents predominantly at 50–55 years, a full 15 years earlier than HCV-related HCC (65–70 years). This disparity is rooted in fundamental oncogenic mechanisms. HBV is a DNA virus that integrates into the host genome, directly expressing oncoproteins like HBx, which dysregulate cell cycle checkpoints and promote genomic instability early in the infection course²⁰. In contrast, HCV is a non-integrating RNA virus that drives hepatocarcinogenesis primarily through long-standing chronic inflammation, fibrosis, and cirrhosis over decades of continuous immune-mediated injury²¹. This age gap has direct clinical implications, suggesting that HCC screening for HBsAg-positive individuals should be initiated earlier than current guidelines recommend, particularly in highly endemic regions²².

Geographically, our weighted estimates reaffirm East Asia, Southeast Asia, and sub-Saharan Africa as the epicenters of HBV-driven HCC, collectively accounting for the majority of the global burden. Conversely, HCV dominance in North Africa and Middle East (primarily Egypt) and high-income North America underscores the differing transmission vectors—historic parenteral anti-schistosomiasis campaigns in the former versus injection drug use in the latter^{23, 24}. Encouragingly, Egypt's rapid decline in HCV prevalence following the establishment of its national treatment strategy in 2006 offers a replicable model for other nations²⁵.

Notably, we identified Central Asia (particularly Mongolia) and Eastern Europe as having the highest HBV/HCV co-infection rates (11.4% and 13.7%, respectively). This synergistic co-infection is biologically devastating; it significantly accelerates fibrosis progression and heightens HCC risk beyond that of either mono-infection through enhanced viral interference and immune exhaustion²⁶. The geographical predilection of this co-burden likely reflects overlapping high-risk exposures, including unsterilized medical equipment and low public awareness. Given that these regions also exhibit the highest overall hepatitis proportion (over 80%), our data strongly advocate for integrated screening strategies (anti-HCV + HBsAg) rather than single-pathogen testing to avoid missed diagnoses and optimize resource allocation in these hotspots²⁷.

Compared with the seminal work by de Martel et al. (2015)²⁸, our study expands the evidence base by nearly 7-fold and extends the geographical coverage to 60 countries. More importantly, the previous study relied on static cross-sectional pooling, whereas our non-linear temporal meta-regression provides a dynamic lens, capturing the recent rebound signals that static analyses would have inherently overlooked. Our use of GLOBOCAN 2022 incidence data for weighting provides greater accuracy for global burden estimation, while the adoption of restricted cubic splines avoids the pitfalls of linear oversimplification, offering a more realistic depiction of real-world epidemiological shifts.

Several limitations warrant consideration. First, substantial heterogeneity persists across studies, largely attributable to differences in diagnostic assays, study periods, and regional healthcare capacities. Although we conducted extensive subgroup analyses, unmeasured confounders may remain. Second, a notable proportion of included studies did not explicitly report HBV/HCV co-infection, potentially leading to an underestimation or misclassification of mono-infection rates. Third, despite our extensive search, data from many LMICs remain sparse, with single-country single-study scenarios limiting the robustness of certain national estimates.

In conclusion, our study not only provides an updated global baseline for viral hepatitis attribution in HCC but also delivers a critical early warning signal through the identification of a post-2010 resurgence in HBV prevalence and the complex “W”-shaped dynamics of HCV. These findings have profound implications for the WHO 2030 elimination agenda: National strategies must pivot from a singular focus on infant vaccination to a dual-pronged approach that includes aggressive screening and antiviral treatment for adults aged 30–60 in high-endemic zones to immediately reduce HCC mortality. Regions like Central Asia require differentiated care models for co-infected populations, while North Africa should consolidate DAA scale-up to prevent future rebounds. The observed rebound mandates the establishment of continuous, standardized longitudinal surveillance systems, particularly in LMICs, to rigorously track viral etiology in HCC and facilitate rapid public health responses.

Declarations

Statement of Ethics

A Statement of Ethics is not applicable because this study is based exclusively on published literature.

Conflicts of interest

All authors declare no competing interests.

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Contributors

LR, YS, BJW, HW, and DZ formulated the research questions and developed the study protocol. BJW and HW conducted a literature search and screened the identified records. WNJ, DZ, CSB, and QHH extracted the data and assessed risk-of-bias, with RL and YS providing supervision. BJW, HW, QHH, and JYW analysed the data. BJW and HW wrote the original draft of the manuscript and LR, YS, CSB, WNJ, and DZ contributed to the review and editing of the manuscript. All authors gave comments and approval on the final version of the manuscript. All authors had full access to all the raw or generated data in the study and had final responsibility for the decision to submit for publication.

Data sharing

The full search strategy and key results used to generate data that inform the conclusion of this systematic review can be found in the appendix. Further enquiries can be directed to the corresponding author.

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Figures

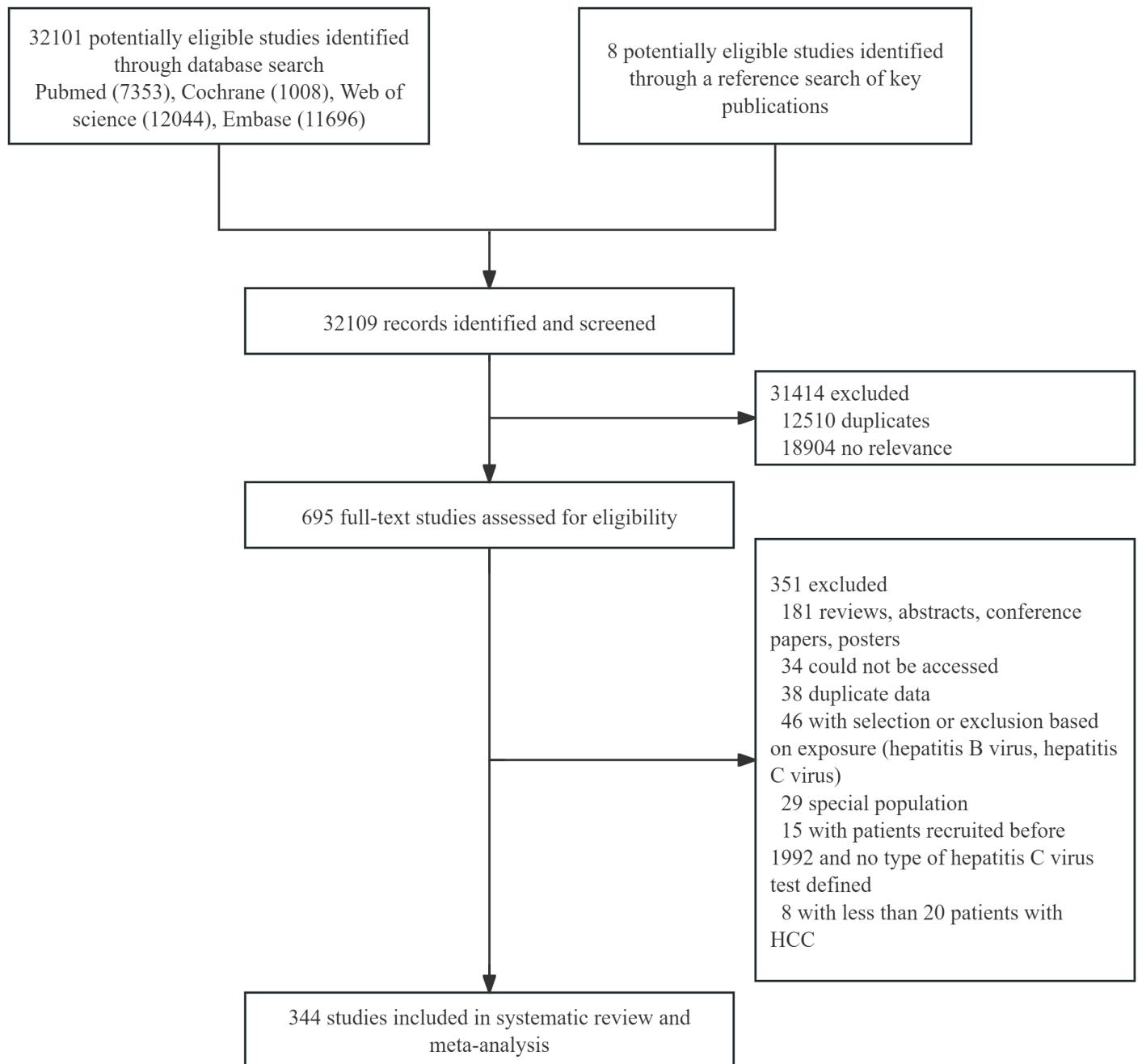


Figure 1

Study selection.

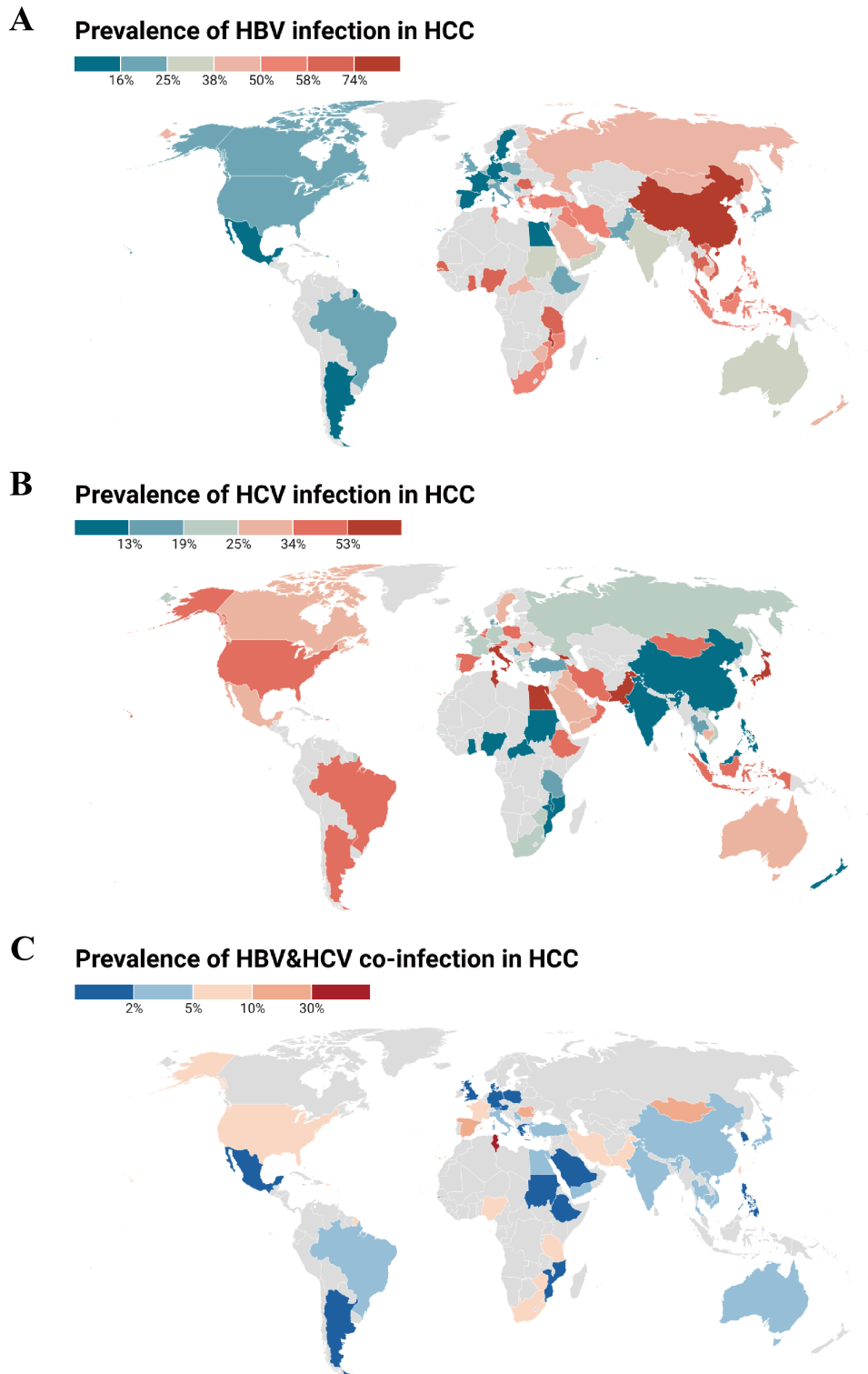


Figure 2

Pooled prevalence of HBV infection (A), HCV infection (B) and HBV&HCV co-infection (C) among HCC patients. The designations used and the presentation of the material in this Article do not imply that we hold any opinion on the legal status of any country, territory, city or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries. HBV=hepatitis B virus, HCC=hepatocellular carcinoma, HCV=hepatitis C virus.

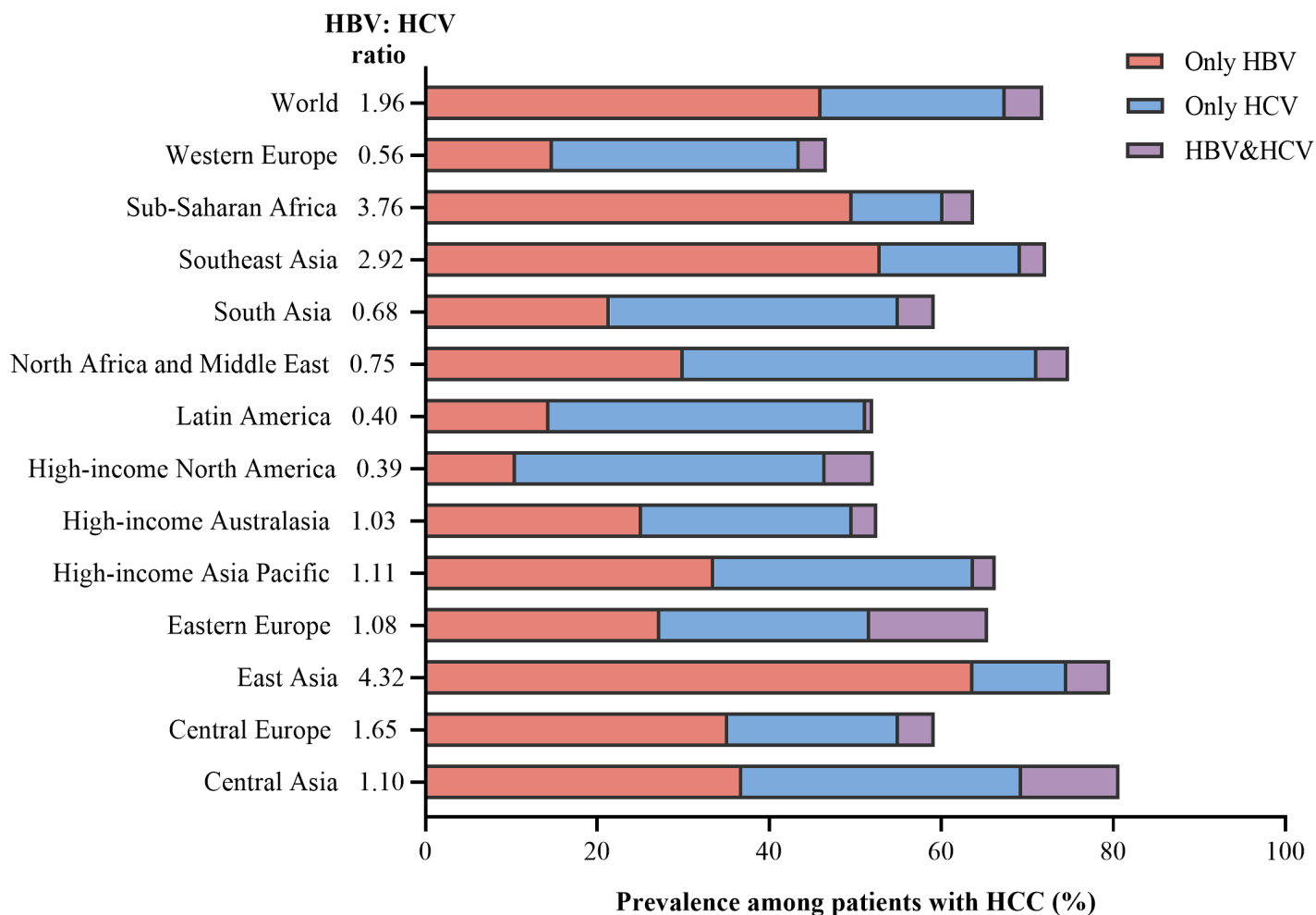


Figure 3

Regional and global pooled prevalence of only HBV infection, only HCV infection and HBV&HCV co-infection among patients with HCC. The HBV:HCV ratio represents the relative importance of HBV over HCV per region and globally. The proportion of only HBV infection is equal to the proportion of HBV infection minus the proportion of co-infection with HBV and HCV; The proportion of only HCV infection is equal to the proportion of HCV infection minus the proportion of co-infection with HBV and HCV; HBV=hepatitis B virus, HCC=hepatocellular carcinoma, HCV=hepatitis C virus.

Restricted Cubic Spline Meta-regression (3 nodes)

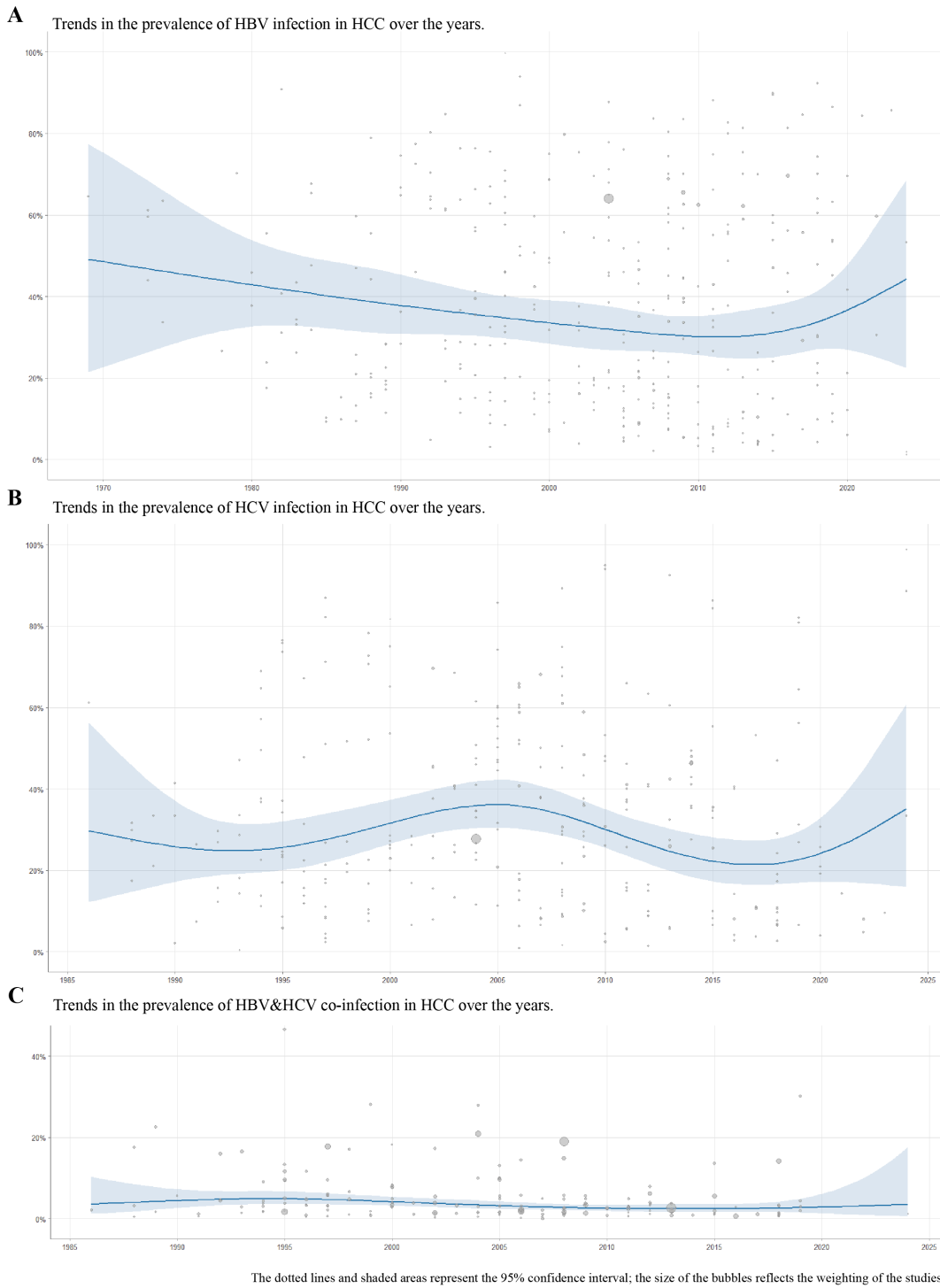


Figure 4

Temporal trends in the proportion of HBV infection (A), HCV infection (B) and HBV&HCV co-infection (C) among HCC patient, as fitted by restricted cubic spline models. The size of the bubbles represents the sample size of a single study. The position of the bubble is determined by the midpoint of the study period and the pooled prevalence. The fitted curve shows the trend in prevalence over time. HBV=hepatitis B virus, HCC=hepatocellular carcinoma, HCV=hepatitis C virus.

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