Journal of Clinical and Translational Hepatology **2024**
DOI: 10.14218/JCTH.2024.00379

Original Article

Dose-dependent Relationship between Alcohol Consumption and the Risks of Hepatitis B Virus-associated Cirrhosis and Hepatocellular Carcinoma: A Meta-analysis and Systematic Review

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Received: October 15, 2024 | **Revised:** November 18, 2024 | **Accepted:** November 20, 2024 | **Published online:** December 17, 2024

Abstract

Background and Aims: The quantitative effects of alcohol consumption on cirrhosis and hepatocellular carcinoma (HCC) in hepatitis B virus (HBV) infection are unknown. This study aimed to establish a dose-dependent model of alcohol consumption on the risks of cirrhosis and HCC. ***Methods:*** PubMed, Embase, the Cochrane Library, Web of Science, and four Chinese databases were searched for studies published from their inception to 15 May 2024. A random-effects model was used to pool the data on the incidence of cirrhosis and HCC, and a dose-dependent model of alcohol's effect on cirrhosis and HCC was established. ***Results:*** A total of 33,272 HBV patients from 45 studies were included. Compared with non-drinkers, the overall pooled odds ratio (OR) for cirrhosis was 2.61 (95% confidence interval [CI]: 1.46–4.66; I^2 = 94%, p < 0.001), and the OR for HCC was 2.27 (95% CI: 1.50–3.43; I^2 = 90%, p < 0.001) among drinkers. Compared with low-level drinkers, the estimated pooled OR for cirrhosis was 2.34 (95% CI: 1.59–3.44; I^2 = 87%, p < 0.001), and the OR for HCC was 2.42 (95% CI: 1.90–3.09; I^2 = 80%, p < 0.001) among high-level drinkers. Furthermore, a linear dose-dependent analysis showed that each daily consumption of 12 g of alcohol increased the risk of cirrhosis by 6.2% and the risk of HCC by 11.5%. ***Conclusions:*** Alcohol dose-dependently increases the risks of cirrhosis and HCC in patients with HBV infection, and patients with daily alcohol consumption of more than 12 g should be strictly monitored.

Keywords: HBV; Alcohol; Hepatocellular carcinoma; Cirrhosis; Risk; Dose-dependent relationship.

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Citation of this article: Wu YP, Yang XY, Tian YX, Feng J, Yeo YH, Ji FP, *et al*. Dose-dependent Relationship between Alcohol Consumption and the Risks of Hepatitis B Virus-associated Cirrhosis and Hepatocellular Carcinoma: A Meta-analysis and Systematic Review. J Clin Transl Hepatol 2024. doi: 10.14218/JCTH.2024.00379.

Introduction

Chronic hepatitis B virus (HBV) infection remains a pressing global health challenge, affecting approximately 296 million individuals worldwide.[1] Despite the implementation of HBV vaccination programs and effective strategies to prevent mother-to-child transmission,[2,3] the prevalence of HBV infection remains alarmingly high. HBV infection is implicated in an estimated 30% of all cases of liver cirrhosis and 45% of all cases of hepatocellular carcinoma (HCC).[4] The World Health Organization set a target in 2016 to eradicate viral hepatitis as a significant public health concern by 2030.[5,6] Specifically, for HBV infection, the World Health Organization has set the goal of a 95% decrease in incident infections and a 65% decrease in associated mortality rates compared with the corresponding numbers in 2015.[6]

HBV is a leading risk factor for the development of cirrhosis and HCC. Prior studies have indicated that, without effective medical intervention, approximately 25% of patients infected with HBV in childhood are likely to develop HCC in adulthood.[7] The health burden is further complicated by alcohol consumption, a well-recognized carcinogen implicated in various types of cancer, including HCC.[8,9] Alcohol consumption is responsible for nearly 30% of all cases of HCC and has been shown to promote HBV replication and weaken anti-HBV immunity *in vitro* and *in vivo*, suggesting that alcohol drinkers have a higher risk of developing cirrhosis and HCC.[10–13]

Several studies have suggested that high alcohol consumption promotes the progression of hepatitis to cirrhosis and HCC in patients with hepatitis C virus or HBV infection.[10,14–20] In patients with hepatitis C virus infection, each alcoholic drink per day is associated with an 11% increase in the risk of cirrhosis.[19] However, the quantitative dose-dependent effects of alcohol consumption on the development of cirrhosis and HCC in patients with HBV infection remain unknown. Therefore, this meta-analysis and systematic review aimed to establish a dose-dependent model of the effects of alcohol consumption on the risks of cirrhosis and HCC in patients with HBV infection.

Methods

Search strategy and selection criteria

PubMed, Embase, Cochrane Library, and Web of Science were searched from inception to 15 May 2024 for relevant prospective or retrospective cohort studies and case-control studies. Four Chinese databases (China National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform, the VIP Information Resource Integration Service Platform, and China Biology Medicine Disc) were also searched, as China has the largest HBV-infected population in the world, with an estimated 86 million patients.[21] This study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines,[22] and the protocol was registered on PROSPERO (CRD42022307917). The full search strategy is provided in Supplementary Table 1.

Studies were included if they met the following criteria: 1) cohort studies involving patients with hepatitis B confirmed based on imaging and clinical manifestations, lifestyle information including alcohol use, antiviral treatment or lack thereof, and laboratory test results; and 2) case-control studies that examined the association between alcohol consumption and cirrhosis or HCC. Studies were excluded if they 1) included patients aged under 18 years; 2) included patients with liver diseases caused by types of viral hepatitis other than hepatitis B; or 3) were conference abstracts, case reports, case series, or review articles.

Data selection

Two reviewers (YPW and XYY) first read the titles and abstracts of the identified studies and omitted irrelevant studies. Then, they read the full texts of the retrieved studies independently to determine their eligibility. Discrepancies were first resolved by discussion between the two reviewers, and if no agreement was reached, the final decision was made by discussing with two other authors (JF and YXT). The following data were extracted and entered into an Excel sheet: 1) study characteristics, such as title, author, publication year, country, and study design; 2) study population characteristics, such as the total number of patients with HBV infection and the countries of the study population; 3) patient characteristics: mean age and sex ratio; 4) alcohol exposure, defined as alcohol consumption per day in grams (in the non-drinker group and at least one exposure group); and 5) number of patients with cirrhosis or HCC, relative risks, odds ratios (ORs), or equivalent measures of risk (such as hazard ratios) for patients with HBV infection, and confidence intervals (CIs) with *p*-values. The study process is presented in Figure 1A.

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies by calculating their risk of bias. The NOS contains three elements: selection with a full score of 5, comparability with a full score of 2, and outcome with a full score of 2. A total score of 7 to 9 is classified as high quality (low risk of bias), 4 to 6 as fair quality (moderate risk of bias), and 1 to 3 as low quality (high risk of bias).[23] The quality of studies was evaluated by two authors (XYY and JF), and any disagreement was resolved by discussion with two other authors (YPW and YXT).

Statistical analysis

We input data into 2×2 contingency tables to generate ORs and 95% CIs for cirrhosis and HCC. We used the Der Simonian–Laird random-effects model to pool the ORs and 95% CIs. Heterogeneity was assessed using Cochran's Q statistic (or the chi-square test). $I^2 > 50\%$ with a p-value < 0.05 was considered to indicate moderate heterogeneity across the included studies. Meta-regression analysis was used to assess the sources of heterogeneity. An estimated overall OR with a p-value < 0.05 was considered to indicate an association between one of the variables and adverse outcomes. Funnel plots and Egger's test were used to assess potential publication bias. Trim and fill analysis was used to assess the stability and reliability of the results. The number of missing studies was estimated iteratively, and meta-analyses were re-run after adding a subset of studies. If the pooled effect size estimates did not change significantly, the effect of publication bias was considered small. Subgroup analyses were conducted according to the quality of studies and the race, age, and sex of the patients. Sensitivity analysis was conducted by removing one study at a time and analyzing the rest of the studies to evaluate whether the results had been affected markedly by a single study.

Based on the Akaike information criterion and Bayesian information criterion statistics, we established a linear dose-dependent model rather than a quadratic or mixed model to calculate the risk estimation OR scales for cirrhosis and HCC attributable to different levels of alcohol consumption (grams per day). The least squares method was used to obtain the equation using 12 g ethanol as the standard daily dose, as recommended in most countries.[24] All analyses were conducted in the metafor package of R statistical software,[25] version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and Stata/SE statistical software, version 11.0 (StataCorp LLC, Texas, USA).

Results

Characteristics of the included studies and patients

In total, 45 studies comprising 33,272 patients with HBV infection met the inclusion criteria, and their basic characteristics are listed in Table 1[15,17,26–68] and Supplementary Table 2. The NOS assessment showed that 23 (51.1%) and 22 (48.9%) studies had a low and moderate risk of bias, respectively (Supplementary Tables 3 and 4). The studies included 36 Chinese studies, four Italian studies, four Japanese studies, and one Korean study, with the majority of studies (n = 41, 91.1%) originating from Asian countries. The sample sizes ranged from 57 to 19,673, and the publication years spanned from 1982 to 2022. Of the studies, 41 (91.1%) had a case-control design and four (8.9%) had a cohort design. Among the patients, 26,687 (80.2%) were male and 6,585 (19.8%) were female. A total of 28,895 (86.5%) patients were alcohol drinkers, while 4,477 (13.5%) were non-drinkers. The cut-off points for categorizing alcohol consumption levels were 20, 40, 50, 60, 80, and 100 g per day in 10,

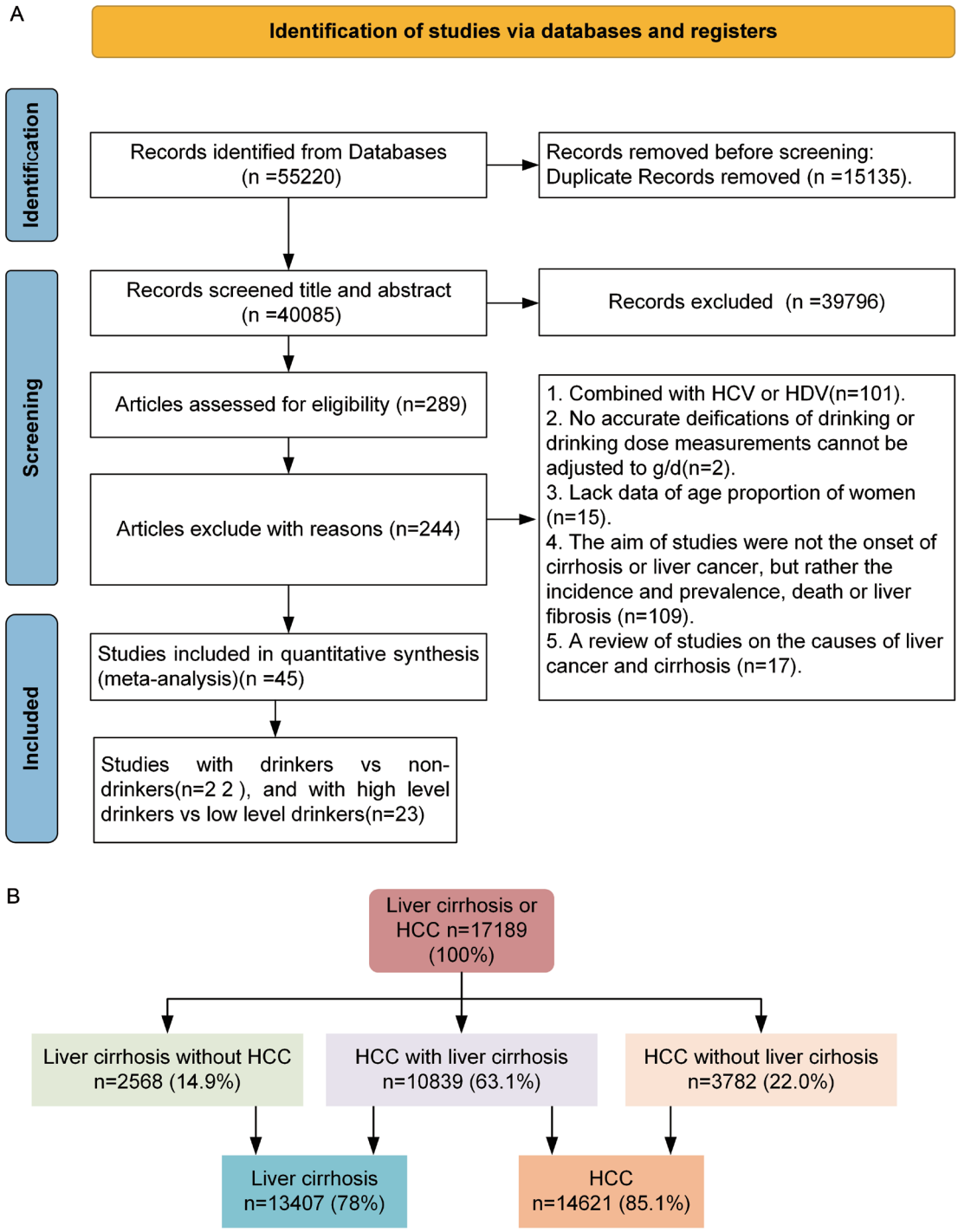

Fig. 1. (A) Study overview: Flow diagram of study selection. (B) Number of patients with chronic hepatitis B. Brick-red, light green, light purple, light brown, light blue, and orange colors represent the populations with adverse outcomes, liver cirrhosis without HCC, HCC with liver cirrhosis, HCC without liver cirrhosis, liver cirrhosis, and HCC, respectively. HCC, hepatocellular carcinoma.

six, five, four, four, and three studies, respectively. The assessment of alcohol consumption varied among the included studies, with most classifying high-level drinkers as those consuming ≥ 40 g of alcohol per day and low-level drinkers as those consuming no alcohol or <40 g per day. A total of 17,189 patients had cirrhosis or HCC, 13,407 had cirrhosis only, 14,621 had HCC only, and 10,839 had both cirrhosis and HCC (Fig. 1B).

Alcohol consumption increases the risk of cirrhosis in a dose-dependent manner

Patients with cirrhosis were included in the analysis of the

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

NO.	Authors (Year)	Country	Study design	T	Mean age	Measure of liver progression	
1[a]	Ikeda *et al.* (1998)[15]	Japan	Cohort study	610	34	Cirrhosis	208 (32.20%)
1[b]	Ikeda *et al.* (1998)[15]	Japan	Cohort study	610	34	Hepatocellular carcinoma	121 (18.80%)
2	Lin *et al.* (2013)[17]	China	Cohort study	764	47	Hepatocellular carcinoma	138 (18%)
3	Hou *et al.* (2016)[26]	China	Case-control	298	43	Hepatocellular carcinoma	141 (47%)
4	Chen *et al.* (2013)[27]	China	Case-control	242	51	Hepatocellular carcinoma	121 (50%)
5	Sun *et al.* (2017)[28]	China	Case-control	283	47	Cirrhosis	89 (31%)
6	Wu *et al.* (2016)[29]	China	Case-control	700	45	Hepatocellular carcinoma	350 (50%)
7	Zhan *et al.* (2016)[30]	China	Case-control	266	52	Hepatocellular carcinoma	133 (50%)
8	Zhang *et al.* (2019)[31]	China	Case-control	238	50	Hepatocellular carcinoma	120 (50%)
9	Yu *et al.* (2015)[32]	China	Case-control	215	42	Cirrhosis	84 (39%)
10[a]	Ohnishi *et al.* (1982)[33]	Japan	Case-control	57	44	Cirrhosis	35 (61%)
10[b]	Ohnishi *et al.* (1982)[33]	Japan	Case-control	57	44	Hepatocellular carcinoma	52 (60%)
11[a]	Xiaerfuhazi *et al.* (2014)[34]	China	Case-control	2,054	50	Cirrhosis	1,334 (65%)
11[b]	Xiaerfuhazi *et al.* (2014)[34]	China	Case-control	2,054	50	Hepatocellular carcinoma	578 (28%)
12	Song *et al.* (2017)[35]	China	Case-control	151	55	Hepatocellular carcinoma	75 (50%)
13	Sun *et al.* (2002)[36]	China	Case-control	470	51	Hepatocellular carcinoma	89 (19%)
14	Lin *et al.* (2013)[37]	China	Case-control	94	55	Hepatocellular carcinoma	47 (50%)
15	Xin *et al.* (2020)[38]	China	Cohort study	343	55	Hepatocellular carcinoma	83 (24%)
16	Nie *et al.* (2017)[39]	China	Case-control	303	51	Hepatocellular carcinoma	137 (45%)
17	Lin *et al.* (2020)[40]	China	Case-control	308	50	Hepatocellular carcinoma	116 (38%)
18	Chen *et al.* (2018)[41]	China	Case-control	331	45	Hepatocellular carcinoma	46 (14%)
19	Wang *et al.* (2019)[42]	China	Case-control	152	51	Hepatocellular carcinoma	72 (47%)
20	Li *et al.* (2015)[43]	China	Case-control	158	52	Hepatocellular carcinoma	138 (87%)
21	Cao *et al.* (2003)[44]	China	Case-control	193	52	Hepatocellular carcinoma	148 (77%)
22	Li *et al.* (2002)[45]	China	Case-control	1,091	55	Hepatocellular carcinoma	626 (57%)
23	Genya *et al.* (2005)[46]	China	Case-control	205	53	Hepatocellular carcinoma	174 (85%)
24	Liu *et al.* (2011)[47]	China	Case-control	80	49	Hepatocellular carcinoma	42 (53%)
25[a]	Villa *et al.* (1988)[48]	Italy	Cohort study	165	52	Cirrhosis	99 (60%)
25[b]	Villa *et al.* (1988)[48]	Italy	Cohort study	165	52	Hepatocellular carcinoma	42 (25%)
26	Nonomu *et al.* (1986)[49]	Japan	Case-control	77	55	Hepatocellular carcinoma	51 (66%)
27	Sun *et al.* (2021)[50]	China	Case-control	80	60	Hepatocellular carcinoma	38 (48%)
28	Xie *et al.* (2021)[51]	China	Case-control	417	53	Hepatocellular carcinoma	57 (14%)
29[a]	Zhang *et al.* (2015)[52]	China	Case-control	715	52	Cirrhosis	281 (39%)
29[b]	Zhang *et al.* (2015)[52]	China	Case-control	715	52	Hepatocellular carcinoma	434 (61%)
30[a]	Kwon *et al.* (2010)[53]	Korea	Case-control	292	53	Cirrhosis	146 (50%)
30[b]	Kwon *et al.* (2010)[53]	Korea	Case-control	292	53	Hepatocellular carcinoma	146 (50%)
31	Bai *et al.* (2021)[54]	China	Case-control	80	43	Cirrhosis	40 (50%)
32	Wu *et al.* (2015)[55]	China	Case-control	240	49	Hepatocellular carcinoma	120 (50%)
33	Abassa *et al.* (2022)[56]	China	Case-control	19,673	52	Hepatocellular carcinoma	8,454 (43%)
34	Cao *et al.* (2018)[57]	China	Case-control	160	44	Hepatocellular carcinoma	20 (12.50%)
35	Stroffolini *et al.* (2010)[58]	Italy	Case-control	62	50	Cirrhosis	12 (19.30%)
36[a]	Zhong *et al.* (2013)[59]	China	Case-control	106	64	Cirrhosis	73 (68.90%)

(continued)

Table 1. *(continued)*

NO.	Authors (Year)	Country	Study design	T	Mean age	Measure of liver progression	
36[b]	Zhong *et al.* (2013)[59]	China	Case-control	106	64	Hepatocellular carcinoma	47 (44.30%)
37	Donato *et al.* (2002)[60]	Italy	Case-control	136	60	Hepatocellular carcinoma	92 (67.60%)
38	Donao *et al.* (1997)[61]	Italy	Case-control	59	60	Hepatocellular carcinoma	41 (69%)
39	Tsutsum *et al.* (1996)[62]	Japan	Case-control	215	50	Hepatocellular carcinoma	92 (43%)
40	Yan *et al.* (2015)[63]	China	Case-control	274	51	Hepatocellular carcinoma	NR
41	Wang *et al.* (2015)[64]	China	Case-control	120	45	Hepatocellular carcinoma	60 (50%)
42	Hao *et al.* (2015)[65]	China	Case-control	170	50	Hepatocellular carcinoma	85 (50%)
43	Shi *et al.* (2013)[66]	China	Case-control	160	49	Hepatocellular carcinoma	80 (50%)
44	Sun *et al.* (2015)[67]	China	Case-control	147	52	Hepatocellular carcinoma	110 (75%)
45	Liao *et al.* (2014)[68]	China	Case-control	318	55	Hepatocellular carcinoma	241 (76%)

[a]Hepatitis B progresses to cirrhosis; [b]Hepatitis B progressed to hepatocellular carcinoma.

association between alcohol consumption and the risk of cirrhosis. Compared with non-drinkers, the pooled OR for the risk of cirrhosis in drinkers was 2.61 (95% CI, 1.46–4.66; I^2 = 94%, p < 0.001) (Fig. 2A). Subgroup analyses showed that drinkers had an increased risk of cirrhosis, with ORs of 2.70 (95% CI: 1.43–5.11; I^2 = 93%, p < 0.001) and 2.15 (95% CI: 0.30–15.64; I^2 = 97%, p < 0.001) in studies with low and moderate risk of bias, respectively (Supplementary Fig. 1). Additionally, the ORs were 3.11 (95% CI: 1.61–6.10; I^2 = 94%, p < 0.001) and 1.76 (95% CI: 0.50–6.19; I^2 = 94%, p < 0.001) for patients aged ≥50 years and <50 years, respectively (Supplementary Fig. 2), and 3.00 (95% CI: 1.73–5.20; I^2 = 94%, p < 0.001) and 0.40 (95% CI: 0.14–1.17) for studies published after and before 2000, respectively (Supplementary Fig. 3).

Compared with low-level drinkers, the estimated overall OR for the risk of cirrhosis in high-level drinkers was 2.34 (95% CI: 1.59–3.44; I^2 = 87%, p < 0.001) (Supplementary Fig. 4). Subgroup analyses showed that high-level drinkers had an increased risk of cirrhosis, with ORs of 2.36 (95% CI: 1.34–4.15; I^2 = 90%, p < 0.001) and 2.31 (95% CI: 1.53–3.49; I^2 = 60%, p = 0.02) in studies with low and moderate risk of bias, respectively (Supplementary Fig. 5). Additionally, the ORs were 2.39 (95% CI: 1.53–3.71; I^2 = 88%, p < 0.001) and 2.32 (95% CI: 0.95–5.70; I^2 = 82%, p < 0.001) for patients aged ≥50 years and <50 years, respectively (Supplementary Fig. 6), and 2.29 (95% CI: 1.54–3.38; I^2 = 87%, p < 0.001) and 5.28 (95% CI: 0.23–122.54; I^2 = 87%, p = 0.005) for patients from Asia and Europe, respectively (Supplementary Fig. 7). Furthermore, the ORs were 2.04 (95% CI: 1.12–3.72; I^2 = 83%, p < 0.001) and 6.88 (95% CI: 4.65–10.16; I^2 = 90%, p < 0.001) for patients with an alcohol consumption history of ≥5 years and <5 years, respectively (Supplementary Fig. 8), and 2.75 (95% CI: 1.86–4.07; I^2 = 88%, p < 0.001) and 0.87 (95% CI: 0.40–1.87; I^2 = 59%, p = 0.09) for studies published after and before 2000, respectively (Supplementary Fig. 9).

Alcohol consumption increases the risk of HCC in a dose-dependent manner

Patients with HCC were included in the analysis of the association between alcohol consumption and the risk of HCC. Compared with non-drinkers, the estimated overall OR for the risk of HCC was 2.27 (95% CI: 1.50–3.43; I^2 = 90%, p < 0.001) for drinkers (Fig. 2B). Subgroup analyses showed that drinkers had an increased risk of HCC, with ORs of 2.15 (95% CI: 1.37–3.36; I^2 = 89%, p < 0.001) and 3.44 (95% CI: 1.17–10.09; I^2 = 92%, p < 0.001) in studies with low and moderate risk of bias, respectively (Supplementary Fig. 10). In addition, the ORs were 2.41 (95% CI: 1.63–3.55; I^2 = 87%, p < 0.001) and 1.64 (95% CI: 0.28–9.68; I^2 = 97%, p < 0.001) for patients aged ≥50 years and <50 years, respectively (Supplementary Fig. 11), and 2.26 (95% CI: 1.47–3.48; I^2 = 91%, p < 0.001) and 2.27 (95% CI: 1.50–3.43) for studies published after and before 2000, respectively (Supplementary Fig. 12).

Compared with low-level drinkers, the estimated overall OR for the risk of HCC was 2.42 (95% CI: 1.90–3.09; I^2 = 80%, p < 0.001) for high-level drinkers (Supplementary Fig. 13). Subgroup analyses showed that high-level drinkers had an increased risk of HCC, with ORs of 2.40 (95% CI: 1.78–3.23; I^2 = 82%, p < 0.001) and 2.51 (95% CI: 1.74–2.04; I^2 = 48%, p = 0.08) in studies with low and moderate risk of bias, respectively (Supplementary Fig. 14); 2.33 (95% CI: 1.72–3.15; I^2 = 81%, p < 0.001) and 2.66 (95% CI: 1.77–3.99; I^2 = 67%, p = 0.002) for patients aged ≥50 years and <50 years, respectively (Supplementary Fig. 15); and 2.46 (95% CI: 1.90–3.18; I^2 = 81%, p < 0.001) and 2.01 (95% CI: 1.15–3.50; I^2 = 0.0%, p = 0.950) for patients from Asia and Europe, respectively (Supplementary Fig. 16). The ORs were 2.45 (95% CI: 1.89–3.18; I^2 = 81%, p < 0.001) and 2.13 (95% CI: 1.45–3.13; I^2 = 0.0%, p = 0.92) for case–control and cohort studies, respectively (Supplementary Fig. 17); 2.59 (95% CI: 2.01–3.34; I^2 = 82%, p < 0.001) and 1.44 (95% CI: 0.40–1.87; I^2 = 45%, p = 0.14) for studies published after and before 2000, respectively (Supplementary Fig. 18); and 1.75 (95% CI: 0.94–3.28) and 3.74 (95% CI: 1.89–7.42; I^2 = 83%, p < 0.001) for patients with an alcohol consumption history of ≥5 years and <5 years, respectively (Supplementary Fig. 19).

Dose-dependent model of the effects of alcohol consumption on the risks of cirrhosis and HCC

The dose-dependent model of the effect of pure alcohol consumption (grams per day) on the incidence of cirrhosis was calculated using the formula log (OR) = 0.004954 × (alcohol intake per day) with p = 0.0318, as determined by the least squares method. According to the formula,

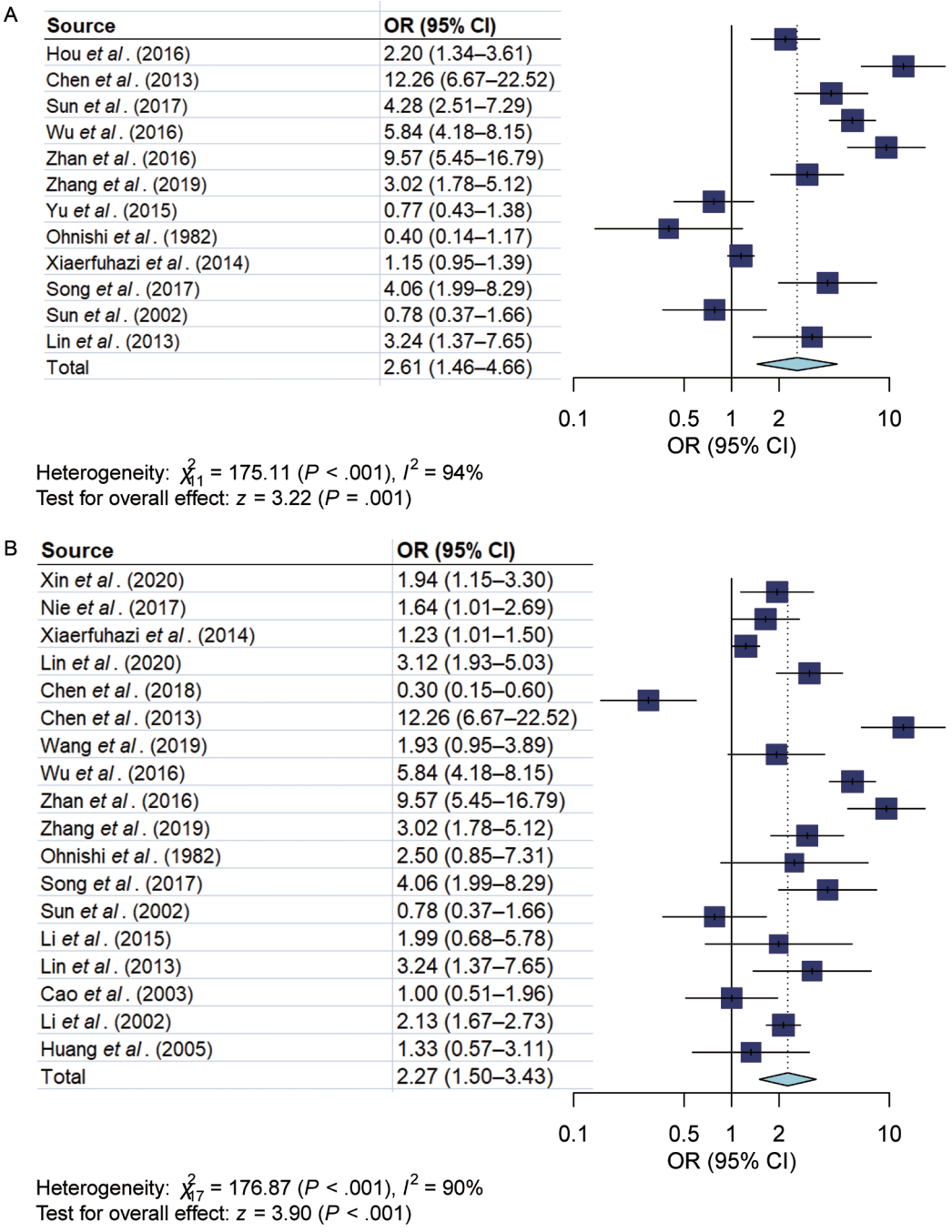

Fig. 2. Forest plot showing study-specific and pooled ORs of (A) cirrhosis and (B) HCC for drinkers versus non-drinkers. Studies are named by author and year of publication.[26–46] Horizontal lines represent 95% CI. The black dots in the middle of line segments represent ORs. Quadrilaterals around the black dots represent weight sizes. The solid line with OR = 1 represents the invalid line. The left and right ends of the lower diamond represent the 95% CI of the pooled results. The dashed line through the diamond represents the pooled OR, and its intersection with the abscissa represents the total OR value. OR, odds ratio; CI, confidence interval; HCC, hepatocellular carcinoma.

each daily consumption of 12 g of alcohol would increase the risk of cirrhosis attributable to HBV infection by 6.2% (Fig. 3A). Meanwhile, the dose-dependent model of the effect of pure alcohol consumption on the incidence of HCC was calculated using the formula log (OR) = 0.009135 × (alcohol intake per day) with p = 0.0005. According to this formula, each daily consumption of 12 g of alcohol would increase the risk of HCC attributable to HBV infection by 11.5% (Fig. 3B).

Publication bias and sensitivity analysis

Funnel plots and Egger's test showed evidence of some publication biases (Supplementary Figs. 20–23 and Supplementary Table 5), and the sensitivity analysis indicated that the

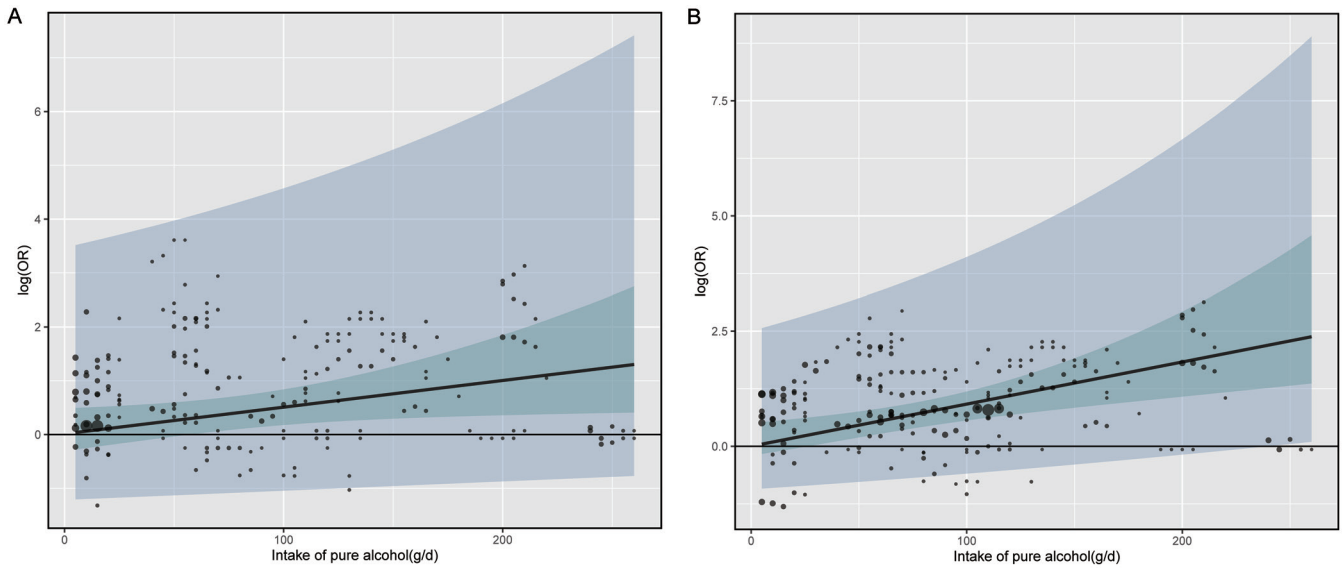

Fig. 3. (A) Dose-dependent model of the effect of alcohol consumption on the risk of cirrhosis. The relationship between the risk of cirrhosis in patients with chronic HBV infection and alcohol intake (grams per day) in log (ORs). (B) Dose-dependent model of the effect of alcohol consumption on the risk of HCC. The relationship between the risk of HCC in patients with chronic HBV infection and alcohol intake (grams per day) in log (ORs). OR, odds ratio; CI, confidence interval; HBV, hepatitis B virus.

results were reliable (Supplementary Figs. 24, 25). We performed sensitivity analyses excluding studies with fewer than 200 patients, considering the total number of patients in the included studies, and those published before 2000, considering the years when nucleoside or nucleotide drugs were developed, and observed that the results had robust reliability (Supplementary Figs. 26–29). In addition, we performed a trim-and-fill analysis to further test the stability and reliability of the results and found that the existence of publication bias did not affect the overall results (Supplementary Fig. 30).

Meta-regression analysis

The age, race, alcohol consumption duration of patients, study design, publication year of the study, and risk of bias were not significantly associated with the heterogeneity of the results in our study, except for publication year, which was a significant contributor to heterogeneity in the results related to patients with liver cirrhosis ($p < 0.05$) when compared with high-level alcohol consumption, as determined by meta-regression analysis (Supplementary Tables 6–9).

Discussion

Alcohol consumption promotes the progression of chronic liver diseases, but the exact quantitative dose-dependent effects of alcohol on the development of cirrhosis and HCC have not been well demonstrated. Our meta-analysis is the first report to show that alcohol consumption increases the risk of cirrhosis and HCC in patients with HBV infection in a dose-dependent manner. Importantly, we established a dose-dependent model of the effects of alcohol consumption on the risks of cirrhosis and HCC, which revealed that each daily consumption of 12 g of alcohol increases the risk of cirrhosis by 6.2% and the risk of HCC by 11.5%.

Alcohol consumption is a leading risk factor for various diseases with serious consequences, accounting for nearly 10% of deaths in populations aged 15–49 years worldwide.[69] Over the past decades, the percentage of drinkers has increased from 45% in 1990 to 47% in 2017 globally.[70] A modeling study from the United States predicted that the age-standardized death rate related to alcohol-associated liver disease would increase from 8.2 deaths per 100,000 patient-years in 2019 to 15.2 per 100,000 patient-years by 2040 if the current trends in alcohol consumption continued.[71] After the COVID-19 pandemic in 2019, the frequency of alcohol consumption further increased by 14% due to various factors such as psychological, economic, and social environments.[72] A recent study suggested that the increase in alcohol consumption during the COVID-19 pandemic could increase the long-term morbidity and mortality of alcohol-associated liver diseases.[73] In the present meta-analysis, we demonstrated that alcohol consumption was closely associated with the occurrence of cirrhosis or HCC in patients with chronic HBV infection. The increased risk attributable to alcohol consumption was independent of age and the quality rating of the included studies for cirrhosis and independent of age, country of the patient population, study design, and quality rating of the included studies for HCC. These findings suggest that alcohol consumption promotes the development of cirrhosis and HCC in patients with chronic HBV infection regardless of their age or the quality rating of the included studies. Mechanistically, alcohol-mediated oxidative stress might contribute to the progression of liver cirrhosis and HCC[74] via the nuclear factor kappa B pathway, which plays an important role in liver injury and regeneration.[75] Furthermore, a systematic review and meta-analysis showed that active alcohol abstinence might decrease the risk of HCC in patients with alcohol-related diseases.[76]

Next, we determined the potential effects of alcohol doses on the incidence of cirrhosis and HCC in patients with HBV infection. We first demonstrated that alcohol consumption increased the risks of cirrhosis and HCC in a dose-dependent manner. In particular, the risks of cirrhosis and HCC were higher in high-level drinkers than in low-level drinkers. Importantly, we established a dose-dependent model of the effects of alcohol consumption on the incidence of cirrhosis and HCC. The model revealed that each daily consumption of 12 g of alcohol increased the risk of cirrhosis by 6.2% and the

risk of HCC by 11.5%. The results are highly consistent with a systematic review of 19 cohort studies published in 2014, which showed that the consumption of more than three alcoholic drinks would increase the risk of HCC by 16% among alcohol drinkers.[77] Therefore, attention should be paid to the effect of alcohol consumption on the development of cirrhosis and HCC in patients with HBV infection, in addition to genetic vulnerability and metabolic risk factors, all of which are known to contribute to the progression of chronic HBV infection to liver cirrhosis or HCC.[78] Patients who consume more than 12 g of alcohol per day should be strictly monitored in the management of HBV infection.

These results should be carefully considered in light of several limitations. First, most of the 45 studies were case-control studies (n = 41, 91.1%), and some studies were published before 2000 (n = 6, 14.6%). The effects of potential biases, including memory bias, changes in diagnostic guidelines, and the discovery of nucleoside or nucleotide drugs, cannot be ruled out. Second, most of the 45 studies were from Asian countries (n = 41, 91.1%), with only four studies from Europe included in the present study, which may not be representative. Third, significant heterogeneity was present among the included studies in our meta-analysis, and the heterogeneity remained even when various subgroup analyses were conducted. The primary studies incorporated into our analysis lacked individual-level data, which compromised the precision of alcohol consumption quantification. This limitation was particularly evident considering the absence of detailed data on adolescent alcohol consumption—an important factor for liver disease—and information regarding periods of abstinence and the chronicity of alcohol intake. These gaps contributed substantially to the high heterogeneity observed in our study, a challenge that persisted even after conducting meta-regression analyses adjusted for age, race, and the methodological rigor of the literature. Despite these efforts, the sources of heterogeneity remained elusive and could not be effectively pinpointed. Therefore, we performed trim-and-fill analysis and sensitivity analysis, finding that the results of the meta-analysis were reliable. In addition, a dose-response meta-analysis could not be performed because only two groups of alcohol doses were present in 76% of the included studies. To establish an appropriate dose-dependent model, we chose a linear dose-dependent model rather than a quadratic or mixed model based on the Akaike information criterion and Bayesian information criterion statistics. In our analysis, we noted that the included studies did not offer detailed quantification of alcohol consumption, particularly for alcohol consumption in adolescents—an important factor for liver disease. Furthermore, the studies lacked comprehensive data on abstinence periods and the chronicity of alcohol consumption. Given the absence of individual-level data, our meta-analysis had limited ability to draw conclusions at the individual level. Instead, we extrapolated our findings to address population-level implications, focusing on broader public health and epidemiological perspectives rather than individual outcomes.

Conclusions

This is the first meta-analysis to report that alcohol consumption increases the risks of cirrhosis and HCC in a dose-dependent manner in patients with HBV infection. The dose-dependent model showed that each daily consumption of 12 g of alcohol increased the risk of cirrhosis by 6.2% and that of HCC by 11.5%. This suggests that patients who consume more than 12 g of alcohol per day should be strictly monitored in the management of HBV infection.

Funding

This work was supported by grants from the National Natural Science Foundation of China (82270631), the ECCM program of the Clinical Research Center of Shandong University (2021SDUCRCB006), and the Young Taishan Scholars (tsqn202103169).

Conflict of interest

FPJ has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2023, MHZ and YCF have been Associate Editors of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Analysis and interpretation of data, drafting of the manuscript (YPW, YXT), data collection (YPW, XYY, FPJ), critical reading (YHY, FPJ, MHZ), conception and design of the study, revision of the manuscript, and leadership responsibility for the research (YCF). All authors have approved the final version and the publication of the manuscript.

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