Original Article

Viral hepatitis increases the risk of cholangiocarcinoma: a systematic review and meta-analysis

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Background: Whether viral hepatitis increases the risk of cholangiocarcinoma (CCA) has been controversial. The reasons for the differences between previous research results may be related to the differences in sample size, region, living environment and course of disease. A meta-analysis is needed to clarify the correlation between them and select the key population for early screening of CCA. Meta-analysis was used to explore the relationship between viral hepatitis and the risk of CCA, so as to provide evidence for the prevention and treatment of CCA.

Methods: We systematically searched EmBase, SinoMed, PubMed, Web of Science China National Knowledge Infrastructure, and Wanfang databases. The quality of the included literature was evaluated using the Newcastle Ottawa Scale. Before merging the effect quantities, the data was first subjected to heterogeneity testing. Heterogeneity testing was evaluated using I^2 (the proportion of heterogeneity variation to overall variation). Subgroup analysis was used to identify sources of heterogeneity in this study. The effect odds ratio (OR) of various studies was extracted or calculated for consolidation. Beta's rank correlation, Egger's Law of Return and funnel plot were used to test publication bias. Conduct subgroup analysis based on the regions included in the literature.

Results: A total of 2,113 articles were retrieved, and a total of 38 articles were included in the meta-analysis. There are 29 case-control studies and 9 Cohort study, including 333,836 cases and 4,042,509 controls. The combined risk estimate of all studies showed a statistically significant increased risk of CCA, extrahepatitis and intrahepatitis incidence with hepatitis B virus (HBV) infection (OR =1.75, OR =1.49, and OR =2.46, respectively). The combined risk estimate of all studies showed a statistically significant increased risk of CCA, extrahepatitis and intrahepatitis incidence with hepatitis C virus (HCV) infection (OR =1.45, OR =2.00, and OR =2.81, respectively). The research points of HCV and CCA were asymmetric, indicating that there may be publication bias in the study of HCV and CCA.

Conclusions: HBV and HCV infection could increase the risk of CCA. Therefore, in clinical practice, attention should be paid to CCA screening and early prevention of HBV and HCV infected patients.

Keywords: Hepatitis B virus (HBV); hepatitis C virus (HCV); cholangiocarcinoma (CCA); meta-analysis

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Introduction

Cholangiocarcinoma (CCA) is a malignant tumor that occurs in the epithelial lining of the biliary system. According to its location, it can be divided into intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) (1,2). CCA accounts for approximately 3–5% of all gastrointestinal cancers and is a common primary liver malignancy with an increasing incidence second only to hepatocellular carcinoma (3). In the Occident, the incidence rate of CCA is 0.3–3.5/100,000, while the incidence rate reaches 90/100,000 in Asian countries (4,5). Despite its low incidence, CCA has a high degree of malignancy. Because of a lack of understanding of its risk factors, low early detection rate, and rapid disease progression, the long-term survival rate of CCA patients is low, and the five-year survival rate is only 5% (4,6). Therefore, it is of great public health significance to perform studies on the etiological mechanism of CCA, explore the risk factors for CCA, and prevent CCA according to the risk factors.

Hepatitis virus infection is a risk factor for various malignancies, including liver cancer, non-Hodgkin lymphoma, multiple myeloma, and thyroid cancer (7-11). The association between viral hepatitis and hepatocellular carcinoma has been recognized. However, the association between viral hepatitis and the risk of other hepatobiliary tumors, such as CCA, ECC, and ICC, remains unclear. The guidelines issued by the Liver Surgery Group of the Chinese Medical Association pointed out that viral hepatitis is a risk factor for CCA (12). However, the "Guidelines for Diagnosis and Treatment of Distal Cholangiocarcinoma and Ampullary Carcinoma of the Chinese Anti-Cancer Association Biliary Tumor Professional Committee" (2011 edition) did not mention hepatitis virus in the risk factors (13). Guidelines issued by the National Comprehensive Cancer Network state that hepatitis B virus (HBV) and hepatitis C virus (HCV) are possible risk factors for the development of ICC, without mentioning ECC (14,15). There has been controversy over whether viral hepatitis increases the risk of developing CCA. We believe that the reasons for the differences between previous research results may be related to differences in sample size, regional differences, differences in living environment, and differences in disease course. A meta-analysis is needed to clarify the correlation between the two and select key populations for early screening of CCA. In this study, meta-analysis was used to explore the relationship between hepatitis viral infections and the risk of CCA and to provide a basis for the prevention and treatment of CCA. We present this article in accordance with the MOOSE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-892/rc).

Highlight box

Key findings

- This study uses meta-analysis to explore the relationship between viral hepatitis and the risk of cholangiocarcinoma (CCA), providing a basis for the prevention and treatment of CCA.

What is known and what is new?

- The association between viral hepatitis and other hepatobiliary system tumors, such as CCA, extrahepatic cholangiocarcinoma (ECC), and intrahepatic cholangiocarcinoma (ICC), remains unclear.
- This meta-analysis suggests that hepatitis B virus (HBV) and hepatitis C virus (HCV) infections may increase the risk of developing CCA.

What is the implication, and what should change now?

- In clinic, we should pay attention to the screening and treatment of HBV and HCV infected patients, and reduce the incidence rate of cholangiocarcinoma to reduce the family, social and economic burden.

Methods

Literature search

We systematically searched the EmBase, SinoMed, PubMed, Web of Science, China National Knowledge Infrastructure (CNKI) and WanFang databases. Using a combination of subject headings and free words, the English and Chinese search terms included "viral hepatitis", "hepatitis A", "hepatitis B", "hepatitis C", "hepatitis D", "hepatitis E", "cholangiocarcinoma", and "biliary tract neoplasm". The literature search time was from the inception of each database to October 27, 2022. The language types were limited to Chinese and English.

Criteria for inclusion and exclusion

All included studies met the following criteria: (I) the research subjects are the whole population, with no age or nationality restrictions; (II) hepatitis virus exposure is used as an exposure indicator; (III) outcome indicators included CCA and intrahepatic CCA. The diagnosis of extrahepatic CCA is clear; (IV) the research types included case-control studies, and cohort studies; (V) the original literature

provides specific case and control data.

The searched literature was excluded if it contained one of the following criteria: (I) a meta-analysis, review, case report, or review; (II) animal and cell studies; (III) unavailable detailed data on case and control groups; (IV) repetitive papers.

Data extraction and quality assessment

The inclusion and exclusion criteria were strictly followed to screen the literature, determine the final included literature, and extract relevant information. Data extraction included the name of the first author, year of publication, country where the study was conducted, type of study design, type of viral hepatitis, type of CCA, and sample size. At the same time, the Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included literature (16). Specifically, the evaluation includes four aspects: selection of the research population, comparability, exposure, and outcome. The evaluation of literature quality by NOS adopts the semi quantitative principle of star rating system. Except for comparability, which can be rated up to 2 points, all other items can be rated up to 1 point, with a maximum score of 9 points. The higher the score, the higher the quality of the research. The full score of the scale is 9 points, with 1–3 points, 4 points, and 7–9 points for high-, medium- and low-risk studies, respectively. Two researchers completed the above process independently, and any inconsistencies were resolved through discussions between the two parties or consultation with third-party experts.

Statistical analysis

Meta-analysis was performed using STATA14.0 statistical software (StataCorp, College Station, TX, USA). Data were first tested for heterogeneity before pooling effect sizes. Heterogeneity tests were assessed using I^2 (the proportion of the variation in heterogeneity in the total variation). I^2=0 indicates no heterogeneity between studies; I^2<50% indicates low heterogeneity between studies; I^2≥50% indicates large heterogeneity between studies. According to the heterogeneity test results, if P≤0.1 and I^2>50%, a random-effects model was selected for meta-analysis; otherwise, a fixed-effects model was used for meta-analysis. High heterogeneity may affect the reliability of the results. This study used subgroup analysis to identify sources of heterogeneity. This study included Case-control study and Cohort study. The Cohort study data corresponds to the Effect size risk ratio (RR), and the Case-control study corresponds to the Effect size OR. We refer to the literature for conversion, RR=OR/[1– P0 × (1–OR)], and P0 refers to the incidence of the disease (17). The combined effect size of each study was expressed by the odds ratio (OR value) and its 95% confidence interval (95% CI), and the test level was α=0.05. Publication bias was tested using Begg's rank correlation, Egger's regression, and the funnel plot method. The type of viral hepatitis and its incidence rate are significantly lower than the difference, so the subgroup analyses were performed according to the geographic region of the included studies. Two-tailed P<0.05 indicates statistical significance.

Results

Selection of studies

A total of 2,113 studies were retrieved from the databases. We excluded 596 duplicate studies, 163 meta-analyses and reviews, 24 case studies and discussions, 1,263 papers with no unrelated topics, 14 animal and cell studies, and 15 studies whose full texts could not be obtained or whose information and data were incomplete. A total of 38 articles were analyzed (see *Figure 1*). The included studies were all on the relationship between HBV and HCV and the risk of CCA. However, the relationship between hepatitis A, D, and E virus infection and the risk of CCA has not yet been reported. The characteristics of the included literature are shown in *Table 1*. All 38 studies had an NOS score of ≥7.

Association of HBV with the risk of CCA

Regarding the association between HBV and the risk of developing CCA, 7 studies were included in the analysis (18,43-45,48,50,51). There was significant heterogeneity across studies (I^2=97.9%). The risk of HBV and CCA was statistically significant when combined using the random effects model. Patients with HBV had a significantly increased risk of developing CCA [OR (95% CI) =1.75 (1.17, 2.59), *Figure 2*].

Regarding the association of HBV with the risk of ECC, 14 studies were included in the analysis (23,25,30, 37,39,40,42,43,45,46,49,51,53,55). There was significant heterogeneity in this meta-analysis (I^2=76.1%), and HBV and ECC morbidity risks were statistically significant when combined using a random effects model. Patients

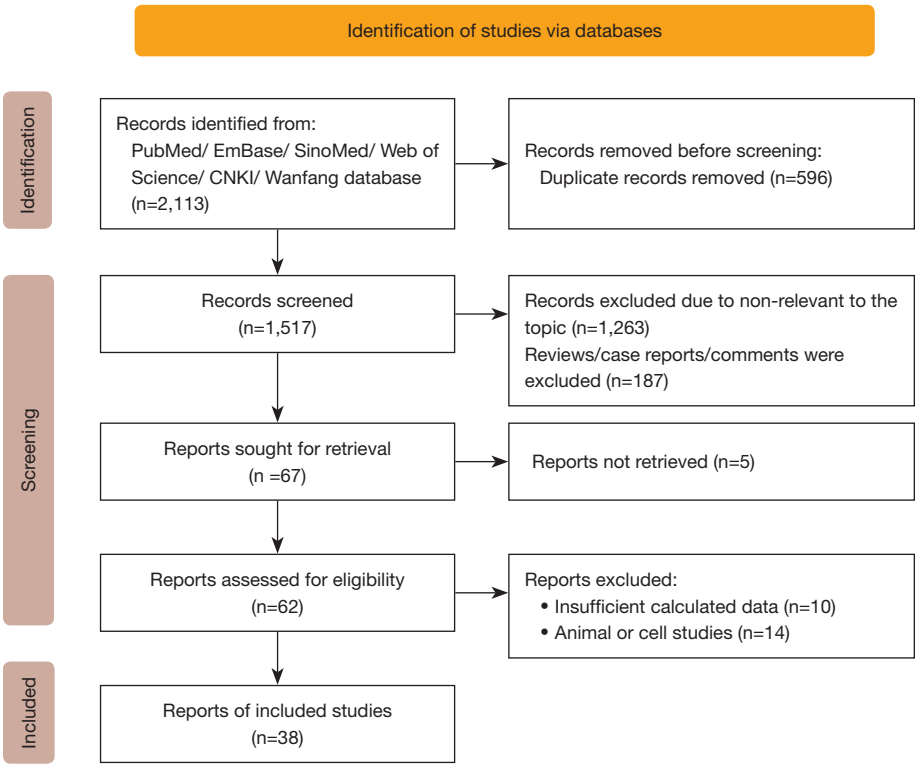


Figure 1 Flowchart of literature screening.

Table 1 Characteristics of the included studies

First author (ref.)	Year	Country	Types of hepatitis	Types of tumors	Cases (n)	Control (n)	Types of studies	NOS scores
Shin (18)	1996	South Korea	HBV/HCV	CCA	41	406	Case-control study	7
Donato (19)	2001	Italy	HBV/HCV	ICC	26	824	Case-control study	9
Yamamoto (20)	2004	Japan	HBV/HCV	ICC	50	205	Case-control study	7
Shaib (21)	2005	USA	HCV	ICC	625	90,834	Retrospective cohort study	8
Choi (22)	2006	South Korea	HBV/HCV	ICC	51	51	Case-control study	7
Shaib (23)	2007	USA	HBV/HCV	ICC	83	236	Case-control study	8
				ECC	163	236		
Welzel (24)	2007	USA	HCV	ICC	743	102,782	Case-control study	8
				ECC	549	102,782		
Hsing (25)	2008	China	HBV/HCV	ECC	134	762	Case-control study	8
Lee (26)	2008	South Korea	HBV/HCV	ICC	622	2,488	Case-control study	7
Zhou (27)	2008	China	HBV/HCV	ECC	129	380	Case-control study	7
El-Serag (28)	2009	USA	HCV	ECC	146,395	572,294	Retrospective cohort study	9
				ICC	146,394	572,293		
Lee (29)	2009	China	HBV/HCV	ICC	160	160	Case-control study	8
Tao (30)	2009	China	HBV/HCV	ICC	61	380	Case-control study	7

Table 1 *(continued)*

Table 1 *(continued)*

First author (ref.)	Year	Country	Types of hepatitis	Types of tumors	Cases (n)	Control (n)	Types of studies	NOS scores
Tanaka (31)	2010	Japan	HBV/HCV	ICC	11	154,814	Retrospective cohort study	8
Zhou (32)	2010	China	HBV	ICC	317	634	Case-control study	8
				ECC	239	478		
Fwu (33)	2011	China (Taiwan)	HBV	ICC	18	1,782,401	Retrospective cohort study	8
Liu (34)	2011	China	HBV/HCV	ICC	87	228	Case-control study	8
Peng (35)	2011	China	HBV	ICC	98	196	Case-control study	7
Welzel (36)	2011	USA	HCV	ICC	743	24,257	Retrospective cohort study	9
Qu (37)	2012	China	HBV	ECC	305	480	Case-control study	7
Chaiteerakij (38)	2013	USA	HBV/HCV	ICC	612	594	Nested case-control study	7
Chang (39)	2013	China (Taiwan)	HBV/HCV	ICC	2,978	11,912	Retrospective cohort study	9
				ECC	2,179	8,716		
Zhou (40)	2013	China	HBV	ECC	239	478	Case-control study	7
Li (41)	2014	China		ICC	183	549	Case-control study	7
Lee (42)	2015	South Korea	HBV/HCV	ECC	81	162	Case-control study	8
			HBV/HCV	ECC	193	386		
			HBV/HCV	CCA	276	552		
Lee (43)	2015	South Korea	HBV/HCV	ICC	83	166	Case-control study	8
Peng (44)	2015	China	HBV/HCV	CCA	3174	3,174	Case-control study	7
Choi (45)	2016	USA	HBV/HCV	CCA	2,395	4,769	Case-control study	8
				ICC	1,169	4,769		
				ECC	995	4,769		
Kamiza (46)	2016	China	HBV/HCV	ECC	501	40,213	Retrospective cohort study	7
Mahale (47)	2017	USA	HCV	ICC	2,936	200,000	Retrospective cohort study	8
				ECC	4,370	200,000		
Meng (48)	2017	China	HBV	CCA	55	926	Case-control study	7
Petrick (49)	2017	USA	HBV/HCV	ICC	2,092	323,615	Case-control study	9
				ECC	2,981	323,615		
Peng (50)	2018	China	HBV/HCV	CCA	2,293	2,293	Nested case-control study	8
Xiong (51)	2018	China	HBV/HCV	CCA	303	606	Case-control study	9
				ICC	136	606		
				ECC	167	606		
Mahale (52)	2019	USA	HCV	ICC	3,401	200,000	Case-control study	7
Zhou (53)	2019	China	HBV	ECC	200	200	Case-control study	8
Lavu (54)	2020	USA	HCV	ECC	412	788	Case-control study	8
Cho (55)	2022	South Korea	HBV/HCV	ICC	821	505,909	Cohort study	9
				ECC	567	505,909		

HBV, hepatitis B virus; HCV, hepatitis C virus; CCA, cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; NOS, Newcastle-Ottawa Scale.

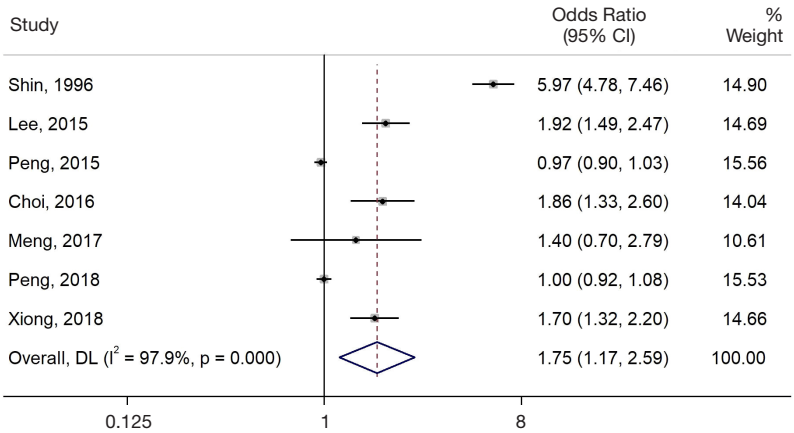


Figure 2 Meta-analysis forest plot of hepatitis B virus and the risk of cholangiocarcinoma. CI, confidence interval.

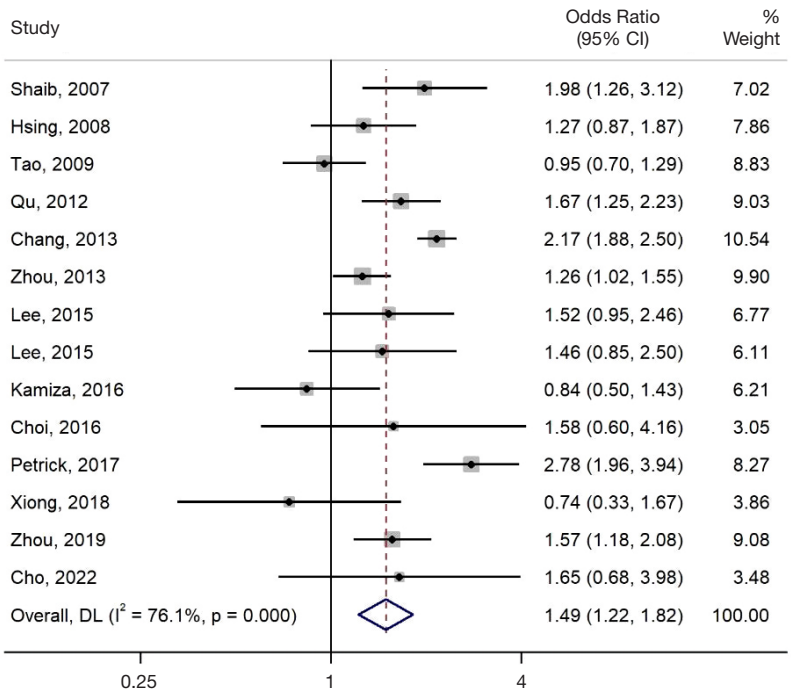


Figure 3 Meta-analysis forest plot of hepatitis B virus and the risk of extrahepatic cholangiocarcinoma. CI, confidence interval.

with HBV had a significantly higher risk of developing ECC [OR (95% CI) =1.49 (1.22, 1.82), *Figure 3*]. For the association between HBC and the risk of ICC, 23 studies were included in the analysis (19,20,22,23,26,27,29-36,38,39,41,43,45,49,51,52,55). This meta-analysis had significant heterogeneity (I^2=79.9%). HBV was positively associated with the risk of developing ICC and was statistically significant when combined using a random effects model [OR (95% CI) =2.46 (2.12, 2.85), *Figure 4*].

Association of HCV with the risk of CCA

A total of 6 studies were included in the analysis on the association between HCV and the risk of developing CCA (8,33-35,40,41). There was significant heterogeneity in this meta-analysis (I^2=93.6%). When combined using the random effects model, the risk of HCV and CCA was statistically significant. Patients with HCV had a significantly increased risk of developing CCA [OR (95%

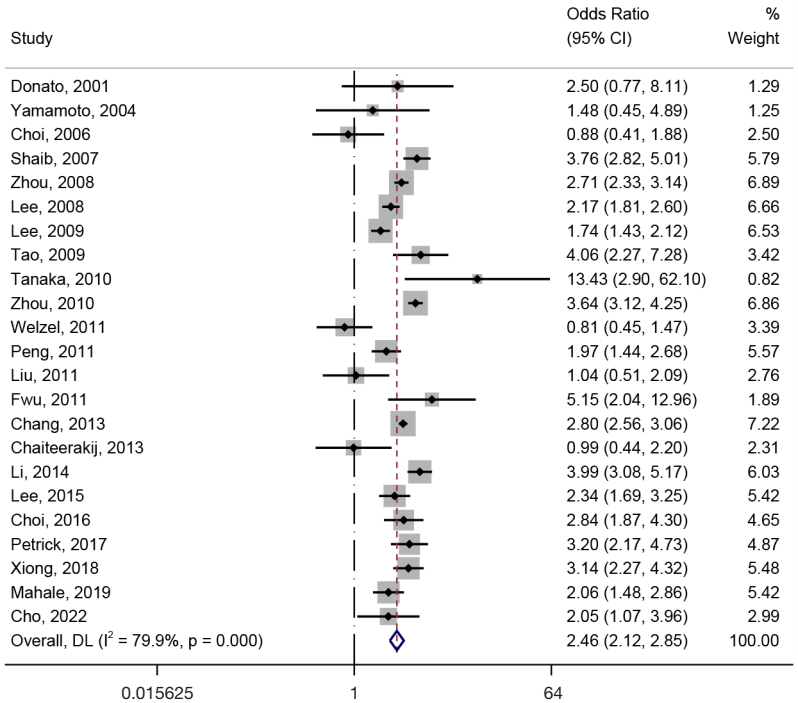


Figure 4 Meta-analysis forest plot of hepatitis B virus and the risk of intrahepatic cholangiocarcinoma. CI, confidence interval.

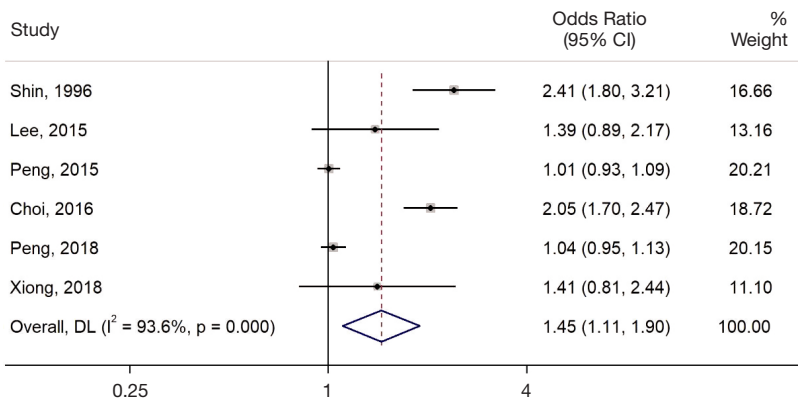


Figure 5 Meta-analysis forest plot of hepatitis C virus and the risk of cholangiocarcinoma. CI, confidence interval.

CI) =1.45 (1.11, 1.90)] (*Figure 5*).

Regarding the association of HCV with the risk of developing ECC, 16 studies were included in the analysis (23-25,28,30,37,39,42,43,45-47,49,51,54,55). This meta-analysis had obvious heterogeneity (I^2=85.4%), and the random effects model was used to combine the risk of HCV and ECC [OR (95% CI) =2.00 (1.50, 2.68)] (*Figure 6*). Regarding the association of HCV with the risk of developing ICC, 21 studies were included in the analysis (19-24,26-31,34,38,39,43,45,47,49,51,55). There was significant heterogeneity in this meta-analysis (I^2=88.2%). When combined using a random-effects model, the risk of HCV and ICC was positively associated [OR (95% CI) =2.81 (2.20, 3.60)] (*Figure 7*).

Subgroup analysis

Subgroup analysis was performed according to the regions (European and American countries, Asian countries) where the trial was conducted in the literature (*Figure 8*).

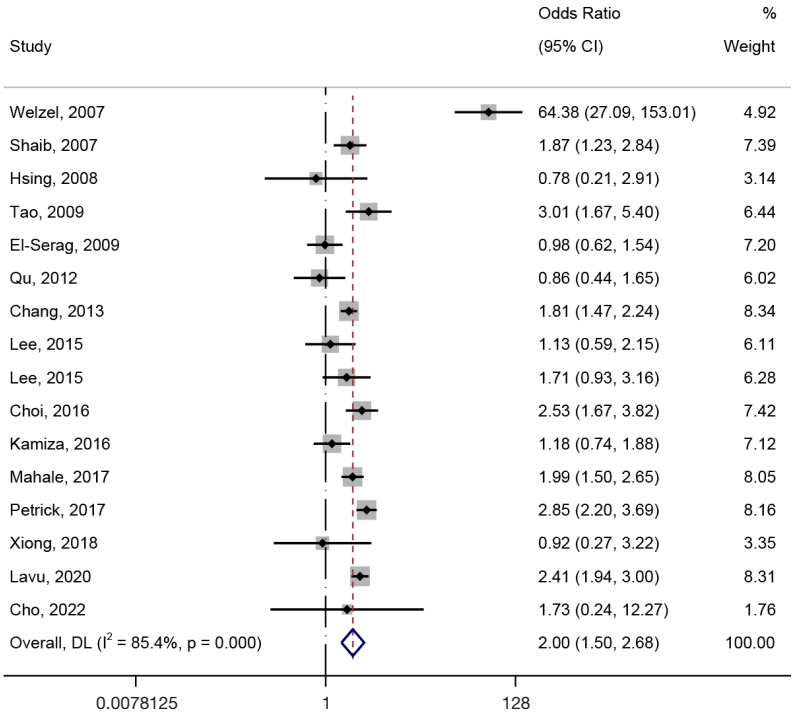


Figure 6 Meta-analysis forest plot of hepatitis C virus and the risk of extrahepatic cholangiocarcinoma. CI, confidence interval.

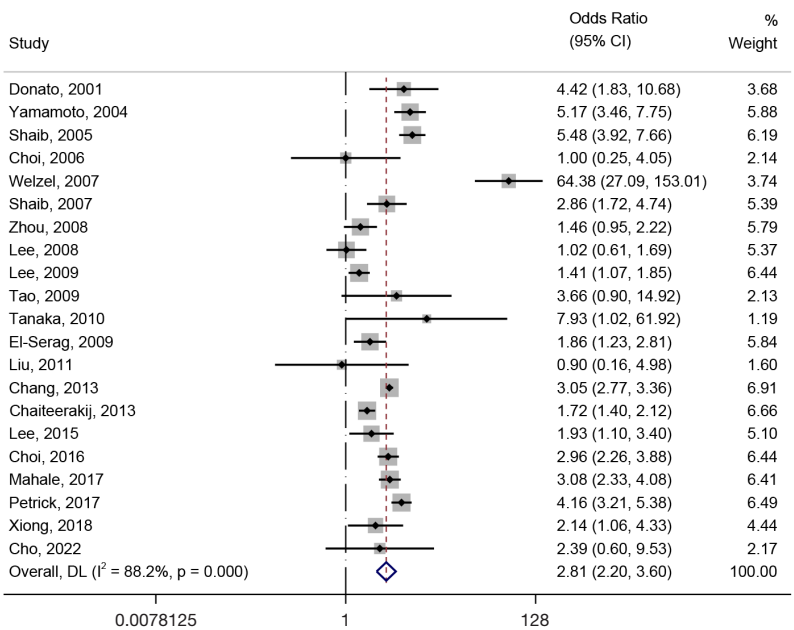
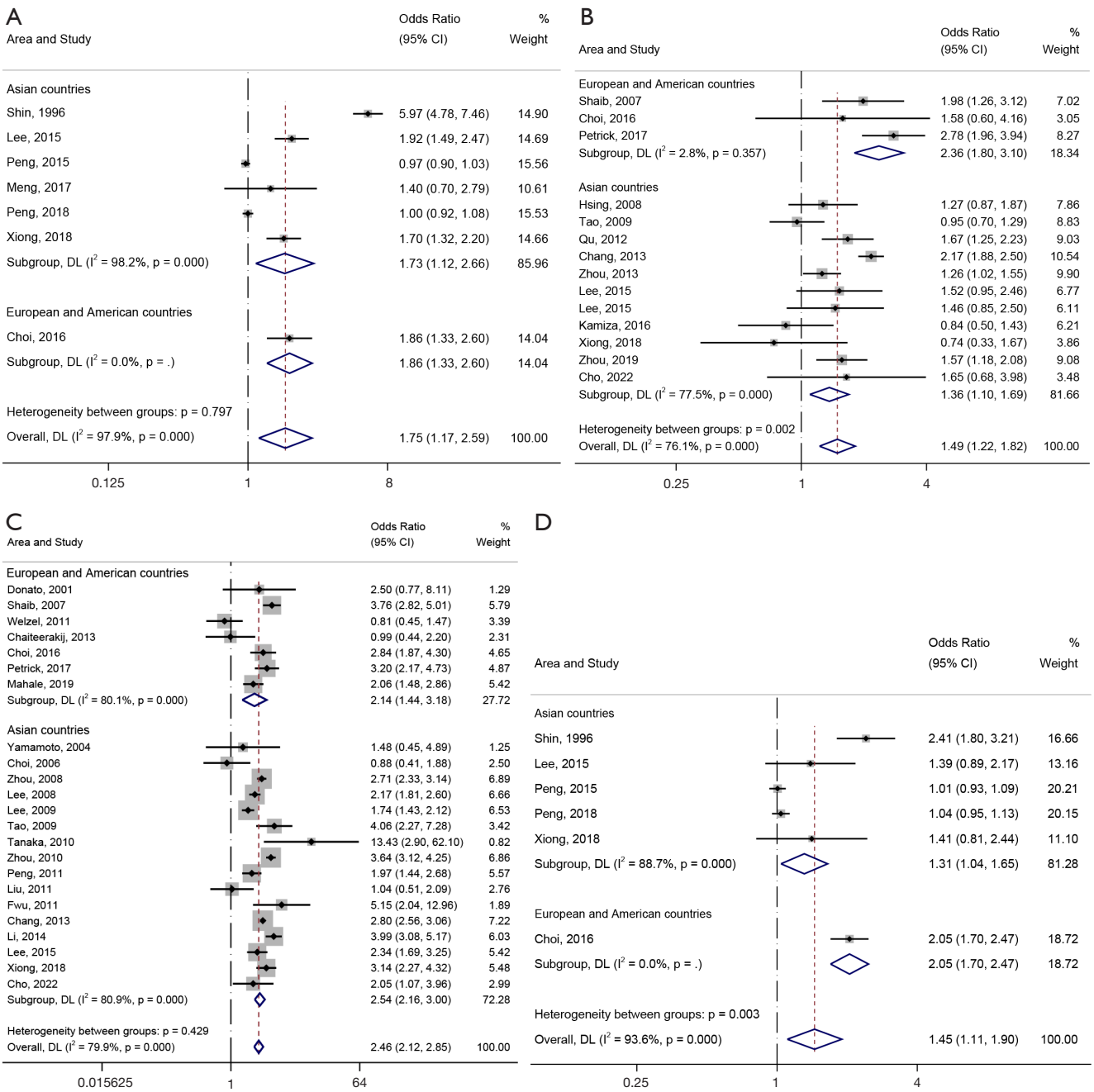


Figure 7 Meta-analysis forest plot of hepatitis C virus and the risk of intrahepatic cholangiocarcinoma. CI, confidence interval.

Compared with European and American countries, the association between HBV and the risk of ICC was more significant in Asian countries [OR (95% CI) =2.54 (2.16, 3.00) *vs.* 2.14 (1.44, 3.18)]. In addition, the association between HBV/HCV and the risk of CCA and ECC was more significant in Europe and the United States [Asian countries *vs.* European and American countries, HBV and CCA: OR (95% CI) =1.73 (1.12, 2.66) *vs.* 1.86 (1.33, 2.60); HBV and ECC: OR (95% CI) =1.36 (1.10, 1.69) *vs.* 2.36 (1.80, 3.10); HCV and CCA: OR (95% CI) =1.31 (1.04, 1.65) *vs.* 2.05 (1.70, 2.47); HCV and ECC: OR (95% CI) =1.47 (1.11, 1.93) *vs.* 2.89 (1.82, 4.60); HCV and ICC: OR



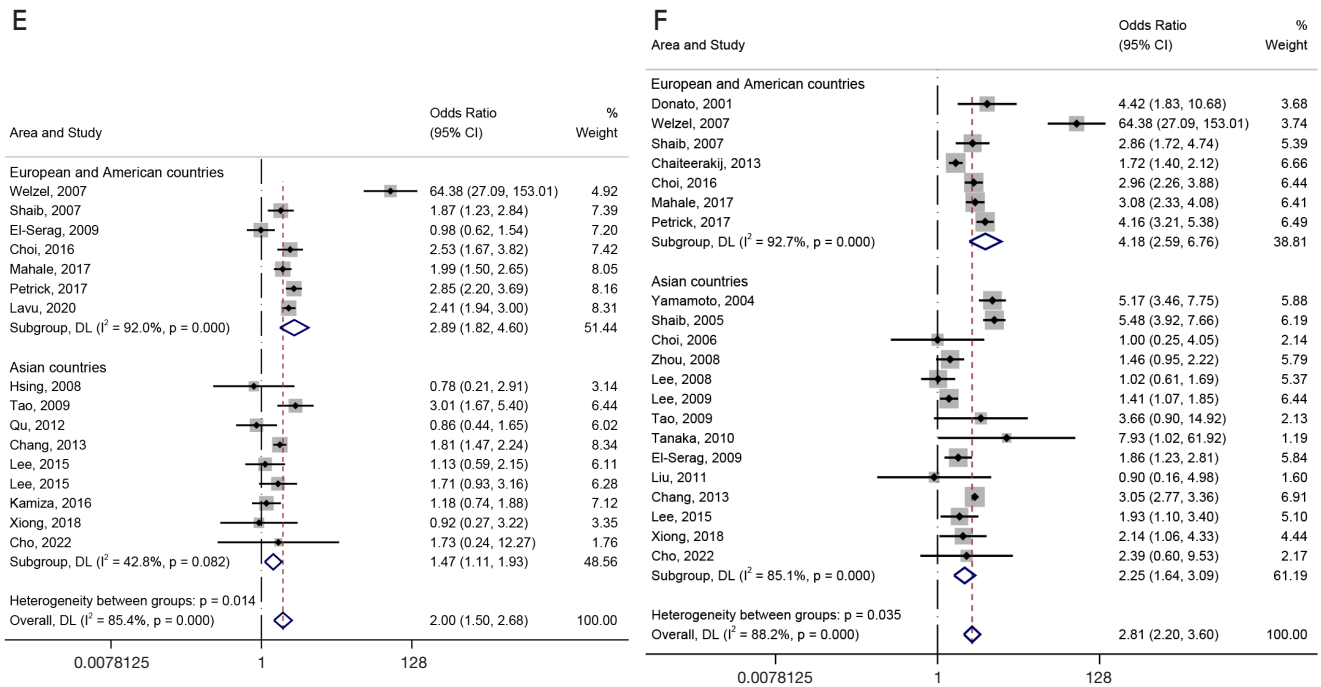


Figure 8 Meta-analysis subgroup analysis of hepatitis B and C virus and the risk of cholangiocarcinoma, extrahepatic cholangiocarcinoma, and intrahepatic cholangiocarcinoma (regions: the Occident and Asian countries). (A) HBV and cholangiocarcinoma; (B) HBV and extrahepatic cholangiocarcinoma; (C) HBV and intrahepatic cholangiocarcinoma; (D) HBV and bile duct cancer; (E) hepatitis C virus and extrahepatic cholangiocarcinoma; (F) hepatitis C virus and intrahepatic cholangiocarcinoma. HBV, hepatitis B virus. CI, confidence interval.

(95% CI) =2.25 (1.64, 3.09) *vs.* 4.18 (2.59, 6.76)].

Publication bias

A funnel plot was used to test the publication bias for the association of HBV and HCV with CCA, ECC, and ICC. The research sites of HCV and CCA were asymmetrical, suggesting possible publication bias in studies on HCV and CCA (*Figure 9*). The remaining images were symmetrical from left to right, suggesting no publication bias. Thus, the results of this meta-analysis are relatively reliable.

Discussion

We performed a meta-analysis of studies on the risk of viral hepatitis and cholangiocarcinoma. A total of 38 studies were included, involving 29 case-control studies and 9 cohort studies, with a total of 333,836 cases and 4,042,509 control patients. In our study, a Case-control study was included. This is because there are fewer Cohort study that meet the screening conditions and cannot provide sufficient sample size to support conclusions. We converted the RR value of the case control to the OR value, and combined with the Cohort study for analysis. To our best knowledge, this study is the largest and most comprehensive meta-analysis to date exploring the association between viral hepatitis and cholangiocarcinoma. The results showed that both HBV and HCV infection were risk factors for cholangiocarcinoma, emphasizing the necessity of screening for cholangiocarcinoma in patients with HBV or HCV infection.

A previous study suggested that hepatitis virus is a hepatocellular virus, and the damage caused by virus replication is limited to the liver (56). However, recent studies have found that hepatitis virus infection can cause damage to extrahepatic tissues, such as the bile duct, gallbladder, kidney, spleen and other organs, through the body's immune response (57-59). Cholangiocarcinoma is an inflammation-related tumor, and related proinflammatory factors can combine with transcriptional activators to activate signal transduction mechanisms, promoting the occurrence and development of tumors (60). In the present study, compared with non-HBV-infected patients, HBV-infected patients had a 75% increased risk of developing

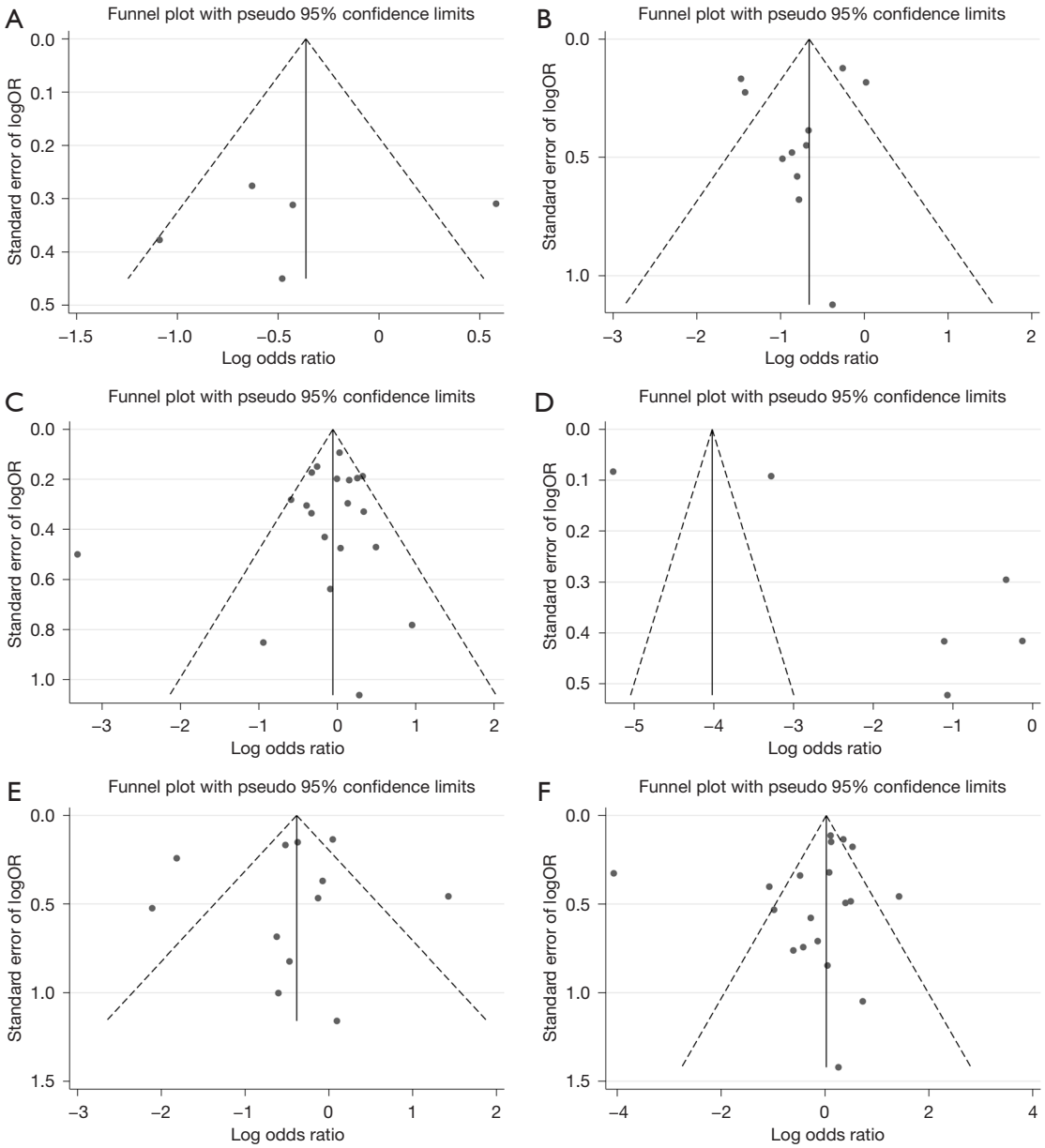


Figure 9 Funnel plot for the risk assessment of study bias. (A) HBV and cholangiocarcinoma; (B) HBV and extrahepatic cholangiocarcinoma; (C) HBV and intrahepatic cholangiocarcinoma; (D) HBV and bile duct cancer; (E) HCV and extrahepatic cholangiocarcinoma; (F) HCV and intrahepatic cholangiocarcinoma. HBV, hepatitis B virus; HCV, hepatitis C virus. OR, odds ratio.

CCA and a 49% and 1.46-fold increased risk of developing ECC and ICC, respectively. Compared with non-HCV-infected patients, HCV-infected patients had a 45% increased risk of developing CCA. The risk of ECC and ICC increased by 1.00 and 1.81 times, respectively. HBV and HCV DNA are found in the nucleus of cholangiocarcinoma cells, suggesting that HBV/HCV may cause cholangiocarcinoma by integrating DNA into host cells (61,62). However, the HCV C protein encoded by the HCV core gene plays a key role in CCA invasion and metastasis by inducing epithelial-mesenchymal transition in CCA cell lines (63,64). Because both hepatocytes and epithelial cells in the bile duct are differentiated from hepatic progenitor cells and the intrahepatic bile duct is adjacent to the liver parenchyma, hepatitis virus infection in the vicinity is more likely to cause ICC.

Because of the significant regional differences in the incidence of cholangiocarcinoma, we divided the included research literature into European and American countries and Asian countries according to the regions where the trials were conducted. Further studies revealed the association of HBV with the risk of ICC was more pronounced in Asian countries. The associations between HBV and CCA/ECC and HCV and CCA risk were more significant in European and American countries. This finding may be related to the more common prevalence of hepatitis C virus in Europe and the United States and the different susceptibilities of people in different regions (65). However, only one study has been published on the association between HBV/HCV infection and the risk of CCA in European and American countries, so more high-quality related studies are still needed to verify the conclusions of this study.

This meta-analysis considered the relationship between viral hepatitis and the risk of cholangiocarcinoma in different anatomical sites and divided cholangiocarcinoma into CCA, ICC, and ECC. Considering the differences in the incidence of cholangiocarcinoma in different regions, subgroup analyses were performed for regions to make the results more detailed and reliable. However, the following disadvantages persist. First, selection and recall bias may have been introduced because the included studies were observational studies. Second, outcomes are often defined differently in different studies (e.g., histological diagnosis, ICD-9, or ICD-10), which may affect pooled estimates. Third, although we performed subgroup analyses, significant heterogeneity was observed in the meta-analysis, possibly reducing the reliability of the results. Finally, we observed potential publication bias by drawing a funnel plot.

Conclusions

HBV and HCV infection may increase the risk of cholangiocarcinoma. Clinical attention should be given to screening and treating patients with HBV and HCV infection to reduce the incidence of cholangiocarcinoma and burden on families and society.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-892/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-892/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-892/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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