Hepatitis D virus dual infection increased the risk of hepatocellular carcinoma compared with hepatitis B virus mono infection: A meta-analysis

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Abstract

Background: Hepatitis delta virus (HDV) is a defective virus that relies on the supply of hepatitis B surface antigen (HBsAg) from hepatitis B virus (HBV) to assemble HDV virions and infect hepatocytes. However, controversy remains in whether the presence of HDV increases the risk of hepatocellular carcinoma (HCC). Our aim is to evaluate the influence of HDV on the risk of HCC through a systematic review and meta-analysis.

Methods: A review of all English-language literature was conducted in the major medical databases using the subject search terms "hepatocellular carcinoma," "liver cancer," "hepatic tumor," and "hepatitis delta." A meta-analysis of the qualifying publications was then performed.

Results: The meta-analysis included 21 studies, which revealed a significantly higher risk of HCC among patients with HDV/HBV dual infection (odds ratio [OR] = 2.08, 95% confidence interval [CI], 1.37-3.14, $p < 0.01$) compared with those with HBV monoinfection. Those with HDV/HBV dual infection remained at higher risk of HCC in the subgroup analysis, irrespective of the status of hepatitis C virus (HCV) or human immunodeficiency virus (HIV) coinfection and in different ethnicities. The HCC risk remained higher in patients with HDV/HBV dual infection with heterogeneous fibrosis stage (OR = 2.04, 95% CI, 1.31-3.17, $p < 0.01$). The difference in the risk of HCC between HDV/HBV dual infection and HBV monoinfection was not statistically significant in patients with cirrhosis or advanced fibrosis (OR = 1.84, 95% CI, 0.48-7.02, $p = 0.37$). However, this subgroup comprised only two studies.

Conclusion: HDV and HBV dual infection significantly increase the risk of HCC development compared with HBV monoinfection.

Keywords: Dual infection; Hepatitis B; Hepatitis delta; Hepatocellular carcinoma; Superinfection

1. INTRODUCTION

Hepatitis delta virus (HDV) is a defective virus that relies on the supply of hepatitis B surface antigen (HBsAg) from hepatitis B virus (HBV) to assemble HDV virions and infect hepatocytes.[1,2] HDV infection can present as coinfection or superinfection. Coinfection is defined as a concurrent infection of HBV and HDV, whereas superinfection is when HDV infection is superimposed on chronic HBV infection.[2]

Chronic HDV infection is associated with more severe liver injury and a higher risk of fulminant hepatitis and fibrosis progression compared with those with HBV monoinfection.[3–6] HDV infection may lead to a high risk of hepatocellular carcinoma (HCC) development and high mortality rate in patients with compensated cirrhosis.[7] In a 28-year study, persistent replication of HDV resulted in cirrhosis, liver decompensation, HCC, and liver-related mortality.[8] In an Italian study, patients with HDV-related HCC were significantly younger than patients without HDV infection, which indicated that HDV infection may be associated with more rapid progression of disease.[9]

HDV infected noncirrhotic patients who had higher levels of HDV RNA were more likely to develop cirrhosis and HCC.[10,11] Coexisting HDV and HBV were reported to increase HCC risk compared with HBV monoinfection in some studies.[12–18] In contrast, several articles suggest that the risk of HCC is similar in patients with HDV dual infection and HBV monoinfection.[19–25]

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However, HDV is still regarded as a group 3 agent that are unclassifiable with respect to their carcinogenicity for humans in the International Agency for Research on Cancer (IARC).[26]

It has been debated whether dual infection of HDV is more likely to cause HCC than HBV monoinfection. Therefore, we performed a systematic review and meta-analysis to estimate the risk of HBV and HDV dual infections regarding the development of HCC.

2. METHODS

2.1. Search methodology and study selection

A literature research was conducted according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analyzes (PRISMA) statement. We searched PubMed, Embase, and the Cochrane Database of Systematic Reviews for articles that were published up to December 2019 using the medical subject heading terms "hepatocellular carcinoma," "hepatitis delta," "hepatitis D," "liver cancer," and "hepatic tumor." The search was limited to English-language literature.

Articles were screened for full text review base on the titles and abstracts. Furthermore, we manually searched the reference lists of the retrieved articles to increase the numbers of possibly relevant articles. Two authors independently looked for all the retrieved papers and assessed their eligibility for inclusion in the present study. Discordant opinions were resolved by consensus with the other coauthors.

2.2. Inclusion and exclusion criteria

We included case control studies, cohort studies, and cross-sectional studies in the meta-analysis. The inclusion criteria were: (1) articles published in full length, (2) inclusion of both HDV/HBV dual infection and HBV monoinfection, and (3) availability of information about HDV and HBV seroprevalence and the incidence of hepatocellular carcinoma (HCC). HDV infection was defined as a positive result for hepatitis delta virus antibody (anti-HDV Ab), and HBV infection was defined as a positive result for hepatitis B surface antigen (HBsAg).

The exclusion criteria were as follows: (1) review articles, (2) lack of a non-HCC control group or HBV monoinfection group for comparison, and (3) incomplete data on the number of cases, controls, and percentage of positive anti-HDV.

The risk of bias was assessed by two authors independently (T.E. Chang and C.W. Su) using the Newcastle-Ottawa Scale (NOS), which evaluates the quality of nonrandomized studies through the selection of the study individuals, comparability of the study groups, ascertainment of the outcome, and the adequacy of follow up.

2.3. Statistical analysis

All statistical analyses were performed using Review Manager version 5.3.5 (RevMan for Windows, 2014; The Cochrane Collaboration, Oxford, United Kigdom). The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to determine the association between the incidence of HCC and HDV/HBV dual infection using a random effect model. Heterogeneity between studies was recognized with a cutoff value of ≥50% using I^2 statistics or $p < 0.10$ with the χ^2 test for Cochran Q statistics. If significant heterogeneity was found, subgroup analyses were performed. Funnel plots were used to assess the publication bias, and subgroup analyses were performed due to high heterogeneity, including coinfection of HCV or HIV, fibrosis status, different ethnic population, study designs, year of study, antiviral treatment, and coinfection or superinfection of HDV.

3. RESULTS

3.1. Search results

A total of 897 citations were identified following the initial main database search. After reviewing abstracts and titles duplicates and unrelated articles were excluded, which left 42 articles. Full-text reviews were performed, and 21 articles were removed according to the exclusion criteria.[7,12–25,27–32] Finally, 21 studies were eligible for the meta-analysis (Fig. 1).

Among the 21 studies, five involved patients with HDV and HBV coinfection, two involved patients with HDV superinfection only, and four involved both coinfection and superinfection patients. Most studies used anti-HDV antibody as the diagnostic method for HDV infection, while two studies used both intrahepatic delta antigen and serum anti-HDV antibody to make the diagnosis (Table 1).

Eight studies involved patients with HIV or HCV coinfection, while four excluded patients with HIV or HCV infection. Two studies included only patients with cirrhosis or advanced fibrosis, and 12 studies involved patients with all stages of fibrosis.

Most of the studies did not indicate whether the included cohorts had received nucleos(t)ide analogue or interferon treatment, the quantitative viral loads, dominant genotypes of HBV and HDV, and the rate of HBsAg clearance (Table 2). The median NOS of enrolled studies was 6 (4–10). Eight of the 21 enrolled studies had a low risk of bias with NOS > 7.

3.2. Comparison of the HCC risk between HBV/HDV dual infection and HBV mono infection

The 21 included studies enrolled 18,497 patients, including 2560 with HDV/HBV dual infections and 15,937 with HBV monoinfection. The risk of HCC was significantly higher in the HDV/HBV dual infection group (OR = 2.08, 95% CI, 1.37-3.14, $p < 0.01$) with high heterogeneity ($I^2 = 69\%$, $p < 0.01$) (Fig. 2A). The funnel plot was symmetrical, which suggests a lower likelihood of publication bias (Fig. 2B).

3.3. Subgroup analysis stratified by the status of virus coinfection, ethnicities, and the stage of liver fibrosis

We grouped the enrolled studies according to whether they looked at concurrent HIV or HCV coinfection, cirrhosis, or advanced fibrosis at baseline, the ethnic populations, and study designs. The HCC risk remained higher in HDV/HBV dual infection group among patients with concurrent HIV or HCV infection (OR = 1.85, 95% CI, 1.13-3.03, $p < 0.01$) and patients without concurrent HIV and HCV infection (OR = 4.19, 95% CI, 2.64-6.63, $p < 0.01$) (Fig. 3A). A significant subgroup difference was noted ($p = 0.02$).

When stratified by the status of liver fibrosis, there was no significant difference in the risk of HCC between HDV/HBV dual infection and HBV monoinfection groups among patients with cirrhosis or advanced fibrosis at baseline (OR =1.84, 95% CI, 0.48-7.02, $p = 0.37$). However, only two studies fit this subgroup. The HCC risk remained significantly higher in patients with HDV/HBV dual infection with respect to heterogeneous fibrosis stage (OR = 1.79, 95% CI, 1.10-2.92, $p = 0.02$) (Fig. 3B). No significant subgroup difference was found ($p = 0.97$).

As for ethnic populations, the risks of HCC were significantly higher in the HDV/HBV dual infection group than in the HBV monoinfection group among Caucasians (OR = 1.97, 95% CI, 1.23-3.16, $p < 0.01$) and Asians (OR = 3.45, 95% CI, 1.41-8.45, $p < 0.01$). But the difference was less significant in Africans (OR = 2.01, 95% CI, 0.73-5.51, $p = 0.18$) (Fig. 3C). To be recorded, Govindarajan et al. listed the risk of HCC in different ethnic populations.[22] Thus, the case numbers presented in this subgroup analysis were numbers for Caucasians only. In cohort studies (OR = 2. 36, 95% CI, 1.56-3.58, $p < 0.01$), the HDV/HBV group had significantly higher risk of HCC compared with the

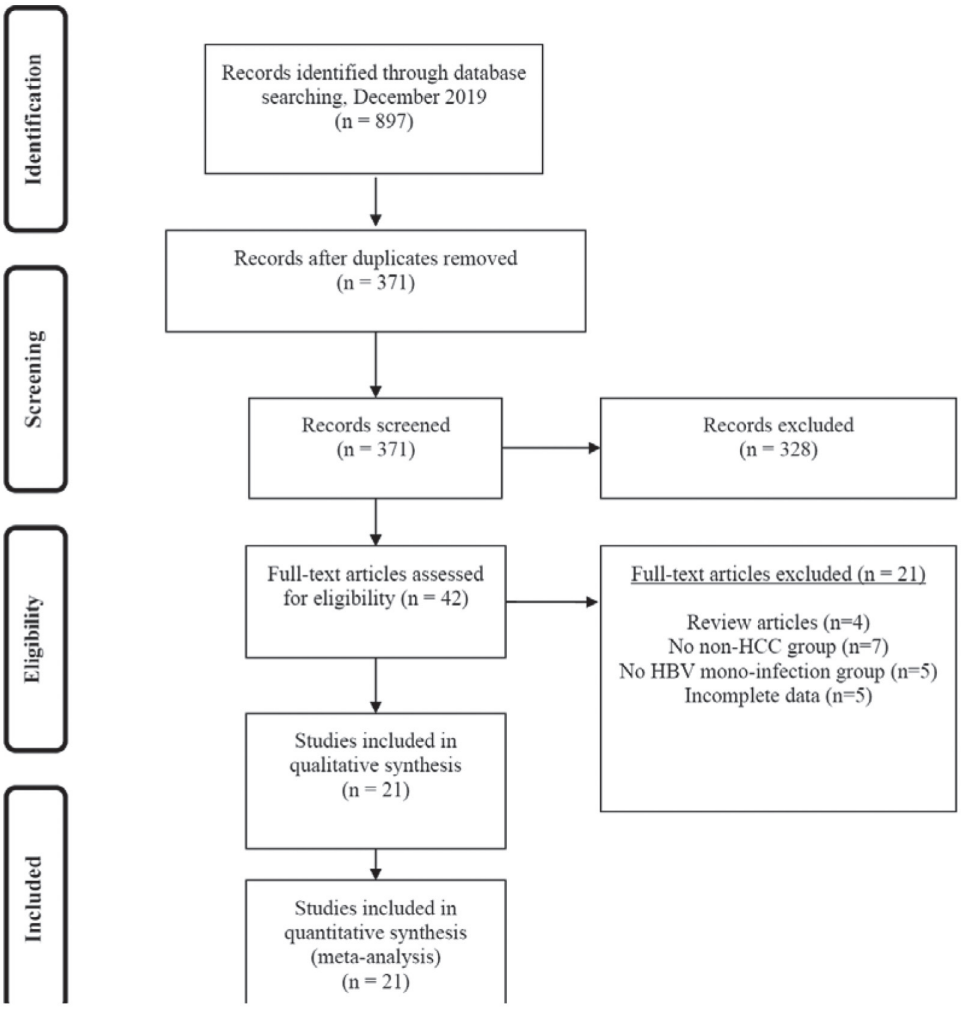


Fig. 1 Flow chart of the selection of eligible studies.

monoinfection group. The risk of HCC did not significantly differ between the two groups in case control studies (OR = 9.03, 95% CI, 0.44-187.0, $p = 0.15$) and cross-sectional studies (OR = 0.76, 95% CI, 0.25-2.34, $p = 0.64$) (Fig. 3D).

Since the periods of the enrolled studies had a wide range, subgroup analysis based on the year of publication was performed. There were trends of an increased risk of HCC development among the dual infection group in the studies before 1990 (OR = 1.40, 95% CI, 0.32-6.18, $p = 0.65$), between 1991 and 2000 (OR = 1.89, 95% CI, 0.79-4.55, $p = 0.15$), and between 2001 and 2010 (OR = 1.57, 95% CI, 0.89-2.79, $p = 0.12$), but without statistical significance. Increased HCC risk was found in the dual infection group among studies published between 2011 and 2019 (OR = 2.54, 95% CI, 1.37-3.14, $p < 0.01$) (Fig. 3E).

Most of the enrolled studies did not mention about antiviral treatment. One study only included patients without antiviral treatment. In the two studies that included only patients who received nucleos(t)ides analogues, a tendency of increased HCC risk was found in the dual infection group compared with the monoinfection group, although the difference was not statistically significant (OR = 2.01, 95% CI, 0.80-5.10, $p = 0.14$). The risk of HCC significantly increased in the dual infection group in the subgroups that enrolled patients who received interferon or nucleos(t)ides analogues (OR = 1.81, 95% CI, 1.18-2.79, $p < 0.01$) (Fig. 3F). However, both subgroups enrolled only small numbers, and the results should be interpreted carefully.

The risk of HCC did not significantly increase in patients with superinfection (OR = 1.61, 95% CI, 0.70-3.67, $p = 0.26$). Instead, the risk of HCC development significantly increased in studies of HDV coinfection (OR = 1.74, 95% CI, 1.23-2.48, $p < 0.01$) and studies including both coinfection and superinfection (OR = 5.11, 95% CI, 2.21-11.79, $p < 0.01$). However, there were still nine studies that did not declare the mode of HDV infection in the article.

4. DISCUSSION

Whether HDV infection increases the risk of HCC development more than HBV monoinfection is still under active debate. This meta-analysis demonstrated that the risk of HCC was higher in the HBV/HDV dual-infected group. The subgroup analysis further demonstrated that the HDV/HBV dual infection remained a significant higher risk for HCC in the presence of HCV or HIV coinfection and in various ethnicities. The risk was less apparent in patients who already presented with cirrhosis or advanced fibrosis.

Our results were generally consistent with a previous meta-analysis by Alfaiate et al.[33] The difference between these two meta-analyses may be caused by the search strategy and the selection criteria. The discrepancy in the number of studies may result in different results in the analysis. Nevertheless, our study provided subgroup analyses of different aspects, including fibrosis stage and different ethnic populations.

Table 1

Characteristics of enrolled studies in order of publication year, including study design, coinfection or superinfection of HDV, genotype, and viral load (n=21)

		Dual infection		Monoinfection						
	Country	HCC	Total	HCC	Total	Study design	Coinfection or superinfection	Diagnostic method of HDV	Genotype	Viral load
Chen 1984[21]	Taiwan	0	3	11	60	Cross sectional	Uncertain	Intrahepatic delta antigen and anti-HDV	No data	No data
Govindarajan 1984[22]	US	1	19	38	77	Cross sectional	Uncertain	Intrahepatic delta antigen and anti-HDV	No data	No data
Cronberg 1984[23]	Senegal	16	26	70	119	Cross sectional	Uncertain	Anti-HDV	No data	No data
Cenac 1987[29]	Niger	14	46	7	26	Retrospective	Superinfection	Anti-HDV	No data	No data
Toukan 1987[12]	Japan	10	47	5	296	Prospective	Both included	Anti-HDV	No data	No data
Trichopoulos 1987[13]	Greece	9	9	78	107	Case-control	Uncertain	Anti-HDV	No data	No data
Tamura 1993[14]	Japan	6	69	29	1058	Prospective	Superinfection	Anti-HDV	No data	No data
Singh 1995[15]	India	2	29	6	175	Cross sectional	Both included	Anti-HDV	No data	No data
Fattovich 2000[7]	Italy	5	39	22	161	Retrospective	Superinfection	Anti-HDV	No data	Tested HBV DNA, no quantitated data
Oyunsuren 2006[30]	Mongolia	46	93	10	31	Prospective	Co-infection	Anti-HDV and HDV RNA	88.7% HBV carrier were genotype D	Tested, no quantitated data
Cross 2008[24]	UK	8	82	66	840	Retrospective	Co-infection	Total HDV antibody, anti-HDV IgM. No HDV RNA.	No data	No data
Ji 2012[16]	Sweden	17	667	46	8556	Retrospective	Both included	Used Swedish Hospital Discharge Register and Outpatient Registry (by ICD-7 code)	No data	No data
Manesis 2013[25]	Greece	1	65	15	1836	Prospective	Both included	Anti-HDV and HDV RNA	No data	Tested HBV DNA
Asmah 2014[27]	Ghana	1	6	18	47	Cross sectional	Uncertain	Anti-HDV	No data	No data
Kushner 2015[17]	US	23	1000*	8	1000	Retrospective	Co-infection	Anti-HDV and HDV RNA	No data	Tested HBV DNA
Amougou 2016[18]	Cameroon	24	25	8	42	Case-control	Uncertain	Anti-HDV	No data	Yes
Béguelin 2017[31]	Switzerland	83	104	462	623	Prospective	Uncertain	Anti-HDV for screening, then HDV RNA were checked (stored samples)	HDV: 94.3% genotype 1; Dual infection: most genotype D HBV	No data
Luma 2017[19]	Cameroon	2	31	6	260	Cross-sectional	Uncertain	Anti-HDV antibody and HDV RNA	No data	Both HBV and HDV viral load presented with median level
Brancaccio 2018 [20]	Italy	17	56	6	56	Prospective	Uncertain	Anti-HDV antibody and HDV RNA	No data	Both HBV and HDV viral load presented with median level
Mahale 2018[32]	Gambia	18	29	165	301	Case control	Co-infection	Anti-HDV antibody and HDV RNA	HDV: 70.6% genotype 5, 29.4% genotype 1	Tested, no quantitate data
Coghill 2018[28]	Australia	14	115	20	264	Retrospective	Co-infection	Anti-HDV	No data	No data

* Documented as person-year in the article.

HCC = hepatocellular carcinoma; HBV= hepatitis B virus; HCV= hepatitis C virus; HDV= hepatitis delta virus; ICD= International Classification of Diseases.

Table 2

Characteristics of enrolled studies in order of publication year, including co-infection of HIV or HCV, cirrhosis or fibrosis status, and antiviral treatment (n = 21)

	HIV/HCV coinfection	Cirrhosis/fibrosis	Cirrhosis at the time of HCC diagnosis	Antiviral treatment	HBsAg loss
Chen 1984[21]	No data	No data	Uncertain	No data	No data
Govindarajan 1984[22]	No data	All cirrhosis in HCC group; 56% cirrhosis in control group	Yes	No data	No data
Cronberg 1984[23]	No data	Yes, unknown proportion	Uncertain	No data	No data
Cenac 1987[29]	No data	Yes, unknown proportion	Uncertain	No data	No data
Toukan 1987[12]	No data	Yes, unknown proportion	Uncertain	No data	No data
Trichopoulos 1987[13]	No data	55.6% HDV (+) HCC patients had cirrhosis; 60.3% HDV (–) HCC patients had cirrhosis	Uncertain	No data	No data
Tamura 1993[14]	No data	Yes, unknown proportion	Uncertain	No data	No data
Singh 1995[15]	No data	Yes, unknown proportion	Uncertain	No data	No data
Fattovich 2000[7]	Yes	All compensated cirrhosis	Median interval between entry and HCC development: Anti-HDV(+)/HBeAg(–): 75 months Anti-HDV(–)/HBeAg(–): 48 months Anti-HDV(–)/HBeAg(+): 40 months 5-year cumulative HCC risk: Anti-HDV(+)/HBeAg(–): 13% Anti-HDV(–)/HBeAg(+): 4% Anti-HDV(–)/HBeAg(–): 2%	Patients with anti-viral treatment during follow up were excluded	No data
Oyunsuren 2006[30]	Yes	No data	Uncertain	No data	No data
Cross 2008,[24]	Yes	22 patients had cirrhosis, 8 of 22 had HCC	Uncertain	IFN-based treatment: 2 patients	No data
Ji 2012[16]	HIV/HCV co-infection excluded	No data	No data	No data	No data
Manesis 2013[25]	HIV/HCV co-infection excluded	Yes, unknown proportion	Baseline cirrhosis: 145 (7.3) in HBV mono-infection and 16 (19.8) in HDV co-infection	46 HDV patients received antiviral treatment, 40 patients received IFN-based therapy	No data
Asmah 2014[27]	No data	Yes, unknown proportion	Known HCC when included	No data	No data
Kushner 2015[17]	59% anti-HDV positive patients have HCV	Yes, unknown proportion	Uncertain	7 (9.6%) HDV patients received IFN-based treatment; 30 (41%) HBV patients received NA.	No data
Amougou 2016[18]	23 HCC patients with positive anti-HCV	No data	Uncertain	No data	No data
Béguelin 2017[31]	All HIV infected. 70% with HCV	Yes, unknown proportion	Cirrhosis as the primary outcomes (liver disease related death)	Tenofovir for HBV suppression	No data
Luma 2017[19]	HIV/HCV co-infection excluded	Yes, fibrosis stages were documented	Uncertain	No data	No data
Brancaccio 2018 [20]	HIV/HCV co-infection excluded	Yes, all cirrhosis or advanced fibrosis	All cirrhosis or advanced fibrosis when included	Entecavir or Tenofovir	HBsAg loss: 4
Mahale 2018[32]	Yes	No data	Uncertain	No data	No data
Coghill 2018[28]	Yes	Yes, unknown proportion	Uncertain	7 (8%) HDV carrier had treatment; 182 (48.5%) HBV carrier received treatment for HBV	No data

HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis delta virus; HIV = human immunodeficiency virus; IFN = interferon; NA = nucleos(t)ide analogues.

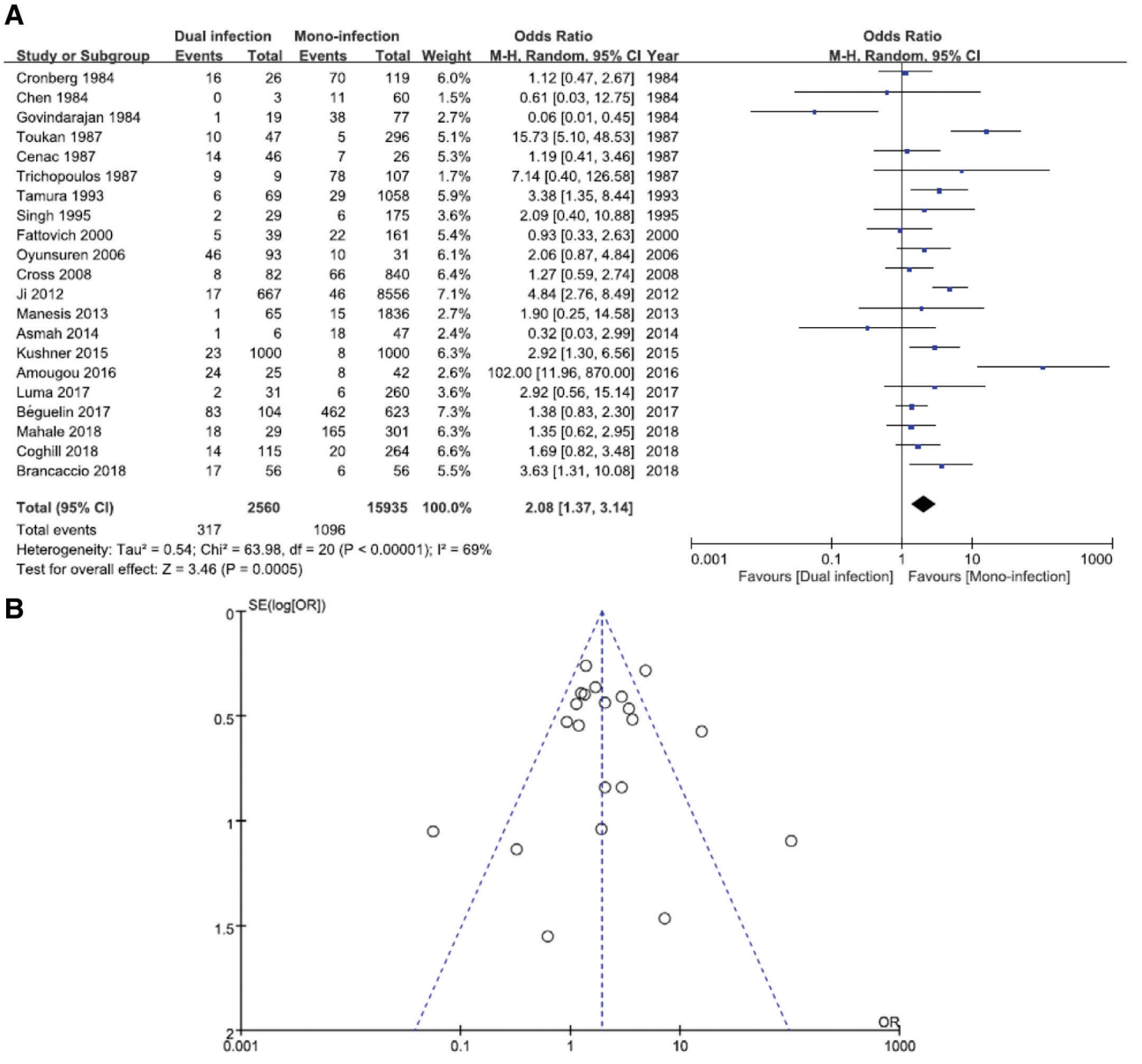


Fig. 2 A, Forest plot of association between hepatitis delta and the risk of HCC in 21 eligible studies using odds ratio. Events denote patients with HCC. B, Funnel plot for the assessment of publication bias. CI = confidence interval; M-H = Mantel-Haenszel.

HDV is a defective virus that needs hepatitis B surface antigen (HBsAg) for the assembly of virions, secretion, and infection of hepatocytes.[2] After invading the host cell, the replication of HDV can carry on without the presence of HBV proteins.[34] HDV superinfection is more likely to become a chronic disease. Chronic HDV infection may accelerate liver fibrosis.[3–6] Enduringly detectable HDV viremia was suggested to have a higher rate of progression to liver cirrhosis and hepatic decompensation.[5,11]

The interaction between HBV and HDV and the factors associated with disease progression during chronic infection has been examined. HDV may trigger an antiviral immune response and suppress the replication of HBV.[35] HDV viremia was associated with the HBsAg level and did not correlate with biochemical activity or histological severity.[36,37]

Our previous study reported that the levels of HDV and HBV viremia varied over time, and the predominance of the viruses fluctuated at different times.[37,38] The presence of HBV or HDV viremia was associated with lower remission rates.[39] Although in most cases, HBV was suppressed and presented with low viremia, there were still cases that presented with HBV reactivation during chronic dual infection.

Furthermore, the carcinogenesis of HCC involves both direct and indirect mechanisms. Immune clearance of infected hepatocytes and regeneration of liver promote HCC in patients with chronic hepatitis B or C.[40,41] The pathogenesis of HDV-associated HCC has yet to be elucidated. HDV might promote HCC development via modifying signaling pathways that may accelerate liver fibrosis and modulate immune response.[35,41–49] The large hepatitis delta antigen (LHDAg) can promote liver fibrosis and HCC.[35,42–44] LHDAg may induce oxidative stress and stimulate nuclear factor kappa B (NF-κB) that sustain inflammation in the microenvironment, which may lead to HCC development.[35,45–47] Small hepatitis delta antigen (s-HDAg) could downregulate the

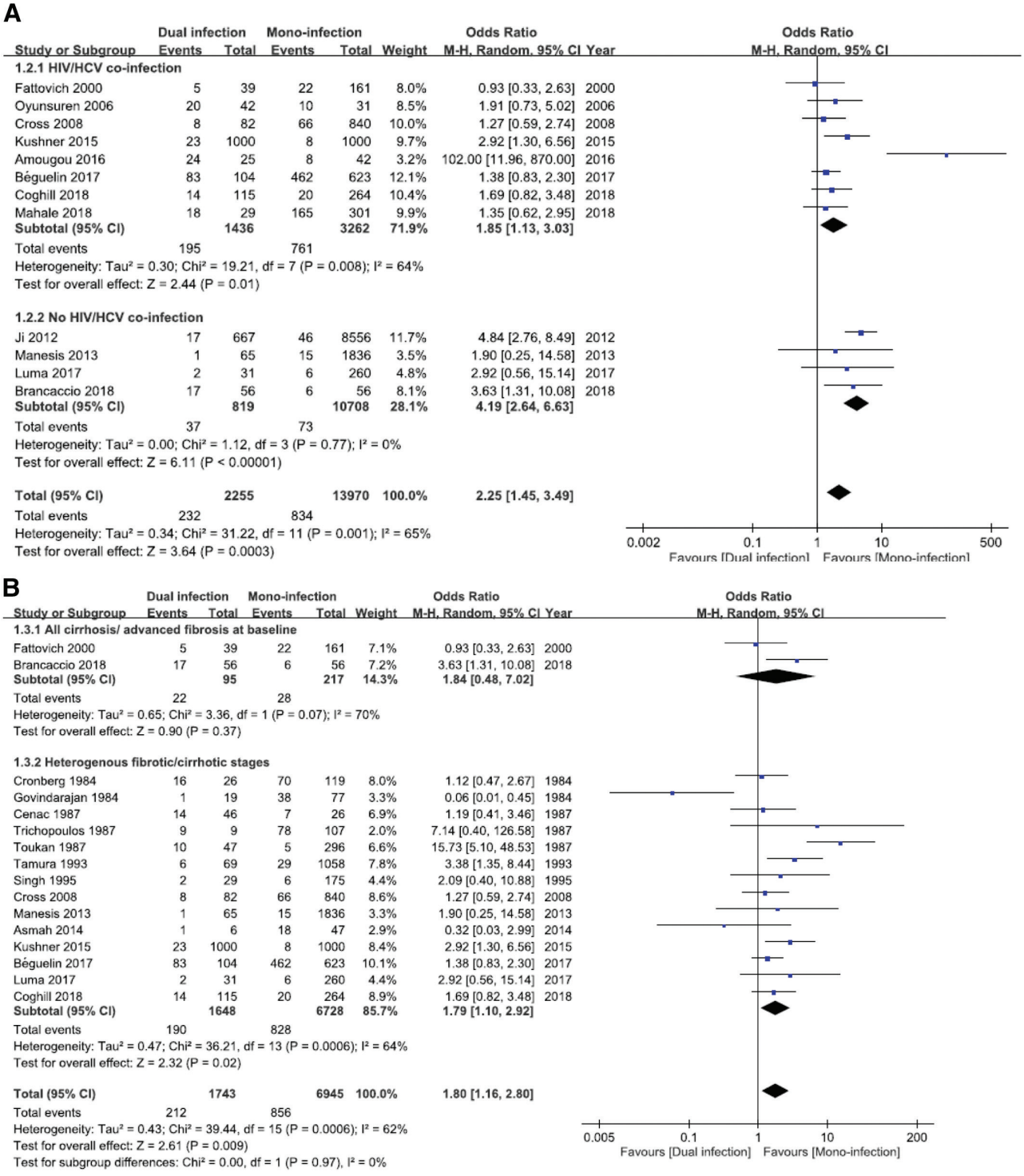
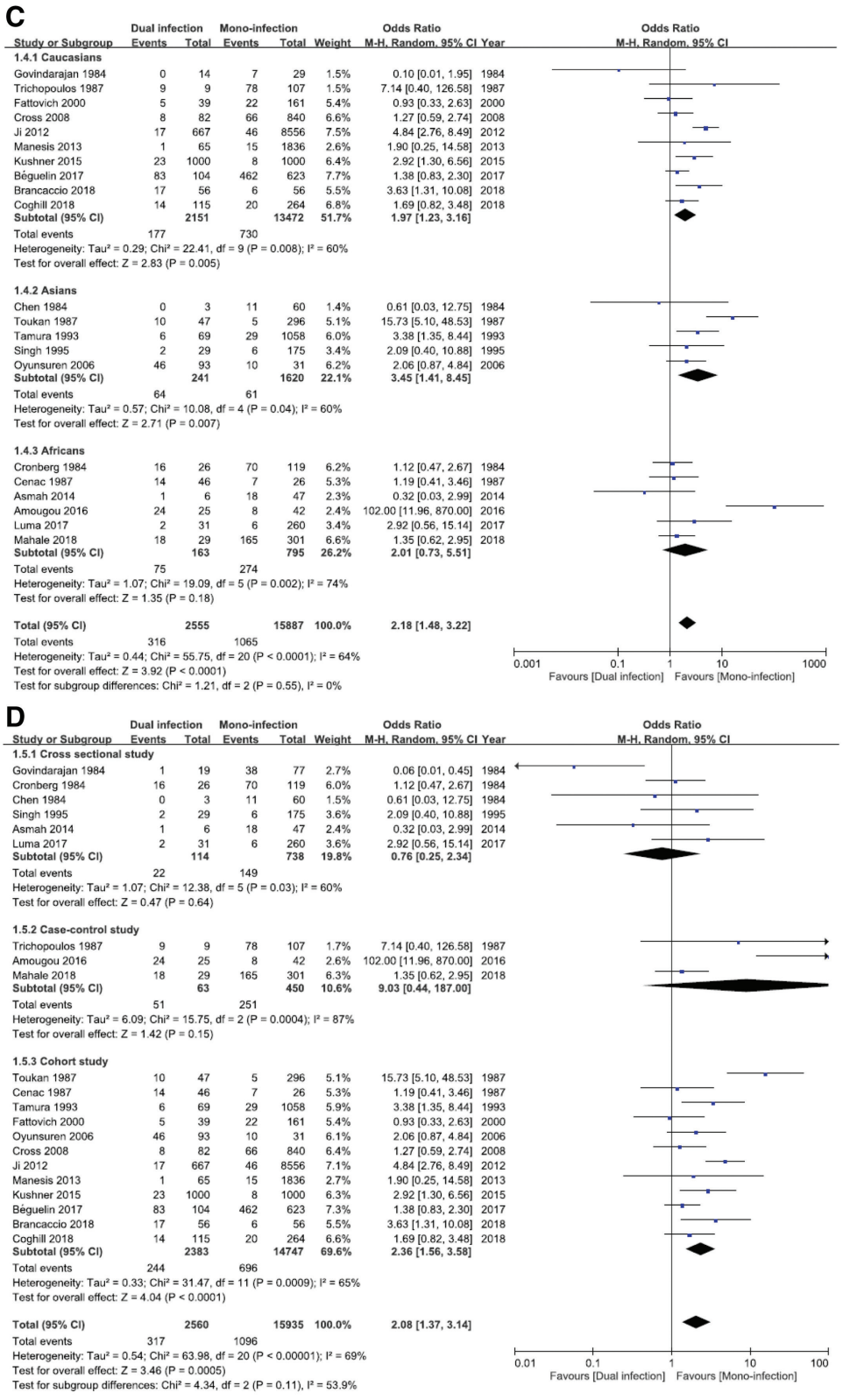


Fig. 3 A, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of HCV or HIV co-infection. Events denote patients with HCC. B, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of advanced fibrosis or cirrhosis. Events denote patients with HCC. C, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of different ethnic populations. Events denote patients with HCC. D, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of different study design. Events denote patients with HCC. E, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of different period of study. Events denote patients with HCC. F, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of antiviral treatment. Events denote patients with HCC. G Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of co-infection or superinfection of HDV. Events denote patients with HCC. CI = confidence interval; M-H = Mantel-Haenszel; IFN = interferon; NA = nucleos(t)ides analogues.



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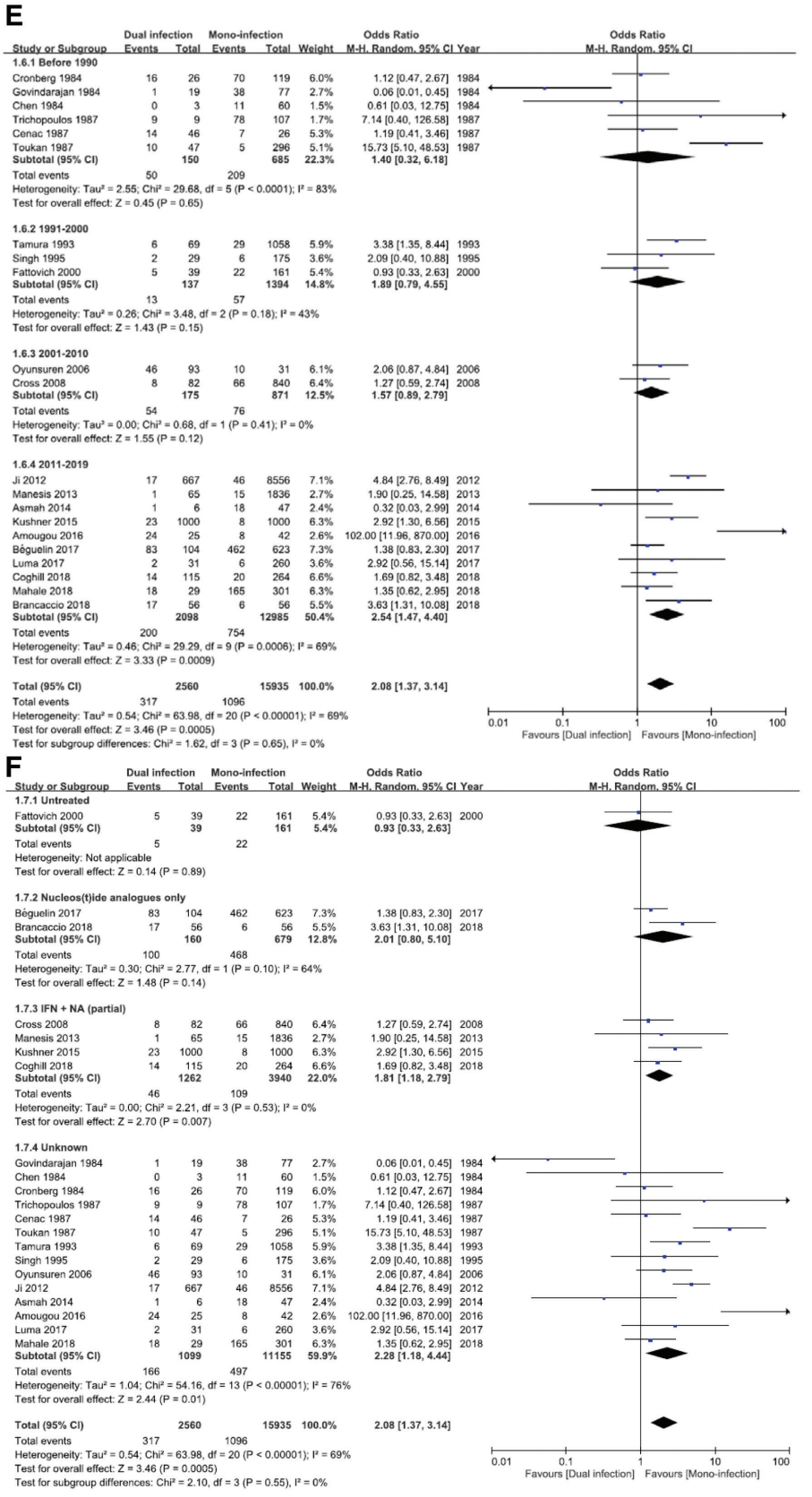

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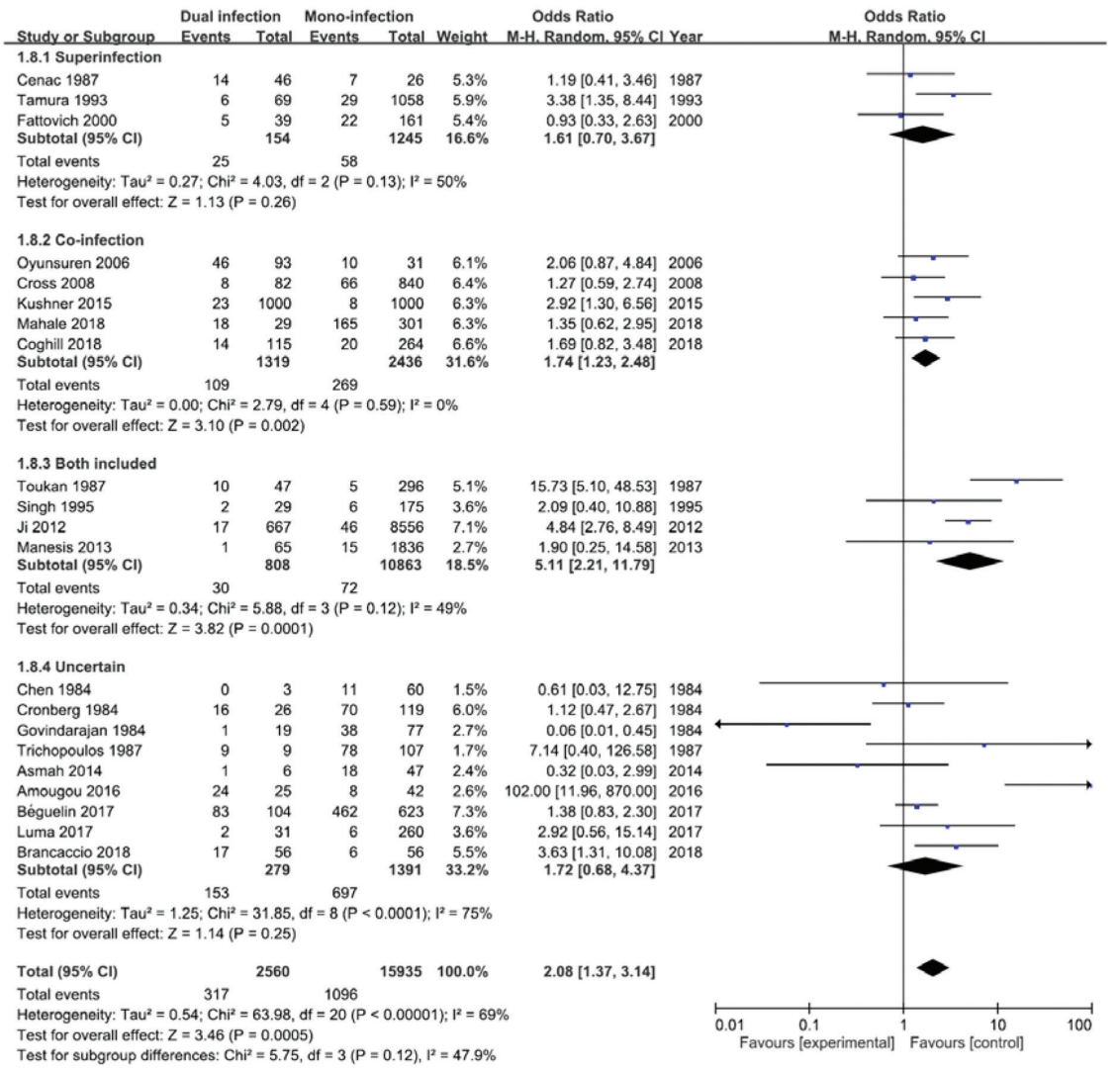

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expression of glutathione S-transferase P1 (GSTP1), and potentially lead to tumor growth.[48] Nevertheless, the direct evidence for the oncogenicity of HDV is still lacking.

HBV and HCV are oncogenic agents for HCC.[26] HIV is believed to increase the risk of HCC in HBV or HCV coinfected patients.[50] HIV coinfection may reduce the rate of viral clearance and promote chronic infection due to defective immunity. To minimize the confounding effects of HCV or HIV infection, we performed a subgroup analysis. The results showed that the risk of HCC development was higher in the HDV/HBV dual infection group in both subgroups. The cohorts excluding HCV or HIV infection had a higher Odds ratio of risk to develop HCC. The presence of HCV or HIV may contribute to HCC risk in both the HDV-infected and the non-HDV-infected group, which may underestimate the influence of HDV. Furthermore, the level of HDV/HIV viremia, antiviral treatment, and the length of infection may affect the results. Besides, some confounding factors of HCC had not been adjusted, including alcohol consumption, primary biliary cholangitis, autoimmune hepatitis, and metabolic dysfunction-associated fatty liver disease. It needs further prospective study to elucidate this issue.

It is difficult to define whether the development of HCC was generated from cirrhosis or triggered directly by HDV infection. Fattovich et al. assessed the influence of hepatitis delta in compensated cirrhotic patients and revealed an increased risk of HCC among HDV-infected patients.[7] A later study enrolled patients with advanced fibrosis or cirrhosis revealed that the rates of death, liver transplantation, liver decompensation, and HCC were significantly higher among HDV-infected patients than HBV monoinfected patients after reached HBV DNA suppression with nucleos(t)ide analogue.[20] However, the subgroup analysis showed no significant difference between HDV/HBV dual infection and HBV monoinfection among patients with advanced fibrosis and cirrhosis. This is not surprising because cirrhosis is a high-risk factor for HCC development.

The time sequence of the development of cirrhosis and HCC was difficult to identify in most of the included studies. Although superinfection of HDV is more likely to be associated with chronic liver disease, the HCC risk did not increase among superinfected patients in the subgroup analysis.[7,14,29] The impact of HDV infection on HCC risk among patients in different stages of liver disease should be further examined.

Persistent HDV viremia was reported to be associated with cirrhosis and HCC in previous studies.[10,11] However, only few studies had documented the level of HDV and HBV viremia,[19,20] or recorded as detectable or undetectable viral loads.[7,17,18,25,30,32]

A subgroup analysis of varying activity of HBV or HDV could not be performed due to inadequate information. Similarly, an analysis for different genotypes of HBV and HDV was not done because lack of the necessary data.

In addition, two of the studies included only patients that received nucleos(t)ide analogue for HBV suppression, and both studies suggested that HDV infection affected HCC development.[20,32] Most of the included studies did not have any record of antiviral treatment. HDV/HBV dual infection did not increase the risk of HCC when patients received nucleos(t)ide analogues.[20,31] Although the activity of viral replication and interaction between HBV and HDV may be crucial for HCC, there was not enough information for analyze.

Subgroup analyses according to the publication year revealed an increased risk of HCC development in the HDV/HBV dual infection group, but only in studies between 2011 and 2019. The cohorts in the studies between 2011 and 2019 were not significantly older or had more advanced liver disease comparing to earlier studies. Yet, the studies published between 2011 and 2019 were mainly cohort studies with a median research time span of 13 years (0.5–27 years) and prospective studies with a median follow-up of 4.3 years (4.2–8.7 years). In contrast, the studies published earlier were mainly cross-sectional studies, or cohort studies with shorter follow-up intervals. These were smaller studies that may not reflect the relationship of HDV infection and HCC in general populations.

There were limitations to this meta-analysis. First, there were inestimable confounding factors of HCC in the enrolled studies. Nearly half of the enrolled studies did not reveal the status of HCV and HIV infection. Second, as mentioned, the viral loads of HBV and HDV were not accurately assessed in most of the studies. We could not assess whether the enrolled patients were inactive carriers with high or low HDV viremia. Third, not all HBV carriers were tested for anti-HDV or HDV RNA, which may lead to underestimation of the HDV infected population. Fourth, the rate of HBsAg clearance was not documented in most of the studies, and it is left to be answered whether the HCC risk remains high in those who have suppressed HBV activity. Fifth, the percentage of HCC cases were varied in the enrolled studies, which may be related to selection bias of these studies. Thus, the data of meta-analysis should be carefully interpretated.

In conclusion, HDV does increase the risk of HCC compared with HBV monoinfection. However, the HCC risk was less apparent in HDV/HBV dual infections if the patients had advanced liver fibrosis or cirrhosis.

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