

Hepatitis D Virus Infection Increases the Risk of Liver Failure: A Systematic Review and Meta-analysis

Yao Gao^{1,*}, Ling Xu^{1,*}, Sisi Chen¹, Yaling Cao¹, Zihao Fan¹, Zhenzhen Pan¹, Zhongping Duan¹,
Feng Ren^{1,#}

¹Beijing Youan Hospital - Beijing Institute of Hepatology, No. 8, XitouTiao Road, Youwai Street, Fengtai District, Beijing 100069, China

Abstract: Hepatitis D virus (HDV) infection causes the most severe form of chronic viral hepatitis in humans, yet whether it elevates liver failure risk remains unclear. To evaluate this association, we conducted a systematic review/meta-analysis searching PubMed, EMBASE, Web of Science, and Cochrane Library using terms "hepatitis Delta," "hepatitis B virus," "liver failure," and "fulminant hepatitis," comparing LF risk in HDV/HBV co-infected versus HBV mono-infected patients. Our analysis of 16 studies (n = 2,990) demonstrated significantly higher LF risk in co-infected patients (OR = 4.41; 95% CI: 2.37–8.18; *P* = 0.000), with subgroup analysis confirming persistently elevated risk irrespective of publication year, geographical region and co-infection status. We conclude HDV/HBV co-infection significantly increases LF risk compared to HBV mono-infection.

Keywords: HDV; HBV; Co-infection; Liver failure; Meta-analysis.

Introduction

Liver failure is a life-threatening condition with high mortality that affects multiple organ systems. It manifests as acute liver failure (ALF), acute-on-chronic liver failure (ACLF), or acute decompensation in cirrhosis^[1]. Hepatitis B virus (HBV) infection represents a core etiology of liver failure^[2]. Globally, over 240 million individuals have chronic HBV infection^[3], and approximately 15–40% of untreated cases progress to cirrhosis^[4], potentially culminating in liver failure.

Hepatitis delta virus (HDV), a defective RNA virus, relies on HBV for envelope protein synthesis^[5]. Clinically, HDV infection occurs as co-infection (simultaneous HBV/HDV acquisition) or superinfection (HDV infection in established HBsAg carriers or chronic HBV patients)^[6]. While approximately 5% of HBsAg carriers worldwide have HDV co-infection^[7], a 2019 meta-analysis reported a prevalence of 10.58%-nearly double prior estimates^[8]. This indicates substantial underestimation of HDV prevalence and neglect of its severe consequences^[9]. Chronic hepatitis D (CHD) constitutes the most severe form of human viral hepatitis^[5]. Compared to HBV mono-infection, HDV co-infection associates with more aggressive hepatitis and accelerated progression to advanced cirrhosis^[10], liver cirrhosis, and end-stage liver disease^[8,11].

Although the increased risk of liver failure in HBV mono-in-

fection is well-established^[12], whether HDV co-infection further elevates this risk remains controversial. Previous studies face limitations including suboptimal design, inadequate power, and descriptive approaches, hindering robust causal inference. A recent meta-analysis of 93 studies (68 case-control, 25 cohort) suggested increased hepatocellular carcinoma (HCC) risk in HBV/HDV co-infected patients^[4,13]. However, no study has comprehensively examined the association between HDV infection and liver failure. We therefore conducted this systematic review and meta-analysis to assess and compare liver failure risks between HBV/HDV co-infected and HBV mono-infected patients.

Methods

This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and was registered in PROSPERO (CRD42022306773).

Search methodology and study selection

Comprehensive database searches were performed across PubMed, EMBASE, Web of Science, and the Cochrane Library through May 2025. This systematic review specifically targeted original studies comparing liver failure incidence between HBV/HDV co-infected and HBV mono-infected cohorts. Search strings incorporated core terms ('hepatitis Delta', 'liver failure', 'hepatitis B virus') alongside related keywords (detailed in [Supplementary Table 1](#)). No language, geographic, publication date, or status restrictions were applied. To ensure literature saturation, we manually screened references of included articles and interrogated the Cochrane Central Register of Controlled Trials for gray literature.

Studies were included in our meta-analysis if they: (1) em-

* These authors contributed equally to this work.

Correspondence: Feng Ren. E-mail: renfeng7512@ccmu.edu.cn. Address: Beijing Youan Hospital - Beijing Institute of Hepatology, No. 8, XitouTiao Road, Youwai Street, Fengtai District, Beijing 100069, China.

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ployed longitudinal designs (cohort, case-control, or randomized controlled trials) reporting primary data; (2) compared HBV/HDV co-infected against HBV mono-infected cohorts within the same study; (3) provided quantifiable effect measures (odds ratios [ORs], relative risks [RRs], hazard ratios [HRs], or calculable effect sizes); (4) reported incident liver failure cases per group; and (5) were peer-reviewed full-text publications.

Data extraction

Literature search results were compiled using EndNote v.10 for reference management. Two independent investigators (Y.G. and L.X.) performed dual screening of titles/abstracts to identify eligible publications, with discrepancies resolved through third-party adjudication (F.R.). From all qualifying studies, we extracted: (1) study characteristics (author, country, publication year, design, follow-up duration, HDV detection methodology, adjusted covariates); and (2) patient profiles (cirrhosis prevalence, cohort sizes for HBV mono-infected and HDV co-infected groups, and liver failure incidence per cohort).

Quality assessment

All included studies underwent quality evaluation using the Newcastle-Ottawa Scale (NOS) for observational and case-control designs. Two independent assessors (Y.G. and L.X.) assigned stars across three domains: group selection (max 4 stars), comparability adjustment (max 2 stars), and outcome ascertainment (max 3 stars). Studies scoring ≥ 7 were deemed high-quality. Discrepancies were resolved through third-reviewer arbitration (F.R.). No exclusions resulted from quality assessment, consistent with Cochrane Handbook recommendations for retaining methodologically diverse evidence.

Data synthesis and analysis

Statistical analysis

Analytical methodology adhered strictly to the Cochrane Handbook for Systematic Reviews of Interventions. We quantified incident liver failure cases in HBV/HDV co-infected versus HBV mono-infected cohorts. Stratified evaluations assessed outcome variations by human immunodeficiency virus (HIV) serostatus, publication era, and hepatic fibrosis severity.

Meta-regression

To identify sources of heterogeneity, we conducted univariable random-effects meta-regressions assessing pre-specified covariates: publication year, geographic region, and HDV infection status. The analysis required ≥ 8 studies per covariate, with $P \leq 0.05$ indicating potential effect modifiers.

Assessment of heterogeneity

Study heterogeneity was quantified via Higgins I^2 statistics and Cochrane's Q-test. I^2 values $>75\%$, $50\text{--}75\%$, and $<50\%$ defined high, moderate, and low heterogeneity, respectively; Q-test $P < 0.10$ indicated significant heterogeneity.

Assessment of publication bias

Publication bias was quantitatively evaluated through funnel plot asymmetry analysis, supplemented by Egger's regression to statistically characterize small-study effects. All statistical procedures were executed in STATA 14.0 (Stata Corp., College Station, Texas), maintaining analytical consistency throughout our meta-analytic framework.

Results

Literature search

Our initial database search yielded 1,576 records through May 2025. After screening titles and abstracts, we excluded unrelated articles, retaining 86 publications. Details of the search databases and keywords can be found in [Supplementary Table 1](#). Following removal of duplicates and case reports, 16 full-text articles were deemed eligible for inclusion^[14–29] ([Fig. 1](#)).

Study selection and characteristics

Sixteen longitudinal studies met prespecified criteria for incorporation into both qualitative assessment and quantitative meta-analysis of liver failure risk in HDV/HBV co-infected cohorts, with the selection workflow graphically outlined in [Fig. 1](#).

The 16 included cohort studies (2 prospective, 14 retrospective) enrolled 2,990 patients from hospital settings between 1969–2022, comprising 929 (31.1%) with HBV/HDV co-infection and 2,061 with HBV mono-infection ([Table 1](#)). Geographically, studies originated from China ($n = 6$), Europe ($n = 6$: France, Sweden, Italy, England, Yugoslavia), India ($n = 2$), Venezuela ($n = 1$), and the USA ($n = 1$). Four were multicenter investigations and twelve were single center. HDV diagnosis was confirmed by anti-HDV antibody positivity or HDV-RNA detection in all studies, with one study additionally utilizing liver tissue HDAg positivity ([Table 1](#)).

Quality assessment

Study quality was generally high, with Newcastle-Ottawa Scale (NOS) scores ranging from 6 to 9 ([Table 2](#)). All studies demonstrated high methodological quality. Two studies implemented 1:1 pair-matching for confounders (age, gender, liver enzymes). Three studies received NOS scores of 5 due to unadjusted confounders (e.g., age, sex) compromising comparative validity.

Scale: a maximum of 4 points can be awarded for selection, 2 for comparability and 3 for outcomes. A score of > 6 indicates a high-quality study.

Risk of liver failure

HBV/HDV co-infection was significantly associated with increased liver failure/fulminant hepatitis risk versus HBV mono-infection (pooled OR = 4.41; 95% CI: 2.37–8.18; $P = 0.000$), though substantial heterogeneity was observed ($I^2 = 87.2\%$). The forest plot is presented in [Fig. 2](#). Visual funnel plot analysis revealed no publication bias ([Fig. 3](#)).

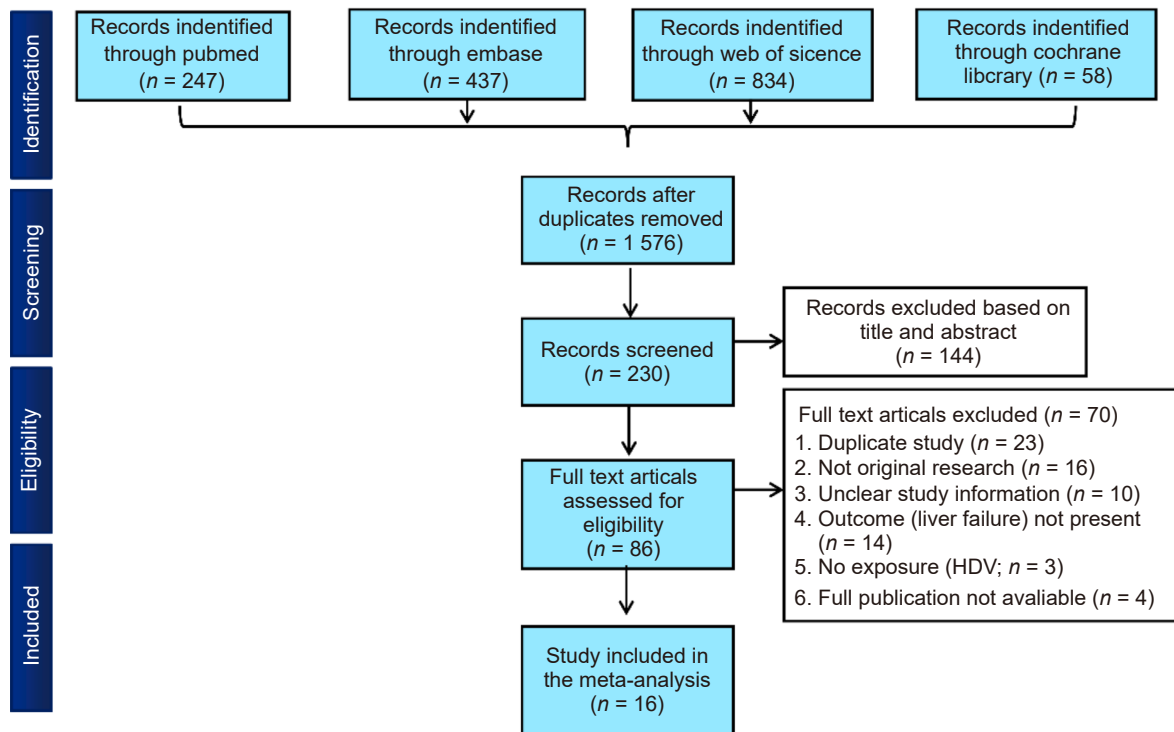


Fig. 1. PRISMA flow diagram outlining search strategy and selection of the studies in the systematic review and meta-analysis.

Table 1. Characteristics of Study Populations in the Included Meta-Analysis.

N.O	Author, Year, Country	Study Design	Enrolment Period	Study Setting	HDV Diagnosis	HBV		HBV + HDV		Coinfection or Superinfection	Definition of Liver Failure
						LF	Total	LF	Total		
1	Smedile et al, 1982, Italy, France England ^[14]	Retrospective	Not mentioned	Multiple center	Anti-HDV IgG + IgM	101	532	43	111	Both included	Fulminant hepatitis
2	Govindarajan et al, 1984, USA ^[15]	Prospective	1969–1983	Multiple center	Anti-HDV IgG + IgM	46	71	19	65	Both included	Fulminant hepatitis
3	Ljunggren et al, 1986, Sweden ^[16]	Retrospective	1979–1984	Multiple center	Anti-HDV IgG + IgM	0	11	4	11	Superinfection	Fulminant hepatitis
5	Lettau et al, 1987 ^[17]	Prospective	1983–1985	Single center	Anti-HDV IgG + IgM	13	135	10	13	Both included	Fulminant hepatitis
6	Krogsgaard et al, 1988, Sweden ^[18]	Retrospective	1970–1985	Multiple center	Anti-HDV IgG + IgM	14	28	14	28	Both included	Fulminant hepatitis
7	Desai et al, 1990 ^[23] , India	Prospective	1985–1989	Single center	Anti-HDV IgG	12	32	20	32	Both included	Fulminant hepatitis
8	Balik et al, 1991, Italy ^[19]	Retrospective	1986–1988	Single center	Anti-HDV IgG + IgM	22	226	9	31	Both included	Severe or Fulminant hepatitis
9	Hadler et al, 1992, Venezuela ^[20]	Prospective	1978–1981	Single center	Anti-HDV IgG + IgM	3	99	28	103	Both included	Fulminant hepatitis
10	Delić et al, 1993 ^[21] , Yugoslavia	Retrospective	1972–1991	Single center	HDAg	35	36	1	36	Not mentioned	Fulminant hepatitis
11	Wu et al, 1994, China ^[22]	Retrospective	1982–1992	Single center	Anti-HDV IgG + IgM + HDV RNA	31	32	12	32	Both included	Fulminant hepatitis
12	Irshad et al, 1996, India ^[24]	Retrospective	1991–1993	Single center	Anti-HDV IgG + IgM	55	175	87	175	Not mentioned	Fulminant hepatic failure
13	Gu et al, 2000, China ^[25]	Retrospective	1988–1998	Single center	Anti-HDV IgG + IgM	22	114	92	114	Not mentioned	Fulminant
14	Gu et al, 2014, China ^[26]	Retrospective	2005–2014	Single center	Anti-HDV IgG + IgM + HDV RNA	23	213	27	92	Not mentioned	Liver failure
17	Fu et al, 2016, China ^[27]	Retrospective	2005–2014	Single center	Anti-HDV IgG + IgM + HDV RNA	2	70	2	22	Not mentioned	Liver failure
15	Xu et al, 2022, China ^[28]	Retrospective	2015–2020	Single center	Anti-HDV IgG + IgM	27	44	17	44	Not mentioned	Liver failure

Table 2. Newcastle-Ottawa Scale for Assessment of the Risk of Bias of the Included Studies.

Author, year	Selection			Comparability		Outcome			Total
	Representativeness	Non-exposed Selection	Ascertainment of exposure	Baseline outcome absent	Comparability (design/analysis)	Outcome Assessment	Follow-up duration	Follow-up adequacy	
Smedile et al, 1982 ^[14]	1	1	1	1	1	1	0	1	7
Govindarajan et al, 1984 ^[15]	1	1	1	0	2	0	1	1	7
Ljunggren et al, 1986 ^[16]	1	1	1	1	2	1	1	1	9
Lettau et al, 1987 ^[17]	1	1	2	2	0	1	1	0	8
Krogsgaard et al, 1988 ^[18]	1	1	2	2	0	0	1	0	7
Desai et al, 1990 ^[23]	1	1	2	1	1	2	1	0	9
Balik et al, 1991 ^[19]	1	1	0	1	1	2	1	1	8
Hadler et al, 1992 ^[20]	1	1	0	1	0	0	1	1	5
Delić et al, 1993 ^[21]	1	1	1	1	0	1	1	0	6
Wu et al, 1994 ^[22]	1	1	0	1	2	0	1	1	7
Irshad et al, 1996 ^[24]	1	1	0	1	0	0	1	1	5
Gu et al, 2000 ^[25]	1	1	0	0	0	1	1	1	5
Gu et al, 2014 ^[26]	1	1	1	1	2	0	1	0	7
Fu et al, 2016 ^[27]	1	2	1	1	1	0	1	0	7
Xu et al, 2022 ^[28]	1	1	1	0	2	1	1	0	7
Zheng et al. 2022 ^[29]	1	1	1	0	0	1	1	1	6

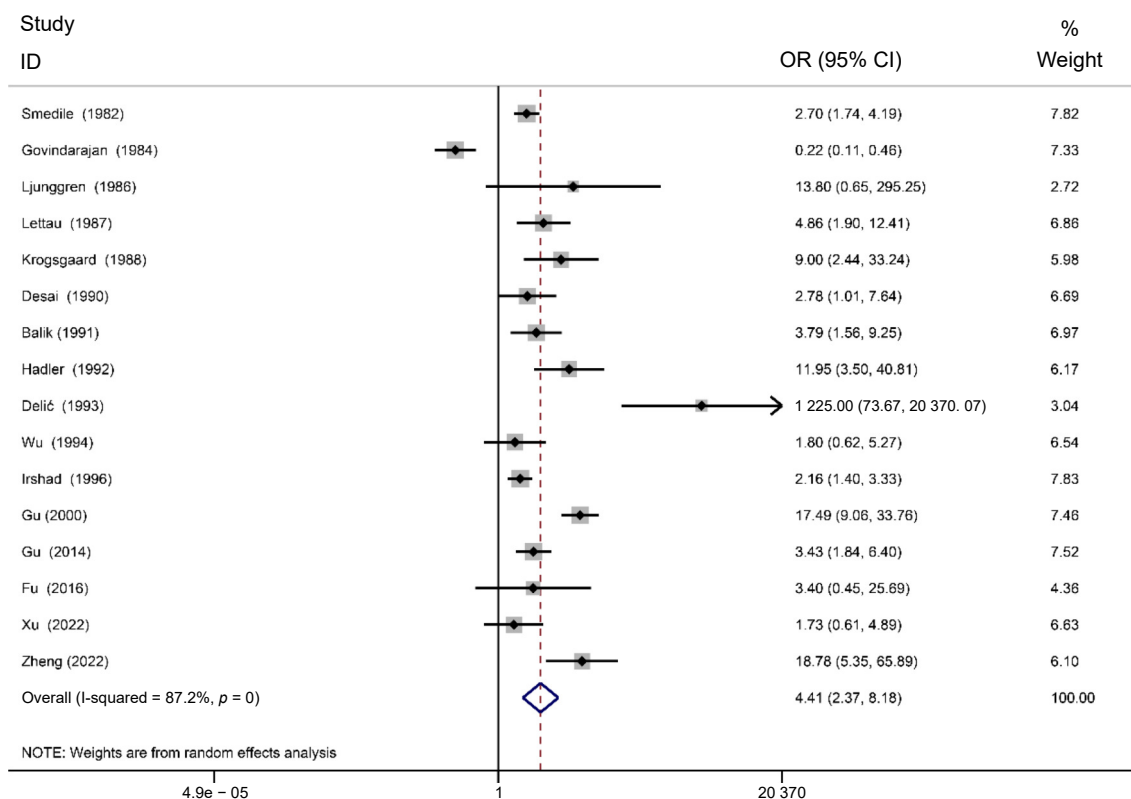


Fig. 2. Funnel plot of the overall meta-analysis. Forest plot of association between HDV and the risk of liver failure in 16 eligible studies using odds ratio. Events denote patients with liver failure.

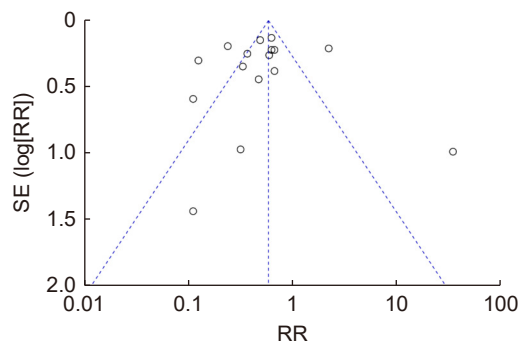


Fig. 3. Funnel plot for the assessment of publication bias. Funnel plot of publication bias in 16 studies assessing the risk of liver failure in hepatitis B virus/hepatitis D virus (HBV/HDV) dual-infected patients compared to HBV mono-infected patients.

Subgroup analyses

Subgroup analysis stratified by publication year (spanning 1969–2022) revealed progressively elevated liver failure risk in HBV/HDV co-infected patients across eras: pre-1990 (OR = 2.62; 95% CI: 0.83–8.33; $P = 0.000$; $I^2 = 89.4\%$), 1991–2000 (OR = 8.08; 95% CI: 2.65–24.7; $P = 0.000$; $I^2 = 89.6\%$), and 2001–2022 (OR = 4.25; 95% CI: 1.66–10.89; $P = 0.036$; $I^2 =$

64.9%), with notably increased risk in studies published between 2011–2019 (Fig. 4).

Participants were stratified by HDV infection status (co-infection vs. superinfection). Five studies evaluating liver failure risk demonstrated no significant association (OR = 0.79; 95% CI: 0.36–1.72; $P = 0.234$; $I^2 = 28.1\%$), indicating comparable risk between HDV infection modalities (Fig. 5).

Given the multinational scope (Asia, Europe, North America, South America), we performed geographic subgroup analysis across 16 studies: Asia ($n = 8$), Europe ($n = 5$), North America ($n = 2$), South America ($n = 1$). Significantly increased liver failure risk with HBV/HDV co-infection was observed in Asian (OR = 4.04; 95% CI: 2.01–8.11; $P = 0.000$; $I^2 = 85.11\%$) and European studies (OR = 9.48; 95% CI: 2.74–32.75; $P = 0.000$; $I^2 = 96.1\%$). Conversely, North American (OR = 1.03; 95% CI: 0.05–20.92; $P = 0.000$; $I^2 = 92.1\%$) showed no significant associations (Fig. 6).

Meta-regression

To assess potential sources of bias, a univariable random-effects meta-regression incorporating all 16 studies was conducted. This analysis demonstrated no significant confounding effect from any study-level characteristic (Supplementary Table 2).

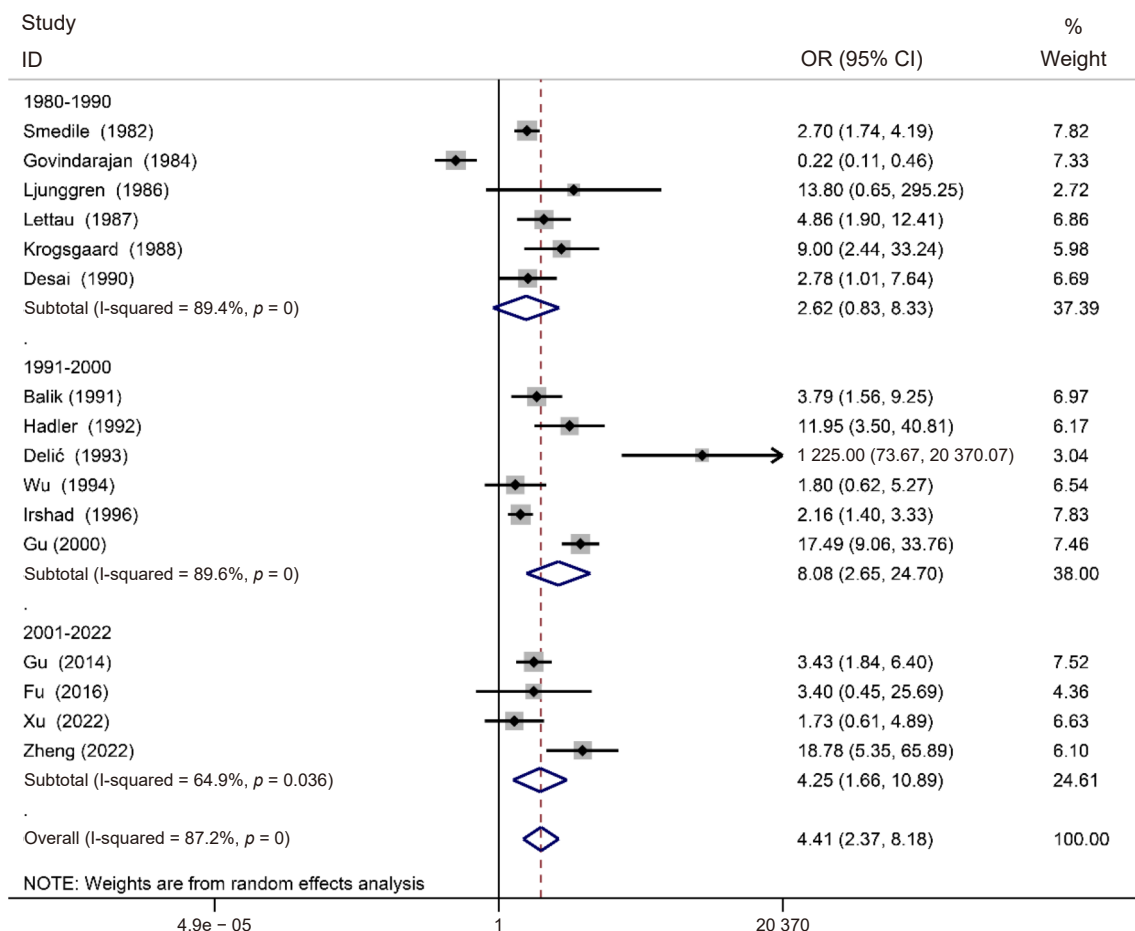


Fig. 4. Forest plot of the subgroup meta-analysis based on date of publication. Odds ratio of HDV infection to liver failure by the subgroup analysis of different date of publication. Events denote patients with liver failure.

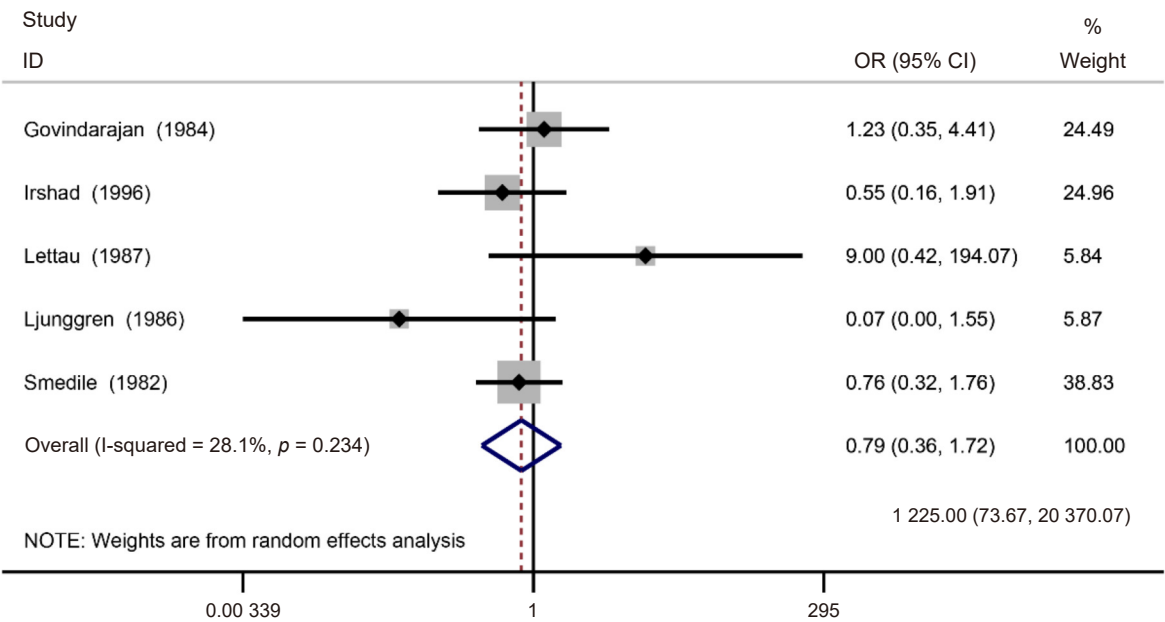


Fig. 5. Funnel plot of the subgroup meta-analysis based on status of HDV infection. Funnel plot of the subgroup meta-analysis based on co-infection and superinfection. Events denote patients with liver failure.

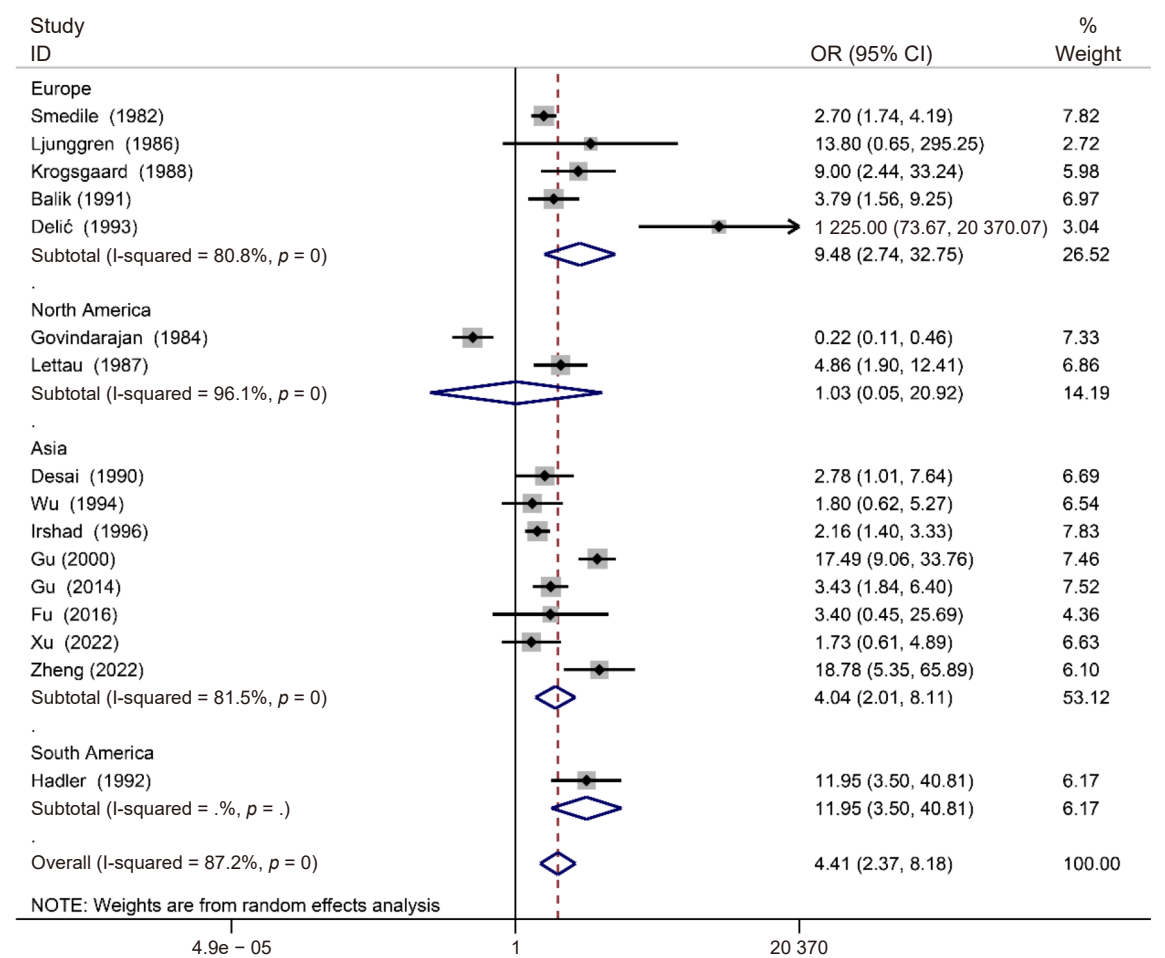


Fig. 6. Funnel plot of the subgroup meta-analysis based on continents. Funnel plot of the subgroup meta-analysis based on the continents where the published articles were from. Events denote patients with liver failure.

Discussion

Whether HBV/HDV co-infection confers higher liver failure risk than HBV mono-infection remains controversial. We conducted this systematic review and meta-analysis to elucidate this association. Broad inclusion criteria identified 16 studies encompassing 2,990 patients. To our knowledge, this represents the first meta-analysis demonstrating significantly elevated liver failure risk in HBV/HDV co-infected versus HBV mono-infected patients. This meta-analysis definitively establishes hepatitis D virus coinfection as a significant independent risk factor for liver failure in patients with chronic hepatitis B. The underlying pathophysiology may involve direct cytopathic effects of HDV and subsequent enhanced host immune responses, leading to accelerated fibrosis progression. Notably, the risk of liver failure persists even in the era of effective HBV suppression with nucleos(t)ide analogue therapy, highlighting the critical role of HDV itself as the primary driver of liver injury.

HDV—a defective virus requiring HBsAg for viral assembly, release, and hepatocyte infection—cannot replicate without HBV proteins^[30]. Consequently, antiviral therapies inhibiting HBV replication may ameliorate end-stage liver disease progression^[31,32]. IFN- γ or nucleos(t)ide analogs (NAs) reduce cirrhosis and HCC risk in HBV-infected patients^[33]. Notably, only two included studies reported antiviral therapy data, potentially biasing comparisons between mono-infected and co-infected cohorts. Despite significant advances in antiviral therapy for hepatitis B virus (HBV), management of liver failure due to HBV/HDV coinfection remains a formidable challenge, as nucleos(t)ide analogues do not counteract the aggressive liver injury driven by hepatitis D virus (HDV)^[34]. Italian registry data underscore this, showing that up to 63% of liver transplants for coinfecting patients are due to HDV-related liver failure, establishing transplantation as the only definitive solution for decompensated disease^[35]. While novel agents like bulevirtide (BLV) suppress HDV replication and improve liver function—offering vital bridging therapy—they may not avert transplantation in fulminant cases^[36]. Thus, alongside developing better therapies, reinforcing comprehensive HBV vaccination remains the most fundamental and cost-effective strategy to prevent HDV coinfection and its severe outcomes at the source.

Publication year-based subgroup analysis revealed increasing liver failure risk in co-infected groups over time. This trend may reflect: evolving HDV detection accuracy across the >10-year study period^[6]; standardization of HBV management (antiviral therapy, regular monitoring) improving compliance and enabling better end-stage outcome documentation^[37,38]; growing HDV risk awareness increasing diagnostic uptake and altering enrollment patterns^[39,40]. However, the lack of universally effective and accessible anti-HDV therapies means the aggressive course of HDV co-infection remains largely unmodified. Consequently, the relative contribution of HDV to liver failure has become more pronounced, creating a widening risk disparity and effectively unmasking the substantial burden of HDV in the contemporary era. This underscores that the rising risk estimate is not an artifact but signals an urgent and unmet clinical need. While successful control of HBV has been achieved, it has simultaneously revealed the severity of challenges in HDV management, making its treatment an increasingly recognized clinical priority.

Consequently, the relative contribution of HDV to liver failure

has become more pronounced, creating a diverging risk profile and effectively "unmasking" the severe burden of HDV in the contemporary era. This underscores that the growing risk estimate is not an artifact but a signal of an urgent and unmet clinical need. It highlights the paradox of modern hepatology: while we have successfully tamed HBV, we have simultaneously unveiled the full magnitude of the HDV challenge, demanding prioritized efforts in screening, drug development, and global access to care.

Our conclusion that HBV/HDV co-infection elevates the risk of liver failure compared with mono-infection should be interpreted in the context of several limitations. First, certain studies provided incomplete characterization of patient profiles; specifically, few reported HIV co-infection status and none reported HCV status, which represent potential confounders for liver failure. Second, the insufficient reporting of HBV and HDV viral loads precluded assessment of a dose–response relationship. Third, HBsAg clearance rates were not consistently documented, limiting insight into liver failure risk among patients with suppressed HBV replication. Furthermore, the high statistical heterogeneity ($I^2 = 89\%$) necessitates cautious interpretation of the pooled estimate. This variability likely stems from differences in patient characteristics and clinical definitions across studies. Although subgroup analyses and meta-regression indicated that factors like geographical region and study design partially explained the heterogeneity, the remaining variability suggests that the pooled risk should be viewed as a representative association range rather than a precise value. Nevertheless, the consistent direction of association across studies strengthens the conclusion of increased risk.

This meta-analysis establishes HDV co-infection as a significant risk factor for liver failure in HBV-infected patients. This finding carries important clinical implications: it underscores the necessity for universal HDV screening in all HBV-infected individuals and reveals the urgent need for developing effective therapies targeting HDV. Future high-quality studies should address biases from HIV/HCV co-infection, antiviral therapies, and HBsAg status through more comprehensive data collection and analysis.

Conclusion

This meta-analysis demonstrates that HDV/HBV co-infection significantly increases the risk of liver failure compared to HBV mono-infection. These findings highlight the critical need for universal HDV screening in HBV-infected patients and the development of effective therapies targeting HDV.

Abbreviations

ACLF, acute-on-chronic liver failure; ALF, acute liver failure; BLV, bulevirtide; CHD, Chronic hepatitis D; HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; HDV, Hepatitis D virus; HR, hazard ratios; LF, liver failure; NAs, nucleos(t)ide analogs; NOS, Newcastle-Ottawa Scale; OR, odds ratios; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, relative risks.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

Authors' contributions

FR and ZPD conceptualized the study and developed the research protocol. YG, LX, ZHF, and ZZZ identified articles for full-text review and extracted data that matched the inclusion criteria. YG, SSC and YLC performed the statistical analyses. YG and LX wrote the paper. FR polished and revised the manuscript.

References

- [1] Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. *Nat Rev Gastroenterol Hepatol*, 2016, 13(3): 131-149.
- [2] Karvellas CJ, Cardoso FS, Gottfried M, et al. HBV-Associated Acute Liver Failure After Immunosuppression and Risk of Death. *Clin Gastroenterol Hepatol*, 2017, 15(1): 113-122.
- [3] Byass P. The global burden of liver disease: a challenge for methods and for public health. *BMC Med*, 2014, 12: 159.
- [4] Chang TE, Su CW, Huang YS, et al. Hepatitis D virus dual infection increased the risk of hepatocellular carcinoma compared with hepatitis B virus mono-infection: A meta-analysis. *J Chin Med Assoc*, 2022, 85(1): 30-41.
- [5] Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. *Lancet*, 2011, 378(9785): 73-85.
- [6] Chen LY, Pang XY, Goyal H, et al. Hepatitis D: challenges in the estimation of true prevalence and laboratory diagnosis. *Gut Pathog*, 2021, 13(1): 66.
- [7] Farci P. Delta hepatitis: an update. *J Hepatol*, 2003, 39: 212-219.
- [8] Chen HY, Shen DT, Ji DZ, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. *Gut*, 2019, 68(3): 512-521.
- [9] Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. *J Hepatol*, 2020, 73(3): 523-532.
- [10] Wu D, Zhang S, Xie Z, et al. Plasminogen as a prognostic biomarker for HBV-related acute-on-chronic liver failure. *J Clin Invest*, 2020, 130(4): 2069-2080.
- [11] Baskiran A, Akbulut S, Sahin TT, et al. Effect of HBV-HDV co-infection on HBV-HCC co-recurrence in patients undergoing living donor liver transplantation. *Hepatol Int*, 2020, 14(5): 869-880.
- [12] Loomba R, Liang TJ. Hepatitis B Reactivation Associated with Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. *Gastroenterology*, 2017, 152(6): 1297-1309.
- [13] Alfaite D, Clement S, Gomes D, et al. Chronic hepatitis D and hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. *J Hepatol*, 2020, 73(3): 533-539.
- [14] Smedile A, Farci P, Verme G, et al. Influence of delta infection on severity of hepatitis B. *Lancet*, 1982, 2(8305): 945-947.
- [15] Govindarajan S, Chin KP, Redeker AG, et al. Fulminant B viral hepatitis: role of delta agent. *Gastroenterology*, 1984, 86(6): 1417-1420.
- [16] Ljunggren KE, Hansson BG. Fulminant delta hepatitis among Swedish drug addicts. *Scand J Infect Dis*, 1986, 18(5): 397-400.
- [17] Lettau LA, McCarthy JG, Smith MH, et al. Outbreak of severe hepatitis due to delta and hepatitis B viruses in parenteral drug abusers and their contacts. *N Engl J Med*, 1987, 317(20): 1256-1262.
- [18] Krogsgaard K, Mathiesen LR, Aldershvile J, et al. Delta infection and hepatitis B virus replication in Danish patients with fulminant hepatitis B. *Scand J Infect Dis*, 1988, 20(2): 127-133.
- [19] Balik I, Onul M, Tekeli E, et al. Epidemiology and clinical outcome of hepatitis D virus infection in Turkey. *Eur J Epidemiol*, 1991, 7(1): 48-54.
- [20] Hadler SC, Alcala de Monzon M, Rivero D, et al. Epidemiology and long-term consequences of hepatitis delta virus infection in the Yucpa Indians of Venezuela. *Am J Epidemiol*, 1992, 136(12): 1507-1516.
- [21] Delić D, Gotić M, Ostrić V, et al. Epidemiology of hepatitis D virus (delta) infection in Yugoslavia. *Liver*, 1993, 13(6): 302-304.
- [22] Wu JC, Chen CL, Hou MC, et al. Multiple viral infection as the most common cause of fulminant and subfulminant viral hepatitis in an area endemic for hepatitis B: application and limitations of the polymerase chain reaction. *Hepatology*, 1994, 19(4): 836-840.
- [23] Desai P, Banker DD. Hepatitis B and delta viruses in fulminant hepatitis. *Indian J Gastroenterol*, 1990, 9(3): 209-210.
- [24] Irshad M, Acharya SK. Hepatitis D virus (HDV) infection in severe forms of liver diseases in north India. *Eur J Gastroenterol Hepatol*, 1996, 8(10): 995-998.
- [25] Gu X, Li Q, Wang Y. The prevalence of serum viral hepatitis markers in patients with hepatitis D virus infection. *J Pract Hepatol*, 2004, 7(3): 135-137.
- [26] Gu X, Li Q, Wang Y. Clinical characteristics of the patients with hepatitis B combining hepatitis D infection. *Zhonghua Gan Zang Bing Za Zhi*, 2014, 9(1): 34-36.
- [27] Fu J, Guo D, Gao D, et al. Clinical analysis of patients suffering from chronic hepatitis B superinfected with other hepadnaviruses. *J Med Virol*, 2016, 88(6): 1003-1009.
- [28] Xu L, Zhang X, Cao Y, et al. Digital Droplet PCR for Detection and Quantitation of Hepatitis Delta Virus. *Clin Transl Gastroenterol*, 2022, 13(7): e00509.
- [29] Zheng RJ, Talafu T, Deng ZR, et al. Sero-epidemiological characteristics of the hepatitis D virus infection among hepatitis B virus infected-patients at a single center in Xinjiang region. *Zhonghua Gan Zang Bing Za Zhi*, 2022, 30(10): 1044-1049.
- [30] Wu JC, Chen PJ, Kuo MY, et al. Production of hepatitis delta virus and suppression of helper hepatitis B virus in a human hepatoma cell line. *J Virol*, 1991, 65(3): 1099-1104.
- [31] Wang J, Yin SX, Zhu L, et al. HBeAg Negativity is Associated with a Higher Risk of Liver-Related Death in Patients with Chronic Hepatitis B Related Liver Cirrhosis. *Dis Res*, 2022, 2(1): 1-8.
- [32] Gan W, Chen Y, Wu Z, et al. Characteristics of Patients with Cryptogenic Cirrhosis: A Retrospective Study. *Dis Res*, 2021, 1(1): 14-17.

- [33] Sung JJ, Tsoi KK, Wong VW, et al. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. *Aliment Pharmacol Ther*, 2008, 28(9): 1067-1077.
- [34] Angelico R, Trapani S, Manzia TM, et al. Liver transplantation for hepatitis D virus/hepatitis B virus coinfection in Italy: An intention-to-treat analysis of long-term outcomes. *Am J Transplant*, 2025, 25(7): 1502-1514.
- [35] Loglio A, Viganò M, Goisis L, et al. Bulevirtide improves liver function in candidates for liver transplant with advanced HDV cirrhosis and severe portal hypertension. *Liver Transpl*, 2025, 31(2): 254-258.
- [36] Degasperis E, Anolli MP, Jachs M, et al. Real-world effectiveness and safety of bulevirtide monotherapy for up to 96 weeks in patients with HDV-related cirrhosis. *J Hepatol*, 2025, 82(6): 1012-1022.
- [37] Ma Z, Wu L, Lu F. Maintenance Mechanism of Chronic HBV Infection and the Strategy for Functional Cure. *Dis Res*, 2024, 4(2): 81-86.
- [38] Vlachogiannakos J, Papatheodoridis GV. Hepatitis B: Who and when to treat? *Liver Int*, 2018, 38 Suppl 1: 71-78.
- [39] Schmidbauer C, Chromy D, Schmidbauer VU, et al. Epidemiological trends of HBV and HDV among Viennese HIV + patients. *Liver Int*, 2021, 41(11): 2622-2634.
- [40] Miao Z, Zhang S, Ou X, et al. Estimating the Global Prevalence, Disease Progression, and Clinical Outcome of Hepatitis Delta Virus Infection. *J Infect Dis*, 2020, 221(10): 1677-1687.