Hepatitis D infection and risk of hepatocellular carcinoma: a systematic review and meta-analysis of observational studies

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1 INTRODUCTION

More than 80% of all cases of **hepatocellular carcinoma** (HCC) can be attributed to chronic viral hepatitis (caused by hepatitis B, C and D viruses – HBV, HCV and HDV respectively) and both HBV and HCV are classified by the World Health Organization as oncogenic viruses.

Hepatitis D, the result of a concomitant infection with both HDV and HBV, is considered the most severe form of chronic viral hepatitis.

The impact of HDV infection on the risk of HCC is, however, debated. It was for long considered that the incidence of HCC in chronic hepatitis D (CHD) patients was similar to that of HBV monoinfected patients, without any contribution of HDV *per se* and that the major complication of CHD was decompensated cirrhosis, not HCC. However, recent evidence from cohort studies suggests a significant increase in the risk of HCC in CHD patients.

2 AIM

We conducted a systematic review and meta-analysis of epidemiological studies to examine whether chronic HDV infection is associated with an increased risk of HCC compared to chronic HBV monoinfection.

3 METHODS

We searched Pubmed, Embase and Web of Science databases for studies indexed from database inception until January 2018, with no language restriction.

Search terms referred to **hepatitis D**, **liver disease progression** and **hepatocellular carcinoma**. We also searched study references and conference proceedings for additional studies.

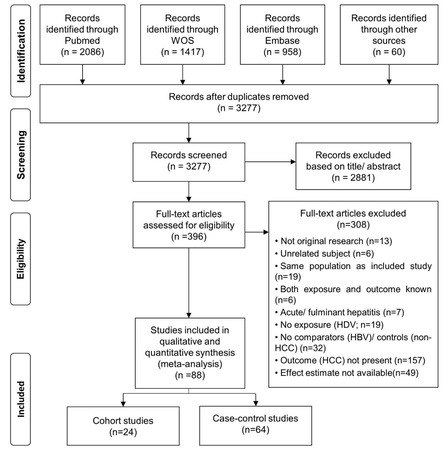
We considered **cohort** and **case-control** studies allowing the calculation of effect estimates for the **association between chronic hepatitis D and hepatocellular carcinoma, in comparison to chronic hepatitis B virus monoinfection.**

The primary exposure was **chronic hepatitis D** and the outcome was any diagnosis of **hepatocellular carcinoma**.

Data extraction was performed independently by two authors using predefined data fields, including quality indicators, according to the Newcastle-Ottawa Scale. Data were pooled using **random-effect models**.

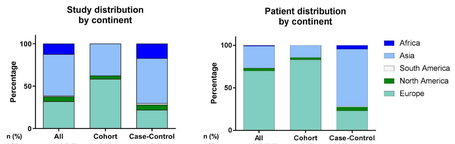
4 RESULTS

A STUDY SELECTION PROCESS



A. PRISMA flow diagram outlining search strategy and selection of the included studies. Eighty-eight studies (**24** cohorts and **64** case-controls) were included in the meta-analysis.

B CHARACTERISTICS OF THE INCLUDED STUDIES

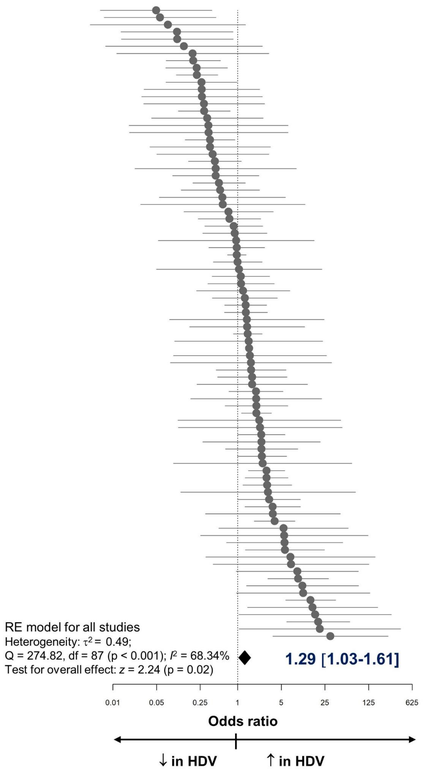


n (%)	All	Cohort	Case-Control
Africa	11 (12.5)	0 (0)	11 (17.2)
Asia	43 (48.9)	9 (37.5)	34 (53.1)
S. America	1 (1.1)	0 (0)	1 (1.6)
N. America	5 (5.7)	1 (4.2)	4 (6.2)
Europe	28 (31.8)	14 (58.3)	14 (21.9)
TOTAL	88	24	64

n (%)	All	Cohort	Case-Control
Africa	897 (0.9)	0 (0)	897 (4.3)
Asia	24661 (25.8)	10662 (14.2)	13999 (67.4)
S. America	190 (0.2)	0 (0)	190 (0.9)
N. America	2914 (3.1)	2008 (2.7)	906 (4.4)
Europe	66942 (70)	62152 (83.1)	4790 (23)
TOTAL	95604	74822	20782

B. Geographical origin of the included studies, by type of study. A total of **95604** patients were included (74822 from cohorts and 20782 from case-control studies). The majority (70%) of the patients were included in European studies.

C OVERALL META-ANALYSIS

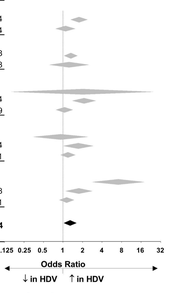


C. Caterpillar plot of the overall meta-analysis for the association between chronic hepatitis D and hepatocellular carcinoma, using chronic hepatitis B as a comparator. Data from each included study (n=88) are represented as OR (dot) and 95% CI (line). Measures of association were pooled as OR and 95% CI using the inverse variance technique. **We identified a significantly higher risk of HCC in patients with CHD, in comparison to HBV monoinfection.**

D SUBGROUP ANALYSIS

Subgroup analysis	Studies (n)	Patients (n)	Pooled OR (95% CI)	p-value	I^2
Study design					
Cohort	24	74822	1.77 (1.31-2.38)	<0.001	63.94
Case-control	64	20782	1.09 (0.77-1.54)	0.64	68.64
Risk of bias					
Low (NOS<5)	67	91565	1.32 (1.04-1.67)	0.02	66.78
High (NOS<5)	21	4039	1.24 (0.62-2.49)	0.55	73.28
Age					
Children	2	131	2.01 (0.16-24.56)	0.58	0
Adults	26	60851	2.11 (1.39-3.2)	<0.001	66.64
Undefined	61	34622	1.05 (0.78-1.41)	0.76	66.69
HCV co-infection*					
Yes	7	102	0.92 (0.35-2.40)	0.86	0
No	22	19453	1.72 (1.01-2.92)	0.04	69.04
Undefined	66	75862	1.19 (0.92-1.55)	0.19	69.31
HIV co-infection					
Yes	4	997	7.13 (2.83-17.92)	<0.001	0
No	11	19781	1.76 (1.10-2.81)	0.02	56.28
Undefined	73	74826	1.14 (0.88-1.48)	0.32	69.81
Overall	**88**	**95604**	**1.29 (1.03-1.61)**	**0.02**	**68.34**

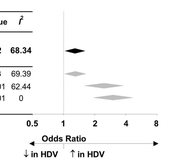
* One hundred and eighty seven HCV+ patients from Béguelin et al 2017 were not included in the analysis as no information was available on the incidence of HCC in this group



D. Forest plots of the subgroup analysis. Studies were classified according to design in **cohorts** and **case-controls**. The **risk of bias** was evaluated using the Newcastle-Ottawa Scale and a cut-off of 5 points was applied to separate studies with high (NOS<5) and low risk of bias (NOS≥5). The **children** subgroup included patients <18 years old; the **adult** group included studies for which it was possible to exclude patients <18 years old based on the information provided and one of the following criteria: lowest value of the age range for all patients ≥18 years old or lower limit of the 95% confidence of the mean ≥ 18 years old. All the studies for which it was not possible to exclude children were grouped as unknown. For **HCV** and **HIV** infection, the same criteria was applied: the non-coinfected group included patients from studies where the presence of a coinfection was an exclusion criteria, as well as, in the case of HCV, subgroups of patients for which it was possible to exclude coinfection. Four of the included cohorts encompassed only HIV infected patients. It was possible to pool data from HCV infected subgroups for 7 studies. Patients from the remaining studies where the presence of coinfection was not evaluated or not enough information was provided to analyze sub-groups, were pooled as unknown.

E SENSITIVITY ANALYSIS

Sensitivity analysis	Studies (n)	Patients (n)	Pooled OR (95% CI)	p-value	I^2
Overall	**88**	**95604**	**1.29 (1.03-1.61)**	**0.02**	**68.34**
Full-text articles	80	91074	1.30 (1.02-1.65)	0.03	69.39
Matched or adjusted studies	11	63755	2.46 (1.59-3.80)	<0.001	62.44
Prospective studies	11	7065	3.02 (1.94-4.70)	<0.001	0



E. Forest plots of the sensitivity analyses. Meta-analysis were conducted including only: studies available as **full-text**; studies adjusting for confounders by **matching or adjustment**; **prospective** studies.

5 CONCLUSIONS

- This review found a significantly **higher risk of hepatocellular carcinoma in patients with chronic hepatitis D**, in comparison to chronic hepatitis B virus monoinfection (**OR 1.29; 95% CI 1.03-1.61; p=0.02**).
- The association was **particularly strong in studies with more robust design**, namely in prospective cohort studies (pooled odds ratio 3.02; 95% CI 1.94-4.7; p=<0.001; I2=63.94%), and in **HIV-infected patients** (pooled odds ratio 7.13; 95% CI 2.83-17.92; p<0.001; I2=0%).
- This observation underlines the burden of hepatitis D virus infection and its additional oncogenic potential and reinforces the need for accrued HDV screening and the development of novel and effective antiviral medicines.

6 ABBREVIATIONS

CHD, chronic hepatitis D
CI, confidence interval
HBV, hepatitis B virus
HCC, hepatocellular carcinoma
HCV, hepatitis C virus
HDV, hepatitis D virus
HIV, human immunodeficiency virus
NOS, Newcastle Ottawa Scale
OR, odds ratio
WOS, Web of Science

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8 CONTACT

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