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

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.

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.

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.

RESULTS
A. PRISMA flow diagram outlining search strategy and selection of the included studies. Eighty-eight studies (34 cohorts and 84 case-controls) were included in the meta-analysis.

B. Geographical origin of the included studies, by type of study. A total of 10,604 patients were included (7,892 from cohorts and 2,712 from case-control studies). The majority (70%) of the patients were included in European studies.

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=48) 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. 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 group as unknown. For HCV and HDV 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 HDV 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. 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.

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 1.34-4.7; p=0.001; I2=63.94%), and in HIV-infected patients (pooled odds ratio 7.13; 95% CI 2.63-17.82; p<.0001; 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 medications.

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