Reviewer’s report

Title: Hepatitis viruses infection and risk of intrahepatic cholangiocarcinoma: evidence from a meta-analysis

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Reviewer: Giovanni Brandi

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Major comments

The systematic review written by Zhou and colleagues tries to address an important question: are hepatitis B virus (HBV) and hepatitis C virus (HCV) associated to the risk of intrahepatic cholangiocarcinoma (ICC)? The relevance of a meta-analysis aimed at answering this question could be high.

Unfortunately, the work by Zhou and colleagues presents severe limitations and in the current form does not provide a reliable answer to the research question.

My suggestion is that the authors should refer to the PRISMA statement and to the PRISMA checklist to improve their work.

The main limitation of the submitted manuscript is the lack of a formal evaluation of the quality (and the risk of bias) of the studies included in the meta-analysis. This process is compulsory when conducting a systematic review (see PRISMA statement or Cochrane Handbook).

Furthermore, the inclusion and exclusion criteria for the studies on HBV/HCV and ICC are not clearly stated by the authors (see again PRISMA checklist).

Also, the search strategy used by the authors is really limited. They searched only two database, as Cochrane Library is not useful for etiological studies (it only index systematic reviews on intervention studies or diagnostic tests).

Moreover, the search string was based only on three MeSH terms (actually, intrahepatic cholangiocarcinoma in a supplementary concept and not a MeSH term). The author should expand their search strategy using a more articulate string (for instance, including terms like “bile duct neoplasms”) and more databases (e.g. Scopus). And why the authors considered only studies in the English language? I think that they should at least include also studies in their native language.

In the manuscript the authors states “Abstracts, letters, editorials and expert opinions, reviews without original data, studies that were not published as full reports, case reports and studies lacking control groups were excluded. Have they used the limit functions in PubMed? If yes, they should reconsider this choice. Using the limit function is a threat to the comprehensiveness of the literature search, as pertinent articles indexed incorrectly could be excluded.

In the manuscript the authors concluded:

“In conclusion, in this meta-analysis of 13 case-control studies and 3 cohorts, we
found that HBV and HCV infection are associated with an increased risk of ICC, but these impacts might be different across different countries or areas.”

I don’t think that such a strong conclusion on the geographical variation is supported by their analysis of the data. The authors only looked for the (statistical) significance of the estimates within countries (e.g. “Both HBV and HCV infection showed significant relation to ICC in Taiwan”). This approach is weak and is opposite to the principles that underlie a meta-analysis.

To formally evaluate a possible geographical gradient a meta-regression should have been performed. Furthermore, they did not evaluate the risk of bias in single studies; hence, are they evaluating a causal geographical variation or a casual variation of biased estimates?

Minor comments
Page 3, line 22, Mesh should be MeSH (Medical Subject Heading).
Page 4, line 14. The paragraph is entitled “Selection of trials”; I suppose that the title should be “Selection of studies”.

Specific questions
1. Is the question posed by the authors well defined? YES
2. Are the methods appropriate and well described? NOT
3. Are the data sound? NOT
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? NOT
5. Are the discussion and conclusions well balanced and adequately supported by the data? NOT
6. Are limitations of the work clearly stated? NOT
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? YES
8. Do the title and abstract accurately convey what has been found? YES
9. Is the writing acceptable? YES

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests