

Jin-Xin Kong  
Science editor,  
World Journal of Gastrointestinal Pathophysiology  
May 21<sup>st</sup>, 2016

**Re: ESPS Manuscript 26369 entitled "Hepatitis C infection and Renal Cell carcinoma: A Systematic Review and Meta-analysis"**

Dear Editor,

Thank you for the thoughtful input and review of our manuscript. The reviewers' inputs are extremely helpful. We believe as a result of this review, our study would have more value for your readers. We revised the manuscript based on the reviewer's suggestions. We have attached our point by point response.

Thank you for your time and consideration. We look forward to hearing from you.

Sincerely,

**Wisit Cheungpasitporn, M.D.**  
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## Response to Reviewer

### Reviewer: 1

#### Comment to the author

The authors attempt to review the published literature by meta-analysis to examine if HCV hepatitis is related to renal cell carcinoma. In the introduction the authors mention the extra-hepatic manifestations of HCV and the connection with non-Hodgkin's lymphoma and also hepatocellular carcinoma. The mechanism of HCC with HCV is by the development of cirrhosis and not as an extra hepatic manifestation and I think this difference needs to be noted. The statistical analysis appears to be robust but needs to be assessed by a statistician. The main criticism I have is of the results. The authors find an increased risk for HCC in patients with chronic HCV hepatitis but after they adjust for the inclusion of studies that have confounder adjustment there is an insignificant trend. In addition there may be a publication bias. The authors also try to explain a biological association between HCV infection and renal cell carcinoma. In summary, I think the manuscript deserves to be published mainly for the reason that it can stimulate further studies to address this possible link. Since we are now in the era of effective oral treatment with direct-acting antivirals it maybe that in the long-term there could be a decrease in the incidence of renal cell carcinoma which has public health benefit. Perhaps a comment on this point may be needed.

Response: We thank you for reviewing our manuscript. We really appreciated your input. We agree with the reviewer and have added the information in our manuscript as following:

We added the mechanism of the association between HCV and HCC. It now reads "chronic HCV infection has been demonstrated to be associated with Hepatocellular carcinoma (HCC) by increased the degree of liver inflammation and fibrosis rather than specific oncogene activation".

Our statistical analysis has been assessed and analyzed by well-trained statisticians who have experiences in analyzing and interpreting data.

We agree with the reviewer that the sensitivity analysis revealed marginally insignificant after including studies with confounder adjustment. The funnel plot demonstrated a small publication bias in this study. However, the sensitivity analysis remains increased pooled risk ratio even though without reaching statistical significance. We believe that it is the consequence of limited number of included studies and lack of power. Therefore, further studies are needed to demonstrate this association. We also addressed the publication bias in limitation part. It now reads "it should be noted that funnel plot was suggestive of a small publication bias in studies

with a positive correlation between HCV infection and RCC. The possibility of selection bias could play a role in chart-reviewed population base study.”

We added the comment from reviewer to the discussion part. It now reads “Since direct-acting antiviral (DAA) agents have been demonstrated to be effective treatment of HCV infection, they may decrease the incidence of RCC in HCV patients in the long term.”

## **Reviewer: 2**

### Comments to the Author

The manuscript is an interesting meta-analysis about the correlation of HCV infection and RCC development. The aim of the meta-analysis is clearly stated and methods are well-described. However, results are too concise and not clearly described; I suggest to better describe the study process and literature review in the results section.

Response: We thank you for reviewing our manuscript. We really appreciated your input. We agree with the reviewer and have added the information in our manuscript as following:

We addressed the reviewer concerns and described the study process in the method and literature review in the result section as following:

Study process has been added more detail. It now reads “Three investigators (K.W., C.T., and W.C.) independently reviewed the titles and abstracts of the studies identified in the search based on inclusion and exclusion criteria. The full text of the included studies from the first phase was reviewed independently to determine whether or not they met the inclusion criteria. We also performed a manual search of conference proceedings from major gastroenterology and hepatology meetings for additional abstract on the topic. When additional information was needed, we contacted the corresponding investigators of eligible studies.”

Literature review process in the result section, we added one study in the literature review process that did not contain data on specific viral hepatitis (Hepatitis B or Hepatitis C). The study demonstrated the association between viral hepatitis and RCC, not viral hepatitis C and RCC. Therefore, we could not include this study to our

meta-analysis. We addressed this study reference in the results part of literature review process. It now reads “Macleod et al study did not contain data on specific viral hepatitis.” We added characteristics of included studies. It now reads “Four studies were conducted in Europe, 2 in the United States, and 1 in Australia.” We also added more details in evaluation of publication bias. It now reads “Two authors (K.W. and W.C.) independently performed the assessment of risk of bias of the included studies. Only minor disagreements between 2 reviewers were present and were resolved by discussion and consensus.”

### **Reviewer: 3**

#### Comments to the Author

The authors present a well-written, well-constructed study of an interesting correlation. It is acceptable for publication, though I wonder why the authors did not include the large study from UW. J Urol. 2013 Nov;190(5):1657-61. doi: 10.1016/j.juro.2013.04.130. Epub 2013 May 9. Risk factors for renal cell carcinoma in the VITAL study. Macleod LC1, Hotaling JM, Wright JL, Davenport MT, Gore JL, Harper J, White E.

Response: We thank you for reviewing our manuscript. We really appreciated your input. We found this article in the literature review process. However, the study did not contain data on specific viral hepatitis (Hepatitis B or Hepatitis C). The study demonstrated the association between viral hepatitis and RCC, not viral hepatitis C and RCC. Therefore, we could not include this study to our meta-analysis. We addressed this study reference in the results part of literature review process. It now reads “Macleod et al study did not contain data on specific viral hepatitis.”

Thank you for great and helpful suggestions.

Sincerely,

**Wisit Cheungpasitporn, M.D.**

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