

Rome, December 1st, 2021

To the Editor

We thank you for the opportunity to submit a revised version of our manuscript. The Reviewers' comments allowed us to greatly increase the quality of the paper, which we hope will be now amenable to publication in the World Journal of Gastroenterology.

Below is the response to the Reviewers' comments.

Reviewer #1:

- 1- Firstly, the information about HDV is one of the parts in the text. However, it is not mentioned in the abstract, core tip, and conclusion. Considering that many reviews regarding HDV-caused HCC have been published in recent years (e.g., PMID: 25914778, 32039360, 34064419, etc.), combined that the authors have not described its mechanism in-depth, it is suggested to delete this part. If the authors don't want to delete it, please add the information about HDV in the abstract, the core tip, and the conclusion section, and extend the mechanism of HDV.

Thanks to the Reviewer for these suggestions, we enriched and extended the description of molecular pathways in HDV-related oncogenesis (page 17 line 25-30; page 18 and 19) and added it in both the core tip (page 2 line 4) and the abstract (page 1 line 12).

- 2- Secondly, from the title, the authors will introduce the risk factors involving viral hepatitis associated with HCC. However, it's not mentioned in the text. On the contrary, the authors focus on the environmental factors in the introduction. It is suggested to demonstrate the risk factors involving viral hepatitis associated with HCC.

Thanks to the Reviewer for this comment, we modified the title accordingly. As we think that the full description of risk factors for viral hepatitis is beyond the aim of the present review, we summarized them in Table 2.

Thirdly, in the text about the molecular pathway of HBV/HCV and HCC development, the authors introduce it according to the classification of viral proteins and different molecular mechanisms. It is suggested to summarize it according to one kind of logic.

Thanks to the Reviewer for this comment, as suggested we organized the text in paragraphs with a more organized structure.

- 3- Fourthly, it is better to add illustrators to exhibit the molecular pathways of HBV and HCV-induced HCC.
- 4- Fifthly, there are some spelling and grammar mistakes in the text. The authors need to check the whole text carefully.

Thanks to the Reviewer for these comments, we added illustrations of molecular pathways in both HBV/HDV and HCV settings and revised the text to avoid grammar mistakes.

Reviewer #2:

- 1. Different in molecular expression of both major viruses (hepatitis B and C)

Thanks to the Reviewer for your precious suggestions, we listed the different pathways involved in HBV, HDV and HCV carcinogenesis in summary Table 5 and 6 and in Figure 1 and 2.

- 2. Different in clinical manifestation and management of both HBV-, HCV-related HCC

Thank you for the comment, we wrote a new paragraph about differences in clinical manifestation between HBV and HCV related HCCs (page 32 lines 3-19). The differences in surveillance were already reported in the specific paragraphs and in Table 4 and 7.

Reviewer #3:

1. Authors may add some informative figures or tables to describe molecular pathways.

Thanks to the Reviewer this suggestion, we added Figure 1 and 2 to describe HBV, HDV and HCV molecular pathways involved in carcinogenesis.

2. The abstract and core tips only mentioned HBV and HCV. In the main text, HDV composes an important part which has not been mentioned.

Thanks for this comment, we mentioned HDV also in the core tip and in the abstract.

Reviewer #4:

1. Better division of Chapters and sub-chapters

Thanks to the Reviewer for this suggestion, we summarized and divided all molecular pathways according to a selection logic; we divided viral factors from environmental factors and classified them to guarantee a better readability to our manuscript.

2. Correction of the many languages and spelling mistakes, the most important of them is writing hepatitis B abbreviations as follows HBsAg, HBeAg, HBcrAg.....and so on

Spelling mistakes were amended in the text.

Reviewer #5:

-However, this MS is more like a textbook.

According to the Reviewer comment, we shortened the length of the manuscript.

- There are 267 references cited, but most of them were published ten or twenty years ago, which cannot exhibit recent advances in this field.

Thanks for this important suggestion, we updated the references, reduced the number and eliminated the older ones.

(1) Science editor:

- reconsider the title as regards the term "clinical management". Indeed, in the manuscript the authors do not specifically address the clinical management of viral hepatitis and/or hepatocellular

carcinoma; but discuss the clinical surveillance for hepatocellular carcinoma in the context of viral hepatitis. Please, consider this point.

Thanks, we reconsidered the title, replacing the term “management” with “surveillance”.

- authors should complete their manuscript with one or more representative figures (see also reviewers’ comments) to summarize their discussion and conclusions

According to this suggestion, we added some informative figures and some tables to describe HBV, HDV and HCV molecular pathways involved in HCC.

- Authors used 267 references: even though the paper is very broad and long, I would suggest the authors to double check and use those who are essential, especially as regards the most dated ones, as observed by one of the reviewers.

As requested, references have been reduced and updated.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

As requested, we edited the table according to the standards.