REVIEWER#1

In this paper, The prognostic role of metformin in diabetes mellitus type 2 patients with hepatocellular carcinoma was studied, which was innovative. This is a good paper about the relationship between metformin and diabetes mellitus type 2 patients with hepatocellular carcinoma. The methods described in sufficient detail for materials, statistical analysis and others. The results of research that support the conclusions. The conclusions is a reasonable extension of the Metformin and relevant impact in preventing adverse effects after HCC treatment. The study's design, data presentation, and citations comply with standard COPE ethical guidelines. Although this manuscript has strong practicability, there are still several points to be explained.

1. Metformin is one of the main drugs for the treatment of diabetes. One item in the user manual is not recommended for patients with severe liver injury. Therefore, the patients with hepatocellular carcinoma in this study may have different degrees of liver injury, which is inconsistent with the drug instructions.
Authors' response: We agree with the Reviewer. We added the following sentence in the part dedicated to the limitations of the study.
"Lastly, HCC patients often present an underlying liver disease, with different degrees of severity. Metformin is contraindicated in patients which severe liver injury, therefore adding a potential bias in the results reported."

2. The quality of the 13 studies included should be scored to illustrate its quality.
Authors' response: We added a figure clarifying the quality of the selected studies.

REVIEWER#2

Comments: Metformin, a low-cost oral hypoglycemic drug, has been proposed to have antitumor effect. Several meta-analyses have shown that metformin can reduce the risk of hepatocellular carcinoma in patients with diabetes. This meta-analysis tried to evaluate the effect of metformin in preventing HCC adverse events (i.e., death, tumor

progression, and recurrence) after HCC treatment. The results showed that the combined ORs were not statistically significant. This research can guide clinical practice and provide direction for future research. However, major revision should be considered before publication as following suggestions.

Introduction 1. Two related meta-analyses have been published recently, and both have positive results (doi: 10.3389/fendo.2021.1060768; doi: 10.1016/j.clinre.2021.101781). The authors can quote and explain the similarities and differences with these studies in introduction or discussion section. In addition, the authors can search the literatures included of previous meta to check whether there is any missing study in his own research.

Authors' response: We checked for the proposed studies. The first one (10.3389/fendo.2021.1060768) identified only 6 articles (vs. 13 in our meta-analysis), all of them coming from Eastern coutries, in which cases receiving almost exclusively curative therapies were considered. Cosequently, despite a larger number of articles was initially considered for the PRISMA process, at the end many relevant articles were missed by the authors. Introducing their research terms on pubmed ("hepatocellular carcinoma" OR "liver cancer" OR "liver tumor" OR "HCC", "type 2 diabetes mellitus" OR "diabetes mellitus" OR "T2DM" OR "DM", "metformin" OR "dimethylguanylguanidine"), only 6 (!) articles have been identifyied, showing a criticism in the selection process.

As for the second study (10.1016/j.clinre.2021.101781), the research was similar to the one performed in the present study (pubmed as research engine). The main difference is that this meta-analysis focused not only on prognosis, but mainly on the diagnosis of HCC (namely the risk of developing HCC receiving or not metformin). Therefore, the articles selected were more. When a separate analysis on post-treatment survival was done, only 9 studies were selected (vs. 13 in our meta-analysis). The differences in the results are caused by the fact that these authors missed some article.

As a consequence, we did not add any comment on the discussion, because the reason for the differences in the results respect to our reported ones derived by the fact that the other meta-analyses missed some studies. However, if the Reviewer thinks that it is relevant to add these considerations more in detail, we can surely do that in a second revision of the article.

Methods 2. If the study has been registered, please provide the registration website name and registration number in the methods section. If not, I suggest that the authors register this meta-analysis.

Authors' response: We thank the Reviewer for the comment. We have registered the study on PROSPERO (code: CRD42023416686).

3. After searching two databases, the authors initially produced 107 documents to be screened. This number is relatively small. The authors can try to search other databases to increase the number of included documents.

Authors' response: We agree that the number of initial studies was small, but looking at the other meta-analyses on the same topic, despite the use of a larger amount of databases, in the end the number of selected studies was even smaller respect to our. So, we think that the problem was not to add duplicate articles at the beginning, but doing a good job in the PRISMA selection process, and to check with attention the references of every selected study.

4. I suggest that the authors conduct sensitivity analysis to further explore the stability of the results. In addition, publication bias should also be tested, especially for more than 10 studies.

Authors' response: We performed as required the sensitivity and the publication bias analyses. We added the funnel plot and the statistical analyses in the text.

Results 5. The authors only used one sentence to describe the quality evaluation of included studies, and I recommend giving a figure or table to show the results more intuitive and convincing.

Authors' response: We added a figure for clarifying the quality of the studies.

6. In "Death in HCC patients with T2DM receiving vs. not receiving metformin" part, the authors only selectively displayed the subgroup received curative therapies, and I suggest that the subgroups that did not receive should also be displayed. In addition,

subgroup analysis can also be carried out by country or race to explore whether there are differences in the role of metformin among different races.

Authors' response: We thank the Reviewer for the comment. We added the analysis focused on patients only receiving a palliative approach. We also performed a sub-analysis focused on the origin of the study (Western vs. Eastern country). We reported the results in the text.

Minor point: Some abbreviations are included in Table 1, 2 and 3. Please give the full name below the table.

Authors' response: We clarified the abbreviations.

REVIEWER#3

I think the topic of study is interesting. In the table number 1(study 2) USA should be written in capital letters.

Authors' response: We thank the Reviewer for the overall positive comments. We modified accordingly.