

4 June 2021

Dear Editor and Reviewer,

Please find enclosed the revised version of our manuscript entitled “Hepatocellular Carcinoma in Patients with Renal Dysfunction: Pathophysiology, Prognosis, and Treatment Challenges”.

Thank you for reviewing our manuscript. We feel that all the comments are very helpful in improving the legibility, objectivity and scientific evaluation of the manuscript.

In the revised manuscript, in accordance with the valuable suggestions of the reviewers, we have made various modifications. All the revised parts are highlighted in red with Microsoft Word “Track Changes” function. The answers made are detailed, point-by-point, in a letter to the reviewer.

We hope that the revised manuscript will retain your attention, and you will judge the revised manuscript to be suitable for publication in *WJG*.

Thank you

Yours truly,
Tzung-Hai Yen

Reviewer#1:

Specific Comments to Authors: This manuscript describes the pathogenesis and treatment challenges of hepatocellular carcinoma with renal insufficiency from many aspects, which is rich in content and combined with clinical practice. However, there are still some problems in this manuscript.

1. In the abstract part, the sentence "this study first summarizes the possible causes of the high morbidity of HCC and renal dysfunction" describes that "this manuscript summarizes the relationship between HCC and renal insufficiency for the first time". The above description is a bit far fetched because many reviews have described "the relationship between HCC and renal insufficiency". For example, "Ho SY, Hsu CY, Liu PH, et al. Survival of Patients with Hepatocellular Carcinoma in Renal Insufficiency: Prognostic Role of Albumin-Bilirubin Grade. *Cancers (Basel)*. 2020 Apr 30;12(5):1130."

Response: We apologize for the inappropriate term. We adopt the word "first" to refer to the initial paragraphs of our article but not that our article is the first relevant work. We have removed the inappropriate term. Please refer to line 6 of the revised abstract and line 2 of the revised conclusion section. Thank you for your comment and the valuable reference.

2. The common immune checkpoints include PD-1, tim3 and CTLA-4. The author only described the relationship between PD-1, CTLA-4 and HCC, but not the relationship between tim3 and HCC.

Response: Thank you for pointing out this important question. Immune-based therapy is an innovative approach that has offered new promise in cancer treatment, and TIM-3 is indeed a potential therapeutic target in addition to the well-known CTLA-4 and PD-1. Although it has not been approved by the FDA, its promising role in anti-cancer treatment really should be included in our review. We thoroughly did a review of the available data on this topic, including mechanisms of its anti-cancer effects and ongoing clinical trials with the possible renal effects. Please refer to the last paragraph of the revised section "5.2 immunotherapy".

3. Jeon MY 等在 2020 年的最新文献讲述了“恩替卡韦和替诺福韦对乙型肝炎病毒相关性肝癌患者肾功能的影响”，而本综述貌似没有提到“恩替卡韦和替诺福韦”，建议将上述参考文献添加进去。（参考文献：Jeon MY, Lee JS, Lee HW, et al.

Entecavir and tenofovir on renal function in patients with hepatitis B virus-related hepatocellular carcinoma. J Viral Hepat. 2020 Sep; 27(9):932-940.) The latest literature of Jeon my et al. In 2020 describes "the effect of entecavir and tenofovir on renal function of patients with hepatitis B virus associated liver cancer", but this review seems not to mention "entecavir and tenofovir", so it is suggested to add the above references.

(References: Jeon MY, Lee JS, Lee HW, et al. Entecavir and tenofovir on renal function in patients with hepatitis B virus-related hepatocellular carcinoma. J Viral Hepat. 2020 Sep; 27(9):932-940.)

Response: Thank you for your impressive comment. Truly antivirals during hepatocellular carcinoma treatment and their effect on renal function are important and debated issues. We had modified our manuscript accordingly and focused on the anti-hepatitis B virus (HBV) nucleos(t)ide analogues (NUCs) with high potency. Please refer to the section "6. Antivirals use during HCC treatment" in the last part of the manuscript. Because of space constraints, we did not cover the hepatitis C virus (HCV) antiviral therapy, which includes various direct antiviral agents (DAAs). However, to our knowledge, the DAAs' effect is not directly related to the risk reduction of HCC, and its prescription during HCC treatment is less frequent than NUCs therapy.

4. The content of this review is very long, but no page number is added.

Response: Thank you for the comment. We have added page numbers to make our article more reader-friendly.

5. The reference "Sarno G, Montalti R, Giglio MC, Rompianesi G, Tomassini F, Scarpellini E, De Simone G, De Palma GD, Troisi RI. Hepatocellular carcinoma in patients with chronic renal disease: Challenges of interventional treatment. Surg Oncol 2020; 36: 42-50" was published in 2021. 2020 should be changed to 2021.

Response: We have corrected the typo error. Thank you for reminding us.

