

## Response to Reviewers

### Response to reviewer #1

**Comment 1:** The study assesses a current, timely topic in HCC. An extensive linguistic revision is required. We believe this article is suitable for publication in the journal although some revisions are needed. The main strengths of this paper are that it addresses an interesting and very timely question and provides a clear answer, with some limitations. Certainly, the authors should better highlight the limitations of the current paper. - The background of the changing scenario of medical treatment in HCC should be better discussed, and some recent papers regarding this topic should be included ( PMID: 32772560; PMID: 37535194; PMID: 36579504 ; PMID: 35031442 ).

**Reply 1:** We greatly appreciate the reviewer's positive comment. Accordingly, we have revised it as follows (Lines 78-91 in the highlight marked manuscript):

“Hepatocellular carcinoma (HCC) is the most devastating type of liver cancer [1], often diagnosed at an advanced stage, with a high mortality rate and aggressive clinical course. The well-known risk factors of HCC include age, sex, alcohol consumption/abuse, environmental toxins, chronic HBV and HCV infection, aflatoxin exposure, and non-alcoholic fatty liver disease [2].

Liver transplantation, radical surgical resection, and radiofrequency ablation are commonly used in early-stage disease. However, most patients do not qualify for radical treatment and are treated with systemic or local treatment instead [3]. Advanced HCC always presents poor prognosis, although several new treatment modalities has been proposed, such as immunotherapy and trans-arterial chemoembolization plus systemic treatments [4-6]. Therefore, exploring effective therapeutic targets for HCC is of great importance to both individuals and society.”

## **Response to reviewer #2**

**Comment 1:** Dear Editor, thank you so much for inviting me to revise this manuscript about HCC. A linguistic revision is needed before eventual publication. A professional service is recommended since it is not possible to accept the paper in its current linguistic form. This paper addresses a current topic. The manuscript is quite well written and organized.

**Reply 1:** Really appreciate the reviewer's positive comment.

**Comment 2:** English should be improved.

**Reply 2:** We have asked a native English speaker to help revise the manuscript.

**Comment 3:** Figures and tables are comprehensive and clear.

**Reply 3:** We have resized the pixels of the Figures and Tables.

**Comment 4:** The introduction explains in a clear and coherent manner the background of this study. We suggest the following modifications: \* Introduction section: although the authors correctly included important papers in this setting, we believe the evolving systemic treatment scenario for HCC should be briefly discussed and some recently published papers added within the introduction ( PMID: 32772560; PMID: 35031442 ; PMID: 33820447; PMID: 37535194 ), only for a matter of consistency. We think it might be useful to introduce the topic of this interesting study. \* Methods and Statistical Analysis: nothing to add.

**Reply 4:** We greatly appreciate the reviewer's positive comment. Accordingly, we have revised it as follows (Lines 78-91 in the highlight marked manuscript):

“Hepatocellular carcinoma (HCC) is the most devastating type of liver cancer [1], often diagnosed at an advanced stage, with a high mortality rate and aggressive clinical course. The well-known risk factors of HCC include age, sex, alcohol consumption/abuse, environmental toxins, chronic HBV and HCV infection, aflatoxin

exposure, and non-alcoholic fatty liver disease [2].

Liver transplantation, radical surgical resection, and radiofrequency ablation are commonly used in early-stage disease. However, most patients do not qualify for radical treatment and are treated with systemic or local treatment instead [3]. Advanced HCC always presents poor prognosis, although several new treatment modalities has been proposed, such as immunotherapy and trans-arterial chemoembolization plus systemic treatments [4-6]. Therefore, exploring effective therapeutic targets for HCC is of great importance to both individuals and society.”

**Comment 5:** \* Discussion section: Very interesting and timely discussion. Of note, the authors should expand some parts, including a more personal perspective to reflect on. For example, they could answer the following questions - in order to facilitate the understanding of this complex topic to readers: What are the knowledge gaps and how do researchers tackle them? How do you see this area unfolding in the next 5 years? We think it would be extremely interesting for the readers. We believe this article is suitable for publication in the journal although major revisions are needed. The main strengths of this paper are that it addresses an interesting and very timely question and provides a clear answer, with some limitations. We suggest a linguistic revision and the addition of some references for a matter of consistency. Moreover, the authors should better clarify some points.

**Reply 5:** Really appreciate the reviewer’s positive comment. Accordingly, we have revised it as follows (Lines 227-233 in the highlight marked manuscript):

“Historically, chronic viral hepatitis was the main etiologies of HCC; however, nonalcoholic fatty liver disease (NAFLD) and related metabolic factors have emerged as the fastest-growing risk factors of HCC in recent years. The relationship between lipid and HCC is complex, so more investigations are anticipated to continue over the next decade. Understanding the role of cholesterol in HCC development will contribute to developing new therapies.”