

Date: 19<sup>th</sup> December, 2023

Dear Editor,

I hope this letter finds you well. I am pleased to submit revision of our manuscript entitled " Global Trends in Hepatitis C-Related Hepatocellular Carcinoma Mortality: A Public Database Analysis (1999-2019)" for consideration for publication in the World Journal of Virology.

The point-by-point response to reviewer questions is included below.

Thank you for considering our submission. I eagerly await feedback and am open to making any necessary revisions.

Warm Regards,

Hassam Ali, MD

Reviewer comments:

I would like to thank the authors for their important work. Notes on the manuscript: Title: is very long and repetitive please modify, I also suggest adding that it is a public accessed database.

**Author response:** Thank you for your valuable feedback. We have revised the title to "Global Trends in Hepatitis C-Related Hepatocellular Carcinoma Mortality: A Public Database Analysis (1999-2019)" to ensure it is succinct and clearly reflects the use of a publicly accessible database.

In the abstract: the authors wrote "We also identified noticeable trends relating to gender, providing insights into demographic groups that are disproportionately affected." >> please clarify what do you mean by "demographic groups that are disproportionately affected" is it that gender is unequally presented?

**Author response:** Thank you for the suggestion. We understand that the mentioned line is part of the Core Tip, not the abstract. The phrase "demographic groups that are disproportionately affected" refers to the unequal presentation of gender in hepatitis C-related HCC mortality rates, as detailed in our analysis.

Introduction: it is not clear what the authors mean by "seismic shift" there is no geological background to the topic.

**Author response:** We intended it metaphorically; However, recognizing that this may lead to confusion, we have revised this word.

Results: the authors wrote first overall males and females then each region without subtitles or any indications where the females and males belong to, please clarify in subtitles.

**Author response:** Thank you for your feedback. To avoid an confusion, we have provided sub headers of regions with overall and gender based rates within one regional subheader only.

Discussion:

1- there is a lot of restating the results previously mentioned, please remove duplication and concentrate on finding the reasons behind the mortality trends and the effects it have on the populations.

**Author response:** We appreciate your feedback on the duplication of results in our manuscript. We have removed some repetitive elements for clarity. However, we retained certain aspects to ensure a smooth flow and coherence in our discussion, which we believe is crucial for comprehensively understanding the reasons behind mortality trends and their effects on populations. Our goal is to provide a detailed yet clear exposition of our findings within the context of wider literature.

2- The authors state “The primary risk factor for HCC in Sub-Saharan Africa is chronic infection with the hepatitis B virus (HBV), particularly prevalent in West Africa. This factor contributes significantly to elevated mortality rates; however, it is essential to note that HCV is not associated with this heightened incidence.” This is out of scope as a reason for HCV related mortality please omit.

**Author response:** Thank you for your insight. This line has been removed.

3- The authors stated “HCV cure is associated with a decreased risk of HCC in Sub-Saharan Africa; however, the risk persists after sustained virological response in patients with cirrhosis, necessitating ongoing surveillance”>> could you add the metaanalysis done on the effect of DAAs on HCC, as there was much debate on this topic, and is very relevant to mention this debate.

**Author response:** Thank you for suggesting the inclusion of studies mentioning the effect of Direct-Acting Antivirals (DAAs) on HCC. We have incorporated these studies.

4- The authors keep repeating the HCV vaccination as the cure to the disease, and fail to compare the actual presentation (in percentages of cure rates) of HCV in the interferon era and the DAAs era, which is a great medical breakthrough. Please don't mention vaccination except in the introduction or once in the discussion as it is not relevant.

**Author response:** Thank you for your comments. We mention the term "vaccination" only once in our manuscript, acknowledging its limited relevance to our study's focus. Our manuscript is more epidemiological in nature, not a review article, and we do not present worldwide data on HCV treatment. We aim to compare HCV incidence and mortality trends across different regions and periods, rather than detailing cure rates or medical breakthroughs. The emphasis on vaccination in our manuscript is minimal and appropriately placed.