# ANSWERING REVIEWERS

**Name of Journal:** World Journal of Experimental Medicine

**Manuscript NO.:** 98543

**Column:** Meta-Analysis

**Title:** Statins decrease the risk of hepatocellular carcinoma in metabolic dysfunction-associated steatotic liver disease: A systematic review and meta-analysis

## Reviewer 1:

Scientific Quality: Grade B (Very good)

Novelty of This Manuscript: Grade A (Excellent)

Creativity or Innovation of This Manuscript: Grade B (Good)

Scientific Significance of the Conclusion in This Manuscript: Grade B (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

**Specific Comments to Authors:**

Thank you for the important research point. You performed a systematic review and meta-analysis to study the effect of statin use on the occurrence of HCC in patients with underlying MASLD and elaborated the role of high dose statins in the prevention of HCC in patients with MASLD. The study concluded that statin use is associated with a reduced risk of HCC in MASLD patients. A higher cumulative daily dose and lipophilic statin decrease the risk of HCC in MASLD patients. This is the first meta-analysis to assess the variation in HCC risk between statin-using and non-statin-using MASLD patients. Two of the included studies were retrospective; one was a case-control, and one was a prospective cohort.

1. The total number of patients in the analysis was 291,684. Of these, 80,246 were statin users, whereas 211,438 were not under therapy with statins. The mean age of the study

population was 57.0 ± 12.2 years. Please correct the percentage: Further, 49.9% (136,804) were male, and 53.1% (154,880) were female; their sum should be 100%.

Response: Thank you for pointing out this error. The correction has been made as: "Further, 46.9% (136,804) were male, and 53.1% (154,880) were female." Please see Section Results, Subsection Literature Search and Study Selection, and Sentence 7.

2. Do all included patients in the study have advanced fibrosis or liver cirrhosis?

Response: The studies we analyzed had patients both with and without cirrhosis. We have now included the details on this point in the revised manuscript. Please see Table 1.

3. Please mention the median duration of follow-up to calculate the risk of HCC.

Response: We have added the follow-up duration in the revised manuscript. Please see Table 1.

4. You studied the effect of lipophilic versus hydrophilic statins on the development of HCC: please mention the names of the drugs in the included studies.

Response: Unfortunately, studies we examined did not specify individual drugs into these classes.

5. Did the included studies mention the side effects of high versus low dose statins particularly in cirrhotic patients?

Response: No, adverse events were not reported.

6. You mentioned in the discussion section that "a few studies have shown that the use of a higher dose of statin has no significant benefit over a lower dose in the prevention of HCC [80,81]." What was the difference in study design and inclusions between these studies and the others that showed that statins reduced the risk of HCC? You analyzed the data based on the dose of statins and concluded that > 600 cumulative defined daily

dose (cDDD) decreases the risk of HCC by 70 % (RR = 0.30, 95%CI: 0.21-0.43), whereas administration of 300-599 cDDD and 30-299 cDDD of statins decreases the risk by 29% (RR = 0.71; 95%CI: 0.55-0.91) and 43% (RR = 0.57; 95%CI: 0.40-0.82), respectively. Thank you so much.

Response: The study performed by Chiu et al. [80] showed no difference based on cumulative statin dose, and they mentioned that the likely reason for not finding the difference was the small number of subjects in the study. The study by Friedman et al. [81] has also not provided a detailed reason. Moreover, they studied the effect of statins on patients with different types of cancers. We have made the modification as: "However, these studies had limitations such as a small sample size and simultaneous inclusion of patients with different types of cancers." Please see Section Discussion, Paragraph 5, and Sentence 8. Thank you for your insightful comments.