

## **Impact of alcohol consumption on treatment outcome of hepatocellular carcinoma patients with viral hepatitis who underwent transarterial chemoembolization**

Dear editor,

We want to thank the editor and reviewers for their constructive criticism and insightful suggestions, which have helped us improve our manuscript. We have revised the manuscript and answered the reviewers' questions point-by-point as suggested. Additionally, we have modified the manuscript according to the editor's suggestion. Please see the responses below.

Reviewer 1

1. Abstract "We hypothesized that alcohol had a synergistic effect with chronic viral hepatitis infection on treatment outcomes after transarterial chemoembolization (TACE) in patients with intermediate-stage HCC". The above sentence needs to be re-written for more clarity so that general reader can also understand

Answer: Thank you for your insightful comment. The word "synergistic effect" has been changed to "additional effect" for more clarity, and we also added the explanation for intermediate-stage HCC as "Barcelona Clinical Liver Cancer [BCLC] B".

The sentence noted in your comment has been justified as follows: "We hypothesized that alcohol had an additional effect with chronic viral hepatitis infection on treatment outcomes after transarterial chemoembolization (TACE) in patients with intermediate-stage HCC (Barcelona Clinical Liver Cancer [BCLC] B)." (Line 52-55)

2. AIM "To evaluate the combinatorial effect of alcohol on treatment outcomes after TACE in HCC patients with chronic viral hepatitis". The combinatorial effect need to be replaced with an alternate term. The above sentence needs to be re-written for more clarity

Answer: Thank you for pointing this out. We have changed the "synergistic effect" to "additional effect" for more clarity. (Line 57-58)

3. Please give clarification for the below point base on the rules and regulation of human ethical studies "The need for informed consent was waived because of the retrospective nature of the study"

Answer: We apologize for the mistake. The need for informed consent was waived because of the study's retrospective nature which minimized the disadvantages that may occur to the participant, and the patient information was de-identified before analysis.

To reduce potential misunderstanding, we have modified the sentence to “The need for informed consent was waived because patient information was de-identified before analysis” (Line 129 - 131)

## RESULTS

4. “The proportion of male patients (66.0% vs. 100%, P=0.007) and mean serum albumin level ( $3.6 \pm 0.7$  vs  $3.2 \pm 0.4$ , P=0.017) in group A were higher than those in group B”. The sentence seems to be with no clarity. connection between male patients and serum albumin level

Answer: Thank you very much, the mentioned sentence has been modified to “The proportion of female patients in group A was higher than that in group B (34.0% vs. 0%, P=0.007). When compared between the two groups, serum albumin level in group A was significantly higher (mean  $\pm$  SD =  $3.6 \pm 0.7$  g/dL vs  $3.2 \pm 0.4$  g/dL, P=0.017), while serum aspartate aminotransferase (AST) level in group B was significantly higher (median [IQR] = 63.0 [42.0 to 116.0] mg/dL vs 96.5 [73.5 to 155.0] mg/dL).” (Line 206-211)

5. “There were no significant differences in tumor characteristics between the two patient groups” Please justify the observation in discussion part

Answer: Thank you for your comment. The tumor characteristics, including the number and size of tumors were not significant between the two groups.

We have noted this observation as follows: “According to the tumor characteristics, there were no significant differences in the number and size of tumors between the two groups. Patients with chronic viral hepatitis concurrent with alcohol consumption developed a lower rate of CR and had decreased survival rate after TACE than those who had chronic viral hepatitis alone.” (Line 254-260)

6. Discussion need a little modification that each result need to be discussed with suitable reference for substantiating the observations

Answer: Thank you very much. Our previous description “Kubo et al. demonstrated that proportion of well-differentiated HCC was higher among those with massive alcohol consumption than those without alcohol use” was wrong. We have corrected it to “proportion of well-differentiated HCC was lower among those with massive alcohol consumption than those without alcohol use” and added more convincing data in this paragraph. (Line 297-300)

7. A graphical abstract will be helpful for understanding the abstract It is better to include graph for few tables.

Answer: We agree with you. However, there is no provision for uploading a graphical abstract in the "World Journal of Hepatology."

Reviewer 2

The paper focused on a very interesting topic. Herein, alcohol was identified as a risk factor which would influence the prognosis of HCC patients with chronic viral hepatitis and TACE treatment.

Some issues to be addressed:

1. The description of "alcohol had a synergistic effect with chronic viral hepatitis infection" might be insuitable. Current evidence only indicated that prognosis of HCC patients with chronic viral hepatitis and alcohol consumption was poorer than those only with chronic viral hepatitis.

Answer: Thank you for pointing this out. We have changed the "synergistic effect" to "additional effect" for more clarity. (Line 57-58)

2. Several studies indicated that clinically relevant portal hypertension was associated with prognosis of HCC patients treated with TACE (PMID: 29218611; 34918471). It was recommended to supplement the presence of portal hypertension in Table 1. Meanwhile, HBV-DNA, AST/ALT and DCP of patients in group A and B should also be supplemented.

Answer: Thank you for this valuable suggestion. The variables of the presence of portal hypertension, HBV DNA viral load, AST, and ALT have been added in Table 1 along with corresponding descriptions. (Line 206-211 and 263-267)

However, because the Des-gamma-carboxy prothrombin was unavailable in our center, we could not add this variable in Table 1.

3. Please update Ref [1-3] and corresponding descriptions.

Answer: We apologize for the use of outdated references. References 1-3 have been replaced with current studies. (Line 101-105)

4. The manuscript needs to be polished. Some of the descriptions are colloquial and not professional. Please pay attention to the grammar and the word spelling.

Answer: Thank you very much. We have modified the tone of the manuscript to be more formal and sent it for editing by a native speaker before submitting the revised manuscript.

We are submitting our revised manuscript for consideration and hope you will agree that our study is of sufficient priority to warrant publication in the "World Journal of Hepatology".

Yours sincerely,

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