Responses to Reviewers

Reviewer #1 (code 02861131)

1. Abstract: it is not gives a delineation of the research background.

Response

We added the sentence regarding the purpose of this study to clarify a delineation of the research background.

2. Introduction: Classically, in this part need to include aim of the study.

Response

We added the aim of this study to the end of the Introduction section.

3. Methods: clear delineated how subjects were selected, how clinical data was collected, how were performed histological evaluation and statistical analysis (methodology) many persons were evaluated before the selection patients for this study?

Response

We retrospectively examined the prevalence of hepatocellular carcinoma occurrence in the NAFLD patients who were diagnosed as NAFLD/NASH by liver biopsy. We added the related statements to the Methods section.

4. Results: Too many section in result- not bad to merge section Comparison of clinicopathological features at the time of biopsy between the HCC and non-HCC groups With Factors related to hepatocarcinogenesis in all NAFLD patients And Comparison of clinicopathological features at the time of biopsy between the HCC and non-HCC groups in NAFLD patients with advanced fibrosis With Factors related to hepatocarcinogenesis in NAFLD patients with advanced fibrosis

Response

We merged paragraphs of the Results sections as possible.

Reviewer #2 (code 03262379)

The authors assessed the risk of hepatocarcinogenesis in NAFLD individuals consuming alcohol less than 20 g in comparison to those without alcohol consumption. They found that the risk of HCC is marginal in the whole cohort however in the patients with advanced fibrosis the drinking habit was significantly associated with increased risk of HCC. This study is presenting interesting and important results regarding life style of patients with NAFLD and can greatly contribute in the management of patients with NAFLD. I have few minor point which should be considered before publication.

Minor Comments:

1. In the title, "non-alcoholic liver disease" should be replaced by "non-alcoholic fatty liver disease".

Response

We are sorry for that. We revised it.

2. In comparison of the groups (drinking and non-drinking) the fibrosis was not significantly different however I guess if the authors compare the cirrhosis (F4) between the 2 groups they will see a significant difference between the groups. I suggest the authors to check it and add it to results.

Response

Thank you for your important suggestion. As you indicated, the prevalence of liver cirrhosis (F4) was higher in the mild drinking group compared to non-drinking groups (9 vs. 8 cases: 10% vs. 4%, P=0.04). We added this finding and the related descriptions to the Results and Discussion sections and Table 1.

3. In figures 1, 2 and 3, the title of parameters of X and Y axes is missing. I suggest authors to add them.

Response

We added the titles of parameters to the respective figure legends.

Reviewer #3 (code 00069130)

I have read the m/s titled "Mild drinking habit is a risk factor for hepatocarcinogenesis in non-alcoholic liver disease with advanced fibrosis" by Kimura T et al. This is an interesting study. The study is well conceived and the manuscript is well written. There is a paucity of literature in this area: whether small amount of alcohol has a carcinogenic effect in a compromised liver. This is very logical. A cirrhotic liver has undergone multiple rounds of futile regenerative cycles and the cells have already accumulated many mutations. In this primed context, if they are exposed to ethanol even in small amounts it will cause great stress-oxinent stress, cell death and replicative stress. Which can cause more mutations (multiple hits) and epigenetic changes resulting in cancer. It is important to note that, the amount of alcohol per hepatocyte is much more in a cirrhotic patient because the total number of healthy hepatocytes are few. The authors are requested to check the tables once again.

Response

We appreciate your comment. According to your comment, we added the following statements to the Discussion sections and cited the related manuscripts.

The net increases in oxidative stress by long-term ethanol consumption may lead to hepatocarcinogenesis in the presence of steatosis, while it is undetermined which factor is most affecting this oncogenic process[33-36]. The impact of ethanol per hepatocyte might be greater in cirrhotic patients because of the decreases in the number and function of hepatocytes. Actually, Vidal et al. reported that ALDH activity was significantly reduced in patients with advanced liver fibrosis compared with those having mild fibrosis[37]. Therefore, we presume that increased acetaldehyde and resultant DNA damage may induce pro-carcinogenic gene mutations and/or epigenetic changes, even with mild drinking, in NAFLD patients with advanced fibrosis.

Lastly, we checked the tables carefully.