**RESPONSE TO REVIEWERS**

Dear Editor

We would like to thank the reviewers for their comments and suggestions. We have revised the manuscript accordingly. Please refer to below for our responses.

**Reviewer #1**

*This retrospective study examined the role of prolonged exposure to PPI in the risk of death/liver transplant in patient with decompensated cirrhosis. Basically, the authors report an increased mortality rate in those treated with PPI for a period exceeding 3 months, having performed a statistical analysis that used propensity scores and Cox model. Data are quite convincing and tend to confirm the resulsts of previous studies. As pointed out by the authors, there are limitations which are inherent to a registry study. However, some important informations are lacking that would be of importance to support the results. 1. We expect long term exposure to PPI to increase dysbiosis, thus leading to increased risk of infections. Were « PPI users » also more « antibiotic users » ? 2. Cause of death must be given 3. It is not clear for me why non diabetic were at increased risk of death..!? 4. Authors included only patients with decompensated cirrhosis: however, the mean MELD is very low in these patients (,~11). This is consistent with ascites as a major cause of decompensation. However, there are very few SBP (that we would expect as a complications of long term PPI exposure…) Any explanations ?*

**Response:**

We would like to thank the reviewer for these insightful observations and comments.

With regards to question 1: Were there more antibiotics users amongst PPI users?

We screened patients for the use of antibiotics for which a total of 19 patients were on long term quinolone for spontaneous bacterial peritonitis prophylaxis (SBP)(mentioned in supplementary table 2). We did not investigate if PPI users were more likely to be on antibiotics than non-users for each hospital admission for decompensation. However, even if PPI users were on long term antibiotics for other diseases with immunocompromised states such as AIDS and malignancies, this would have been adjusted for in our analysis using propensity scoring.

With regards to question 2: Cause of death?

The cause of death is difficult to ascertain in this retrospective study, therefore all-cause mortality was used as an objective measurement of outcome. To illustrate this difficulty with an example, when a decompensated patient was admitted for hepatic encephalopathy (HE) but developed aspiration pneumonia and SBP then subsequently passed away, it was unclear from reviewing the patient's clinical notes and documentation if the cause of death was pneumonia or a liver related death from SBP. Due to this ambiguity, we decided on measuring all-cause mortality instead, after adjusting for baseline comorbidities making up the charlson index (Table 1).

With regards to question 3: Why were non-diabetics at increased risk of death?

The result of non-diabetic patients having a higher risk of mortality for PPI users suggests that within the non-diabetic group, PPI users had a 3.38 times higher risk of death than non-diabetic, non-users. From this, we interpreted that within the diabetic (DM) group, there was no difference in mortality whether patients were PPI users or non-users. This could be explained by diabetic patients being more likely to have cardiovascular disease with concurrent treatment on clopidogrel or aspirin. Thus, warranting PPI use and possibly the overall influence of PPI on mortality which may then be less significant. In order to minimize further confusion for the readers, we have removed the DM and non-DM groups from the tables in the main manuscript and shifted it to the supplementary data.

With regards to question 4: Are there any explanations for our fewer than expected number of patients with SBP?

The small number of patients with SBP mentioned was on index admission. We agree with the reviewer that PPI increases the risk of SBP but this is expected after PPI use and not at index event. Nonetheless there are several reasons for the smaller number. In our cohort, we removed those who used PPI more than 3 months prior to the index admission for decompensation to minimize bias. This is because PPI use has been shown to increase hospital readmissions within 3 months. Doing so would remove a proportion of patients with SBP. Also, there were fewer patients with "index event of SBP" or "history of SBP" because we only included patients who had significant PPI use within the 6 months landmark period of hepatic decompensation. After PPI use, the outcomes measured were mortality and hospital readmissions for any decompensation. SBP was not measured as an outcome.

**Reviewer #2**

*This is an interesting and well written paper regrading the impact of PPIs in mortality and hepatic decompensation events in patients with decompensated cirrhosis. The authors evaluated 295 decompensated cirrhosis patients, 238 were PPI users and 57 non-users and they found that PPI users had higher mortality compared to non-users, while longer PPI use was associated with higher mortality, compared to non-users. Finally, PPI users had a higher incidence of hospitalization for hepatic decompensation.*

We would like to thank the reviewer for the insightful comments and observations. Please refer to our responses below.

*Major issues:*

1) *The authors did not provide the causes of mortality (liver related or not)*

As explained in our response to the first reviewer above, the cause of death is difficult to ascertain in this retrospective study, therefore all-cause mortality was used as an objective measurement of outcome. To illustrate this difficulty with an example, when a decompensated patient was admitted for hepatic encephalopathy but developed aspiration pneumonia and SBP then subsequently passed away, it was unclear from reviewing the patient's clinical notes and documentation if the cause of death was pneumonia or a liver related death from SBP. Due to this ambiguity, we decided on measuring all-cause mortality instead, after adjusting for baseline comorbidities making up the charlson index (Table 1).

2) *Although the authors used propensity score, important baseline characteristics were different between PPI users and non-users.*

The Table 1 data represents baseline characteristics **before** propensity scoring was done for analysis, the differences found were adjusted for.

3) *"In the 6-month landmark cohort, 102 of 238 (42.9%) PPI users and 43 of 57 (75.4%) non-users died" but after adjustment the result was the opposite ("PPI users had a higher risk of overall mortality, compared to non-users with adjusted HR…". How did the authors explain this great change after adjustment?*

We have reviewed our results and this is a typographical error. We sincerely apologize for the confusion. 13 of 57 (22.8%) non-users died during the median follow up period of 551 (IQR 231-1017) and 584 (289-1152) days, respectively. This has been amended.

4) *Can the authors provide more data regarding decompensation events (SBP, encephalopathy, infections etc)*

We have decided to omit this data in our manuscript because current evidence already supports the increased risk of SBP and HE with PPI use. Furthermore, a patient admitted to the hospital for decompensated cirrhosis could also have multiple hepatic events eg variceal bleeding and HE in the same setting. It would be difficult to tabulate these separately over the study follow up period. Thus, we simplified our data presented to risk of hospital admissions.

5) *The authors should add more clinical studies regarding this topic and discuss their findings*

Thank you very much for the suggestion, we will look into this.