



Gyongyi Szabo, M.D., Ph.D.

*Worcester Foundation for Biomedical Research Chair
Associate Vice Provost for Interprofessional Education in Research
Associate Dean for Clinical and Translational Sciences
Director MD/PhD Program
Professor and Vice Chair for Research
Department of Medicine
364 Plantation Street, LRB 208
Worcester, MA 01605-4321
Tel: 508-856-5275 Fax: 508 856-4770
Gyongyi.Szabo@umassmed.edu*

Koo Jeong Kang, MD, PhD, Professor
Department of surgery
Keimyung University Dong-San Medical Center
Daegu 41931, South Korea

Nikolaos Pyrsopoulos, FACP, FRCP (C), MD, PhD, Director, Professor, Research Scientist
Gastroenterology and Hepatology
Rutgers New Jersey Medical School, University Hospital
Newark, NJ 07103, United States

March 5, 2019

Dear Dr. Kang and Dr. Pyrsopoulos:

Thank you for the opportunity to submit the revision of our original manuscript entitled "Proton Pump Inhibitor use Increases the Severity of Hepatic Encephalopathy in Cirrhotic Patients: A Single Academic Center Experience". We greatly appreciate the positive comments and enthusiasm of the reviewers for our work. In the enclosed revised version, we have addressed all of the concerns and questions raised by the Reviewers. Below we provide point-by-point responses for your convenience.

Reviewer #1:

This study seeks to evaluate a hot topic right now, which is the association of the use of PPIs to any particular disease. This topic in special (hepatic encephalopathy), although, has a good background research and this association might be a casual one, but more studies are still needed to define as such, mostly prospective ones, since sometimes the cause of the outcome is the reason for the patient to be on PPIs. The proposed study meets its aim, analyzing thoroughly the gathered data. It is well known that PPIs should not be prescribed lightly, and this study comes to aid us in such decision. Although, some points need to be looked at:

Comment 1: Abstract: The first two sentences can be removed and the third sentence kept as AIM. In the objective session, describe the type of study and design.

Response 1: These changes were made to the manuscript.

Comment 2: Introduction: some abbreviations first used are not explained. The introduction is long, but it is effective in explaining the purpose of the study. You could consider to remove some basic information, since the article is meant to be published in an Hepatology journal.

Response 2: We have clarified all abbreviations in this section and would like to keep the short discussion paragraph on the basic science relevance as it stands now. We respectfully suggest that discussion some of the possible mechanistic explanations behind the biology for our findings will be useful information for clinical hepatologists.

Comment 3: Methods: You certainly have found through an ICD search more than 103 patients. Please describe the number of total patients found and the reasons for them to be excluded from the study. I suggest to present the data regarding each grade of encephalopathy as a table.

Response 3: We have attached an additional Table (Table 3) with the information requested by the Reviewer.

Comment 4: Results: Very well described.

Comment 5: Discussion: I suggest that in the text or in the limitations paragraph, you should stress that this study is unable to define causality, but just association. As we have found in previous studies regarding PPI and some diseases, sometimes the association does mean cause. Sometimes the reason for the patient to be using PPIs might be the cause of the outcome. Overall, it is also well written.

Response 5: We agree that this is a very important point and we have included this now point in the limitations section as the Reviewer have suggested.

Comment 6: References: You need to review them. For instance, in the text you cite Hung et al. and put the number 23 in the end of the phrase. Reference number 23 does not refer to the cited article in the text, which would be (<https://www.ncbi.nlm.nih.gov/pubmed/29551615>). You also should cite one of the most important papers on the subject (<https://www.ncbi.nlm.nih.gov/pubmed/27474889>).

Response 6: We appreciate the Reviewer's comment and apologize for the mistake in the citations.. These changes were made and reflected in the revised Reference section.

Reviewer #2:

I would like to make important Specific Comments related your work: 1) We noticed in your study: Original findings: PPI use in cirrhotic patients is associated with more severe degree of hepatic encephalopathy compared to those not on a PPI. In addition, PPI use was associated with a longer hospital stay and higher percentage of patients requiring an ICU admission. 2) We noticed also: Clinical importance: management of cirrhotic patients Conclusion: summarize appropriately the study data Key problem: - Retrospective review limit (e.g. follow up evaluation) - Uneven distribution about PPI user and no PPI user patients - Small sample size (Power lack): impacting on some secondary outcomes 3) Future direction: Further randomized-controlled, prospective studies are needed to help confirm above observation.

Comment 1: The reviewer requested evidence of alcohol-induced microbiota translocation across the intestinal barrier.

Your work could have been related to a retrospective study focused on the association between Proton Pump Inhibitors (PPIs) and Hepatic Encephalopathy (HE) severity in cirrhotic patients with HE status. Your manuscript looks like ARRIVE Checklist. Please, see my comments:

1) Study motivation/context statement is enough well documented as well as the method.

2) The study limits are described.

3) Observation related manuscript writing and/or presentation:

a. Observations or mistakes to take into account:

- Title page: I noticed you do not describe clearly author's contributions. I would have wished you describe the roles related primary, secondary and senior author in your work.

Response 1: We have made these changes and they are reflected in our manuscript and title page.

Comment 2: Institutional review board statement: you noticed "none" however you provided IRB form.

Response 2: We have updated the title page to include: The study was reviewed and approved by the University of Massachusetts Medical School Institutional Review Board Approved Protocol # H00012102

Comment 3: Abstract: Conclusion: line 3: Please, delete the mark "-"

Response 3: This has been fixed and corrected in the abstract section

Comment 4: Method section: Patient selection: line 2 and 3: Please delete the coma "," (for instance: January 1"," 2012). Data collection: "semi-stupor" instead "semistupor"

Response 4: These changes have been made in the patient selection and data collection section.

Comment 5: Results section: demographics sub-section: you noticed the frequencies for demographics and drug use data (PPI, lactulose). I would have wished you consider "demographics and clinical characteristics" or "demographics and drug use data". In this "results section" you noticed data about "lactulose" without describe it in anywhere "above section". You provided also the "table 2" that's not noticed in the text.

Response 5: We have made the changes suggested by the Reviewer in the results section. We also clearly marked the reference to Table 2.

Comment 6: Format: Reference in the text does not match the journal requirement (for instance Introduction section: line 5: ".....world ^[1]" instead ".....world (1)"

Response 6: We have changed the references as suggested.

Comment 7: Reference: - Text: I have difficult to browse Ref 2 "The neurological changes in the more common types of severe liver disease" from Google and Pubmed may be very hold reference.

Response 7: We agree, this appears to have been written in the 1950's which may be difficult to find and is not in pubmed. Thus, we have deleted one of the references that was not readily discoverable by Google search.

Comment 8: Some reference citation in reference section need to be explicit and/or complete: issue number miss often. I would have wished you consider these observations.

Response 8: We have included the complete issue number for all references as suggested.

Comment 9: In addition I would like to make important Specific Comments related your work:

1) We noticed in your study:

Original findings:

PPI use in cirrhotic patients is associated with more severe degree of hepatic encephalopathy compared to those not on a PPI. In addition, PPI use was associated with a longer hospital stay and higher percentage of patients requiring an ICU admission.

Response 9: We have included these comments in our work and hope they are clear to the reader.

Comment 10: 2) We noticed also:

Clinical importance: management of cirrhotic patients

Conclusion: summarize appropriately the study data

Key problem:

- Retrospective review limit (e.g. follow up evaluation)
- Uneven distribution about PPI user and no PPI user patients
- Small sample size (Power lack): impacting on some secondary outcomes

Response 10: We have included these in our limitation section and again stress the need for further randomized-controlled, prospective studies

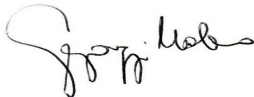
Comment 11: Future direction:

Further randomized-controlled, prospective studies are needed to help confirm above observation.

Response 11: We have again stressed this in our limitations section as well as our conclusion

We trust that, with the specific responses to the Reviewers' concerns, the revised manuscript will reach the scientific standards of *World Journal of Hepatology* for publication. On behalf of the authors, thank you for your time with the editorial decisions.

Yours truly,



Gyongyi Szabo, MD, PhD