

October 24<sup>th</sup>, 2021

**Re: Manuscript entitled “In-Hospital Mortality of Hepatorenal Syndrome in the United States: Nationwide Inpatient Sample”**

Manuscript number: 71356

Dear Editor,

Thank you for the thoughtful input and review of our manuscript. We believe as a result of this review, our study will have more value for your readers. We revised the manuscript based on the reviewers' suggestions. We have attached our point-by-point response.

Thank you for your time and consideration. If you have any additional questions or comments, please let us know.

Sincerely,



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**Response to Reviewer#1**

It's a well written paper

Response: We thank you for reviewing our manuscript. We appreciate the reviewer's expertise.

## Response to Reviewer#2

### Comment #1

I would like to thank the authors for their efforts searching National Inpatient Sample database for evaluation of in hospital mortality of patients with hepatorenal syndrome that is a major complication for patients with liver cirrhosis and grave outcomes. The use of weighting is advantageous in sampling of patients, the authors used discharge weight provided by the Healthcare Cost and Utilization (HCUP) to estimate the total number of hospital admissions for hepatorenal syndrome. In the results section they mentioned that there were 4,938 hospital admissions with hepatorenal syndrome as the primary diagnosis in the unweighted sample and 23,973 admissions in the weighted sample. The difference is very big as we are talking about hospital admissions not individual patients with multiple admissions throughout their disease course. I hope the authors could clarify the cause of this difference to the readers.

Response: We appreciate the reviewer's important points and the expertise. We agree with the reviewer and the following statements have been added to the statistical analysis section

**"The NIS database contains hospitalization data from a stratified sample of 20% of hospitals in the United States. As such, we used discharge weight provided by the Healthcare Cost and Utilization (HCUP) to estimate the total number of hospital admissions for hepatorenal syndrome."**

### Comment #2

Also, in table 1 the numbers in the second column are for unweighted sample while the third column is the percentage of the weighted sample. The authors should separate weighted from unweighted as performed in table 2.

Response: The reviewer raises important point. We agree with the reviewer and Table 1 has been changed as suggested.

### Comment #3

Kindly provide footnote for tables and figures with the abbreviation used.

Response: Footnotes for tables and figures to describe abbreviations used have been added as suggested.

### Comment #4

There are few writing mistakes probably typos errors for example; the repetition of the word "and" in the introduction, second paragraph, line 8; "male" in the first paragraph of the results section should be (males) and "coverted " at the end of data collection should be (converted).

Response: We appreciate the reviewer's thorough review. These errors have been corrected

Comment #5

Minor polish is needed. The documentation and reporting of in the patient mortality of hepatorenal syndrome is crucial but, I have another inquiry for the authors about the time frame (Why exactly the time frame chosen for this study was from 2005 to 2014 and not just the 10 years before the pandemic for example?)

Response: We agree with the reviewer. The NIS dataset is available upon purchase from HCUP. When we obtained the NIS dataset used in this study, the data was only available up to year 2014. In addition, although the NIS data in more recent years are later available (currently up to 2017), the NIS dataset starting from year 2015 used ICD-10 for diagnosis and procedure codes. In contrast, the NIS dataset from 2005 to 2014 in this study used ICD-9. Therefore, the difference in coding systems might lead to heterogeneity in identification of hepatorenal syndrome, other medical diagnoses, and procedures between period before and after 2015.

### Response to Reviewer#3

#### Comment #1

Why is paracentesis associated with reduced mortality? please discuss.

Response: We thank you for reviewing our manuscript. We appreciate the reviewer's expertise. We agree with the reviewer and additionally added discussion on reduced hospital mortality among patients who received paracentesis as suggested.

**“Possible mechanisms underlying reduced mortality among patients who received paracentesis were that those who had abdominal paracentesis received more aggressive treatments such as albumin and vasopressors, TIPS, and liver transplantation than those who received palliative care. Furthermore, abdominal paracentesis may have led to the diagnosis and treatment for spontaneous bacterial peritonitis (SBP).”**

#### Comment #2

Add the definitions of neurological disorders and coagulopathy considered for the current study.

Response: The diagnosis of neurological disorders, coagulopathy, and all other medical conditions in this study are based on ICD-9 diagnosis codes. The list of ICD-9 codes for medical diagnoses and procedures are shown in Table S1.

#### Comment #3

Hepatic encephalopathy (HE) is known to be associated with mortality (PMID: 30076614 DOI: 10.1002/hep.30208). Is it HE or other neurological disorders as well?

Response: The reviewer raises important point. We agree and thus added this discussion with suggested reference (updated reference #47) in our manuscript as suggested.

**“Hepatic encephalopathy (HE) is known to be associated with mortality,[47] and thus this could be the underlying reason for association between neurological disorder and increased in-patient mortality for HRS.”**

#### Comment #4

Discuss the reason for pulmonary failure in these patients (PMID: 33065772 DOI: 10.1111/liv.14703 can be useful.

Response: We appreciate the reviewer's important point. We agree and thus added the discussion on respiratory failure with also suggested reference (updated reference#43).

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**“Unfortunately, as of 2020, the FDA has not yet approved the use of terlipressin for HRS in the United States. Results from the phase 3 trial terlipressin did not show any significant survival benefit and its use was associated with adverse events, such as respiratory failure.[42, 43]”**

Comment #5

The treatment of HRS is not assessed in the study. If there is any data on vasoconstrictors should be added. As non-response to vasoconstrictors can also predict mortality. Please elaborate this major limitation-Maiwall R, Sarin SK, Moreau R. Acute kidney injury in acute on chronic liver failure. Hepatology international. 2016 Mar 1;10(2):245-57. Kulkarni A, Sowmya T, Sharma M, et al IDDF2020-ABS-0192 Terlipressin non-response predicts mortality in acute-on-chronic liver failure-a prospective cohort study Gut 2020;69:A87-A88.

Response: The following statements have been added to the limitation section. We also found suggested references (updated references 40 and 49) helpful and used as suggested.

**“In addition, treatment of hepatorenal syndrome was not assessed in this study.[40, 49] Data on medications including midodrine, octreotide, vasopressor, albumin infusion were not available in the database. Thus, we could not assess the effects of these agents and the response to treatments on the outcomes of HRS.”**

Comment #6

Was the MELD data not captured? MELD is considered as a predictor of mortality in patients with AKI-HRS (PMID: 30076614 DOI: 10.1002/hep.30208)

Response: The NIS database did not capture MELD data. The following statements have been added to the limitation section with suggested reference.

**“The database did not contain Model for End-stage Liver Disease (MELD) score, which predicted mortality in HRS patients.[48]”**

## Response to Reviewer#4

Kaewput et al. present the result of a nationwide, retrospective cohort study evaluating in-hospital mortality of hepatorenal syndrome in the United States. They found that in-hospital mortality among patients admitted for hepatorenal syndrome significantly improved during the analyzed period. Moreover, they identified several predictors for hospital mortality. The overall scientific quality of the manuscript is excellent and the authors must be praised for their extensive work on the subject. I have only a few comments regarding the manuscript.

Response: We thank you for reviewing our manuscript and your critical evaluation.

### Comment #1

In the results section, the length of hospital stay and hospitalization cost are presented as median values whereas in table no 1 they appear as mean +/- SD.

Response: We apologized for this error. We summarized the length of hospital and hospitalization cost as mean  $\pm$  SD in both the result section and table for consistency as suggested.

### Comment #2

In table no 1 an asterisk appearing after SE does not have an explanation below the table.

Response: We apologized for error. Asterisk was deleted. Footnote has been added.

### Comment #3

The definition of the hepatorenal syndrome has changed over the years. I understand that the national registry may not provide all the necessary answers but can authors elaborate on the diagnostic criteria of hepatorenal syndrome and whether it was uniform in the studied population?

Response: The reviewer raises very important point. We agree with the reviewer's important point and thus added this important point in the limitation of our study as suggested.

**“HRS was identified by ICD-9 diagnosis code. Given definition of the HRS has changed over the years, these changes in definition may have affected the incidence of HRS in our study overtime.”**

### Comment #4

I do agree that there are no clear indications on the use of TIPS in patients with HRS. Since mortality in patients with HRS undergoing TIPS is driven mainly by poor liver function it may be possible that there was a population selection bias and these patients had initially better liver function resulting in better survival.

Response: We greatly appreciate the reviewer's extremely helpful insight. We agree with the reviewer and thus added this important point in the discussion of our manuscript.

“Specific to this topic, there is a clear need for additional randomized controlled trials, however, in the interim, there are an increasing number of small studies demonstrating positive outcomes in select HRS patients receiving TIPS.[24, 46, 47] **Since mortality in patients with HRS undergoing TIPS is driven mainly by poor liver function it may be possible that there was a population selection bias and these patients had initially better liver function resulting in better survival.**”

**Thank you for your time and consideration. We greatly appreciated the reviewer's and editor's time and comments to improve our manuscript. The manuscript has been improved considerably by the suggested revisions.**