

Dear Dr. Ma,

We would like to sincerely thank you again for considering our article titled "Nonselective beta-blocker use is associated with increased hepatic encephalopathy-related readmissions in cirrhosis " for publication in World Journal of Clinical Cases.

We also would like to thank you, the other members of editorial staff and the reviewers for reviewing our article. Incorporation of the comments has significantly improved the quality of our article. Our point-by-point responses to the comments and questions listed in your letter are mentioned below and the manuscript is revised accordingly.

Sincerely,

On behalf of the authors,

Mohammad Amin Fallahzadeh, MD MPH

Reviewer 2:

1. Whether the use of NSBB is associated with the risk of different grades of hepatic encephalopathy-related readmissions (e.g. grades II, or III, or IV, respectively)?

-As the study was performed in a retrospective manner, details of overt HE grades were not available for all of the patients and no conclusion can be made about the NSBB association with grades of HE-related readmissions. The following sentence in 3rd paragraph of “Reconciling Data” section of Discussion was revised as follows to reflect this limitation:

“Furthermore, blood pressure, ammonia levels, precipitant factors for HE, association of NSBB use with different overt HE grades, indications/contraindications for NSBB use and diuretic/proton pump inhibitor use were not explored in our study.”

2. Is there any association between duration or dose of NSBB use and risk of hepatic encephalopathy-related readmissions?

-In performing Cox regression analysis to evaluate the factors associated with the first HE-related readmissions, the duration of taking NSBB while being in our study is already included and adjusted for in our analysis. Furthermore, as mentioned in the limitations section, the exact start and end dates of NSBB and SBB use in our patient population were not determined in all cases. So, a separate analysis evaluating the association between duration of NSBB use and risk of hepatic encephalopathy-related readmissions could not be performed. The following sentence in 3rd paragraph of “Reconciling Data” section of Discussion was revised as follows to reflect this limitation: “Although the exact start and end dates and compliance with NSBB and SBB use in all cases and hence the association between duration of NSBB use and risk of HE-related readmissions were not determined, stable estimates across a variety of subsets showed similar results.”

Considering the dose of NSBB, there were 3 different NSBB medications used in our patient population with different doses in different patients. Due to limited sample size for an individual NSBB medication and lack of a universal dose-conversion guideline for different NSBBs, a meaningful analysis exploring the association of different doses of NSBBs and risk of HE-related readmissions could not be performed in our study. The following sentence was added to 3rd paragraph of “Reconciling Data” section of Discussion to reflect this limitation:

“Due to limited sample size for an individual NSBB medication and lack of a universal dose-conversion guideline for different NSBBs, a meaningful analysis exploring the association of different doses of NSBBs and risk of HE-related readmissions could not be performed in our study.”

3. How about the stability of NSBB prescription? Is there any patients quit the NSBB use or newly prescribed NSBB during follow up?

As this study included data collected during the liver-related hospitalizations, we were only able to assess whether the patients were on NSBB right before and after the hospitalizations and not during the intervals between the hospitalizations. The following sentence in 3rd paragraph of “Reconciling Data” section of Discussion was revised as follows to reflect this limitation:

“Although the exact start and end dates and compliance with NSBB and SBB use in all cases and hence the association between duration of NSBB use and risk of HE-related readmissions were not determined, stable estimates across a variety of subsets showed similar results.”

Furthermore, we did not include the patients whose status of NSBB/SBB use got changed after the start of the study. The following sentence was added to “Study Variables” section of Materials and Methods to address this issue:

“Patients with a change in their NSBB or SBB status after the first liver-related hospitalization were not included in our study.”

4. Whether quitting NSBB use is associated with a decreased risk of hepatic encephalopathy-related readmissions?

We did not include the patients whose status of NSBB/SBB use got changed after the start of the study. The following sentence was added to “Study Variables” section of Materials and Methods to address this issue:

“Patients with a change in their NSBB or SBB status after the first liver-related hospitalization were not included in our study.”