Stefan Chiriac, MD, PhD
"Grigore T. Popa" University of Medicine and Pharmacy
St. Spiridon Clinical Emergency Hospital
1 Independentei Street, Iasi 700111, Romania
Tel +40 745 236 409, Fax +40 232246611
E-mail address: stefannchiriac@yahoo.com

Professor Lian-Sheng Ma
Founder and Chief Executive Officer
Editor-In-Chief
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: l.s.ma@wjgnet.com

Dear Editor-In-Chief,

Thank you for the response and for the valuable observations regarding our manuscript NO.: 59872 entitled "The Role of Ammonia in Predicting the Outcome of Patients with Acute-on-Chronic Liver Failure". We thank the Reviewer for analyzing our manuscript and for providing these useful comments and observations. As a result of applying these recommendations the quality of our manuscript has improved. All of the changes that we made to the original manuscript are highlighted in red. We offer a detailed point-by-point response to the Reviewer's concerns in Italics.

1. In Mortality analysis, what is the time point to calculate death?

Response:

We determined the in-hospital mortality. We added the text "The mean survival of the deceased patients was 5 (3-10) days" in the "RESULTS" section, "Mortality analysis" subsection, paragraph 1.

2. High VA is a common indicator for the diagnosis of HE. And HE is a complication for ACLF which has a prognosis role. Therefore, high VA as an inexpensive predictor of in-hospital mortality in patients with ACLF is lack of novelty. The important discovery in this paper is to find the cut-off value of VA. However, I do not consider this a point new finding can support the publication of

this manuscript. I hope that based on this big data, the authors could find more in this study, such as building a prognosis model.

Response:

We thank the reviewer for the excellent suggestion of building a prognosis model. Although we considered building a prognosis model, the absence of a validation population would not allow us to adequately validate the model. However, although building a prognosis model was not the aim of this study we would surely build it in a subsequent study.

3. It is interesting that the presence of HE was not associated with increased mortality in this study. Please make a deeper explanation.

Response:

We thank the reviewer for this comment. In our study we did not find an increased risk for mortality in patients with any-grade HE; however, patients with grade III or IV HE presented an increased risk for in-hospital death, as presented in the results section.

We added the following text ***in the "DISCUSSION" section,*** *paragraph 4: "These results are in accordance with the findings reported by Bajaj et al. The authors analyzed 1560 patients, from which 516 presented HE, 371 grade 1-2 and 145 grade 3-4. Grade 3-4 but not grad 1-2 HE was associated with both higher in-hospital and 30-day mortality rates[27]."*

In the "Refferences" section *we updated accordingly:*

We added:

"27 Bajaj JS, O'Leary JG, Tandon P, Wong F, Garcia-Tsao G, Kamath PS, Maliakkal B, Biggins SW, Thuluvath PJ, Fallon MB, Subramanian RM, Vargas HE, Lai J, Thacker LR, Reddy KR. Hepatic Encephalopathy Is Associated With Mortality in Patients With Cirrhosis Independent of Other Extrahepatic Organ Failures. Clin Gastroenterol Hepatol 2017; 15: 565-574 [PMID: 27720916 DOI: 10.1016/j.cgh.2016.09.157]"

We replaced:

"13 Joshi D, O'Grady J, Patel A, Shawcross D, Connor S, Deasy N, Willars C, Bernal W, Wendon J, Auzinger G. Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. Liver Int 2014; 34: 362-366 [PMID: 23844567 DOI: 10.1111/liv.12257]"

With:

"13 Hu C, Huang K, Zhao L, Zhang F, Wu Z, Li L. Serum ammonia is a strong prognostic factor for patients with acute-on-chronic liver failure. Sci Rep 2020; 10: 16970 [PMID: 33046732 DOI: 10.1038/s41598-020-73603-1]"

4. Please add liver background information in to the Table 1.

Response: *We added "Etiology of liver disease" in Table 2.*

5. Please add the cause of death for this study.

Response: *We added the causes of death in the "RESULTS" section, "Mortality analysis" subsection, paragraph 1.*

6. Some number in the Table2 is not matched, such as Child-Pugh class, n (%).

Response: *Some records from our database were not complete and did not allow the calculation of the Child-Pugh Class, thus they were not presented in the tables; this explains the unmatched Child-Pugh class numbers.*

We changed the order of the column information in Table 2, Row: "Venous ammonia > 152.5 µmol/L, n (%)", from 24 (70.6) 75 (19) to: 75 (19) 24 (70.6), as it was not correctly placed.

7. The Non-survivors group is 35 and Survivors group is 411. I have to say this data cannot have a good balance in this two groups.

Response: *Thank you for this observation. We agree with the reviewer that the groups of survivors and non-survivors do not have similar numbers; however, we did not specifically chose the number of patients from these groups. We did not actively populate these groups but rather performed an in-depth analysis of our main group regarding the mortality by sub-dividing this group into two sub-groups, containing survivors and non-survivors. Thus, we could not anticipate this difference.*

We thank the Science Editor for the comments and suggestions; regarding the issues raised we enclose a point-by-point response:

(1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: *Our only figure has been generated in SPSS, not in PowerPoint and thus, it cannot be fully editable in vectorial form. We have uploaded a partially editable image in power point as well as a .spv file generated by SPSS.*

(2) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text

Response: *We added the “Article Highlights” section at the end of the main text.*

The authors should provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.

Response: *We provided and uploaded the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.*

The Written informed consent is not right.

Response: *We uploaded the informed consent that was signed by all of the patients at admission.*

Best regards,

Chiriac Stefan, MD, PhD