

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "International normalized ratio and model for end-stage liver disease score predict short-term outcome in cirrhotic patients after the resolution of hepatic encephalopathy" (tracking number 48148). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have read the comments carefully and have made correction which we hope meet with approval. Revised portions are marked in red with track changes. The main corrections in the paper and the responds to the reviewers' comments are as following:

Reviewer 1 (Number ID:03253490)

Hu et al. aimed to determine predictors of early readmission and of mid-term mortality in cirrhotic patients discharged after the resolution of HE in this study. INR cut-off value for the study is well designed and the manuscript is well written. Thank you opportunity to review this study.

Response: Thanks for the reviewer's comment!

Reviewer 2 (Number ID 02871607)

1-How hypoalbuminemia (n=3) is cause of re-admission?

Response: Thanks for the reviewer's question. Actually these three cirrhotic patients had edema of both lower extremities caused by hypoalbuminemia, so we replaced "hypoalbuminemia" by "**edema of both lower extremities**" in both manuscript and study data file.

2-Is there difference between patients with first attach of HE and patients with recurrent attaches?

Response: Thanks for the reviewer's question. We divided all patients (n=213) into two groups (recurrent attaches group vs. first attach group). First, we performed a univariate analysis, finding that PTA at discharge (44 ± 15 vs. 54 ± 16 (%), $P=0.002$), INR at discharge (2.0 ± 0.6 vs. 1.7 ± 0.5 , $P=0.002$), hemoglobin at discharge (85 ± 14 vs. 93 ± 21 (g/L), $P=0.004$), INR layering (INR > 1.62 and INR ≤ 1.62) at discharge (24.7% vs. 8.3%, $P=0.001$) were significantly different between two groups. Secondly, we performed logistic regression analysis between two groups. It should be noted that we could just include either INR or INR layering at discharge in logistic regression analysis because they are the different forms of the same variable. When we included INR at discharge in multivariate analysis, we found that PTA at discharge (OR=0.965, $P=0.01$) was the only independent predictor of recurrent attaches of HE, suggesting that patients with lower PTA level at discharge were more likely to have recurrent attaches of HE. However, the OR value of 0.965 was very close to 1, which made this parameter far from a powerful indicator, so we did not discuss this finding in the manuscript.

When we included INR layering at discharge in multivariate analysis, we found that INR layering at discharge (OR=3.12, $P=0.006$) was the only independent predictor of recurrent attaches of HE, suggesting that patients with INR > 1.62 at discharge were more likely to have recurrent attaches of HE than those with INR ≤ 1.62 . In the manuscript, we have mentioned that INR cut-off value of 1.62 could be used to predict readmissions of all causes and HE is among the causes, so we did not discuss this finding in the article.

Overall, PTA level at discharge was the difference between two groups when INR was included in multivariate analysis; INR layering (INR > 1.62 and INR ≤ 1.62) at discharge was the difference between two groups when INR layering was included in multivariate analysis.

Note: We have added a categorical variable named **recurrent attaches of HE** in study data file.

3- Is there any effect of vitamin K therapy in your study?

Response: Thanks for the reviewer's question. From the study by Meyer AV et al^[1], we knew that administration of vitamin K did not affect INR changes in the cohort of hospitalized patients with cirrhosis (n=276), however, it is a single-center retrospective investigation, the efficacy of this strategy still needs verifying in trials of higher evidence, and for the rigor of our study, we are still skeptical about this finding. Meanwhile, after reviewing all the patients in our study, we found no one had received vitamin K therapy during the hospitalization and follow-up period. Therefore, we supplemented the content of "**or received vitamin K therapy**" (exclusion criteria vii) in line 18 of *Patients* part.

Editors

Response:

1. We have provided language certificate by a professional English language editing company (Elsevier Language Editing Services), and the title in the certificate is a previous one of this paper.
2. We have submitted an audio core tip whose format is mp3 on the system (File name: 48148-Audio core tip.mp3).
3. We have provided figures whose parts are all movable and editable, organized them into a PowerPoint file, and submitted as "48148 - image files.ppt" on the system.

4. Our manuscript was prepared with word-processing software, using 12 pt Book Antiqua font and 1.5 line spacing with ample margins.
5. We have added our manuscript number (48148) in the title page.
6. We have changed the abbreviations in the title to their full names.
7. We have added a running title as “Predictors of outcome in cirrhotic patients” in the title page.
8. We have modified the content of author contributions accordingly.
9. We have deleted the “S” in the “CONCLUSIONS” in the abstract.
10. We have explained all the abbreviations in the core tip.
11. We have distinguished between the title of the article series and modified second subtitles to italic ones.
12. We have modified all the P values accordingly.
13. We have added article highlights accordingly.
14. For references, we have modified the format of them accordingly; we have replaced reference 11 with another one; we have added DOI citation to reference 13 and PMID to reference 14; we have revised some parts of reference 14 according to Pubmed; and we have deleted the PMCID of reference 15 and reference 20.

15. For figures, we have used distinct colors with comparable visibility; we have changed the abbreviations in titles of table 2 and table 5 to their full names; we have explained all the abbreviations of each figure/table under each piece of figure/table legends; and we have used superscript numbers for illustration.

16. We have created another file for the supplementary Excel form and table and named the file as “48148-Supplementary material.pdf” Besides, we have modified the citation of the supplementary material in the article. (Line 23 in *Patients* part and Line 26 in *Study design* part, respectively)

17. We have added an Open-Access statement, the timeline of article publication processes and the copyright statement.

18. We have modified the citation of the article according to the file named Format for Manuscript Revision: Observational Study.

Reference:

1. **Meyer AV**, Green M, Pautler HM, Korenblat K, Deal EN, Thielke MS. Impact of Vitamin K Administration on INR Changes and Bleeding Events Among Patients With Cirrhosis. *Ann Pharmacother* 2016; **50**: 113-117 [PMID: 26586854 DOI: 10.1177/1060028015617277] [IF:2.765]

Your help and assistance is highly appreciated and I am looking forward to hearing from you.

Best regards

Yours sincerely,

Jian Gao