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OPEN PEER REVIEW

Development and Validation of a Prognostic Nomogram Based on Fibrosis-4 Index to Predict 3-Month Mortality in Patients with Hepatic Encephalopathy

Yunxuan Guan, Kai Liu, Xiujun Zhang, Caoyan Qi, Xiaolu Chen, Wenhui Zhang, Yan Chen, Yu Ma, Lina Pu, Jiahong Yuan, Niansen Lu, Chaochao Zhang, Yuan Xue

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About this report

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1 Original submission

3 comments · 14 Mar 2023 – 9 Apr 2023

Associate Editor

MINOR REVISION 14 Mar 2023

The present study constructed a non-invasive nomogram to predict 3-month mortality in patients with hepatic encephalopathy (HE). The model consisted of FIB-4 and complications including HRS, SBP and UGIB. The results showed that the newly constructed model was superior to other models such as MELD and so on. The study was overall well conducted and had clinical potential. Some minor points are listed below.
1. The inclusion criteria for the subjects should be specified in the Methods section.
2. The results of internal validation should be demonstrated.
3. What about the performance of other prognostic models such as CLIF-SOFA, COSSH-ACLF and so on?

Associate Editor

MAJOR REVISION 8 Apr 2023

First of all, I should congratulate you on this article on an interesting topic. It would be interesting to determine the prognostic values of the Fibrosisl-4 Index for predicting 3-month mortality in patients with hepatic encephalopathy.
However, the manuscript needs to be revised in terms of the introduction, methodological details, results, discussion, and mainly the language.

Abstract:
1- Please check all the keywords in PubMed/MeSH. You have to write the keywords based on MeSH. Not all of them are based on MeSH!!

Introduction:
Please do not use abbreviations at the beginning of the abstract.
Method:
1-Could you explain the missing data? Did you lose a patient to follow-up?
2- What is the difference between the survival and non-survival groups? You should explain more about these 2 groups. How did you separate the patients? What was your goal? Based on which criteria did you form the 2 groups?
Result:
1-You mentioned that: “HRS, SBP, UGIB and FIB-4, but not APRI and GPR, were independent”. What does that mean? Are these independent factors for death or HE?
You mentioned in the Discussion that: “including UGIB, SBP, and HRS, were significantly associated with the prognosis of HE”.
Please explain what you mean by independent and associated.
3-You write in the first paragraph, "There was no significant difference in HE grades between the two groups”. You did not specify how you measured the grade. How did you measure the grade?
4-You talked about the differences between the two groups, but you didn't specify in the Method section on what basis you formed the two groups or what the differences were between them.

Discussion:
1- In the second paragraph, you write "fibrosis in patients with CHB". What do you mean by CHB? You should explain it and then use the abbreviation!!
2- You mentioned that "data from univariate analyses show that age is related to HE outcomes", but you didn't mention it in your results!!! How did you find it?

3- You mentioned, "Because a high incidence of SBP occurs in patients with UGIB and ascites, antibiotics such as rifaximin may reduce the risk of SBP and mortality in HE".
Your title is not about therapy or prevention of HE!!!
Could you please mention previous articles or indicate whether the independent factors in your article are the same as those in other articles?
Or this sentence: “In addition, dehydrating agents such as mannitol are routinely used to prevent encephaledema”!!!

4- Have previous studies examined NSS and other complications related to the prognosis of 3-month mortality in patients with DC and HE?

Reference:
The references are outdated; please use more current and related references for the article, especially for the discussion section.

Editor-in-Chief

MAJOR REVISION 9 Apr 2023

Dear Authors,

Please follow the peer-review comments and submit the revision.

Regards,
EIC

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Changzhou, April 17th, 2023

Dear Editors,

We appreciate greatly the Editors and Reviewers for their helpful comments and suggestions for improving this manuscript. We have addressed the comments and suggestions and made manuscript text modifications that are presented in a revised manuscript. The changes in the revised manuscript text are highlighted. Point-by-point responses are included below and shown as blue text for ease of review.

Point-by-point response to Reviewers

Associate Editor 1:

The present study constructed a non-invasive nomogram to predicting the 3-month mortality in patients with hepatic encephalopathy (HE). The model consisted of FIB-4 and complications including HRS, SBP and UGIB. The results showed that the newly constructed model was superior to other models such as MELD and so on. The study was overall well conducted and of clinical potential. Some minor points are listed as below.

1. The inclusion criteria of the subjects should be specified in the Methods section.

Thank you for the professional comment. The inclusion criteria of the subjects have been added in the first paragraph of Methods section in the revised manuscript.

2. The results of internal validation should be demonstrated.

Thank you for the critical suggestion. Considering that the sample size was not large, we performed an internal validation using bootstrap sampling method. In the revised manuscript, we have added the AUROCs of FIBC to show its accuracy in predicting3-month mortality in the training and internal validation groups (Figure 3A and 3B). In addition, both the discrimination and calibration curves were also added to show the accuracy of the nomogram (Figure 4).

3.What about the performance of other prognostic models such as CLIF-SOFA, COSSH-ACLF and so on?

Thank you for the professional comment. CLIF-C ADs and COSSH-ACLF IIs have been added in the Methods and Results sections. The results showed that AUROCs of MELD, CLIF-C ADs, COSSH-ACLF IIs, FIB-4, APRI and GPR were 0.675, 0.637, 0.662, 0.676, 0.667 and 0.692, respectively. The AUROC of FIBC was significantly higher than those of the other indicators (all P <0.01) (Figure 4C and 4D in revised manuscript). We agree with the Reviewer that it is interesting to investigate the accuracy of CLIF-SOFA, however, it could not be scored because of the lack of variables about circulatory and respiratory systems in our study.

Associate Editor 2:

First of all, I should congratulate you for this article with interesting topic. It would be interesting to determine Prognostic values of Fibrosisl-4 Index to predict 3-month Mortality in Patients with Hepatic Encephalopathy. However, the manuscript needs to be revised in terms of introduction, methodological details, results, Discussion and mainly in the language.

ABSTRACT

1. please checks all of Key word in PubMed/Mesh. You have to write the keywords based on the Mesh. All of them are not base on Mesh!!

Thank you for the professional comment. We have searched keywords from the Mesh list, and replaced the original keywords with “Hepatic Encephalopathy; End Stage Liver Disease; Complications; Nomograms; Survival Analysis”.

INTRODUCTION

1.Please do not write the abbreviation at the beginning of the abstract.

We have added full names instead of abbreviations in the abstract.

METHODS

1. Could you explain the missing data? Did you miss a patient during follow-up?

Thank you for the critical comment. We have added the exclusion criteria in the revised flow chart (Figure 1) and Method section. In the retrospective study, more than half of the patients lost to follow-up, had insufficient data for analysis, or had underlying malignancies, were excluded.

2.What is the difference between survival and non-survival? You should explain more about these 2 groups. How did you separate the patients? What was your goal? Based on which criteria did you make 2 groups?

In the revised Method section, we have specified the endpoint of the present study, and the patients were divided into two groups according to the 3-month outcomes of those patients. Thank you.

RESULTS

1.You mentioned that: “HRS, SBP, UGIB and FIB-4, but not APRI and GPR, were independent” what’s that mean? These are independent factor for death or HE?

Thank you for the critical comment. The sentence has been corrected as “multivariate analysis showed that HRS, SBP, UGIB and FIB-4, but not APRI and GPR, were independent risk factors for 3-month mortality of HE” to be clearer.

2. Because you mentioned in Discussion that: “including UGIB, SBP, and HRS, were significantly associated with the prognosis of HE, please explain the independent and associated.

Univariate analysis showed that HRS, SBP and UGIB, FIB-4 and TBil were significantly associated with the 3-month mortality. Thereafter, the five variables mentioned above had $P < 0.05$ after univariate analysis were included in a multivariate analysis, suggesting that HRS, SBP, UGIB and FIB-4 were independent risk factors for 3-month mortality of HE. We have corrected the sentence as “complications including UGIB, SBP, and HRS, were independent

risk factors for the mortality of HE" to be clearer.

3. You write in the first paragraph, "There was no significant difference in HE grades between the two groups". You did not specify how you measured the grid? How did you measure the grid?

Thank you for the professional suggestion. We have added the criteria of HE grades in the first paragraph of the Methods section. "OHE was graded from I to IV based on West-Haven criteria [2]: Grade I: Cognitive/ behavioral decay but oriented in time and space; Grade II: Disoriented for time combing other mentioned symptoms, such as apathy or lethargy; Grade III: Unconscious but responding to stimuli; Grade IV: Coma with no response to pain."

4.You talked about the differences between the two groups, but you didn't specify in the method on what basis you formed the two groups and what the differences were between them.

Thank you for the critical comment. In the third paragraph of the revised Methods section, we have added the endpoint of the study, and the patients were divided into two groups according to the 3-month outcomes. The differences between the survivor and non-survivor groups were described in the first and second paragraphs of the Results section.

DISCUSSION

1. In the second paragraph you write that "fibrosis in patients with CHB", what you mean about (CHB)?? you should explain it and then use the abbreviation!!

We have corrected the abbreviation to "chronic hepatitis B" in the revised manuscript.

2. You mentioned that "data from univariate analyses show that age is related to HE outcomes", but you didn't mention it in your results!!! How did you find it?

Considering that FIB-4 was calculated using age as an indicator in the formula, age was not included in the multivariate analysis. While multivariate analyses were performed using GPR or APRI, age was included and data showed that neither GPR nor APRI was an independent

risk factor for 3-month mortality of HE (Table S1 and S2). It suggests that FIB-4 may be superior to GPR and APRI in predicting the outcomes of HE. We have revised the sentence in the second paragraph of the Discussion section. Thank you.

3. You mentioned, "Because a high incidence of SBP occurs in patients with UGIB and ascites, antibiotics such as rifaximin may reduce the risk of SBP and mortality in HE".
Your title is not about therapy or prevention of HE!!!
Could you please mention the previous article or independent factors in your article which are same with others or not?
Or this sentence “In addition, dehydrating agents such as mannitol are routinely used to prevent encephaledema”!!!

Thank you for the professional comment. Sentences about therapy and prevention of HE have been deleted in the revise manuscript. It is much more concise and clearer after deleting of these sentences.

4. Have previous studies examined NSS and other complications related to the prognosis of 3-month mortality in patients with DC and HE?

To the best of our knowledge, there is no study concerning the comparison of FIB-4, GPR and APRI in predicting outcomes of HE. Cui et al. has reported that HRS and UGIB are independent risk factors for 3-month mortality in patients with HE, but SBP is scarce in predicting outcomes of HE. Collectively, a new model incorporating FIB-4 and complications of DC is novel. We have mentioned the novelty of the present study in the Introduction and Discuss section. Thank you very much for the useful comments.

REFERENCES
The references are outdated; please use more current and related references for the article, especially for the discussion section.

We have updated the references and replaced them with more current and related references.

2 Revision 1

2 comments · 21 Apr 2023 – 23 Apr 2023

Associate Editor

ACCEPT 21 Apr 2023

Thank you very much for your answers!

Editor-in-Chief

ACCEPT 23 Apr 2023

Dear Authors,

I am delighted to inform you that your manuscript is accepted for publication.

Regards,
EIC