List of Responses

Dear Editors and Reviewers:
Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "*Development and validation of a nomogram for predicting overall survival in cirrhotic patients with acute kidney injury*". 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 studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in ***BOLD and ITALIC*** in the paper.

Responds to the reviewer#1's comments:

1. On "Short title", the main body of the article is "cirrhosis", so it should not be ignored, but should be included in the Short title.

Reply: Thank you very much for pointing this out, which is important for our manuscript. We have revised the Short title to "Prognosis prediction of cirrhosis with AKI" due to the rule of no more than 6 words.

2. 250 eligible patients were randomly divided into training cohort (n = 173) and validation cohort (n = 77). The difference in the number of cases between the two groups was more than twice. What method is used here? It should be clear.

Reply: Thank you very much for pointing it out. The 250 eligible patients were randomly divided into training cohort (n = 173) and validation cohort (n = 77) using the built-in random packet function of SPSS 23.0 software (Chicago, IL, USA) according at a ratio of 1:2. Previous studies were randomly divided in a ratio of 1: 2 at the discretion of the researchers (doi: 10.3389/fped.2021.641318; DOI: 10.1016/j.intimp.2018.01.007). We have revised the issue. Please see paragraph 2 of the Methods section, which were highlighted in BOLD and ITALIC.

3. In Figure 1, the total number of cirrhotic patients with AKI is 382, compared with 305 in the text (page 5). Why? Please clarify.

Reply: We are very sorry for this input mistake. As we can see, this input mistake did not affect our analysis and results. We confirm that the total number of cirrhotic patients with AKI is 382 cases. We have revised the issue. Please see paragraph 2 of the Methods section, which were highlighted in BOLD and ITALIC.

4. The logarithm based on constant e is a natural logarithm and should be recorded as lnN instead of logeN. The latter is not concise enough and should be modified. **5.** In "Calculations of the CTP, ……" section, there are four times signs (×) symbol is in Chinese format, please change it to the Western format.

Reply: Thank you for your comments and we agree with your opinion. We have revised this issue according to your comments. Please see paragraph 8 of the Methods section, which were highlighted in BOLD and ITALIC.

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6. This is a retrospective research, the cases were selected from January 2015 to December 2016, but the ICA consensus, one of the diagnostic criteria cited by the author, was published in April 2015 (according to Ref. 1). Its publication time later than the starting point of the study. How to deal with the previous cases? The author should make an explanation. Similarly, it has been more than 6 years since 2015. Why does the author limit the time to 2016 instead of now? If the research time is up to now, the number of cases can be greatly increased. Please clarify.

Reply: Thank you for your questions. In fact, these data were collected during 2016 to 2017, thus, the ICA classification was applicable to all cases at that time in this retrospective study. These patients were decided to be enrolled in a long-term follow-up then. However, during our follow-up we found that the risk factors for the short-term and long-term prognosis of cirrhotic patients with AKI may be different. The nomograms for predicting short-term and long-term prognosis should be developed and validated separately. Therefore, we first analyzed the data of the short-term follow-up. I will sort out and analyze the data of the long-term prognosis which will be published in the future.

7. Throughout the full text, all percentages expressed as (n = 190, 76.0%) or 69.6% (n = 174) should be modified to (190/250, 76.0%) or 69.6% (174/250). All confidence limits expressed as "95% CI 1.081 – 1.787" should be modified to "95% CI, 1.081 – 1.787", or "95% CI = 1.081 – 1.787", or "95% CI: 1.081 – 1.787". Choose any one and keep the full text consistent.

Reply: Thank you very much for your valuable comments, which is very helpful for us to revise the manuscript. The issues have been corrected in the full text.

8. With regard to patient selection, cirrhosis should be the first, followed by AKI. Therefore, the order of inclusion criteria (1) and (2) should be adjusted to each other.

Reply: Thank you for your comment and we agree with your opinion. We have revised the issue. Please see paragraph 1 of the Methods section, which were highlighted in BOLD and ITALIC.

9. It is equally a quantitative observation indicator. Why only the heart rate and peak SCr given the cut-off values, while other indicators do not? What is the basis for the selection of their cut-off values? Please clarify. In Figure 3, the unit of peak SCR should not be "mg/ml", but the "times baseline".

Reply: Thank you for your comments. Currently, there is no consensus on whether the quantitative variables need to be transformed into categorical variables by using cut-off values. It usually needs to be determined by its clinical implication. For example, the heart rate of 55-100 bpm is considered to be normal, while the heart rates less than 55 or more than 100 bpm are considered to be abnormal. Similarly, many studies have showed that sCr > 1.5 mg/dl was considered to be an independent risk factor for mortality of cirrhotic patients with AKI (DOI: 10.1007/s12664-020-01086-z; DOI: 10.1007/s12072-016-9756-z; DOI: 10.1016/j.clinre.2019.07.004). In addition, patients with peak SCr > 1.5 mg/dl had a higher short-term mortality rate than those with SCr ≤ 1.5 mg/dl (DOI: 10.1002/hep.20405; DOI: 10.1016/j.jhep.2013.04.036). As a result,

SCr > 1.5mg/dl has an important impact on the prognosis of these patients. Therefore, a cut-off value of 1.5mg/dL of SCr level was decided in our study, and the unit of peak SCr is “mg/ml” in the nomogram.

10. It may be more reasonable to change the “independent predictors” into “potential risk factors” in this paper.

Reply: Thank you for your comment and we agree with your opinion. We have corrected the issue in the full text.

Responds to the reviewer#2’s comments:

I read with interest the manuscript entitled "Development and validation of a nomogram for predicting overall survival in cirrhotic patients with acute kidney injury". The findings of the study are original and I think that they would be of interest for the readers of the Journal. 2. The concept they propose could be used in clinical practice to help clinicians in identifying high-risk vs. low-risk patients with cirrhosis and AKI.

Reply: We are very pleased that you show an interest in our study and appreciate your valuable comments very much.

I have come comments and questions:

1. It is not clear to me, if all patients were hospitalized or not. At some point in the discussion authors state, that they also included patients with "compensated cirrhosis", which was surprising since AKI (and 60% ACLF) is usually diagnosed in the context of acute decompensation and highly likely a hospitalisation. Authors should elaborate on the inclusion criteria, routine controls, or hospital admissions?

Reply: Thank you for your questions. Based on ICA criteria for AKI, patients with compensated cirrhosis could also developed AKI (doi: 10.1016/j.jhep.2014.12.029). Moreover, a study showed that the incidence of AKI increased gradually with progression of chronic liver disease, compensated cirrhosis and decompensated cirrhosis (doi: 10.1186/s12879-021-05991-2). In our study, the inclusion criteria were as follows: (1) Patients who were diagnosed with cirrhosis and (2) patients who met the criteria for at least one of the RIFLE, AKIN, KDIGO and ICA criteria. These patients were hospitalized. According to the inclusion criteria, patients with compensated cirrhosis was not excluded in our study. Among 250 patients who were included, however, only 7 (2.8%) patients had compensated cirrhosis, and 243 (97.2%) patients had decompensated cirrhosis. Considering that a small number of patients with compensated cirrhosis may contribute little to the overall mortality rate in this study. Therefore, the description may be more appropriate in the discussion section that patients with cirrhosis who were diagnosed with AKI in the study by Kumar U et al. only met the ICA criteria, and those patients in the studies by Fang JT et al. and Pan HC et al. only met the RIFLE criteria, while the study population in our cohort met the criteria for at least one of the main four classifications. We have revised the issue. Please see paragraph 1 of the Methods section, paragraph 1 of the Results section and paragraph 5 of the Discussion section, which were highlighted in BOLD and ITALIC.

2. What was the principle etiology of AKI in these patients, are there any data on that? Did AKI etiology actually influence the prognosis? (AKI-HRS vs. prerenal AKI).

Reply: Thank you for pointing this out and are help for us to revise the manuscript. In this study, the main causes of AKI were hypovolemia (136/250, 54.4%), followed by infections (54/250, 21.6%), nephrotoxicity (21/250, 8.4%) and other causes (39/250, 15.6%). As we all known, the presence of AKI is closely associated with the prognosis of cirrhotic patients. So far, the influence of different etiology of AKI on the prognosis of cirrhosis has been uncleared yet. However, different subtypes of AKI, which was usually divided into three subtypes: pre-renal AKI, acute tubular necrosis (ATN) and hepatorenal syndrome (HRS), have different prognosis. A retrospective study showed that compared with non-AKI patients, patients with prerenal AKI had a 2.37-fold higher risk of in-hospital death, patients with ATN had a 6.878-fold higher risk, and patients with HRS had a 12.98-fold higher risk (DOI: 10.1080/00365521.2018.1545423). Moreover, studies have demonstrated that patients with HRS-AKI have a worse prognosis than those with non-HRS-AKI (DOI: 10.3748/wjg.v27.i26.3984). The results seem to indicate that patients with AKI-HRS have a higher risk of death. In our study, we focused on developing a prognostic nomogram in predicting the prognosis of these patients. The nomogram could be used to calculate the scores corresponding to each potential risk factor, and the predicted probability corresponding to the sum of the scores represented the risk of death for patients with cirrhosis and AKI. It was applicable to predict the prognosis of any subtype of AKI in patient with cirrhosis, which may be more convenient, comprehensive and accurate to assess the prognosis of these patients. We have revised the issue. Please see paragraph 1 of Result section, paragraphs 3 and 6 of Discussion section, which were highlighted in BOLD and ITALIC.

3. The nomogram is included, but I am not sure how to use it in practice, could authors describe more in detail, how to calculate it in practice - mathematical formula is usually included.

Reply: Thank you for your comments. Previous studies on establishing model did produce a mathematical formula, but if there were many variables in this model, which will make the mathematical formula complex and difficult to be used in clinical practice (DOI: 10.7717/peerj.8497; DOI: 10.1007/s12072-016-9756-z). Nomogram is essentially a statistical visualization of the mathematical formula, which makes it more convenient and practical. The nomogram could be used to calculate the scores corresponding to each potential risk factor, and the predicted probability corresponding to the sum of the scores represented the risk of death for patients with cirrhosis and AKI. For example, patients with cirrhosis presenting AKI and diabetes had SCr level of 2 mg/dl, INR 2, grade 1 HE and blood sodium level of 130 mmol/L. The total score of the patient was approximately 118 points (SCr level of 2 mg/dl, approximately 11 points; INR 2, approximately 26 points; grade 1 HE, approximately 21 points; diabetes, approximately 22.5 points; and blood sodium level of 130 mmol/L, approximately 37.5 points.), and the probability of the overall survival at 30, 90 and 180 days was approximately 53%, 23% and 15%, respectively. We have revised the issue. Please see

paragraph 6 of Discussion section, which were highlighted in BOLD and ITALIC.

4. Were any patients of these patients liver transplanted? If so, how many, and how were they handled statistically?

Reply: Thank you very much for pointing this out. No patients who underwent liver transplantation in our study. We have revised the issue. Please see line 229 in page 9, which were highlighted in red. Please see paragraph 6 of Discussion section, which were highlighted in BOLD and ITALIC

Responds to the reviewer#3's comments:

This is a very interesting manuscript that deals with prognosis of patients with liver cirrhosis who have acute kidney injury.

Reply: We are very pleased that you show an interest in our study and appreciate your valuable comments very much.

My concern is the following: Acute kidney injury is caused by numerous different factors, e.g. nephrotoxic antibiotics, X-ray contrast media, diuretics, among others.

1. How is the underlying cause of AKI considered in the present manuscript?

Reply: Thank you for pointing this out and are help for us to revise the manuscript. In this study, the main causes of AKI were hypovolemia (136/250, 54.4%), followed by infections (54/250, 21.6%), nephrotoxicity (21/250, 8.4%) and other causes (39/250, 15.6%). Please see paragraph 1 of Results section, which were highlighted in BOLD and ITALIC.

2. The "functional kidney failure" - the hepato-renal syndrome is categorized in type 1 (bad prognosis) and type 2 (better prognosis). Does the nomogram reflect this difference.

Reply: Thank you for pointing this out and we agree with your opinion. In this study, our main objective was to focus on developing a nomogram in predicting the short-term prognosis of cirrhotic patient with AKI, rather than distinguishing the types of HRS. However, the prognosis of cirrhotic patients was affected by not only types of AKI, but also other factors, such as increased INR, the presence of HE and jaundice, sepsis, serum sodium level and other complications (DOI: 10.1007/s12664-020-01086-z; DOI: 10.1093/ndt/gfm914; DOI: 10.3748/wjg.v25.i26.3426; DOI: 10.1111/hepr.12412). If patients with cirrhosis and type 2 HRS are accompanied by hyponatremia, HE and other complications, the prognosis of these patients may be worse than those with type 1 HRS. in the present study, the nomogram could be used to calculate the scores corresponding to each potential risk factor, and the predicted probability corresponding to the sum of the scores represented the risk of death for patients with cirrhosis and AKI. It was suitable for any type of AKI patients in our study. Thus, we consider that the nomogram may be more convenient, comprehensive and accurate to assess the prognosis of these patients. We have revised the issue. Please see paragraph 6 of Discussion section, which were highlighted in BOLD and ITALIC.

3. There are many measures to treat AKI in liver cirrhosis. The high rate of patients

with ascites suggests that diuretics were given to the patients. What's about terlipressin? Influence on the nomograms?

Reply: Thank you for your comments. In this study, a comprehensive medical intervention was administered to every patient, including supportive therapy, prevention and treatment for complications, and reduction or withdrawal of all unnecessary nephrotoxic medications. Patients also received albumin, vasoconstrictors (norepinephrine and terlipressin), intravenous antibiotics, diuretics, proton pump inhibitors or continuous renal replacement therapy if required. However, the majority of patients in this study could not afford terlipressin because of the national medical insurance policy that year. In addition, many studies have demonstrated that terlipressin was effective for the improvement of HRS, but it did not seem to reduce mortality (DOI: 10.1056/NEJMoa2008290; DOI: 10.1111/apt.13912; DOI: 10.1007/s00134-018-5267-9; Gastroenterology 2016; 150: 1579-1589. e2). Please see paragraph 9 of Methods section, which were highlighted in BOLD and ITALIC.

Responds to the reviewer#4's comments:

I would like to thank for the opportunity to revise this manuscript. This was a retrospective, single center study which investigated the prognostic role of AKI in patients with cirrhosis admitted to the hospital. The Authors consecutively considered 250 patients, who were further divided in a training and a validation cohort. A nomogram was created from the training cohort to predict mortality in patients with AKI. The paper is of interest, well-written and easy to understand. The topic in of interest, although not novel.

Reply: We are very pleased that you show an interest in our study and appreciate your valuable comments very much.

1. I do not understand why the Authors used many different criteria for diagnosis of AKI. This point does not make, in my opinion, these data suitable for reproducibility in other centers. As the Authors stated, there are several definitions of AKI in cirrhosis. I suggest to revise this paper using one of these definitions (e.g., ICA classification).

Reply: Thank you for your comments and we agree with your opinion. Currently, there are four main criteria for AKI, including RIFLE, AKIN, KIDGO and ICA criteria. However, a single criterion that comprehensively evaluates and diagnoses AKI is still unavailable. As we all known, AKI is closely associated with the prognosis, and the incidence and mortality of AKI greatly varied among studies (DOI: 10.1038/srep23022; DOI: 10.5114/aoms.2019.85148; DOI: 10.1080/00365521.2018.1545423). Based on the above reasons, the main purpose of our study is to focus on developing the prognostic nomogram to predict the prognosis of these patients who met any of these four criteria. The risk factors for death of cirrhotic patients with AKI were identified and the nomogram incorporating these risk factors was developed to predict their prognosis, and was used to select patients with a high risk of death in this study. In addition, a study focused on cirrhotic patients with AKI who meet the ICA criteria is carrying out by our team and will be published in the future.

2. I do not understand the role of liver transplantation: how many patients underwent

LT? All of these were at least evaluated for transplant? This is an important point, in my opinion, because transplant can be considered a competing event with death in such patients, if they were suitable for transplant.

Reply: Thank you for pointing this out and we agree with your opinion. Liver transplantation was a competing event of death in patients with cirrhosis. However, there were no patients who underwent liver transplantation in the present study. We have revised the issue. Please see paragraph 1 of Results section, which were highlighted in BOLD and ITALIC.

3. The study focused on AKI at any stage. Therefore, the nomogram could be useful both for AKI I and III. Furthermore, this nomogram can be used for any type of AKI (ATN, HRS, pre-renal AKI), even if, as the Authors said, the outcome of these types of AKI significantly differs. I suggest more granularity about these points.

Reply: Thank you very much for pointing this out, which is very helpful for me to revise the manuscript. Different subtypes of AKI, which was usually divided into three subtypes: pre-renal AKI, acute tubular necrosis (ATN) and hepatorenal syndrome (HRS), have a different prognosis of patients with cirrhosis. A retrospective study showed that compared with non-AKI patients, patients with prerenal AKI had a 2.37-fold higher risk of in-hospital death, patients with ATN had a 6.878-fold higher risk, and patients with HRS had a 12.98-fold higher risk (DOI: 10.1080/00365521.2018.1545423). Moreover, studies have revealed that patients with HRS-AKI have a worse prognosis than those with non-HRS-AKI (DOI: 10.3748/wjg.v27.i26.3984). The results seem to indicate that patients with AKI-HRS have a higher risk of death. In our study, we focused on developing a prognostic nomogram in predicting the prognosis of these patients. The nomogram could be used to calculate the scores corresponding to each potential risk factor, and the predicted probability corresponding to the sum of the scores represented the risk of death for patients with cirrhosis and AKI. The nomogram includes not only SCr level, but also four other factors to visually evaluate the prognosis of cirrhotic patients with AKI, which may be more convenient, comprehensive and accurate to assess the prognosis of these patients. Please see paragraphs 3 and 6 of Discussion section, which were highlighted in BOLD and ITALIC.

4. Similarly, it would be interesting to see if patients died of renal-related causes or not. How many patients were discharged within 180-d?

Reply: Thank you very much for pointing this out. In this study, the overall mortality rate was 76.4% (191/250) within 180 days. Among these patients who died, the most common cause of mortality was hepatic failure (74/191, 38.7%), followed by infections (41/191, 21.5%), renal failure (34/191, 17.8%), and variceal bleeding (24/191, 12.6%), others (19/191, 9.9%). The length of hospital stay ranged from 2 to 145 days, 131 patients died during hospitalization, and 119 patients were discharged. We have revised the issue. Please see paragraph 2 of Results section, which were highlighted in BOLD and ITALIC

5. I do not understand if patients admitted to ICU for CVVH or patients undergoing CRRT due to AKI were included or not.

Reply: Thank you for your comments. We were excluded patients who underwent renal replacement therapy (RRT) (including hemodialysis and peritoneal dialysis) before admission, because RRT could affect the baseline of SCr in these patients, thereby causing the bias of results. Twenty-six patients (10.4%) received continuous replacement therapy due to the progression of AKI. Moreover, RRT recommendations for cirrhosis patients are the same as for the general population (refractory volume overload, refractory electrolyte imbalance, refractory acidosis, uremia, or intoxication) (DOI: 10.1016/j.jhep.2018.03.024). In addition, studies have shown that RRT could not improve mortality (DOI: 10.1016/j.jcrc.2015.05.006; DOI: 10.1007/s11255-013-0527-7). We have revised the issue. Please see lines 130-132 and 178-184 in pages 6 and 8, which were highlighted in red. Please see paragraphs 1 and of Methods section, which were highlighted in BOLD and ITALIC.

6. When was diagnosed HE? At time of AKI, during hospitalization?

Reply: Thank you for your comments. HE was diagnosed during hospitalization. Moreover, 64 (25.6%) cirrhotic patients presented AKI at the time of admission, 186 (74.4%) developed AKI during hospital course. We have revised the issue. Please see lines 216-218 in page 9, which were highlighted in red. Please see paragraph 1 of Results section, which were highlighted in BOLD and ITALIC.

7. Discussion section. The Authors said that they included patients with compensated and decompensated cirrhosis. Nevertheless, the mean CHILD Pugh was 10, reflecting patients with decompensated disease. Moreover, the short-term outcome mirrors the outcome of a cohort of decompensated patients more than compensated ones.

Reply: Thank you for pointing this out and we agree with your opinion. Based on ICA criteria for AKI, patients with compensated cirrhosis could also developed AKI (doi: 10.1016/j.jhep.2014.12.029). Moreover, a study showed that the incidence of AKI increased gradually with progression of chronic liver disease, compensated cirrhosis and decompensated cirrhosis (doi: 10.1186/s12879-021-05991-2). In our study, the inclusion criteria were as follows: (1) Patients who were diagnosed with cirrhosis and (2) patients who met the criteria for at least one of the RIFLE, AKIN, KDIGO and ICA criteria. These patients were hospitalized. According to the inclusion criteria, patients with compensated cirrhosis was not excluded in our study. Among 250 patients who were included, however, only 7 (2.8%) patients had compensated cirrhosis, and 243 (97.2%) patients had decompensated cirrhosis. Considering that a small number of patients with compensated cirrhosis may contribute little to the overall mortality rate in this study. Therefore, the description may be more appropriate in the discussion section that patients with cirrhosis who were diagnosed with AKI in the study by Kumar U et al. only met the ICA criteria, and those patients in the studies by Fang JT et al. and Pan HC et al. only met the RIFLE criteria, while the study population in our cohort met the criteria for at least one of the main four classifications. In addition, the result of our study showed that short-term mortality rate was still high, indicating that most patients

were in the stage of advanced cirrhosis. We have revised the issue. Please see paragraph 1 of the Methods section, paragraph 1 of the Results section and paragraph 5 of the Discussion section, which were highlighted in BOLD and ITALIC.

8. I agree with the Authors when they said that this nomogram could be useful to select those patients who are at highest risk of death. What could be the best treatments to be offered to these patients? Early RRT?

Reply: We are very pleased that you agree the ideal of our study and appreciate your valuable comments very much. Guidelines and consensus have been recommended on the treatment of AKI in patients with cirrhosis (DOI: 10.1136/gutjnl-2014-308874; DOI: 10.1007/s00535-021-01788-x). Moreover, RRT recommendations for cirrhosis patients are the same as for the general population (refractory volume overload, refractory electrolyte imbalance, refractory acidosis, uremia, or intoxication (DOI: 10.1016/j.jhep.2018.03.024). Furthermore, studies have shown that RRT could not improve mortality (DOI: 10.1016/j.jcrc.2015.05.006; DOI: 10.1007/s11255-013-0527-7). In addition, several independent risk factors for death were identified in the present study, including serum sodium level, INR, peak SCr level > 1.5 mg/dl, the presence of HE and diabetes, and the nomogram incorporating these risk factors was developed to evaluate the prognosis of these patients. Early diagnosis and interventions of AKI are very important for improving prognosis. Therefore, these risk factors for death should be treated as soon as possible. For example, monitoring and control of blood glucose levels in diabetes, control of blood ammonia, correction of electrolyte imbalances and coagulation dysfunction, the improvement of liver function, removel of potential factors of renal injury (such as controlling infection and correcting hypovolemia). These measures and treatments may improve the prognosis of these patients to some extent.

9. Minor comments - There are some typos to be corrected (Table 1: live-→ liver) - Table 1: not all patients had Hep B cirrhosis.

Reply: We are very sorry for these typos, and thank you very much for pointing this out. We have revised the issue in the Tables.

Responds to the reviewer#5's comments:

The manuscript attempted to identify predictors of mortality in patients with cirrhosis and acute kidney injury and establish a nomogram for predicting overall survival in cirrhotic patients with AKI. A nomogram incorporating predictors including presence of diabetes, HE, INR, serum sodium and peak SCr levels were developed and showed good predictive discrimination and calibration for the mortality of such patients. The idea of the manuscript is novel, and the research results have certain clinical value

Reply: We are very pleased that you show an interest in our study and appreciate your valuable comments very much.

1. How about the Child-Turcotte-Pugh (CTP), the model for end-stage liver failure (MELD) and MELD-Na score exhibited in predicting mortality in previous studies?

Reply: Thank you for your comments and are help for us to revise the manuscript. Few studies have focused on predicting the prognosis of cirrhotic patients with AKI. Kumar U et al demonstrated that the AUROCs of CTP and MELD scores were 0.82 and 0.84, respectively, for predicting 30-day mortality in cirrhotic patients with AKI who met ICA classification (doi:10.1007/s12664-020-01086-z). Fang JT and colleagues reported that CTP and MELD scores had AUROC of 0.61 and 0.757, respectively, for predicting in-hospital mortality of cirrhotic patients with AKI (DOI: 10.1093/ndt/gfm914). Another prospective study conducted by Pan HC et a indicated that CTP and MELD scores had AUROCs of 0.622 and 0.776, respectively, for predicting the in-hospital mortality of cirrhotic patients with AKI who met the RIFLE classification (DOI:10.1371/journal.pone.0051094). In the present study, the AUROCs of CTP and MELD scores were 0.694 and 0.669, respectively, for predicting 30-day mortality of cirrhotic patients with AKI in the training cohort, respectively. The discriminative ability of CTP and MELD scores differed among studies, which may be explained by the analysis of different patients. Patients with cirrhosis who were diagnosed with AKI in the study by Kumar U et al. only met the ICA criteria, and those patients in the studies by Fang JT et al. and Pan HC et al. only met the RIFLE criteria, while the study population in our cohort met the criteria for at least one of the main four classifications. We have revised the issue. Please see lines 412-431 in pages 15-16, which were highlighted in red. Please see paragraph 5 of the Discussion section, which were highlighted in BOLD and ITALIC.

2. A nomogram incorporating predictors including presence of diabetes, HE, INR, serum sodium and peak SCr levels were developed and showed good predictive discrimination and calibration for the mortality of patients with cirrhosis and acute kidney injury. Please explain the possible reasons why every factor could play a role to predictive discrimination.

Reply: Thank you for your comments. In our study, serum sodium level, INR, peak SCr levels, and presence of diabetes, HE were considered to be independent risk factor for death of cirrhotic patients with AKI, and these risk factors play critical role in predicting the prognosis of these patients. As we all known, liver has numerous biological functions in the body, mainly including synthetic function and metabolic function. Liver failure can cause a synthetic and metabolic dysfunction, which is closely associated with prognosis. The increase in INR is one of the manifestations of synthesis dysfunction in liver. Similarly, HE is an important feature of liver failure. Once HE occurs in patients with chronic liver disease, the prognosis is very poor, with a 1-year survival rate of less than 50% and a 3-year survival rate of less than 25% (DOI: 10.3748/wjg.v25.i26.3426). Studies have shown that INR is associated with death of cirrhotic patients (DOI: 10.3748/wjg.v25.i26.3426; DOI: 10.1111/jgh.13917). Serum sodium imbalance was very common in cirrhotic patients with AKI and affects the prognosis of these patients (DOI: 10.1111/hepr.12412; DOI: 10.1002/hep.20405). SCr represents the status of renal function. A study conducted by Kumar U showed that SCr > 1.5 mg/dl at the admission was independent predictors for mortality of cirrhotic patients with AKI (doi: 10.1007/s12664-020-01086-z). Moreover, patients with a peak SCr > 1.5 mg/dl had a higher short-term mortality rate than those with a peak SCr ≤ 1.5 mg/dl

(DOI: 10.1016/j.jhep.2013.03.039; J Hepatol 2013;59:474–481). The results have demonstrated that peak SCr > 1.5 mg/dl was closely associated with the prognosis of patients with cirrhosis. Diabetes was also considered an independent risk factor for mortality in cirrhotic patients with AKI in this study. Although the mechanisms underlying the relationship between diabetes and mortality in cirrhotic patients with AKI remain unclear, several studies have documented that the presence of diabetes and poorly controlled blood glucose levels are associated with the prognosis of patients with cirrhosis. (DOI: 10.3748/wjg.15.280; DOI: 10.1080/15321819.2021.1911813; DOI: 10.1111/jgh.12790). Studies have shown that Diabetes is an independent risk factor for the development of AKI or acute kidney disease (DOI: 10.1002/hep4.1840; DOI: 10.1111/liv.15154). As a result, the presence of diabetes was associated with the prognosis of cirrhotic patients with AKI. Collectively, we consider that serum sodium level, INR, peak SCr level > 1.5 mg/dl, the presence of diabetes and HE play a critical role in predicting prognosis of these patients. We have revised the issue. Please see paragraph 4 of the Discussion section, which were highlighted in BOLD and ITALIC.

3. Figures and tables should be improved to make it easier for readers to understand and make the manuscript look better. What is the x-coordinate of Figure4 d?

Reply: Thank you for pointing this out. The X-coordinate of Figure4 d is nomogram-predicted probability of 6-month mortality, and the Y-coordinate of Figure4 d is actual 6-month mortality. We have revised the issue in the Figures and Tables according to your comments.

4. In this manuscript, INTRUDOCTION and DISCUSSION should be well organized, and the logic is not good. The authors need to cite and discuss some recent findings as follows in the discussion and introduction to enhance my above concerns: 1. Hu L, Gao L, Zhang D, Hou Y, He LL, Zhang H, et al. (2022). The incidence, risk factors and outcomes of acute kidney injury in critically ill patients undergoing emergency surgery: a prospective observational study. BMC Nephrol, 23:42. 2. Sun D, Wang J, Shao W, Wang J, Yao L, Li Z, et al. (2020). Pathogenesis and Damage Targets of Hypertensive Kidney Injury. J Transl Int Med, 8:205-209. 3. Martins CB, De Bels D, Honore PM, Redant S (2020). Early Prediction of Acute Kidney Injury by Machine Learning: Should We Add the Urine Output Criterion to Improve this New Tool? J Transl Int Med, 8:201-202.

Reply: Thank you for your comment and we agree with your opinion. We have carefully read these three articles. We have cited and discussed two of the three literatures in the Introduction and Discussion sections. However, the paper "Pathogenesis and Damage Targets of Hypertensive Kidney Injury" mainly discussed the pathogenesis and mechanism of hypertensive kidney injury, a chronic kidney disease, which seems to not closely associated with this study focused on predicting the prognosis of cirrhotic patients with AKI. We have revised the issue in the Introduction and Discussion sections.

Responds to the science editor's comments:

This manuscript attempted to identify predictors of mortality in patients with cirrhosis and acute kidney injury and to develop a nomogram predicting overall survival in patients with cirrhosis with AKI. The selected cases in this manuscript are patients from six years ago; please specify the inclusion criteria, routine control or hospitalization; and supplement the relevant information on liver transplantation in patients; please cite and discuss some recent findings in the Discussion and Introduction.

Reply: Thank you very much for your valuable comments. In this study, the inclusion criteria were as follows: (1) Patients who were diagnosed with cirrhosis and (2) patients who met the criteria for at least one of the RIFLE, AKIN, KDIGO and ICA classifications, and these patients were hospitalized. There were no patients who underwent liver transplantation in the present study. Please see lines 125-127 and 229 in pages 6 and 9, which were highlighted in red. Please see paragraph 1 of the Methods section and paragraph 1 of the Results section, which were highlighted in BOLD and ITALIC. We have revised the Introduction and Discussion sections according to your comments and other reviewer's suggestions.

Responds to the company editor-in-chief's comments:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Reply: We are very pleased that you show an interest in our study and appreciate your valuable comments very much. We have revised the format of Figures and legends, and provided a decomposable Figures in the PowerPoint file according to your comments.