

Dear Editors and Reviewers:

Thanks for the reviewers' comments concerning our manuscript entitled "Prognostic value of risk scoring systems for cirrhotic patients with variceal bleeding" (ID: 51656). These comments are all valuable and very helpful for revising and improving our paper. We have given the comments serious consideration and revised the manuscript according to the suggestions of the Editors and Reviewers. The modified part can be easily identified because we adopted the Microsoft Word review mode.

We again appreciate the kindness of the Editors and Reviewers in helping with improvement of the manuscript. All authors have reviewed and agreed to the submission of the revised manuscript. We hope that the revised manuscript will meet your expectations. If some contents or formats cannot meet the requirements, we are very willing to revise our manuscript once again.

Thank you very much for your consideration.

Yours sincerely,

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Reviewer #1:

We thank Reviewer #1 for the constructive suggestions. Here is a point-by-point response to the reviewer's comments and concerns.

Comment 1: *Regarding the manuscript entitled "Validation of the prognostic value of risk scoring systems for cirrhotic patients with acute variceal bleeding: A retrospective cohort study", the study has some interesting points; well-written and coherent. however, I have some points: 1- What is the significance of this manuscript even the similarity with other previous studies, <https://doi.org/10.5604/16652681.1222107> and DOI: 10.1016/j.cgh.2009.08.011.*

Response: Thanks for your kind question. Some previous studies thought that these tested scores may be useful for predicting short-term outcomes in patients with variceal bleeding, while others did the opposite^[1-6]. These conclusions are

still controversial. Therefore, this study aimed to validate the overall performance of these prognostic scoring systems in Chinese patients with variceal bleeding. Motola-Kuba et al.^[2] (10.5604/16652681.1222107) also performed a similar study, while our study included more patients and more comprehensive scoring systems. In addition to higher statistical power, our study will help hospitals of different grades to select suitable models to screen high-risk patients. As we all know, China is a country with the most liver disease patients^[7]. In fact, many primary hospitals still do not have good medical conditions to support the timely treatment of high-risk patients. Our study provides some simple models, which can quickly identify some high-risk patients. Then, these high-risk patients can be transferred to high-level hospitals to get appropriate treatments. Our results are different from the study by Motola-Kuba et al.^[2], and this may be mainly due to the different characteristics of included patients. Augustin et al.^[8] (10.1016/j.cgh.2009.08.011) developed a new model using three variable(Child-Pugh score, creatinine level, and infection)to predict the risk of 6-week mortality in patients with variceal hemorrhage, and their study purpose was different from ours. We have added some discussions about this point in the revised manuscript. **(See revised manuscript Page 13, Line 373-385)**

Comment 2: *2- Statistical analysis should be revised.*

Response: Thank you for your comments. The statistical analyses of the study were guided by a professional statistician. If you have specific suggestions for the statistical analysis, would you mind telling us more information about this part? Thank you again for your criticism.

Reviewer #2:

Comment: *None*

Response: We thank Reviewer#2 very much for reviewing our article.

Reviewer #3:

We thank Reviewer#3 for these very useful comments. Here is a point-by-point response to the reviewer's comments and concerns.

Comment 1: *Tantai et al. aimed to validate and compare the overall performance of selected prognostic scoring systems for predicting in-hospital outcomes in cirrhotic patients with variceal bleeding. The topic is interesting. Some issues raised: 1-In abstract and introduction: Some abbreviations have no descriptions (for example CTP, CANUKA).*

Response: We have made correction according to the Reviewer's comments **(See revised manuscript Page 3, Line 90-92; Page 6, Line 158-159).**

Comment 2: *2 – In method and results: Variceal bleedings have different patterns according to the localization of the varices. So the mortality and the morbidity rates are different. In this study, all variceal bleedings are included (gastric?esophageal?). The authors must give more information about this point. Endoscopic treatments used for variceal bleeding are also effect the mortality and the morbidity rates. So the authors must give information about these treatments. Statistics should be renewed after these changes. Thank you for givinig opportunity to review this study. Yours sincerely.*

Response: We thank the reviewer's good suggestions, and the comments are very helpful for us to improve our paper. We have provided the information about the localization of the varices **(See revised manuscript Page 9, Line 255-257; Page 20, Table 1)**. According to the reviewer's suggestions, additional analyses were performed focusing on patients with esophageal variceal bleeding and patients receiving endoscopic treatments, and corresponding statistical analysis was also be updated **(See revised manuscript Page 8, Line 239-241; Page 11, Line 313-326)**. In addition, sensitivity analyses focusing on patients with gastric variceal bleeding cannot be performed due to the small effective sample size. We have added this point as a limitation of the study in our discussion section **(See revised manuscript Page 14, Line 414-418)**.

Reviewer #4:

We are deeply grateful to Reviewer#4 for taking the time to provide quite valuable suggestions. Here is a point-by-point response to the reviewer's comments and concerns.

Comment 1: *The authors validated and compared the overall some effectiveness of well-known prognostic scoring systems for predicting in-hospital outcomes in cirrhotic patients with variceal bleeding. Indeed, recent international recommendations endorsed using Rockall risk scoring score (CRS), AIMS65 score (AIMS65), Glasgow-Blatchford score (GBS), modified GBS as well as the new scoring system CANUKA for the management of NON-VARICEAL UGIB patients. However, it is well recognized that patients with variceal bleeding constitute a specific and high risk group, with outcome largely dependent on the values of the hepatic venous pressure gradient (HVPG), measured within 24 hours after stabilization of hemodynamics, exceeding 20 mm Hg, as well as the severity of underlying liver disease as assessed by the Childs-Turcotte-Pugh (CTP) score or model for end stage liver disease (MELD). In addition, these predictors include impaired renal function, bacterial infection, hypovolemic shock, active esophageal variceal bleeding during endoscopy and early relapse with the need for transfusion of more than 4 doses of packed red blood cells, the presence of hepatocellular carcinoma and portal vein thrombosis. Therefore, the use of for predicting in-hospital outcomes in cirrhotic patients with variceal bleeding of prognostic scoring systems the management of NON-VARICEAL UGIB in my perception is not correct.*

Response: Thanks for your valuable comments. In fact, the CRS, AIMS65, CANUKA and GBS scoring systems were established using unselected UGIB patients, and both patients with variceal bleeding and those with nonvariceal bleeding were enrolled for model building. In the subsequent validated studies, many studies have confirmed the predictive value of these scores in patients with nonvariceal bleeding, and the latest 2019 International Guideline^[9] has suggested using a Glasgow Blatchford score of 1 or less to identify patients who are at very low risk for rebleeding or mortality and thus may not require hospitalization or inpatient endoscopy. However, the conclusions of previous studies exploring the predictive value of these scores in patients with variceal bleeding were controversial. Some studies believed that those scores were useful for predictive of rebleeding in patients with variceal bleeding^[2,4,5], while others did the opposite^[1,3,6]. In our study, these scoring systems were found to be more suitable for predicting in-hospital death than in-hospital rebleeding. As you commented, the component variables of these scores indicate that they are unsuitable for predicting short-term rebleeding, we have also discussed this point in the discussion section (**See revised manuscript Page 13, Line 389-398**). We agree with you that some specific variables should be used for developing a model in patients with variceal bleeding, and this will be our next research

work.

Comment 2: *I have a few questions. 1. Did the treatment of patients with variceal bleeding meet current requirements and what was it?*

Response: As a tertiary teaching hospital, and all patient management in our hospital was in line with Chinese guidelines for the diagnosis and treatment of esophageal and gastric variceal bleeding in cirrhotic portal hypertension^[10]. (See revised manuscript Page 6-7, Line 183-196). Patient management process can be seen in Figure 1.

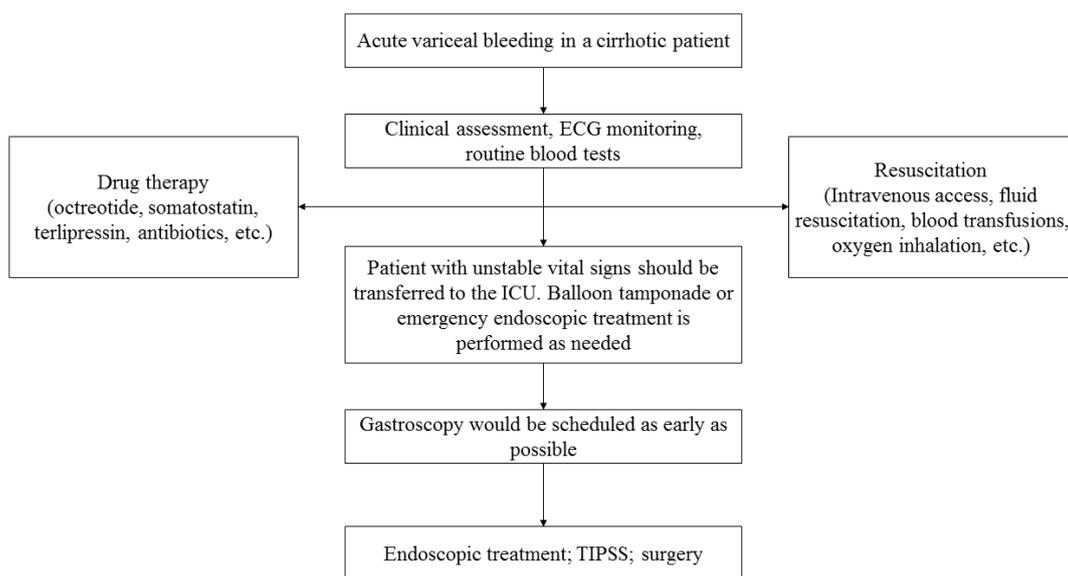


Fig.1 Algorithm for the management of acute variceal bleeding in cirrhosis

Comment 3: *2. How was portal pressure evaluated? If HVPG was not measured, were alternative methods used? The study has a number of limitations which are indicated by the authors themselves.*

Response: Special thanks to you for your good questions. Without doubt, portal pressure is an important factor, which is associated with short-term rebleeding and death in patients with variceal bleeding. As an invasive method, HVPG measurements are rarely used in our clinical practice. In addition, many studies have shown that measurements of liver and spleen stiffness closely correlates with HVPG. However, transient elastography was introduced to our

department for just several years, and this noninvasive method was only used by a few patients. Several noninvasive liver fibrosis indexes, such as AST-to-platelet ratio index (APRI) and FIB-4, may be associated with portal hypertension and easy to calculate, but their predictive accuracies were not good enough^[11,12]. Furthermore, a study found that these noninvasive indexes had no ability to predict variceal bleeding^[13]. Our study aimed to validate the overall performance of tested prognostic scoring systems for predicting in-hospital outcomes. We have to admit that we cannot perform the relevant subgroup or sensitivity analysis due to lack of data of portal pressure. We have added this point as a limitation of this study in our discussion section (**See revised manuscript Page 14, Line 414-418**).

Reviewer #5:

We thank Reviewer #5 for her/his valuable comments and constructive suggestions. Here is a point-by-point response to the reviewer's comments and concerns.

Comment 1: *A well written manuscript dealing with critical issue in cirrhotic patients. but some points to be discussed: 1- In the demographic data the endoscopic finding must be clarified eg grading of esophageal varices , Types of gastric varices and No of each*

Response: We have made correction according to the Reviewer's comments (**See revised manuscript Page 9, Line 257-260; Page 20, Table 1**).

Comment 2: *2- the relation of recurrence of bleeding to the grading and types of varices*

Response: The grading and type of varices may be associated with rebleeding, and it deserves further study. However, this investigation was not among the aims of our study. The aim of our study was to validate the performance of tested eight scoring systems for predicting in-hospital outcomes in patients with variceal bleeding. We may be able to perform subgroup or sensitivity analyses based on the grading and types of varices. However, after the patients are regrouped, further analysis cannot be performed due to the small effective sample size. We have added this point as a limitation of the study in our

discussion section(See revised manuscript Page 14, Line 414-418).

Comment 3: 3- some studies need to be added to the discussion: • A large multinational prospective trial demonstrated the GBS to be superior to the AIMS65 in predicting need for intervention (transfusion, endoscopic treatment, IR, or surgery) or rebleeding, although the AIMS65 remained a better predictor of mortality (Stanley 2017). - Vinaya et al observed statistically significant correlation between AIMS65 score and length of hospitalization and mortality in noncirrhotic patients. We found that AIMS65 score paralleled the endoscopic grading of lesion causing UGIB in noncirrhotics. AIMS65 score correlated only with mortality but not the length of hospitalization or endoscopic stigmata of bleed in cirrhotics. (Vinaya Gaduputi, Molham Abdulsamad, Hassan Tariq, et al., "Prognostic Value of AIMS65 Score in Cirrhotic Patients with Upper Gastrointestinal Bleeding," *Gastroenterology Research and Practice*, vol. 2014, Article ID 787256, 8 pages, 2014. <https://doi.org/10.1155/2014/787256>).

Response: According to the Reviewer's suggestions, these studies have been added to our discussion section (See revised manuscript Page 12-13, Line 360-368).

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