

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Clinical-radiomics nomogram for predicting esophagogastric variceal bleeding risk noninvasively in patients with cirrhosis" (Manuscript NO.80823). We were pleased to know that our work was rated as potentially acceptable for publication, subject to adequate revision. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have read the comments carefully and have made correction which we hope meet with approval. We have also sent our revision to a professional English language editing company for language polishing further. The point-by-point responses to the comments are listed below this letter, and all amendments are highlighted in red in the revised manuscript.

This manuscript has been under scientific editing by Medjaden Inc.

Your help and assistance are highly appreciated and we hope that the revision is acceptable for the publication in your journal.
We are looking forward to hearing from you soon!

With best wishes,
Yours sincerely,
Jian Gao

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Replies to Reviewer #1 (Number ID: 05394499)

1.You developed a clinical-radiomics nomogram for the prediction of esophagogastric variceal bleeding in patients with liver cirrhosis. Have you selected patients with a stable liver cirrhosis or participants who underwent a hospital admission due to an acute liver cirrhosis decompensation?

Response: Thank you for your valuable comments. The acute decompensation of cirrhosis is defined as first or recurrent grade 2 or 3 ascites, acute hepatic encephalopathy, acute gastrointestinal hemorrhage and acute bacterial infection in a short-term period(reference 1, in the bottom of the answering letter). These decompensated events can occur simultaneously or can influence each other's progression. Our study was a retrospective study, and to reflect the true prevalence, consecutively included patients with cirrhosis and esophagogastric varices who were first hospitalized between 2017 and 2021, some of whom suffered acute decompensation events such as ascites, hepatic encephalopathy, and hemorrhage. Hemorrhage mainly occurred in bleeding group, ascites and hepatic encephalopathy were present in both bleeding group and non-bleeding group. To whether the included patients

suffered decompensation events, we have added in the result. The details can be found *in Line 258-261, Page 10*, please check it.

2. If your participants suffered an acute liver cirrhosis decompensation, please mention the trigger factor. Was it a bleeding episode or an infection etc.?

Response: In our study, some of the included patients suffered acute decompensation events which included hemorrhage, ascites and hepatic encephalopathy. Bleeding risk was the target of our study, and we supplemented ascites, hepatic encephalopathy, and Child-Pugh scores in the table of baseline characteristics to further characterize the decompensated events. The details can be found in *TABLE 1*, please check it.

3. Was your model able to predict a variceal bleeding in esophagogastric junction or also bleeding coming from gastric fundus varices?

Response: Thank you for raising this valuable issue. Our study included patients with cirrhosis consecutively hospitalized between 2017 and 2021, and they all have undergone endoscopy examination to determine the presence of both esophageal and gastric varices. We explored the overall bleeding risk of esophagogastric varices and the results demonstrated our model had good predictive performance. The bleeding group in the study included variceal bleeding at the esophagogastric junction (EGJ) and the gastric fundus, with 29 patients having bleeding at the esophagogastric junction and 27 ones at the gastric fundus. Thus, our model was able to predict the risk of variceal bleeding in the EGJ and gastric fundus to some extent. Due to the small amount of relevant included data, we were not able to perform further subgroup analysis of both, which can be further prospectively explored and analyzed in follow-up studies. We have made the relevant additions in the discussion, and the details can be found *in Line 337-343, Page 13*. please check it, thank you!

4. You included patients who have received a triple-phase enhanced CT scan within a week after endoscopy but excluded patients who underwent an endoscopic therapy of the esophageal varices. Your participants were bleeding or non-actively bleeding, according to Figure 1 (flow-chart study population). Your reading audience comes, therefore, to the conclusion that actively bleeding patients did not receive any endoscopic intervention and after a week underwent a CT-scan control. Please explain this crucial point.

Response: Thanks for your careful question. As clearly stated in the abstract, the population included in our study was patients who had undergone the triple-phase CT scan within one week before endoscopy. We are very sorry for causing the ambiguity and misunderstanding, and have modified the corresponding parts in the manuscript to make the expression more accurate

and clearer (*Line 171-172, Page 7*). Please check it.

5. Please start the following paragraph as such: "The Baveno VII consensus workshop"

Response: We have modified this part according to your suggestion (*Line 115, Page 5*), please check it.

Replies to Reviewer #2 (Number ID: 03765308)

1. Abstract should be reduced to <350 words.

Response: Thank you for your kindly suggestion. Since the journal requires an abstract of no less than 350 words for retrospective research manuscripts at the Guidelines and Requirements for Manuscript Revision, we have simplified the abstract of the manuscript before submission. We are sorry that we have to observe the journal's word count requirement for abstract, but we have still streamlined the abstract (*Line 40-80, Page 3-4*). Please check it.

2. How many patients were diagnosed with liver cirrhosis and varices between 2017 and 2021?

Response: Our study enrolled cirrhotic patients who were admitted to hospital for the first time, and all patients were diagnosed with esophagogastric varices by endoscopy. The purpose of this study was to predict the possibility of the risk of bleeding in people with esophagogastric varices. Between 2017 and 2021, a total of 586 patients were diagnosed with cirrhosis and varices by CT and endoscopy during their initial hospitalization at our institution, of which 204 were esophageal varices, 93 were isolated gastric varices, and 289 were esophagogastric varices. Based on your suggestion, we have appropriately modified the flow chart of the inclusion and exclusion process *in Figure 1*, from which you can find out the exact process. Please check it.

3. Please give the numbers of patients received liver histology study. For the rest of patients, please describe how cirrhosis is diagnosed by image. The variceal bleeding seems to be based on endoscopic findings. How to handle patients with recent history of bleeding but without endoscopic evidence of bleeding at time of study?

Response: Thank you for raising such a valuable question.

1) We added to the number of patients diagnosed with cirrhosis by pathological histological examination *in Line 255-257, Page 10*. Most of the included patients were diagnosed with cirrhosis by a combination of history, clinical manifestations, laboratory tests and CT image manifestations.

According to your suggestions, we provided a supplementary description of the CT imaging manifestations of cirrhosis, and the details can be found *in Line 128-134, Page 6*. please check it.

2) When patients have a recent history of hemorrhage, it may not be caused by esophagogastric variceal bleeding. Ulcers and portal hypertensive gastropathy may also result in upper gastrointestinal bleeding. In this study, our assessment of variceal bleeding was established based on the Baveno consensus (reference 4,16 in the manuscript). When patients had a recent history of bleeding and endoscopy failed to find evidence of varices as a potential bleeding cause, we consider the possibility of bleeding led by other reasons such as portal hypertensive gastropathy. We made the relevant additions as detailed *in Line 185-189, Page 8*. please check it.

4. This is a retrospective study. What were the indications for endoscopic and CT scan studies?

Response: Thanks for your kindly question. The guidelines recommend routine endoscopy to screen for the presence and assess the severity of varices in all patients with a confirmed diagnosis of cirrhosis, which is the indication for endoscopy (reference 4 in the manuscript). CT can assist in the diagnosis of cirrhosis when there is lack of pathologic histological examination. Also, follow-up review of imaging examinations such as CT in patients with cirrhosis can assess the status of liver, spleen, variceal size, shunts, and portal vein thrombosis(reference 2, in the bottom of the answering letter). In clinical practice, we recommend endoscopic and CT examinations to evaluate the condition of patients without contraindications such as severe cardiopulmonary disease, contrast or anesthetic allergy. Cirrhotic patients with esophagogastric varices were included in our retrospective study. Endoscopy can accurately assess their varices and determine whether to further endoscopic treatment, while CT scanning before endoscopy can preliminarily evaluate the conditions of varices, extraluminal lesions and shunt.

5. Cirrhosis may be well compensated or decompensated. Please give the Child Pugh classification data in Table 1.

Response: Thanks for your very valuable suggestion, we have added Child-Pugh scores to the **TABLE 1 and TABLE 2**.

6. How were portal vein thrombosis, AV shunting, spleen upper and lower pole diameter, spleen thickness, spleen diameter in Table 1 be diagnosed or measured?

Response: We have added the description about the diagnosis and

measurement of the above indicators in the text. The details can be found *in Line 202-211, Page 8*. Please check it. Thank you!

7. The bar chart in the Figures is too small to be seen clearly.

Response: We are very sorry for the lack of clarity in the bar chart, and we have revised all of the figures to make them clear, please check them *in Figure2-7*.

8. RadScore was based on CT features, 5 from liver and 3 from spleen. Please give a description of these features.

Response: Thank you for your insightful suggestion. We have added descriptions of the features in the manuscript (*Line 312-315 and 317-323, Page 12*) and the specific formula of RadScore is shown *in the supplementary material*. Please check it.

9. In Table 1, most of the patients were HBV related cirrhosis. Why was there a female predominant?

Response: Thank you very much for discovering this error. We are very sorry that we have made mistake to fill in the column of 'Sex' as 'Female', which should be filled in as 'Male' in reality. As previously described in the main text, 131 males and 80 females were included in the study, which is also consistent with the liver disease epidemiology. We have corrected the error in the *TABLE 1*, please check it.

10. Please give a missing data percentage in each parameter of Table 1.

Response: Thanks for your careful attitude. In this study, we excluded patients with missing clinical or imaging data and finally excluded 5 patients who was lack of clinical data (Figure 1, in the manuscript). The excluded ones contained only demographic data features, and the amount of missing data was less than 2% of the total data, which had little impact on the overall data bias. Data for all 211 patients eventually included in our study were complete, with no missing data.

11. Platelet counts were higher and total bilirubin levels were lower in the bleeding group. Please discuss these findings by matching with Child Pugh classification.

Response: Thank you for raising this worthy comment. Child Pugh score is composed of five parameters including hepatic encephalopathy, ascites, serum albumin level, serum total bilirubin level and prolonged prothrombin

time. It can reflect the liver reserve function, often as a prognostic indicator in patients with cirrhosis. When there is hepatic function damage, the remaining endotoxin will affect platelet aggregation and number. Meanwhile, the reduction of thrombopoietin synthesis, hepatitis virus, immune destruction and other factors may combine to lead to thrombocytopenia. Our study was retrospective, in which most of the included patients had splenomegaly and hypersplenism, and the Child Pugh scores were predominantly grade B in both the bleeding and non-bleeding groups. Although the former had a higher platelet count and lower total bilirubin, there was no significant difference in Child Pugh score, platelet count and total bilirubin level between the two groups in subsequent logistic regression analysis ($P > 0.05$), which were not the independent risk indicators for predicting bleeding risk. The similar result was also reflected in some previous studies (references 3,4, in the bottom of the answering letter). These were the results of our single-center study, which need to be further validated in large, multicenter, prospective researches in the future. We have added relevant contents to the discussion (*Line 369-374, Page 14*), please check it. Thank you!

12. In Figure 4, there are 5 types of line in the figure, but only 3 line-marks were seen.

Response: In Figure 4 we have depicted the 5 line-markers actually and we are sorry for the blurring of the image due to the light color. We have adjusted the colors of the lines to make them clear and reordered the figures, please check it *in Figure 5*.

13. Is it possible to compare RadScore with elastography in some cases?

Response: Thank you for such thoughtful suggestion. Elastography can predict portal hypertension and esophagogastric varices to some extent by measuring the values of liver stiffness and spleen stiffness. Lin's study has compared elastography and radiomics, which showed that radiomics-related model was superior in predicting high-risk gastroesophageal varices (reference13 in the manuscript). The existing radiomics models developed to predict variceal bleeding were lack of comparing with elastography. In our retrospective study, the majority of patients did not receive elastography examination, and we failed to obtain relevant data during retrieval. This is a limitation of our study and it is necessary to further analyze and explore this field in the future. We have made relevant additions to the discussion section in the manuscript. The details can be found *in Line 377-386, Page 14-15*. Please check it. Thank you again!

Replies to Reviewer #3 (Number ID: 06409430)

The authors failed to have a native English speaker revise and finalize the

entire manuscript! The authors must have a native English speaker revise and finalize the "entire" manuscript sentence by sentence again to improve the accuracy, clarity, conciseness and style of the text and title! Thank you. Several examples of the inappropriate statements requiring revision are as follows: - Title: "Esophagogastric varices bleeding"? - Abstract section & Core tip: "However, there are no standardized non-invasive predictive models available in clinical practice. " is not fully accurately addressed. We hepatologists are aware of Baveno criteriae, etc. "gastroscopy"? -Materials and Methods: "Endoscope"? "It was considered strong reproducibility and dependability when the ICC values exceeded 0.75, which was included in subsequent studies."? more... - Numerous errors can be spotted by a person speaking ESL throughout the entire manuscript; e.g., Core tip: "can personalized management"? Materials and Methods: "patients lack of complete clinical or imaging data" more...

Response: Thank you for pointing out the language problems with the manuscript. Before submitting the manuscript, we have sent the whole text to a professional English editing company for language polishing and have provided the language certificate. We are sorry that the language expression failed to meet the requirement. We have corrected the grammatical problem of the title based on your suggestion. Furthermore, we have sent the revised manuscript for professional language polishing again and resubmitted a new language certificate. We really hope that the flow and language level have been substantially improved.

The BavenoVI consensus recommended that the compensated cirrhotic patients with the value of LSM <20 kPa and platelet count >150 G/L may be spared endoscopic screening. However, it also has some limitations. The low specificity for ruling out the high-risk varices (HRV) leads to some patients requiring a subsequent endoscopy to detect possible HRVs(reference 5, in the bottom of the answering letter). The results of ultrasound elastography are impeded by ascites, obesity, flatulence, and other clinical issues (Line 116-117, Page 5, in the manuscript). The above reasons limit the application of Baveno criteria in clinical practice. The Baveno criteria is mainly used for screening of high-risk varices, and its predictive value for bleeding risk is unclear. We have added and modified the relevant content (*Line 44-45, Page 3; Line 89-90, Page 4; Line 117-120, Page 5*), please refer to it, thank you!

References

1. D'Amico G, Bernardi M, Angeli P. Towards a new definition of decompensated cirrhosis. *Journal of Hepatology*. 2022 Jan 1;76(1):202–7.
2. Aubé C, Bazeries P, Lebigot J, Cartier V, Boursier J. Liver fibrosis, cirrhosis, and cirrhosis-related nodules: Imaging diagnosis and surveillance. *Diagnostic and Interventional Imaging*. 2017 Jun 1;98(6):455–68.

3. Li J, Li J, Ji Q, Wang Z, Wang H, Zhang S, et al. Nomogram based on spleen volume expansion rate predicts esophagogastric varices bleeding risk in patients with hepatitis B liver cirrhosis. *Front Surg*. 2022 Nov 16;9:1019952.
4. Liu H, Sun J, Liu X, Liu G, Zhou Q, Deng J, et al. Dual-energy computed tomography for non-invasive prediction of the risk of oesophageal variceal bleeding with hepatitis B cirrhosis. *Abdom Radiol (NY)*. 2021 Nov;46(11):5190–200.
5. Stafylidou M, Paschos P, Katsoula A, Malandris K, Ioakim K, Bekiari E, et al. Performance of Baveno VI and Expanded Baveno VI Criteria for Excluding High-Risk Varices in Patients With Chronic Liver Diseases: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2019 Aug;17(9):1744-1755.e11.