

Author response:

Reviewer: 1

Dear Reviewer:

Thank you very much for your recognition, careful review and valuable suggestions of my article. I have learned a lot and have done it according to your suggestions.

According to each of your suggestions, modify as follows:

1. Limited Sample Size and Single-Center Study: The study is a retrospective single-center study with a limited sample size. This could limit the generalizability of the findings to a broader population. The results might not apply to patients from different geographical locations, ethnic backgrounds, or healthcare systems.

**Response:** Thank you very much for the limitations that you have proposed. We will add the limitations you mentioned to the limitations writing paragraph in the discussion section of this article. In future studies, this model can be verified in different dimensions and applied in multiple scenarios.

2. Lack of Nutritional Factors in Current Models: The authors mention that current prediction models do not consider nutritional factors. However, they do not provide a detailed explanation or evidence to support why dietary factors, specifically sarcopenia, should be included in the prediction models.

**Response:** Nutritional status may affect patient prognosis, and nutritional factors are a factor that can be intervened. At present, sarcopenia is recognized as a better quantifiable and objective indicator to evaluate liver nutrition, so this study focuses more on including sarcopenia into the prediction model.

3. Retrospective Study Design: The study's retrospective nature could introduce bias, as the data was not collected with the specific research question in mind. This could affect the reliability and validity of the results.

**Response:** There is a possibility of bias in the retrospective study, which is a common problem, so it is expected to further expand the sample to include multicenter for prospective study.

4. Lack of External Validation: Although the authors used a separate group of patients for validation, these patients were from the same hospital as the training cohort. An external validation with a completely independent dataset from a different center would have strengthened the model's reliability.

**Response:** Regarding the verification of the model, in the early stage of the model establishment, to ensure the homogeneity of the data, such as checking the equipment, reagents and checking the threshold, to ensure the validity and feasibility of the model. Therefore, in the validation stage, we still selected patients in the center first, but the difference was that we used patients in two different wards of the center (the second and third wards of hepatobiliary surgery) to ensure that the data was not from the repeated data set. It is expected that further validation of multi-center and multi-background population can be performed in future studies.

5. Lack of Comparison with Other Models: The authors claim that the SAMD model is superior to other models but do not provide a detailed comparison. A head-to-head comparison with other models using the same dataset would have provided a clearer picture of the SAMD model's performance.

Response: We compared three models: AS score; ERASL-pre score and pre-MORAL score; and used these models to score our data set, distinguishing high-risk and low-risk groups from the three models to compared their recurrence free survival time and the HR for predicting recurrence.

6. Potential Confounding Factors: The study does not seem to account for potential confounding factors that could influence the results, such as the patient's overall health status, lifestyle factors, or other comorbidities.

Response: Thank you very much for the limitations that you have proposed. We will add the limitations you mentioned to the limitations writing paragraph in the discussion section of this article.

7. Selection Bias: The study only included patients with a history of chronic hepatitis B with positive hepatitis B surface antigen (HBsAg), which may not represent the entire population of patients with HCC. This could introduce selection bias and limit the model's applicability to a broader HCC patient population.

Response: In Asian population, hepatitis B is still the first cause of liver cancer. Therefore, the subject selects hepatitis B population as the research population.

8. Inclusion and Exclusion Criteria: The exclusion of patients with a history of other treatments for HCC (such as transcatheter arterial chemoembolization or chemotherapy) could also limit the generalizability of the findings. These criteria may exclude a significant portion of the HCC patient population undergoing such treatments.

Response: This study focuses on patients after liver cancer radical surgery. To maintain consistency in preoperative factors, patients with a history of other HCC treatments (such as transcatheter arterial chemoembolization or chemotherapy) prior to resection were excluded in order to control the impact of these preoperative treatment factors on the recurrence of patients after resection. Further comparisons can be designed in the future.

9. Diagnostic Criteria for Sarcopenia: The study uses specific diagnostic criteria for sarcopenia based on the Japan Society of Hepatology Guidelines for Sarcopenia in Liver Disease. This may not be universally applicable or accepted, and different criteria could yield different results.

Response: At present, there is no unified diagnostic standard for sarcopenia; The Japanese Society of Hepatology has specified diagnostic criteria for sarcopenia in its guidelines. As Japan and we belong to the same Asian population, we chose the Japanese Society of Hepatology's diagnostic criteria for sarcopenia in terms of

population fitness.

10. Follow-up Protocol: The follow-up imaging results were reviewed every 3-6 months, which may need to be more frequent to detect all cases of recurrence promptly. A more frequent or standardized follow-up protocol could provide more accurate data on recurrence.

Response: In the follow-up program, I agree with your point that more frequent follow-up can indeed detect all recurrent cases in a timely manner, but it may not be feasible in terms of economic benefits and practical scenarios. At the beginning of this experimental design, we focused more on establishing effective models for earlier and more proactive postoperative interventions, while maintaining close follow-up for high-risk populations through predictive models.

11. Statistical Analysis: While the study used various software, the methods and assumptions underlying these analyses are not detailed in the search results. Any limitations in the statistical methodology could affect the validity of the model.

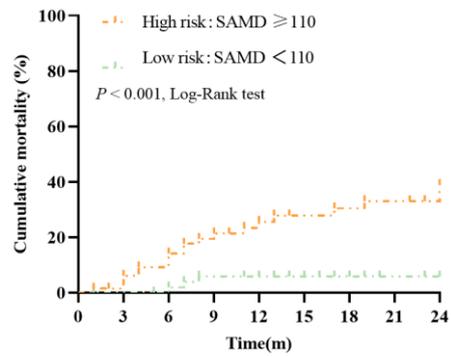
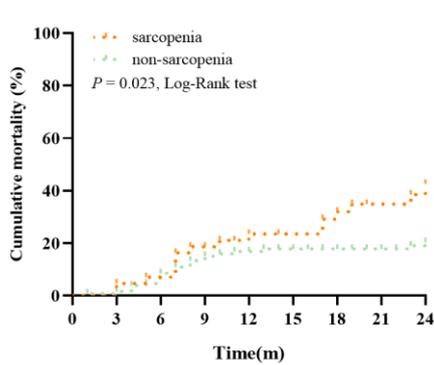
Response: Thank you for the reviewer's reminder. We will include it in the limitations section.

12. Data Collection: As a retrospective study, the data collection was based on records, which may not have been gathered systematically or with the current research question in mind. This could lead to information bias.

Response: There is indeed a possibility of bias in retrospective studies, which is a common issue in such studies. This article is based on the impact of nutrition on outcomes in liver diseases dominated by sarcopenia, ensuring the completeness of core data. In the future, higher quality prospective studies can be designed. Include as many outcome related indicators as possible and further expand the sample to include multiple centers for validation.

13. Outcome Measures: The study focuses on recurrence-free survival (RFS) but does not discuss overall survival or quality of life post-surgery, which are also important outcomes for patients with HCC.

Response: Thank you for the reminder from the reviewing experts. Overall survival or postoperative quality of life is indeed an important outcome for HCC patients. As shown in the figure, we also conducted an analysis of overall survival within 2 years and found that patients with sarcopenia have a higher risk of death, and the high-risk population for recurrence in the SAMD model also has a higher mortality rate.



However, based on the endpoint we set in this study, which is recurrence free survival (RFS), early assessment of recurrence is more effective in improving survival prognosis. Therefore, the results of overall survival or postoperative quality of life are not presented or discussed in this article.

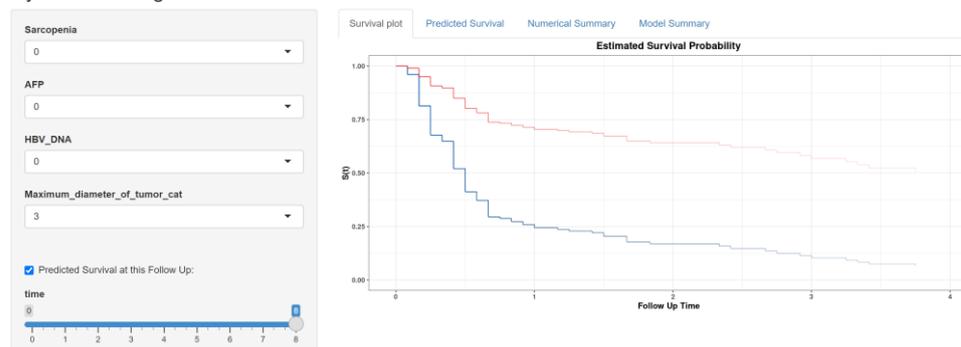
14. Model Calibration and Validation: Although calibration curves indicated good consistency between predicted and observed results in the training and validation cohorts, the need for external validation in a different clinical setting or population remains a concern.

Response: One of the limitations of this study is the single center, which has been discussed that the model will be validated and generalized in multiple centers and can be applied to different clinical settings.

15. Online Calculator: An online calculator was developed for the model, but its accessibility, usability, and accuracy in a real-world clinical setting are not discussed.

Response: Thank you for the reviewer's suggestions. An online calculator was developed for the model and has been attempted to be used in our clinical practice, making it easier for us to see visualized survival probability.

Dynamic Nomogram



16. Comparison with Other Models: The study compares the SAMD model with other preoperative models using AUC, but it does not discuss the clinical relevance or practical differences that might affect the choice of model in clinical practice. In summary, while the study by Peng and Lei et al. contributes to the field by proposing

a new model for predicting HCC recurrence post-hepatectomy, the limitations outlined above and in the initial question suggest that further research is needed to confirm the model's effectiveness and generalizability.

**Response:** Our model is superior to other models, and it is recommended to be applied to liver cancer based on hepatitis B.