Peer Review File

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Reviewer A:

In this study, developed two novel nomograms based on inflammation-related indicators and clinical parameters to predict OS and RFS in HCC patients undergoing radical resection, which will help individualized follow-up and adjuvant treatment after surgery. The study performed a detailed analysis and the work is suitable for publication in the journal. Then, there are some minor issues in the article that need to be improved. These comments are described below.

1. This article studies whether the inflammatory indicators take into account the effects of chronic hepatitis and cirrhosis on inflammatory cells. Because the progress of liver cancer has part of this effect.

Response: We thank the reviewer for their constructive comments. These inflammation-related indicators (neutrophil times γ-glutamyl transpeptidase to lymphocyte ratio (NrLR),(1) platelet-to-lymphocyte ratio (PLR),(2) prognostic nutritional index (PNI),(3) γ-glutamyl transpeptidase to platelet ratio (GPR),(4) and systemic immune-inflammation index (SII)(5)) comprise serum albumin, platelet count and GGT level. Serum Albumin is an important indicator of liver function. Hypoalbuminemia not only contributes to impaired liver function due to the underlying chronic liver disease but is also associated with a sustained systemic inflammatory response.(6)The low platelet count noted in a considerable proportion of patients with cirrhosis is a well-known indicator of portal hypertension.(7) A high level of GGT was associated with liver cirrhosis.(8) Thus, we took into account the effects of chronic hepatitis and cirrhosis on inflammatory cells, which are associated with the progress and prognosis of liver cancer.

2. There are also different geographical areas and etiology mentioned in the article that need to be further verified, which can better explain the conclusions.

Response: We thank the reviewer for their constructive comments. As suggested, we added different subgroups, including in patients with different aetiology (non-viral hepatitis and viral

hepatitis) and liver cirrhosis status (non-liver cirrhosis and liver cirrhosis) in the revised manuscript (see Page 16, line 334-341, Table S3, Table S4).

3. Liver function and blood cells, neutrophils, etc. are also affected by other factors whether this effect has been ruled out.

Response: We thank the reviewer for their constructive comments. First, the majority of surgically treated patients with HCC have Child-Pugh A liver function, which accounted for more than 95% of patients in this study. Second, blood samples were obtained for routine laboratory tests for liver function within the 14 days before surgery. Thus, this effect has been ruled out.

Reviewer B:

Zeng *et al* developed two novel nomograms integrating inflammation-related indexes and accessible clinical parameters to predict OS and RFS in HCC patients who underwent radical resection. It is a relatively large and interesting study. There are several comments that should be taken into consideration.

1. In this study, how many people lose follow-up? How many people died from HCC and other diseases, respectively? The detailed information should be provided.

Response: We thank the reviewer for their constructive comments. In this study, 661 people were lost to follow-up within 5 years. HCC-related deaths occurred in 801 cases, liver-related death is 254 cases and deaths related to other diseases in 138 cases. As suggested, we have included detailed information in the revised manuscript (see Page 13, line 266-270).

2. Kaplan-Meier analysis of all included patients should be performed.

Response: We thank the reviewer for their constructive comments. As suggested, we have added a Kaplan-Meier analysis of all the included patients to the revised manuscript (see Page 13, line 270-272, Figure S2).

3. In the method, how to detect and quality control the inflammation-related index?

Response: We thank the reviewer for their constructive comments. In this study, blood samples

were obtained for routine liver function and blood cell laboratory tests within the 14 days before surgery, which can detect and quality control the inflammation-related index. As suggested, we have added the sentence to the revised manuscript (see Page 8, line 174-175).

4. In the included patients, are there some patients received chemoradio-therapy? The authors may consider the factor and adjusted this factor in the Cox regression.

Response: We thank the reviewer for their constructive comments. Patients who underwent preoperative anticancer treatment, including TACE, radiotherapy, and sorafenib, were excluded from this analysis. Postoperative adjuvant radiotherapy is not performed to treat HCC. As suggested, we have incorporated postoperative adjuvant TACE into the Cox regression (see Table S2).

Reviewer C:

The author developed and validated novel nomograms to predict post radical resection mortality of HCC patients using the local cohort of HCC patients. Two novel nomograms integrating inflammation-related indexes and accessible clinical parameters (The hepatitis, AFP, ALBI, NrLR, PLR, PNI, GPR, tumor size, tumor number, microvascular invasion and Edmondson-Steiner grade) were developed to predict OS and RFS in HCC patients who underwent radical resection.

This research work is very interesting, but there are a few questions for the author to clarify.

1. Before establishing a prognostic model, it is best to use the feature selection method to select the optimal factors for modeling, which could minimize the number of factors included in the model.

Response: We thank the reviewer for their constructive comments. We used univariate and multivariate Cox regression analysis to identify the optimal factors for modeling. The factors with $p < 0.05$ were included in the model, which minimized the number of factors.

2. As mentioned in the manuscript, the nomograms were built based on the result of multivariable analysis in the training cohort, the author needs to explain what modeling

methods (the Logistic Lasso or Ridge Regression) are used.

Response: We thank the reviewer for their constructive comments. In this study, we used univariate and multivariate Cox regression analysis to build the prognostic nomograms.(9, 10) We have modified the text as advised (see Page 10, line 214-215).

3. As we all know, Age and gender are important factors affecting inflammatory markers, I think the authors need to look at the predictive effects of prognostic models in different age and gender groups. This part can be placed in the supplementary materials section.

Response: We thank the reviewer for their constructive comments. As suggested, we added different subgroups based on age (≤ 50 years and > 50 years) and gender (male and female) in the revised manuscript (see Page 16, line 334-341, Table S3, Table S4). The results showed that the nomograms' performance was good in these populations.

Reference

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