Peer Review File

Article information: https://dx.doi.org/10.21037/jgo-2024-914

Reviewer A

The authors established a nomogram which predict early recurrence of HCC patients based on serum markers and radiomic score. It seems that this model could predict the prognosis of patients, however, there are major concerns that need to be addressed.

1) It is hard to understand the radiomic features of CT findings. What does it reflect the HCC characteristics? I guess that it is associated with pathological findings such as microvascular invasion as mentioned in Discussion. However, there is no description of the relation of radiomic features to pathological data. Also, imaging score formula is too complex to be understood by the physicians except for radiologists.

Reply: Thank you so much for your comment. We have supplemented the "###Feature extraction" section of the methodology with information on the association between CT radiomic features and pathological characteristics of HCC, such as microvascular invasion. We recognize that the formula might indeed be challenging for non-radiological clinicians to understand. Therefore, we have revised the "Feature Reduction and Selection" section in our methods to use simpler and more comprehensible language. This revision explains how we filtered and calculated this scoring formula from a large set of radiomic features, aiding readers in better understanding the construction process of the formula. Furthermore, to facilitate the broader application of our research in future studies, we are exploring the use of machine learning techniques to simplify the model-building process. This initiative aims to reduce the complexity for clinicians applying such models, making them more accessible and easier to use in routine medical practice.

Changes in the text: page 6-7/line 189-219.

2) Except for radiomic score, variables selected for nomogram are commonplace for prediction model of HCC patients. Consequently, I don't think that this model can provide better accuracy compared with conventional model including pathological data.

Reply: Thank you so much for your comment. In this study, the radiomic score, combined with conventional clinical and pathological parameters, formed a multidimensional assessment model. The AUC of this model reached 0.9265 in the training set and 0.9255 in the internal testing set, significantly outperforming a model that only included conventional clinical and pathological data. Furthermore, the introduction of the radiomic score allows the model to provide predictive information on key pathological features, such as microvascular invasion, preoperatively, which is typically only confirmed postoperatively through pathological results in routine clinical

practice. Therefore, although our model incorporates some conventional variables, by integrating the innovative radiomic score, we are able to offer a tool with higher predictive accuracy and more comprehensive information, providing valuable support for the management and treatment decisions of HCC patients. We have added the innovative aspects of this study in the introduction and included a comparison of the AUC values with other traditional prediction models in the discussion section.
Changes in the text: page 5/line 135-143; page 11/line 355-356; page 12/line 375-380.

3) Why the patients were divided into 8:2? Usually, they are divided into 2 (training set) : 1 (validation set).
Reply: Thank you so much for your suggestion. Due to the relatively small sample size in this study (n = 156), we chose an 8:2 split ratio to retain more data in the training set, ensuring that the model could learn a more comprehensive feature representation. Using a 2:1 split ratio might lead to insufficient data in the training set, potentially affecting the model's robustness. Although a 2:1 split ratio is common in many studies, an 8:2 ratio is also widely used in research focused on internal validation. This split ratio ensures that the model is adequately trained while preserving enough data in the validation set to effectively assess the model's predictive performance. The high predictive ability of our model in both the training set (AUC = 0.9265) and the validation set (AUC = 0.9255) indicates that the 8:2 split ratio is reasonable and did not affect the model's generalization ability or predictive accuracy.
Changes in the text: None.

4) This is a retrospective study, therefore, it should be written according to STROBE declaration.
Reply: Thank you for your valuable comment. We have revised and supplemented the manuscript according to the guidelines of the STROBE statement.
Changes in the text: Full text checked and revised.

Reviewer B

The study primarily developed a nomogram model to predict early postoperative recurrence in hepatocellular carcinoma (HCC) patients using preoperative CT imaging radiomic features and serum biomarkers related to microvascular infiltration. The main findings indicate that the nomogram model, which includes key predictive factors such as Kiel 67 (Ki-67) levels, tumor diameter, alpha fetoprotein (AFP), vascular endothelial growth factor A (VEGF-A) levels, fibrosis-4 index, multifocality, abnormal enhancement around the tumor, and a derived radiomics score, effectively predicts

early postoperative recurrence in HCC patients. The model demonstrated excellent predictive accuracy with area under the curve (AUC) values of 0.9319 and 0.8993 for the training and internal test sets, respectively. However, the study is a single-center study with a relatively small sample size, which may affect the generalizability and external validity of the results. The study did not account for postoperative lifestyle, emotional states, or adherence to medical advice, which could be relevant factors in HCC recurrence. My major concern regarding the methodology of this study is the lack of external validation sample. In the title, I suggest the authors to indicate the development of the nomogram. In the abstract, the authors did not explain why the combination of preoperative CT imaging radiomic features and serum features related to microvascular infiltration could be used to develop the prediction model in the background, did not describe the inclusion of participants, data collection of preoperative CT imaging radiomic features and serum features related to microvascular infiltration, follow up procedures, and the outcome measurement of early postoperative recurrence in the methods, did not describe the baseline characteristics of the study sample in the results, and tone down the current conclusion due to the lack of evidence on the external validity of the nomogram. In the introduction, the authors need to review the clinical needs for the prediction model of HCC re-occurrence, available prediction models and their predictors and predictive accuracy, and the clinical needs for new prediction models. Further, please explain why there is a need to combine preoperative CT imaging radiomic features and serum features related to microvascular infiltration, not alone. In the methodology, please describe the clinical research methodology, sample size estimation, follow up procedures, and how the re-occurrence was diagnosed. In statistics, please describe the details of assessing the predictive accuracy and the threshold AUC values for a good prediction model. Please cite several related papers: 1. Zeng J, Zeng J, Lin K, Lin H, Wu Q, Guo P, Zhou W, Liu J. Development of a machine learning model to predict early recurrence for hepatocellular carcinoma after curative resection. Hepatobiliary Surg Nutr 2022;11(2):176-187. doi: 10.21037/hbsn-20-466. 2. He T, Zou J, Sun K. The efficiency of pathological response after preoperative transcatheter arterial chemoembolization for microvascular invasion and early tumor recurrence in hepatocellular carcinoma. Hepatobiliary Surg Nutr 2023;12(1):142-143. doi: 10.21037/hbsn-22-359. 3. Zhang S, Xu L, Dai F, Wang P, Luo J, Zhang M, Xu M. Construction of a predictive nomogram and bioinformatic investigation of the potential mechanism of postoperative early recurrence of hepatocellular carcinoma meeting the Milan criteria. Ann Transl Med 2022;10(16):866. doi: 10.21037/atm-22-3390. 4. Zhao QY, Liu SS, Fan MX. Prediction of early recurrence of hepatocellular carcinoma after resection based on Gd-EOB-DTPA enhanced magnetic resonance imaging: a preliminary study. J Gastrointest Oncol 2022;13(2):792-801. doi: 10.21037/jgo-22-224.

Thank you so much for your valuable comments. Below are our responses to the reviewer's comments and the corresponding revisions:

1. However, the study is a single-center study with a relatively small sample size, which may affect the generalizability and external validity of the results. The study did not account for postoperative lifestyle, emotional states, or adherence to medical advice, which could be relevant factors in HCC recurrence. My major concern regarding the methodology of this study is the lack of external validation sample.

Reply: Thank you so much for your valuable comment. We acknowledge that the single-center nature of the study and the small sample size are limitations of this research. We have added a discussion of this limitation and proposed suggestions for addressing it in future studies. The exclusion of factors such as postoperative lifestyle, emotional status, and patient adherence to medical advice is indeed another important limitation. We plan to consider these variables in future research and explore their impact on HCC recurrence.

Changes in the text: page 11-12/line 364-375.

2. In the title, I suggest the authors to indicate the development of the nomogram.

Reply: Thank you so much for your valuable comment. The title has been changed to "Development and nomogram prediction of early postoperative recurrence in hepatocellular carcinoma based on preoperative CT imaging radiomic features and serum features related to microvascular infiltration".

Changes in the text: page 1/line 3.

3. In the abstract, the authors did not explain why the combination of preoperative CT imaging radiomic features and serum features related to microvascular infiltration could be used to develop the prediction model in the background, did not describe the inclusion of participants, data collection of preoperative CT imaging radiomic features and serum features related to microvascular infiltration, follow up procedures, and the outcome measurement of early postoperative recurrence in the methods, did not describe the baseline characteristics of the study sample in the results, and tone down the current conclusion due to the lack of evidence on the external validity of the nomogram.

Reply: Thank you so much for your valuable comment. We have revised the abstract based on the suggestions.

Background: We added an explanation of why combining preoperative CT radiomic features and serum biomarkers related to microvascular invasion helps in developing the predictive model, thereby enhancing the logical flow of the background.

Methods: We provided a detailed description of the inclusion criteria for participants,

the process of collecting preoperative CT radiomic and serological feature data, the follow-up procedures, and the outcome measurements for early postoperative recurrence.

Results: We further clarified the characteristics of the study sample.

Conclusion: We added a note indicating that the model requires further external validation.

Changes in the text: page 1-3/line 31-69.

4. In the introduction, the authors need to review the clinical needs for the prediction model of HCC re-occurrence, available prediction models and their predictors and predictive accuracy, and the clinical needs for new prediction models. Further, please explain why there is a need to combine preoperative CT imaging radiomic features and serum features related to microvascular infiltration, not alone.

Reply: Thank you so much for your valuable comment. We have revised the introduction section to explain why it is necessary to combine preoperative CT radiomic features and microvascular invasion-related serological features, rather than using them separately.

Changes in the text: page 4-5/line 123-143.

5. In the methodology, please describe the clinical research methodology, sample size estimation, follow up procedures, and how the re-occurrence was diagnosed.

Reply: Thank you so much for your valuable comment. Due to the single-center nature of this study and the limitations of the research timeline, a total of 156 HCC patients who met the inclusion criteria were included. Given the limited sample size, no sample size estimation was performed in this study. To avoid overfitting, it is generally recommended that each variable corresponds to at least 10 events (such as recurrence cases). In this study, the number of 60 early recurrence patients meets the minimum sample size requirement for developing a multivariable predictive model. The follow-up process and how recurrence was diagnosed are detailed in the 'Follow-up assessment' section.

Changes in the text: None.

6.In statistics, please describe the details of assessing the predictive accuracy and the threshold AUC values for a good prediction model.

Reply: Thank you so much for your valuable comment. We have revised the statistical analysis methods and added content regarding the evaluation of predictive accuracy and threshold AUC values.

Changes in the text: page 7-8/line 228-235.

7. Please cite several related papers: 1. Zeng J, Zeng J, Lin K, Lin H, Wu Q, Guo P, Zhou W, Liu J. Development of a machine learning model to predict early recurrence for hepatocellular carcinoma after curative resection. Hepatobiliary Surg Nutr 2022;11(2):176-187. doi: 10.21037/hbsn-20-466. 2. He T, Zou J, Sun K. The efficiency

of pathological response after preoperative transcatheter arterial chemoembolization for microvascular invasion and early tumor recurrence in hepatocellular carcinoma. Hepatobiliary Surg Nutr 2023;12(1):142-143. doi: 10.21037/hbsn-22-359. 3. Zhang S, Xu L, Dai F, Wang P, Luo J, Zhang M, Xu M. Construction of a predictive nomogram and bioinformatic investigation of the potential mechanism of postoperative early recurrence of hepatocellular carcinoma meeting the Milan criteria. Ann Transl Med 2022;10(16):866. doi: 10.21037/atm-22-3390. 4. Zhao QY, Liu SS, Fan MX. Prediction of early recurrence of hepatocellular carcinoma after resection based on Gd-EOB-DTPA enhanced magnetic resonance imaging: a preliminary study. J Gastrointest Oncol 2022;13(2):792-801. doi: 10.21037/jgo-22-224.

Reply: Thank you so much for your valuable suggestion. The above references haven been cited in the manuscript.

Change in the text: reference 5, 8, 9, 14.

Reviewer C

1. Please check if Ref.18 and Ref.21 were duplicated.

Reply: Thank you for your reminder. These two references are indeed duplicated. The reference numbers have been adjusted accordingly.

2. Mao seems not the first author of Ref.16, please check and revise.

528 For instance, Mao et al. (16) showed that radiomic features can be used to non-
529 invasively indicate the potential relationship between CT images and HCC pathological

Reply: Thank you for your reminder. It has been changed to "Mao et al (20)".

3. Please check if more references should be given in this sentence since you've mentioned "recent studies".

466 recurrence following treatment. Recent studies have categorized HCC recurrence into
467 early recurrence and late recurrence (13). Early recurrence is often associated with

Reply: Thank you for your reminder. "Studies" has been changed to "study".

4. Table 1: Please define this type of data either inside the table or in table footnote.

Age (years)	60.00 (55.00, 65.00)	61.00 (54.75, 66.00)	−1.5191	0.13

Reply: Thank you for your reminder. The presentation format of such data has been added to the captions of Tables 1 and 4.

5. Please also define FIB-4 in Table 3-4 footnotes.

Reply: Thank you for your reminder. The full name of FIB-4 has been added in footnote.