Peer Review File

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Reviewer A

Comment 1: The authors are congratulated on their work on the predictive nomogram for HCC recurrence after liver transplantation. However, there's one major issue that requires clarification before the acceptance of their paper. Usually, a training set of data is explored in advance (retrospectively), and a nomogram is derived. Eventually, the nomogram validity is tested in a validation set prospectively or retrospectively. Now, the authors used a different methodology. I think they should discuss their design in light of the existing literature.

Reply 1: While most studies in traditional radiomics focus on dichotomous problems, this study creatively uses COX survival analysis to fully utilize disease-free survival data from patients receiving long-term follow-up care, both to explore whether the patients recur or not after liver transplantation, and to predict the possibility of recurrence at 1, 2, and 3 years after surgery. This better solves the most concerned problem of clinicians - the possibility of postoperative recurrence and the prediction of disease-free survival, and can guide clinicians to take shortened follow-up period, postoperative adjuvant chemotherapy, and other measures to provide early proactive intervention for the patients, rather than until the follow-up found that the patients have recurrence and then carry out passive interventions.

The five factors involved in the clinical model, pathologic model, radiomics model, and nomogram model in this study were all obtained from the COX survival analysis, and therefore, the same methodology was applied to the creation of all four models. Multiple factors that could impact the patients' prognosis were taken into account for the COX survival analysis. Subsequently, a single and multiple survival variable analysis was conducted to identify five independent predictors of recurrence: AFP, ALP, tumor number, Ki-67, and radiomics score. Finally, a clinical model was composed of AFP and ALP, a pathological model was composed of tumor number and Ki-67, a radiomics model was composed of radiomics score, and a nomogram model was composed of the five factors.

The essence of the nomogram model in this study is a comprehensive predictive model containing five independent predictors related to recurrence, which was finally constructed to be easily understood and used by clinicians, taking advantage of the characteristics of the nomogram's visibility, ease of understanding, and convenience. Finally, the AUC and C-index of the four models were compared, and it was found that the nomogram model performed the best in both the training and validation cohorts; to validate its predictive performance again, the Kaplan-Meier survival curve analysis was used to find that there was a significant difference between the disease-free survival of patients in the high- and low-risk groups, and the disease-

free survival of the patients in the low-risk group was longer, which indicated that the nomogram model had a better risk stratification ability, and it can accurately identify the high-risk group for recurrence, to carry out more active follow-up and treatment strategies.
Later, to further validate the model, data from transplant departments of other hospitals will also be collected for external validation.
Changes in the text: None.

Comment 2: Additionally, ALP's predictive validity is rather unusual compared to that of the available predictive systems. Wasn't there a center bias?

Reply 2: ALP is a common indicator in patients' inpatient liver function tests. Unlike AFP, which reflects patients' tumor load, its value better reflects patients' liver function in non-lesion areas of the liver, and patients with good liver function generally have better preoperative physical function and relatively faster postoperative recovery.
In the study of reference 10, ALP was found to be one of four independent predictors of patient overall survival. In the study in reference 33, ALP was found to be an independent predictor affecting patients' overall survival and disease-free survival, and preoperative ALP levels can also be used to monitor and predict recurrence in patients with high-risk HCC.
In this study, firstly, the enrolled patients were randomized according to the training cohort: validation cohort of 7:3, and the p-value of ALP was 0.64, which represented comparable data between the two cohorts; subsequently, the COX survival analysis for the training cohort incorporated the patients' gender, age, HBsAg, Child-Pugh classification, AFP, ALP, tumor number, maximum tumor diameter, Ki-67, radiomics score, and several other factors that may affect prognosis, and a single and multiple survival variable analysis was performed; finally, the results also showed that ALP was one of the independent predictors associated with patient recurrence. The results of this study are in general agreement with the results of the references.
Reference
10. Yeh CN, Chen MF, Lee WC, et al. Prognostic factors of hepatic resection for hepatocellular carcinoma with cirrhosis: univariate and multivariate analysis. J Surg Oncol. 2002;81(4):195-202.
33. Yu MC, Chan KM, Lee CF, et al. Alkaline phosphatase: does it have a role in predicting hepatocellular carcinoma recurrence? J Gastrointest Surg. 2011;15(8):1440-1449.
Changes in the text: None.

Reviewer B

Comment: The authors provide a very interesting clinical work. They developed and validated a nomogram model constructed from radiomics, clinical features, and pathological indicators to predict DSF after liver transplantation in HCC patients. The introduction provides a brief but concise overview of the clinical problem as well as the research question addressed in this work. The methods section is detailed and clear and the results obtained follow a central thread. The authors provide a technique to screen for and evaluate early recurrence in liver transplant patients after HCC, a crucial aspect in planning follow-up care in those patients. Nice work. There remains just two minor questions:

Reply: First of all, I would like to especially thank the reviewers for recognizing the work of this study, and I will answer the reviewers' questions in detail below.

Comment 1: Could the authors elaborate, why they decided for the follow-up cutoff date to be in 2020? And would there be a possibility to get the most recent data for those patients (e.g., cutoff date 2023 for longer FU time)?

Reply 1: Our unit was formerly the General Hospital of the Armed Police, and after organizational restructuring in 2018, it was renamed the Third Medical Center of the General Hospital of the People's Liberation Army, and the specialities direction shifted to urology and ophthalmology, and the original organ transplantation surgery were also gradually shifted to other medical centers, therefore, our hospital shifted from being focused on liver transplantation operation to being focused on postoperative follow-up and adjuvant treatment of patients from December 2018 onwards.

Of the 139 patients enrolled, the first patient received liver transplantation in January 2013, and the last patient received liver transplantation in December 2018, so the longest follow-up period for patients was up to 7 years, and the shortest follow-up period was 1 year; and reference 6 also pointed out that the prognosis of patients with recurrence 1 year after liver transplantation was poor. Since there were no patients with liver transplantation after December 2018, it was decided to set the follow-up cutoff date in January 2020 in this study.

Subsequently, we will also collaborate with transplantation departments of other hospitals to collect data on liver transplantation patients in recent years, conduct a multicenter study, and externally validate the performance of this prediction model.

Reference

6. Sapisochin G, Goldaracena N, Astete S, et al. Benefit of Treating Hepatocellular Carcinoma Recurrence after Liver Transplantation and Analysis of Prognostic Factors for Survival in a Large Euro-American Series. Ann Surg Oncol. 2015;22(7):2286-2294.

Changes in the text: None.

Comment 2: The final cohort consisted of 139 patients, while 273 patients underwent LT for HCC in the study period. What happened to those patients that were not included? And do you think, this might be a major bias in your data?

Reply 2: A total of 134 patients were not included in this study, including 15 patients without CT-enhanced images; 98 patients who had received local or systemic antitumor therapy before liver transplantation; 13 patients with incomplete laboratory test items, demographic data, and follow-up information; and 8 patients who had no recurrence in less than 1 year of follow-up. During the follow-up cycle, 57 disease-free surviving patients were not enrolled, and the percentage of non-recurrence was 42.54%, which was roughly similar to the percentage of non-recurrence in enrolled patients, which was 42.17%, with no statistical difference.

To further prove that the data collection of the enrolled patients did not have the occurrence of bias, the independent predictors related to recurrence obtained in this study were counted, and among the non-enrolled patients, the percentages of AFP <200 ng/mL were 66.45%, ALP <135 U/L were 72.39%, the number of tumors was single was 40.30%, and the Ki-67 <10% was 56.72%, which were the same as the corresponding percentages of enrolled patients were 70.5%, 66.19%, 34.53%, and 55.4%, respectively. There was no statistically significant difference in the percentages of the four factors.

Therefore, we believe that the non-inclusion of patients did not bias the conclusions of this study.

Changes in the text: None.