

Peer Review File

Article Information: <https://dx.doi.org/10.21037/jgo-24-285>

Reviewer A

In this study, a nomogram for prediction of survivals of patients undergoing large HCC was developed using public data, which was validated using independent cohort. Although this study does not harbor many novel findings, this is a well-written paper and valuable for readers in this field.

Comment 1: This study is retrospective, and the manuscript should be written based on STROBE, which recommends that there is no patient data in Materials and Methods. Also, patient selection should be described using flow-chart.

Reply 1: Thank you for your expert guidance. We have deleted the patient data in Materials and Methods. In addition, we have added a flow-chart to describe the patient selection.

Changes in the text: We have deleted the patient data (see Page 8, line 135). We have added a flow-chart to describe the patient selection (see Figure 1).

Comment 2: Chemotherapy in Table 1 was performed before or after operation?

Reply 2: Thank you for your meticulous work. Due to the small sample size after further further division, we did not distinguish whether chemotherapy was performed before or after surgery.

Comment 3: There is no data on operation factors such as curative surgery, surgical margin, and amount of bleeding etc, despite of surgical paper. If they are not available, it should be written in limitations in Discussion.

Reply 3: Thank you very much for your valuable comment. Due to the limitations of the SEER database, we are unable to obtain more information about surgery such as curative surgery, surgical margin, and amount of bleeding etc. We have added this content in limitations in Discussion.

Changes in the text: We have added the related contents in limitations in Discussion (see Page 14, line 271-273).

Comment 4: Also, there is no data on treatments after recurrence, which would have affected patients survivals.

Reply 4: Thank you for your professional advice. Data on treatments after recurrence is also unavailable in SEER database. We have also taken this into consideration, so the main outcome of this research is cancer-specific survival. We plan to combine multi-center data in future studies to predict postoperative recurrence of hepatocellular carcinoma and investigate the best intervention after recurrence.

Reviewer B

Comment 1: First of all, my major concern for this study is the small sample size of the external validation sample, n=21, which is far insufficient to be the validation sample. My

other major concern is the limiting of the follow up dates in the SEER dataset, between 2010 and 2015, but the external validation sample's follow up dates were 2012-2019.

Reply 1: Thank you for your professional advice, which has been of great help to the improvement of our article.

First, although we have collected a relatively complete sample of eligible patients who underwent surgery at our hospital, the external validation sample size is small. The external validation of this research is only for preliminary validation. We have also searched for other studies that included external validation. We found that 21 patients could serve as an external validation. Researches based on small sample external validation have been published recently. (Reference: 1. Yuan C, Zou S, Wang K, Hu Z. Establishment and external validation of prognosis prediction nomogram for patients with distant metastatic intrahepatic cholangiocarcinoma: based on a large population. *BMC Cancer*. 2024;24:227. 2. Sun W, Zhang X, Qiu Z. Survival trends and conditional survival in primary non-metastatic esophageal cancer: a SEER population-based study and external validation. *Transl Cancer Res*. 2023;12:2693 – 705. 3. Song X, Xie Y, Lou Y. A novel nomogram and risk stratification system predicting the cancer-specific survival of patients with gastric neuroendocrine carcinoma: a study based on SEER database and external validation. *BMC Gastroenterol*. 2023;23:238.) We expect to have more patients as external validation in future studies.

Second, we included patients diagnosed with HCC between 2010 and 2015. In order to increase the sample size as much as possible in external validation cohort, we included patients diagnosed with HCC between 2012 and 2019. As shown in the Result part, The median follow-up time of patients was 53 months. In this research, we established a nomogram to evaluate the survival rate of patients with large HCC at 12, 24, and 36 months. Therefore, follow-up data is suitable.

Comment 2: Second, the title did not indicate the prognosis outcome to be predicted.

Reply 2: Thank you for your valuable comment. We have revised the title based on your suggestion.

Changes in the text: We have revised the title (see Page 1, line 2-4).

Comment 3: Third, the abstract is inadequate. The background did not describe the current knowledge gap and the clinical needs for this research focus. The methods need to specify the training, internal validation, and external validation samples, inclusion criteria, potential clinical predictors, follow up procedures, and measurement of prognosis outcome. The results need to briefly summarize the clinical characteristics of the three samples used, as well as the cancer-specific survival rates. Also, AUC values for both the internal and external validation samples should be reported. The current conclusion needs to be tone down since the accuracy findings in the external validation sample is not convincing and the present study had methodology limitations.

Reply 3: Thank you for your professional advice, which has been of great help to the improvement of our article. We have revised the abstract according to your suggestions.

Changes in the text: We have revised the abstract (see Page 2, line 22-53).

Comment 4: Fourth, the background of the main text is inadequate. Please review what has

been known on the prognosis of patients with large hepatocellular carcinoma undergoing surgical resection, factors associated with such prognosis, available prognosis predictive models and their predictors, and limitations of prior studies.

Reply 4: Thank you for your meticulous advice, which has been of great help to the improvement of our article. We have added the background about what has been known on the prognosis of patients with large HCC.

Changes in the text: we have added the related contents in the Introduction part (see Page 6, line 88-102).

Comment 5: Fifth, in the methodology of the main text, the clinical research methodology of this study should be clearly described. The authors need to describe the sources of the training and internal validation samples in detail including how the cohort was established, settings, clinical factors, follow up procedures, and how the prognosis outcomes were measured. In statistics, please describe the threshold AUC values for a good prediction model, also I suggest the authors to calculate the sensitivity and specificity of the prediction model.

Reply 5: Thank you for your meticulous advice, which has been of great help to the improvement of our article. We have adjusted and improved the relevant contents according to your comment, which greatly enriched our methodological description and results and made our research more rigorous. In addition, we have added a flow-chart to describe the patient selection.

Changes in the text: we have added the related contents in the methodology part (see Page 7, line 110-123; page 8, line 140-141; page 9, line 161-162), Figure 1, and result part (page 10, line 188-194; page 11, line 209-210).

Comment 6: Finally, please cite several related papers: 1. Shah RM, Sheikh S, Shah J, Vivian E, Mejia A, Shahin I, Mantry PS. Prognostic factors of unresectable hepatocellular carcinoma treated with yttrium-90 radioembolization: results from a large cohort over 13 years at a single center. *J Gastrointest Oncol* 2021;12(4):1718-1731. doi: 10.21037/jgo-20-435. 2. Yang J, Shang X, Li J, Wei N. Comparative study on the efficacy and safety of transarterial chemoembolization combined with hepatic arterial infusion chemotherapy for large unresectable hepatocellular carcinoma. *J Gastrointest Oncol* 2024;15(1):346-355. doi: 10.21037/jgo-23-821. 3. Cai YS, Wu H. Is FOLFOX-HAIC superior to transarterial chemoembolization in treating large hepatocellular carcinoma? *Hepatobiliary Surg Nutr* 2022;11(1):164-165. doi: 10.21037/hbsn-21-503. 4. Hakkakian K, Golse N. Resection post-radio-embolization in patients with single large hepatocellular carcinoma. *Hepatobiliary Surg Nutr* 2024;13(2):307-310. doi: 10.21037/hbsn-24-3.

Reply 6: Thank you for your professional advice, which has been of great help to the improvement of our article. We have carefully read these relevant papers and cited them.

Changes in the text: We have cited relevant papers (see Reference 14, 15, 24, 25).