Peer Review File

Article information: https://dx.doi.org/10.21037/tcr-23-1786

Reviewer A

Comment 1: The authors have used a sound and interesting methodology, however the patient cohort being analyzed is far too heterogeneous with respect to treatment era with varying chemotherapy regimens and surgical approaches.

Reply 1: Thank you! As indicated by the reviewer, the patient cohort examined in this study was too heterogeneous in the treatment era, involving different chemotherapy regimens and surgical modalities. However, it is worth noting that liver tumours are a rare malignant occurrence in children. The study's data collection originated from the SEER database, collated from 18 centres in the United States. In the end, only 409 cases fulfil the study's criteria, despite nearly 20 years of data. Furthermore, the particular surgical methods and chemotherapy regimens were not specifically addressed in this study. The sole focus was the investigation of the impact of surgery and chemotherapy, or lack thereof, on the prognosis of paediatric patients.

Comment 2: Additionally much of what is concluded is not additive to the established literature. For example it is well established that the presence of metastatic disease confers a poorer prognosis on patients. Similarly a binary yes/no paradigm for surgery adds little to the literature. Hepatoblastoma is a cancer for which surgery is necessary. It stands to reason that patients who did not receive surgery would do worse.

Reply 2: Thank you. Our research involved conducting multivariate and univariate Cox regression analyses to identify independent prognostic markers for both Cause-Specific Survival (CSS) and Overall Survival (OS). Based on the results obtained from these analyses, we developed nomograms for CSS and OS by incorporating the identified independent prognostic variables into our assessment. Whilst there have been reports of poorer prognosis amongst children with distant metastasis and without surgical intervention, our multivariate regression analysis found that distant metastasis and surgery were not independent prognostic factors for children with hepatoblastoma. Therefore, they were not included in our model construction.

Comment 3: Finally the effect of age on outcomes has been well established by the CHIC consortium. In the current AHEP1531, age is used to stratify patients with patients under 3 YOA having a better prognosis. This analysis suggests that patients age greater than 2 have inferior outcomes however is not more granular than that.

Reply 3: Thank you. The AHEP1531 trial investigated the treatment of hepatoblastoma or liver cancer in children and young adults following surgery. In contrast, the present study focuses on children exclusively with hepatoblastoma. The X-tile method is applied to determine the age cutoff value. X-tile is a software developed by Yale University, which determines the optimal cutoff value of continuous variables and facilitates the drawing of Kaplan-Meier curves.

Comment 4: Finally I fail to understand what the distinction between systemic therapy and chemotherapy is. To me they are synonymous in the treatment era included here.
Reply 4: Thank you. We apologize for any inconvenience caused. In this study, systemic therapy is defined as the administration of chemotherapy and surgical treatment, regardless of their order. A definition of systemic therapy has been included in the Methods section of the study. (see Page 5, line 109-111)

Reviewer B

Comment 5: In this paper, the authors developed a nomogram-based models to assess the outcome of children with hepatoblastoma. This model seems to estimate survival in patients with hepatoblastoma. However, the nomogram is based on age, presence or absence of surgery and/or chemotherapy, and tumor size. From a clinical point of view, it is questionable why distant metastasis is not included into the factors of this system. Patients with an unresectable tumor may undergo liver transplantation to achieve complete resection, and tumor location is also important for surgical decision making. Thus, it has not been reported that tumor size had prognostic value in hepatoblastoma.
Reply 5: Thank you. As previously discussed with Reviewer A, while it has been reported that children with distant metastasis and without surgical intervention have a poorer prognosis, our univariate Cox analysis supports this finding. However, in our multivariate regression analysis, distant metastasis and surgery do not emerge as independent factors that impact the prognosis of children with hepatoblastoma. So, we have excluded them from the model's construction. While this discovery may be contentious, it is factual to our research, which drew data from the publicly available SEER database.

Comment 6: One can generally estimate survival rates based on age, PRETEXT stage, presence or absence of metastasis. The author’s model does not seem to me more useful than the preexisting prognostic factors and potent to change clinical decision in hepatoblastoma.
Reply 6: Thank you. Survival rates were approximated based on age, PRETEXT stage and presence or absence of metastasis. However, our model provides accurate individual survival rate calculations. Our model demonstrated good discrimination and calibration in both the training and validation cohorts. To increase accessibility, a web-based survival rate calculator using our nomogram was developed. This tool allows healthcare professionals and patients undergoing medical treatment to determine the long-term overall survival.