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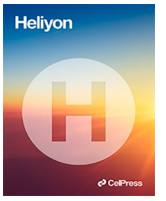

Research article

Impact of treatment on the prognosis of childhood in hepatoblastoma: A SEER based analysis

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ABSTRACT

Background: The prognosis of patients with hepatoblastoma has been unsatisfactory. This study analyzed the effects of different treatment methods on cancer-specific survival (CSS) in children with hepatoblastoma.

Method: From 2000 to 2018, patients with hepatoblastoma were included in the Surveillance, Epidemiology, and End Results (SEER) database. CSS was estimated using the Kaplan–Meier method. Cox regression analysis assessed prognostic factors. The predictive models were validated using the concordance index (C-index), calibration curve and receiver operating characteristic (ROC) curve.

Result: Of the 785 included patients, 730 (93.0 %) underwent chemotherapy, 516 (65.7 %) underwent liver tumour resection and 129 (16.4 %) underwent liver transplantation. Both chemotherapy and surgery could significantly improve the CSS rate (all $p < 0.001$). However, there was no difference in CSS rate between the two surgical methods (liver tumour resection and liver transplantation) ($p = 0.613$). Further subgroup analysis revealed that children who underwent liver tumour resection or liver transplantation based on chemotherapy (all $p > 0.05$) had a similar prognosis. Multivariate analysis revealed that age ($p = 0.003$), race ($p = 0.001$), operative method ($p < 0.001$), chemotherapy ($p < 0.001$), distant metastasis ($p < 0.001$) and tumour size ($p < 0.001$) were independent factors related to CSS. The C-index of the new nomogram was 0.759, and its consistency was good. The ROC curves verified that the nomogram had a better prediction ability for 1-, 3- and 5-year CSS rates.

Conclusion: In children with hepatoblastoma, there was no statistically significant difference in CSS between chemotherapy combined with liver transplantation and liver tumour resection. The nomogram we constructed demonstrated satisfactory CSS prediction ability.

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1. Introduction

Hepatoblastoma is a highly malignant embryonal hepatocellular carcinoma caused by abnormal development of pluripotent hepatic stem or progenitor cells. Hepatoblastoma is a rare disease, accounting for two-thirds of all liver tumour cases in children [1], with an incidence of 2.3 cases/million children/year [2,3]. According to the literature, 90 % of hepatoblastomas occur in children <5 years old, most of whom are <3 years of age [4]. Hepatoblastoma is treated primarily with liver transplantation, liver resection and chemotherapy. However, the prognosis of patients with hepatoblastoma remains poor, with the 5-year event-free survival (EFS) being approximately 65 % [5]. High-risk hepatoblastoma and a poor prognosis should be identified in the early stages to help formulate appropriate treatment plans.

Previous studies have indicated that only 30 % of patients with hepatoblastoma can undergo one-stage radical resection treatment, and the survival rate is approximately 20%–30 % [6,7]. However, only 60 % of these tumours can be resected following treatment with neoadjuvant chemotherapy, with a 5-year survival rate that has improved to more than 75 % [8]. Liver transplantation is an important treatment option for unresectable tumours after chemotherapy. The effect of liver transplantation remains controversial. There are relatively limited research data on hepatoblastoma, particularly a prognostic model for hepatoblastoma that can assist clinicians in predicting the prognosis of patients with hepatoblastoma.

The Surveillance, Epidemiology, and End Results (SEER) database collects and stores cancer incidence, survival, and treatment data across the United States. Clinical data are abundant and of great value for studies on cancer epidemiology, etiology, diagnosis, and treatment. Therefore, compared to the hepatoblastoma data from the research center, the number of patients and clinical data in the SEER database are more comprehensive; thus, conclusions drawn from these data are more reliable. This study was performed using patients with hepatoblastoma in the SEER database as the research objects to compare the prognosis of patients under different treatment methods, and we built a prediction model for cancer-specific survival (CSS) of hepatoblastoma to identify adverse clinical outcomes in patients with early-stage disease and provide personalized and regularly updated dynamic prognostic information for clinicians and patients.

2. Materials and methods

2.1. Patients and ethics

We used the SEER database and SEER-stat software (SEER*Stat 8.3.9) to identify and collect the data of patients with confirmed hepatoblastoma aged 0–18 years between 2000 and 2018 according to the International Classification of Diseases for Oncology (ICD-*O*-3). A total of 833 patients were preliminarily assessed to meet the study conditions. Of the 833 patients, 48 were excluded from this study for the following reasons: (1) 7 patients without complete follow-up (2) The diagnosis of 20 patients was not confirmed based on pathological examination and (3) 21 patients were over the age of 18 years. After these exclusions, the remaining 785 patients were included in the study group (Fig. 1). The data used in this study were obtained from open data resources provided by the SEER database, which were anonymised in terms of patients' personal information. Therefore, ethical approval was not required.

2.2. Definition of variables

The data were classified as follows: Age at diagnosis was divided into three groups: <3 and ≥ 3 years [9,10]. Sex was divided into male or female, and race was divided into three categories: white, black and other/unknown. Surgery type (no, liver resection, liver transplantation and unknown), chemotherapy status (yes and no) and the presence or absence of distant metastasis (yes, no and

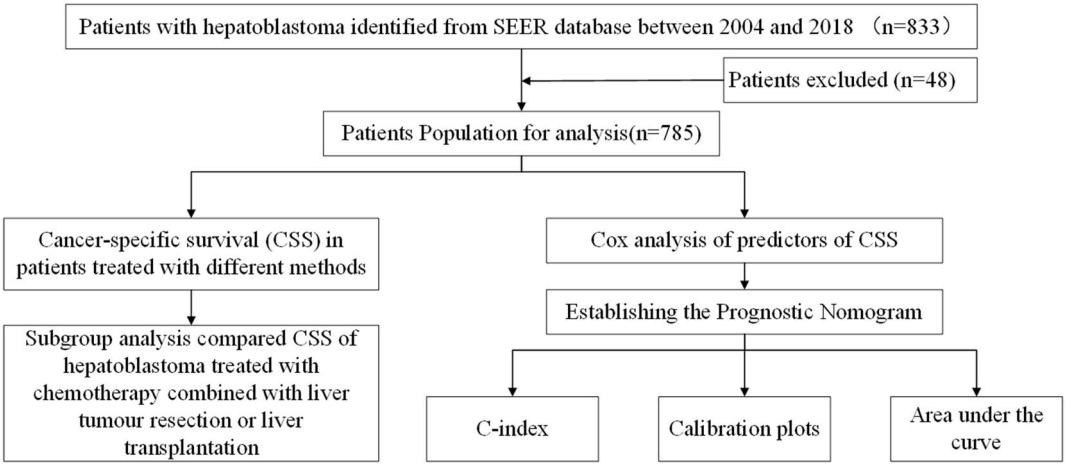

Fig. 1. Flow chart of the overall study design.

unknown) were recorded. Tumour size was divided into three categories: <5 cm, ≥5 cm [11,12] and unknown. Serum alpha-fetoprotein (AFP) levels were divided into three categories: elevated, normal and unknown.

2.3. Statistical analysis and nomogram construction

The primary result for this study was CSS. Survival curves were generated using Kaplan–Meier curves and statistical comparisons were performed using the log-rank test. Patient characteristics were compared between cohorts using chi-square tests. PH hypothesis tests for all included factors were $p > 0.05$. Clinical indicators with $p < 0.05$ in the univariate analysis were incorporated into the multivariate Cox regression analysis. Clinicopathological features correlating with the survival rate were screened. A subgroup analysis was conducted for patients undergoing chemotherapy combined with liver resection or transplantation in the SEER database. The relationship between the treatment and prognosis was screened for each subgroup. A forest map was plotted to present the results.

Concordance index (C-index) and calibration curves were used to evaluate the performance of the nomogram. The larger the C-index value, the more accurate the prediction [13]. Internal validation was performed using 1000 bootstraps resamples. Concordance between predicted and actual survival was quantified using calibration curves of the nomogram for 1-, 3- and 5-year CSS. Furthermore, the area under the ROC curve was used to accurately predict 1-, 3- and 5-year survival.

In this study, R (version 3.6.3 and 4.0.3) was used for statistical analyses. The "survival" package was used for univariate and multivariate Cox regression analyses, and the "survminer" package was used for forest mapping. Hazard ratios (HRs) > 1 indicated risk factors, and HRs <1 indicated protective factors. All tests were two-sided, and *p*-values <0.05 were considered statistically significant.

3. Results

1. Patient Characteristics

A total of 785 patients were included in this study and their clinical characteristics are summarised in Table 1, comprising 481 females (61.3 %) and 304 males (38.7 %). The median age at the time of diagnosis was 1 year (interquartile range [IQR], 0–18 years).

Among the 785 included patients, 645 (82.1 %) received surgical treatment for hepatoblastoma, of which 516 (65.7 %) underwent liver tumour resection and 129 (16.4 %) underwent liver transplantation. The majority of the children (93.0 %) underwent chemotherapy.

Table 1
Characteristics of hepatoblastoma patients.

Variable	Data, n (%)
Total	785(100.0)
Age (year)	
<3	619(78.9)
≥3	166(21.1)
Gender	
Female	304(38.7)
Male	481(61.3)
Race	
Black	67(8.5)
White	593(75.5)
Others/Unknown	125(16.0)
Surgical therapy	
None	130(16.6)
Liver resection	516(65.7)
Liver transplantation	129(16.4)
Unknown	10(1.3)
Chemotherapy	
No	55(7.0)
Yes	730(93.0)
Distant	
No	398(50.7)
Yes	122(15.5)
Unknown	265(33.8)
Tumor size (cm)	
<5	167(21.3)
≥5	406(51.7)
Unknown	212(27.0)
Serum AFP	
Elevated	507(64.6)
Normal	11(1.4)
Unknown	267(34.0)

Abbreviations: AFP= Alpha fetoprotein.

2. Cancer-Specific Survival in Patients with Hepatoblastoma Treated with Different Methods

Fig. 2A and B present the CSS rate of patients with hepatoblastoma after receiving different treatment methods. Patients with hepatoblastoma who received chemotherapy had a significantly improved prognosis than those who did not receive chemotherapy ($p < 0.001$), and the 1-, 3- and 5-year CSS rates were 71.2 % vs. 91.2 %, 66.1 % vs. 84.6 % and 66.1 % vs. 83.4 %, respectively. The CSS of patients who underwent surgery was significantly better than that of patients who did not ($p < 0.001$).

However, there is no significant difference between liver tumour resection and liver transplantation ($p = 0.613$), and the 1-, 3- and 5-year CSS rates were 58.5 % vs. 95.9 % vs. 96.9 % vs. 75.0 %, 44.8 % vs. 91.6 % vs. 90.0 % vs. 50.0 % and 42.6 % vs. 90.5 % vs. 90.0 % vs. 50.0 %, respectively. Subgroup analysis was performed to compare the CSS of patients with hepatoblastoma treated with chemotherapy combined with hepatectomy or liver transplantation (Fig. 3). The results revealed that there was no significant difference in the prognosis of children who underwent liver tumour resection or liver transplantation based on chemotherapy (all $p > 0.05$).

3. Prognostic Factors Affecting CSS

Univariate analysis revealed that age ($p = 0.003$), race ($p = 0.001$), surgical therapy ($p < 0.001$), chemotherapy ($p < 0.001$), distant metastasis ($p < 0.001$), tumour size ($p < 0.001$) and AFP status ($p < 0.001$) were related to CSS. Age ≥3 years ($p < 0.001$), black ($p < 0.001$), no surgery ($p < 0.001$), no chemotherapy ($p < 0.001$), distant metastasis ($p < 0.001$) and tumour size ≥5 cm ($p = 0.008$) were independently associated with poor CSS (Table 2).

4. Establishing the Prognostic Nomogram Model

Nomograms were generated via Cox proportional hazards regression analysis to predict the incidence of CSS in patients with hepatoblastoma at 1, 3 and 5 years (Fig. 4). As an example for explaining the application of the model, taking a 2-year-old patient with hepatoblastoma (55 points) as an example. His race (59 points) and preoperative tumor size (70 points) are unknown, but he is accompanied by distant metastasis (61 points), and he received chemotherapy (55 points) and liver transplantation (50 points). The total risk value for this patient was 350, with a downward trend on the '1-year, 3-year and 5-year overall survival' axis. The 1-, 3- and 5-years survival rate were 92.2 %, 86.2 % and 85.1 %, respectively.

The C-index of the nomogram was 0.759 (95 % CI: 0.736–0.782), and the accuracy of the nomogram was verified by using self-lifting sampling (1000 iterations). Calibration plots demonstrated good agreement between the actual 1-, 3- and 5-year CSS rates and the survival rates predicted by nomograms (Fig. 5A–C). In addition, the accuracy of the model for predicting the 1-, 3- and 5-year CSS rates was assessed based on the area under the curve (AUC) values (Fig. 5D–F). The AUC values of the nomogram for predicting 1-, 3- and 5-year CSS were 0.86, 0.81 and 0.81, respectively.

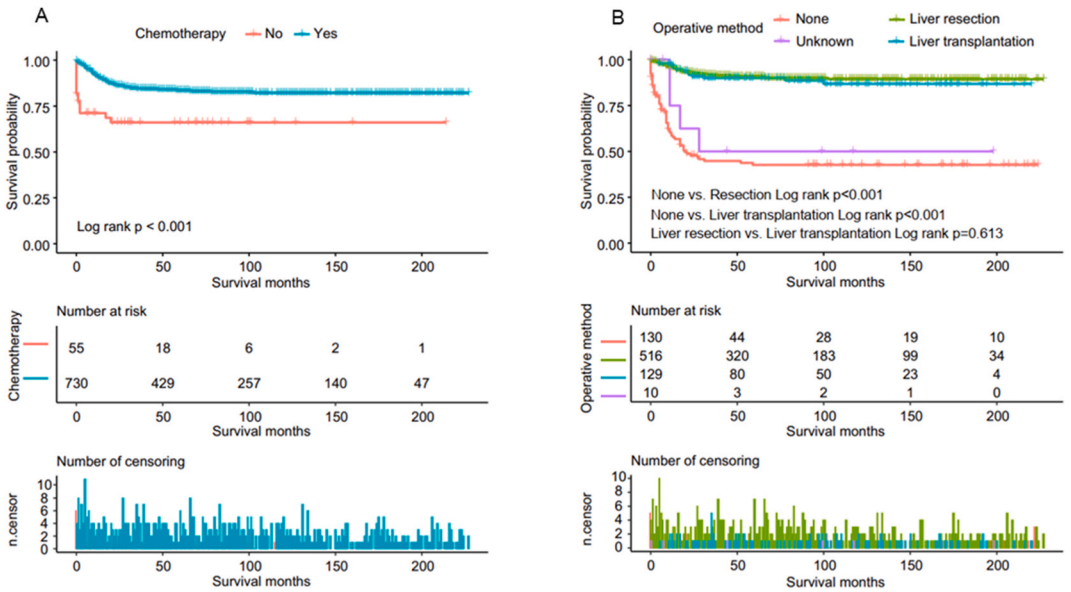

Fig. 2. Survival curves for the CSS of patients with hepatoblastoma with different treatments. K–M curves for CSS with (A) chemotherapy vs. no chemotherapy groups and (B) surgery vs. no surgery groups. The number of at-risk cases in each group at 0, 50, 100, 150 and 200 months is indicated. Abbreviations: CSS: Cancer-specific survival; K–M: Kaplan–Meier.

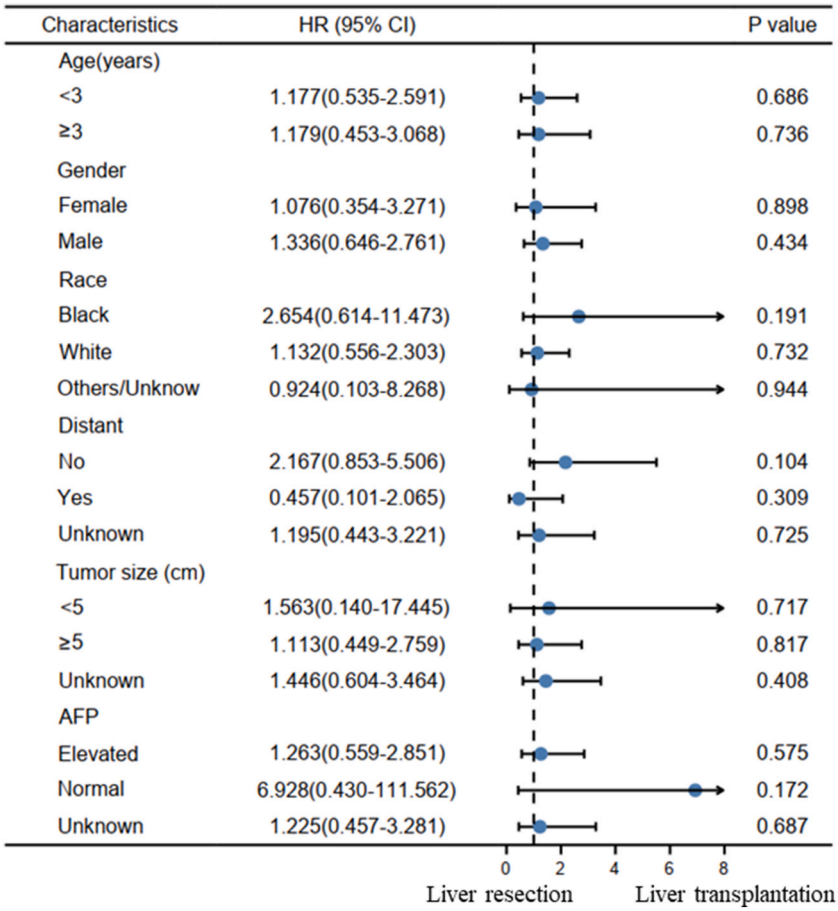

Fig. 3. Subgroup analysis of CSS between patients with hepatoblastoma with chemotherapy combined with hepatectomy and liver transplantation, hazard ratio ±95 % confidence interval. Abbreviations: CSS: Cancer-specific survival; CI: Confidence interval; HR: Hazard ratio; AFP: Alpha-fetoprotein.

4. Discussion

Hepatoblastoma is the most common liver tumour in children with a dismal prognosis. This study revealed whether undergoing surgery and chemotherapy is associated with the patient's survival and whether they are independent risk factors for hepatoblastoma prognosis (all $p < 0.001$). However, liver transplantation shows a tendency towards inferior CSS outcomes when compared to liver resection, although this disparity does not reach statistical significance ($p = 0.613$). Using the results of multivariate analysis, a nomogram model is established to predict CSS in one year, three years and five years. The new prediction model was consistent and exhibited good discrimination (C-index = 0.759).

In this study, 93 % of the patients underwent chemotherapy. Chemotherapy significantly improved prognosis, and the 5-year CSS rates were 66.1 % vs. 83.4 % ($p < 0.05$). Multivariate Cox regression analysis indicated that whether patients received chemotherapy was an independent prognostic factor. Complete surgical resection is currently the first-line treatment for hepatoblastoma; however, approximately 50%–60 % of tumours are unresectable at diagnosis [14], and approximately 20 % of patients with hepatoblastoma present with distant metastasis at diagnosis [15]. Chemotherapy forms a vital backbone of hepatoblastoma therapy. Neoadjuvant chemotherapy reduces tumour size and shortens tumour stage, allowing certain patients to undergo surgery [16–18].

Postoperative adjuvant chemotherapy can improve survival and reduce the incidence of recurrence and metastasis. It has been reported that the 5-year survival rate of stage III and IV patients with hepatoblastoma who underwent tumour resection following neoadjuvant chemotherapy was 88 % [19]. Currently, the commonly used first-line chemotherapy agents include CFVD (cisplatin + 5-fluorouracil + vincristine + doxorubicin), C5V (cisplatin + 5-fluorouracil + vincristine) and ICE (Ifosfamide + carboplatin + etoposide). Routine chemotherapy should be administered according to the treatment guidelines [20]. At present, the optimal chemotherapy regimen for hepatoblastoma is yet to be determined, and further investigation is required in this field.

However, because the SEER database does not provide details pertaining to the chemotherapy sequence or specific chemotherapy regimen, the importance of chemotherapy for CSS of hepatoblastoma could not be evaluated. There is great controversy about the impact of liver tumour resection and liver transplantation on the prognosis of hepatoblastoma. In this study, 66.7 % of patients

Table 2
Variables associated with CSS according to the Cox proportional hazards regression model.

Variable	Univariable analysis		Multivariable analysis	
	Hazard ratio (95 % CI)	*P* value	Hazard ratio (95 % CI)	*P* value
Age (year)				
<3	Reference	–	Reference	–
≥3	1.741(1.206–2.513)	0.003	2.013(1.375–2.946)	<0.001
Gender				
Female	Reference	–	–	–
Male	1.331(0.924–1.917)	0.124	–	–
Race		0.001		<0.001
Black	Reference	–	Reference	–
White	0.392(0.246–0.625)	<0.001	0.370(0.226–0.605)	<0.001
Others/Unknown	0.410(0.222–0.758)	0.004	0.438(0.234–0.820)	0.010
Surgical therapy		<0.001		<0.001
None	Reference	–	Reference	–
Liver resection	0.116(0.080–0.169)	<0.001	0.173(0.114–0.263)	<0.001
Liver transplantation	0.135(0.076–0.241)	<0.001	0.201(0.110–0.370)	<0.001
Unknown	0.661(0.241–1.814)	0.422	1.232(0.435–3.487)	0.695
Chemotherapy				
No	Reference	–	Reference	–
Yes	0.332(0.199–0.554)	<0.001	0.357(0.205–0.623)	<0.001
Distant		<0.001		<0.001
No	Reference	–	Reference	–
Yes	3.826(2.446–5.984)	<0.001	2.663(1.644–4.313)	<0.001
Unknown	2.632(1.741–3.978)	<0.001	2.066(1.024–4.168)	0.043
Tumor size (cm)		<0.001		0.009
<5	Reference	–	Reference	–
≥5	2.336(1.115–4.893)	0.025	3.044(1.343–6.902)	0.008
Unknown	5.479(2.625–11.436)	<0.001	3.638(1.569–8.433)	0.003
AFP		0.001		0.703
Elevated	Reference	–		
Normal	1.268(0.311–5.173)	0.741	1.012(0.242–4.224)	0.987
Unknown	1.953(1.381–2.762)	<0.001	0.782(0.439–1.393)	0.404

Abbreviations: CI= Confidence interval; AFP= Alpha fetoprotein.

underwent liver tumour resection, while 23 % of patients underwent liver transplantation. Regardless of whether surgical treatment had a significant effect on the rate of CSS ($p < 0.05$), the 5-year CSS rate of liver tumour resection and liver transplantation was similar (90.5 % vs. 90.0 %, $p = 0.613$). Subgroup analysis further proved that there was no significant difference between liver tumour resection and liver transplantation ($p > 0.05$). Currently, the efficacy of liver transplantation in hepatoblastoma is yet unknown. Liver transplantation is preferred for patients with local or distant lesions and multiple satellite lesions [21,22]. McAteer et al. reported a disease-specific 5-year overall survival rate of children with hepatoblastoma was 85.7 %, and the patients undergoing resection and transplantation had the same survival rate (85.6 % vs. 86.5 %, $p = 0.66$) [23]. Jincheng et al. reported the percentages of patients with a 10-year OS were comparable between those undergoing liver tumour resection (n = 341) and liver transplantation (n = 84) (89.3 % vs 90.1 %, $p = 0.891$) [12].

However, for patients with inoperable tumours, liver transplantation combined with chemotherapy is the best option for long-term disease-free survival [24]. Thus, we observed a slight upward trend in modern liver transplant survival rates. The overall survival rate of patients with liver transplantation (100 %) was higher than those with liver tumour resection [25]. Paloma et al. reported that overall survival 1 and 5 years after transplantation were 93.3 % and 86.4 %, respectively [26]. Combined with the analysis of the data of hepatoblastoma transplantation group of COG and SIOPEL [27,28], it is found that there is no difference in the prognosis between the liver transplantation group and the liver resection group, which may be related to many patients with recurrent resection and extrahepatic metastasis in the transplantation group. These patients are indeed poor candidates for transplantation. In this study, liver transplantation was not associated with improved overall survival compared to liver tumour resection in paediatric patients with hepatoblastoma who received chemotherapy. This may be related to the fact that patients undergoing liver transplantation were generally high-risk patients, with high tumour stage, often accompanied by distant metastasis, endless resection of liver tumours, insensitivity to chemotherapeutic drugs and there was no guide reference. In conclusion, we believe that intensive surgical resection must be completed in order to achieve good long-term success. If complete resection cannot be achieved, liver transplantation should be carried out as the main resection. Liver transplantation should not be considered if the tumour relapses or there is extrahepatic non chemotherapy reactive metastasis.

In this study, we observed that distant metastasis at the visit is independent of prognostic factors for CSS. Currently, there are different views on the impact of distant metastasis on the prognosis of hepatoblastoma. According to previous studies, distant metastasis represents a high-risk stratification and a poor overall prognosis [29]. However, some reports have proved that there is no significant difference in the prognosis of hepatoblastoma, which may be related to the removal of distant metastases through neo-adjuvant chemotherapy if the tumour is sensitive to chemotherapy. Therefore, more research is needed to determine determine whether distance can be used to predict the prognosis of hepatoblastoma. The age of <5 years old was observed to be a favourable

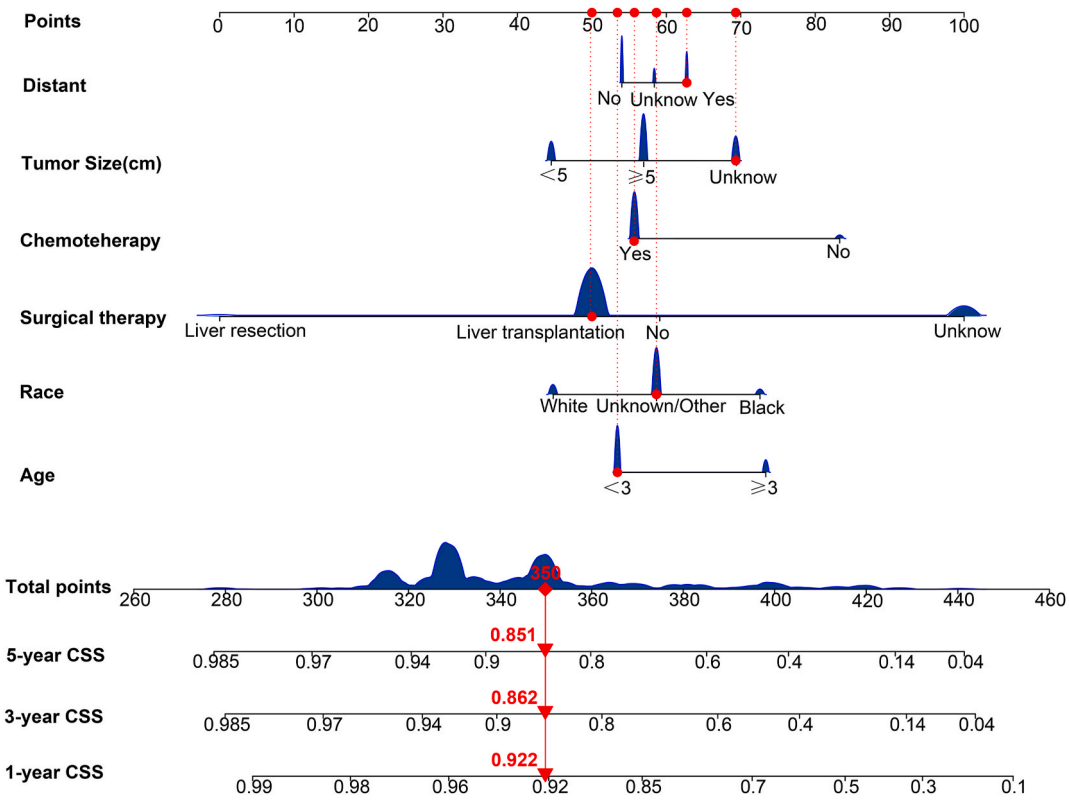

Fig. 4. The 1-, 3- and 5-year CSS probability is calculated by determining the sum of the risk points, which are based on Cox proportional hazards regression analysis. For each parameter, the number of associated risk points can be determined by drawing a vertical line from each variable axis upwards to the points axis (0–100). The total score projected on the bottom scale represents the probability of CSS rates of 1-, 3- and 5-years. Abbreviations: CSS: Cancer-specific survival.

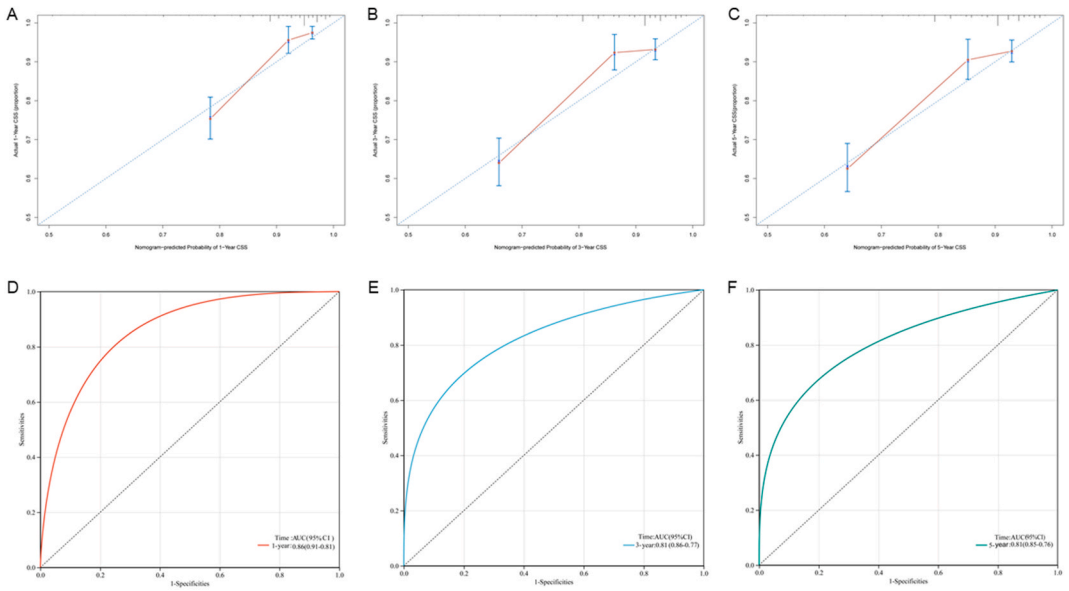

Fig. 5. Development and performance of the nomogram. Calibration curves to assess the 1- (A), 3- (B) and 5- (C) year CSS rates. AUC values to predict CSS rates at 1- (D), 3- (E) and 5- (F) years. Abbreviations: CSS: Cancer-specific survival; AUC: Area under the curve.

factor for prognosis, which is consistent with previous studies [30]. However, there is no clear cut-off to define how much age has an impact on prognosis. Felix et al. reported that age <2 years as a favourable prognostic factor [31]; Tian et al. believe that children aged <1 year have a better prognosis and survival in hepatoblastoma [32]. However, the younger the age at the initial diagnosis, the better the prognosis.

Based on the results of multivariate Cox analysis, we successfully constructed the nomogram CSS prediction map for 1-, 3- and 5-year CSS prognosis in patients with hepatoblastoma. The nomogram reveals the impact of chemotherapy and surgery on CSS. Patients who did not undergo chemotherapy had a worse prognosis. Surgery had an important role in the incidence of CSS. Surgical patients have higher rates of CSS than non-surgical patients ($p = 0.003$). To our knowledge, this is the first study to create a CSS model for predicting hepatoblastoma. The nomogram demonstrated better discrimination in predicting CSS, with a C-index of 0.759. Internal validation was performed using 1000 bootstrap resampling. The calibration model revealed a good concordance between the predicted values and the actual values. However, real-world clinical validation and genetic markers are lacking. These issues should be addressed in future studies. We aim to establish clinical data for patients with liver tumours at our research center to improve and validate the feasibility of this predictive model.

This study had some limitations. First, missing data in samples inevitably introduce potential selection bias and accuracy loss. Second, the SEER database lacks information on chemotherapy sequence, tumour recurrence, details of chemotherapy regimen, spontaneous rupture, targeted therapy, immunotherapy, and perioperative mortality. Third, since the SEER database does not provide PRETEX staging, it is impossible to compare survival conditions with other clinical studies using this staging method. Therefore, these parameters were not included in the regression model. Fourth, the Cox regression model might potentially overestimate the risk associated with tumor-specific mortality. Fifth, the limited sample size of children with unkonwn surgical therapy may result in potential deviations and overestimations of their risk profiles. Lastly, this was a retrospective study, and further prospective, multicentre and large-scale studies are required to verify our findings. Currently, diverse treatment methods for hepatoblastoma are under development, and future research can further compare the effects of various treatment methods (radiotherapy, targeted therapy, and immunotherapy) on the prognosis of patients with hepatoblastoma.

5. Conclusion

Surgery and chemotherapy can improve the overall prognosis of hepatoblastoma. However, there is no significant difference in the improvement of CSS rate between patients with liver transplantation and those with liver tumour resection. The CSS nomogram model established based on Cox multivariate analysis has good prediction accuracy and consistency and can help doctors in accurately estimating the survival rate of patients, formulate personalized treatment plans and provide better clinical benefits for patients.

Data availability statement

All data used in this paper may be accessed and analyzed via the SEER*Stat web program following the submission of a request for access to the data at https://seer.cancer.gov/and from the corresponding authors upon reasonable request.

Consent for publication

Not applicable.

Ethics declarations

Informed consent was not required for this study because since the SEER database is public, the approval of the ethics committee is not required. The SEER database has hidden the patient's identity information, so the patient's informed consent is not applicable.

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CRediT authorship contribution statement

Sihan Huang: Writing – original draft, Software, Methodology, Data curation. **Yaobin Lin:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis. **Shan Liu:** Validation, Supervision, Methodology, Investigation, Conceptualization. **Jin Shang:** Supervision, Investigation. **Zhihong Wang:** Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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