Original Article

Clinical features and a prognostic nomogram based on the SEER database for hepatoblastoma, hepatocellular carcinoma, and embryonal sarcoma among children and adolescents

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Background: Hepatoblastoma (HB), hepatocellular carcinoma (HCC), and embryonal sarcoma (ES) are the three main types of liver tumors in children and adolescents. At present, epidemiological knowledge and predictors of these three liver tumor types in multi-ethnic populations are limited. This study aimed to outline the clinical features and construct a prognostic nomogram for these tumors, which can contribute to the prediction of dynamic overall survival probability during the follow-up period.

Methods: A total of 1,122 patients liver tumor patients between 2000 to 2019 in Surveillance, Epidemiology, and End Results (SEER) database were enrolled for the current study, and separated into 824 HB, 219 HCC, and 79 ES according to the type of pathology. Independent prognostic factors were screened by univariate and multivariate Cox regression analysis, and a prognostic nomogram was constructed for overall survival. The accuracy and discriminative abilities of the nomogram were evaluated by concordance index as well as time-dependent receiver operating characteristic curves and calibration curves.

Results: Race (P=0.0016), surgery [hazard ratio (HR): 0.1021, P<0.001], and chemotherapy (HR: 0.27, P=0.00018) are independent prognostic factors for hepatoblastoma. Pathological tissue grading (P=0.00043), tumor node metastasis (TNM) staging (P=0.00061), and surgery are independent prognostic factors for hepatocellular carcinoma. Household income and surgery (HR: 0.1906, P<0.001) are independent prognostic factors for embryonal sarcoma. All of these prognostic factors are significantly associated with prognosis. A nomogram consisting of these variables was established, which showed a good concordance index (0.747, 0.775, and 0.828 in hepatoblastoma, hepatocellular carcinoma, and embryonal sarcoma, respectively). Also, the 5-year area under curve (AUC) of the nomogram were 0.738, 0.812, and 0.839 in hepatoblastoma, hepatocellular carcinoma, and embryonal sarcoma, respectively. In the calibration diagram, an optimal agreement between the nomogram-predicted and actual observed survival was evident.

Conclusions: We developed an effective prognostic nomogram for overall survival prediction in hepatoblastoma, hepatocellular carcinoma, and embryonal sarcoma in children and adolescent patients, which will further benefit the assessment of long-term outcomes.

Keywords: Hepatoblastoma; hepatocellular carcinoma; embryonal sarcoma; nomogram; children and adolescents

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Introduction

Compared with other malignant conditions in children and adolescents, liver tumors are relatively rare. A previous retrospective analysis suggested that the incidence rate was 1.8/million per year (1). Hepatoblastoma (HB), hepatocellular carcinoma (HCC), and embryonal sarcoma (ES) are the top three most frequent liver tumors in children and adolescents (2-4). Health problems in children cannot be ignored, and the spectrum of liver disease predisposing to liver tumors in children differs from that in adults. In recent years, there has been an increasing amount of literature on the incidence and screening of the prognostic factors in HB, HCC, and ES among children and adolescents. Up to now, Justin's study has indicated that HB incidence increased, meanwhile, age, race or ethnicity, and stage were the prognostic factors in 5-year relative survival (5). HCC is the second most common primary liver malignancy in a pediatric setting, which is diagnosed more commonly in adolescents (10–14 years). Long term outcomes indicated that survival of younger (0–4 *vs.* ≥5 years) and male has a better prognosis (6). ES is a rare and aggressive pediatric malignancy. Complete tumor removal remains the key element of its treatment. Combination chemotherapy, as an effective approach to cure children with ES, can facilitate complete surgical resection (7). Thus, clarifying the clinical features and prognostic factors is a promising approach to contribute to the management of liver tumors in this population. There is a growing body of literature that recognizes the importance and convenience of prediction models in childhood and adolescent diseases (8,9). The epidemiology and outcomes for pediatric patients with liver tumors have not been well documented. Therefore, the present article aims to outline the clinical features and prognostic prediction for the three aforementioned types of liver tumors. We present the following article in accordance with the TRIPOD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-679/rc).

Highlight box

Key findings

- Race, household income, surgery, chemotherapy, pathological tissue grading, and tumor node metastasis staging are the independent prognostic factors for malignant liver tumors among children and adolescents.

What is known and what is new?

- Hepatoblastoma, hepatocellular carcinoma, and embryonal sarcoma are the main types of liver tumors among children and adolescents.
- Different kinds of liver tumors have various prognoses and prognostic factors. Race, surgery, and chemotherapy are independent prognostic factors for hepatoblastoma. Pathological tissue grading, tumor node metastasis staging, and surgery are independent prognostic factors for hepatocellular carcinoma. Household income and surgery are independent prognostic factors for embryonal sarcoma.

What are the implications, and what should change now?

- Nomograms were constructed according to the prognostic factors, which can be used to calculate the estimated risk of individual patients and contribute to their treatment.

Methods

Data source

We performed a retrospective cohort analysis by querying the Surveillance, Epidemiology, and End Results (SEER) database to identify patients diagnosed with malignant liver tumors from 2000 to 2019 (primary site: C22.0; all patients ≤18 years old). SEER is an authoritative source of information on cancer incidence and survival in the United States, covering approximately 48.0% of the U.S. population. The detailed process of the study is shown in *Figure 1*. The clinical pathological information is public and anonymous, so our study did not require ethical approval or patient consent. The study method complies with the regulations of the SEER database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Clinical variables

Patient demographic information (age, sex, race, income), tumor characteristics (tumor grade, cancer-specific factors, tumor size, pathological type, staging), treatment (surgery, radiotherapy, chemotherapy, systemic therapy), and follow-up information (survival status, cause-specific death, survival time) were collected. Annual household income was collected and estimated in a time-dependent manner using data from the US Census American Community Survey 5-year files. The annual median household income was inflation-adjusted to 2018 US dollars and categorized into four groups: <$40,000, $40,000 to $54,999, $55,000 to $69,999, and ≥$70,000. The following exclusion criteria were applied to HCC patients in this study: (I) age >18 years old; (II) those whose tumor was not the first

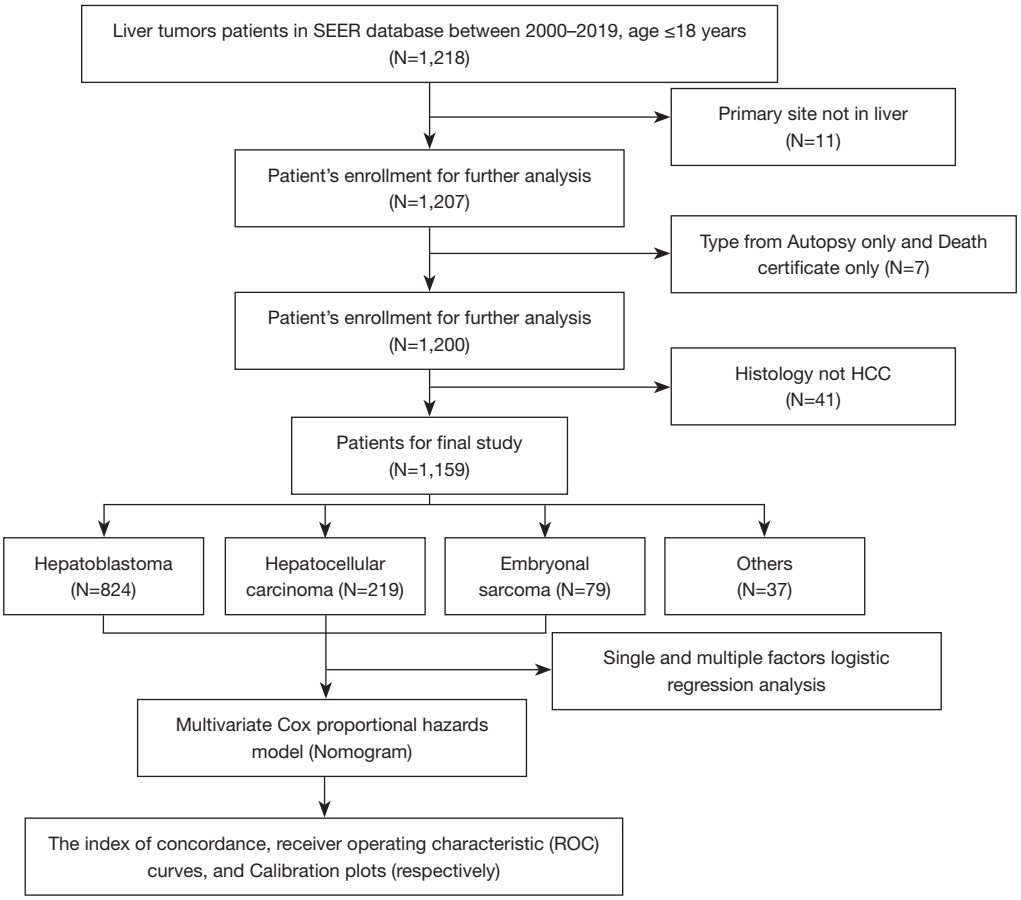

Figure 1 Flow chart of patient selection from the SEER database. The data of 1,218 child and adolescent liver tumor patients diagnosed between 2000 and 2019 was downloaded from the SEER database. After screening, 1,159 eligible patients were included in this study. These eligible patients were divided according to the tumor type: hepatoblastoma (N=824), hepatocellular carcinoma (N=219), and embryonal sarcoma (N=79).

malignant primary indicator; (III) the type of reporting source was only autopsy and death certificate; and (IV) histologic type were not in the liver tumors types. Cases of blank variables were classified as unknown.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD) values and analyzed using unpaired *t*-tests, categorical variables were expressed as the frequencies and proportions, and the Chi-square or Fisher's exact test was used to compare categorical variables. Survival curves were generated by the Kaplan-Meier method, and the prognostic factors were screened by stepwise regression according to the Akaike information criterion (AIC) (10). The nomogram was constructed using the multivariate Cox proportional hazards model to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), and the risk groups underwent digital quantization using the variable scores. The predictive accuracy and discriminative ability of the nomogram were determined by the concordance index (C-index) as well as time-dependent receiver operating characteristic (ROC) curves and calibration curves. The C-index and AUC >0.7 were considered to be sufficiently discriminative. The accuracy of the nomogram was tested by calibration plots with 1000 bootstraps resamples. All analyses were conducted using R software version 4.1.1 (www.r-project.org). A two-sided P-value <0.05 was considered statistically

significant.

Results

Epidemiological and clinical features of cancer types

A total of 1,159 patients listed in the SEER dataset met our eligibility criteria. We estimate that there were 824 HB, 219 HCC, and 79 ES patients from 2000 to 2019 (*Table 1*). There were significantly more males than females in this cohort. Also, new cases of liver tumors were almost consistent in number per year (*Figure 2*).

According to the follow-up information, all of the liver tumors could be divided into two groups; in the HB cohort, the median age was 1 year old, and the median survival time was 66.5 months. Patients who survived were more likely to be younger (1.63 *vs.* 2.30 years, P=0.002), have a smaller tumor size (100 *vs.* 110 mm, P=0.021), received more effective chemotherapy and systemic therapy (all P<0.001), and have undergone surgery (P<0.001). Here, survival was also related to race (P=0.009) (Table S1).

In the HCC cohort, the median age was 14 years old, and the median survival time was 33 months. Patients who survived were more likely to be younger (11.58 *vs.* 13.49 years, P=0.003), have a smaller tumor size (81 *vs.* 124.5 mm, P=0.01), received more effective chemotherapy and systemic therapy (P<0.001, P=0.02, respectively), be at an early stage (P<0.001), and have undergone surgery (P<0.001) (Table S2).

In the ES cohort, the median age was 9 years old, the median survival time was 79 months. Patients who survived were more likely to have a smaller tumor size (140 *vs.* 188.5 mm, P=0.047), received more effective systemic therapy (P=0.032), and have undergone surgery (P=0.005) (Table S3).

Prognostic factors distinguished by cancer types

Using univariate and multivariate Cox regression analysis, the predictors of survival among patients in the three types of liver tumors were respectively assessed. According to the AIC (10), there are three factors that play a role in HB, and survival is enhanced significantly in the patients who receive surgery (HR: 0.1021, 95% CI: 0.06458–0.1614, P<0.001) and chemotherapy (HR: 0.27, 95% CI: 0.13605–0.5357, P=0.00018). Meanwhile, survival is significantly worse in Black patients (P=0.0016). In the HCC cohort, survival was markedly better in patients who had undergone surgery (HR: 0.1906, 95% CI: 0.1069–0.3399, P<0.001) but was significantly worse in the patients of an advanced stage (P=0.00061) and pathological tissue grading III (P=0.00043). In the ES cohort, survival was notably enhanced in the patients who had undergone surgery (P=0.014) and those from a high-income family (P=0.0007). All of the prognostic factors were validated according to the overall survival (OS) and cancer-specific survival (CSS) (*Figures 3-5*).

Construction and validation of a prognostic nomogram

Our prognostic nomogram integrated all of the significant independent factors determined by the multivariate analyses mentioned above. In the HB cohort, The C-index of the nomogram was 0.747 (95% CI: 0.70584–0.78816), and the nomogram achieved time-dependent ROC-AUCs of 0.782, 0.738, and 0.738 for the prediction of progression risks at 1, 3, and 5 years, respectively (*Figure 6*). In the HCC cohort, the C-index of the nomogram was 0.775 (95% CI: 0.73972–0.81028), and the nomogram achieved time-dependent ROC-AUCs of 0.83, 0.821, and 0.812 for the prediction of progression risks at 1, 3, and 5 years, respectively (*Figure 7*). In the ES cohort, the C-index of the nomogram was 0.828 (95% CI: 0.70648–0.94952), and the nomogram achieved time-dependent ROC-AUCs of 0.883, 0.883, and 0.839 for the prediction of progression risks at 1, 3, and 5 years, respectively (*Figure 8*). Moreover, the excellent accuracy of the nomogram's prediction value was also assessed by the calibration curves at 1, 3, and 5 years of survival, and an optimal consistency between the nomogram-predicted and actual observed values was evident in all three cohorts (*Figure 9*).

Discussion

Primary liver tumors comprise 1–2% of all pediatric tumors, which can make research delays problematic. An accurate and effective prognostic prediction for cancer patients is very important for clinical treatment and guideline formulation. Herein, we constructed an accurate nomogram based on a large retrospective case series to predict the OS children and adolescents with liver tumors. This novel nomogram provides an important quantitative indicator and reference for clinical decision-making and the management of treatment regimens.

In our cohort, it was obvious that HB was the most common primary liver tumor, accounting for 71.1% of primary hepatic malignancies in children and adolescents. Surgery, chemotherapy, and race were identified as

Table 1 Characteristics of the study cohort: children and adolescents with liver tumors, 2000–2019

Characteristics	Level	Embryonal sarcoma (n=79)	Hepatoblastoma (n=824)	Hepatocellular carcinoma (n=219)	Others (n=37)	P
Age, mean (SD)		8.67 (3.85)	1.76 (2.45)	12.58 (4.79)	10.32 (6.41)	<0.001
Gender (%)	Female	43 (54.4)	315 (38.2)	89 (40.6)	21 (56.8)	0.007
	Male	36 (45.6)	509 (61.8)	130 (59.4)	16 (43.2)	
Grade (%)	Grade I	0 (0.0)	28 (3.4)	32 (14.6)	0 (0.0)	<0.001
	Grade II	0 (0.0)	5 (0.6)	43 (19.6)	4 (10.8)	
	Grade III	1 (1.3)	7 (0.8)	18 (8.2)	7 (18.9)	
	Grade IV	60 (75.9)	15 (1.8)	3 (1.4)	2 (5.4)	
	NA	18 (22.8)	769 (93.3)	123 (56.2)	24 (64.9)	
Tumor size (mm), median [IQR]		148.00 [116.50, 181.00]	100.00 [70.00, 120.00]	100.00 [59.00, 145.00]	87.00 [51.75, 112.50]	<0.001
AFP (%)	NA	42 (53.2)	309 (37.5)	93 (42.5)	22 (59.5)	<0.001
	Negative	34 (43.0)	11 (1.3)	51 (23.3)	9 (24.3)	
	Positive	3 (3.8)	504 (61.2)	75 (34.2)	6 (16.2)	
Fibrosis score (%)	Moderate fibrosis	8 (10.1)	36 (4.4)	19 (8.7)	1 (2.7)	<0.001
	NA	71 (89.9)	784 (95.1)	190 (86.8)	35 (94.6)	
	Severe fibrosis	0 (0.0)	4 (0.5)	10 (4.6)	1 (2.7)	
Lymph nodes surgery (%)	NA	11 (13.9)	124 (15.0)	31 (14.2)	6 (16.2)	0.994
	None	44 (55.7)	473 (57.4)	123 (56.2)	21 (56.8)	
	Yes	24 (30.4)	227 (27.5)	65 (29.7)	10 (27.0)	
Radiotherapy (%)	No	69 (87.3)	822 (99.8)	203 (92.7)	29 (78.4)	<0.001
	Yes	10 (12.7)	2 (0.2)	16 (7.3)	8 (21.6)	
Chemotherapy (%)	No/Unknown	5 (6.3)	65 (7.9)	87 (39.7)	6 (16.2)	<0.001
	Yes	74 (93.7)	759 (92.1)	132 (60.3)	31 (83.8)	
Systemic therapy (%)	NA	26 (32.9)	239 (29.0)	61 (27.9)	6 (16.2)	<0.001
	No	4 (5.1)	111 (13.5)	107 (48.9)	15 (40.5)	
	Yes	49 (62.0)	474 (57.5)	51 (23.3)	16 (43.2)	
Race (%)	Black	7 (8.9)	71 (8.6)	18 (8.2)	6 (16.2)	0.268
	Other (American Indian/AK Native, Asian/Pacific Islander)	7 (8.9)	125 (15.2)	31 (14.2)	4 (10.8)	
	Unknown	2 (2.5)	11 (1.3)	8 (3.7)	0 (0.0)	
	White	63 (79.7)	617 (74.9)	162 (74.0)	27 (73.0)	
AJCC7 (%)	I	0 (0.0)	0 (0.0)	17 (7.8)	1 (3.3)	<0.001
	II	0 (0.0)	0 (0.0)	9 (4.1)	0 (0.0)	
	III	0 (0.0)	0 (0.0)	10 (4.6)	0 (0.0)	
	IV	0 (0.0)	0 (0.0)	24 (11.0)	2 (6.7)	
	NA	55 (100.0)	540 (100.0)	159 (72.6)	27 (90.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Level	Embryonal sarcoma (n=79)	Hepatoblastoma (n=824)	Hepatocellular carcinoma (n=219)	Others (n=37)	P
Survival months, median [IQR]		79.00 [21.50, 147.50]	66.50 [17.00, 130.25]	33.00 [8.00, 83.50]	13.00 [6.00, 77.00]	<0.001
Income (%)	High income	29 (36.7)	323 (39.2)	94 (42.9)	14 (37.8)	0.97
	Low income	2 (2.5)	23 (2.8)	7 (3.2)	2 (5.4)	
	Median high income	37 (46.8)	352 (42.7)	86 (39.3)	15 (40.5)	
	Median low income	11 (13.9)	126 (15.3)	32 (14.6)	6 (16.2)	
Surgery (%)	No	10 (12.7)	145 (17.6)	86 (39.3)	17 (45.9)	<0.001
	Yes	69 (87.3)	679 (82.4)	133 (60.7)	20 (54.1)	
Status (%)	Alive	67 (84.8)	660 (80.1)	105 (47.9)	16 (43.2)	<0.001
	Dead	12 (15.2)	164 (19.9)	114 (52.1)	21 (56.8)	

SD, standard deviation; NA, not available; IQR, interquartile range; AFP, alpha fetoprotein.

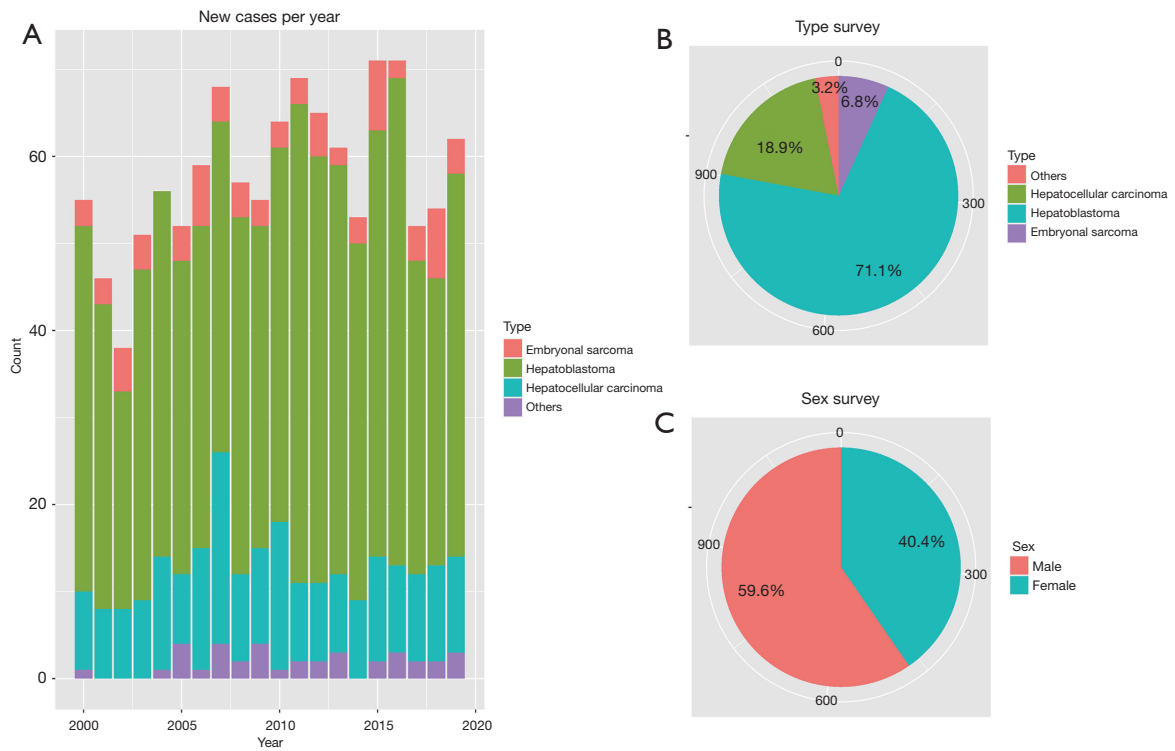

Figure 2 Trends in liver tumors incidence are illustrated by (A) years, (B) pathological type, and (C) sex. Hepatoblastoma, hepatocellular carcinoma, and embryonal sarcoma are the most frequent types of liver tumors in children and adolescents, with the incidence in males being higher than that in females.

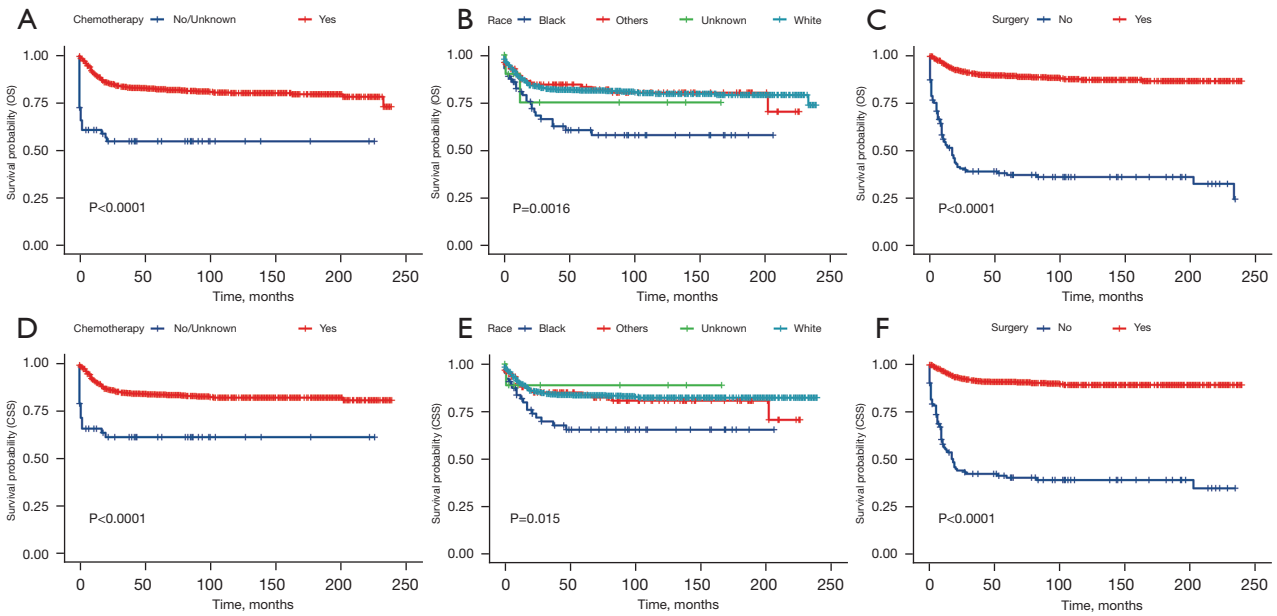

Figure 3 The OS and CSS according to the prognostic factors in hepatoblastoma. OS, overall survival; CSS, cancer-specific survival.

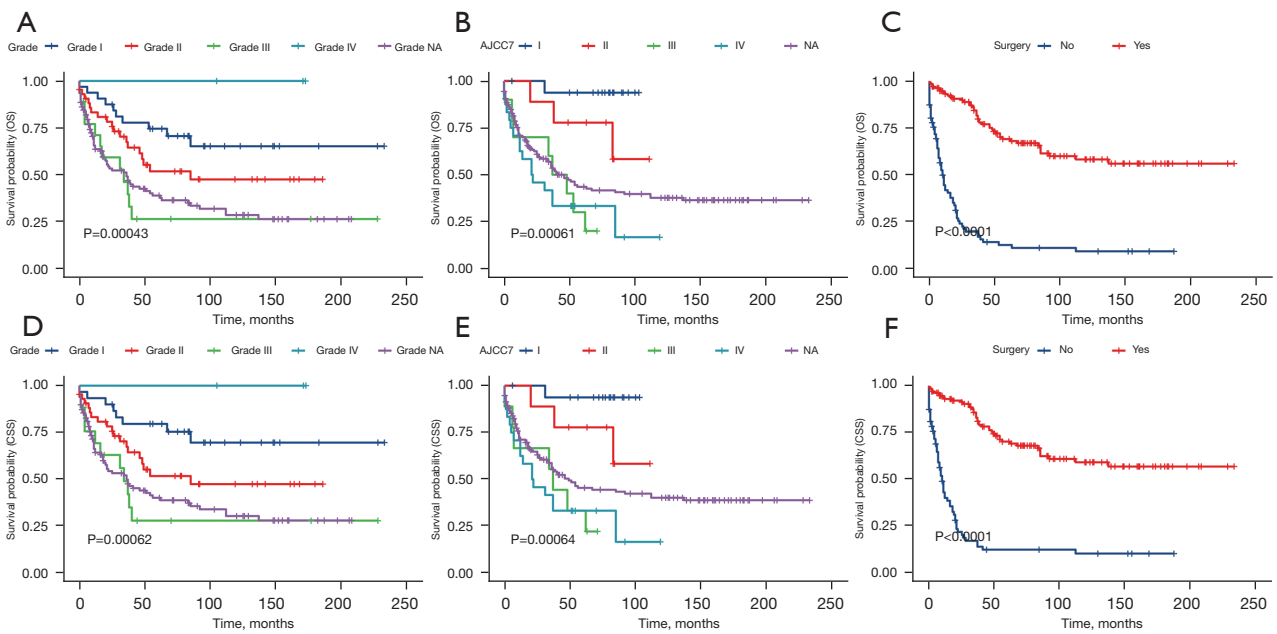

Figure 4 The OS and CSS according to the prognostic factors in hepatocellular carcinoma. OS, overall survival; CSS, cancer-specific survival. AJCC, American Joint Cancer Committee.

independent prognostic factors in patients with HB. The social factor (race) is an independent prognostic factor for HB. Similar findings were also noted in a previous study conducted in the USA (11). Black patients tend to have poor outcomes. Surgery remains the mainstay of treatment for HB, and complete resection is the only way to achieve a cure (12). The 5-year OS rate for HB is as high as 91% for patients who receive partial hepatectomy (13). However, 40–60% of HB patients are considered inoperable (14). Chemotherapy is a well-known and effective treatment for various kinds of

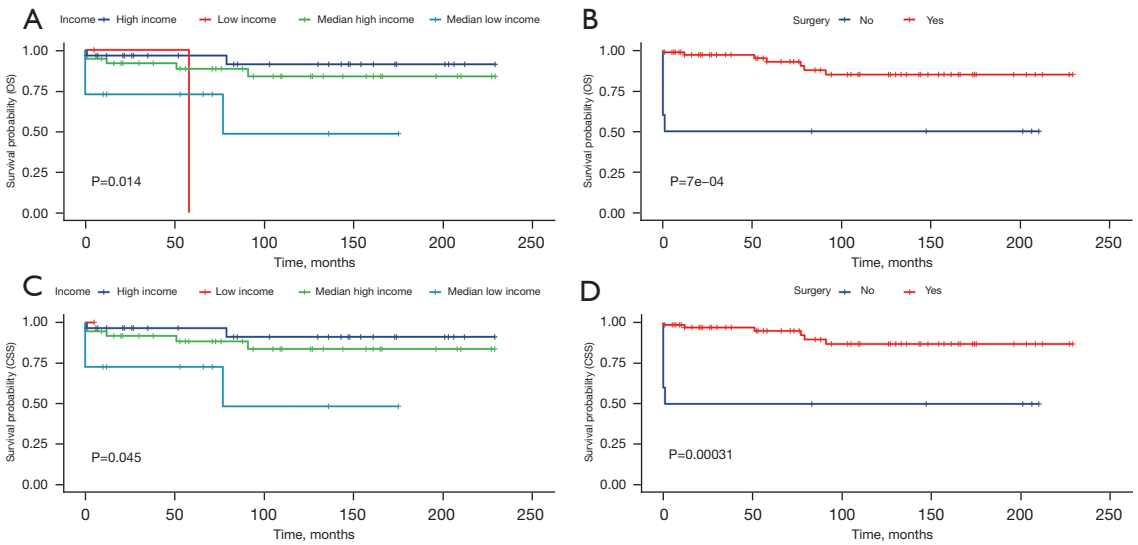

Figure 5 The OS and CSS according to the prognostic factors in embryonal sarcoma. OS, overall survival; CSS, cancer-specific survival.

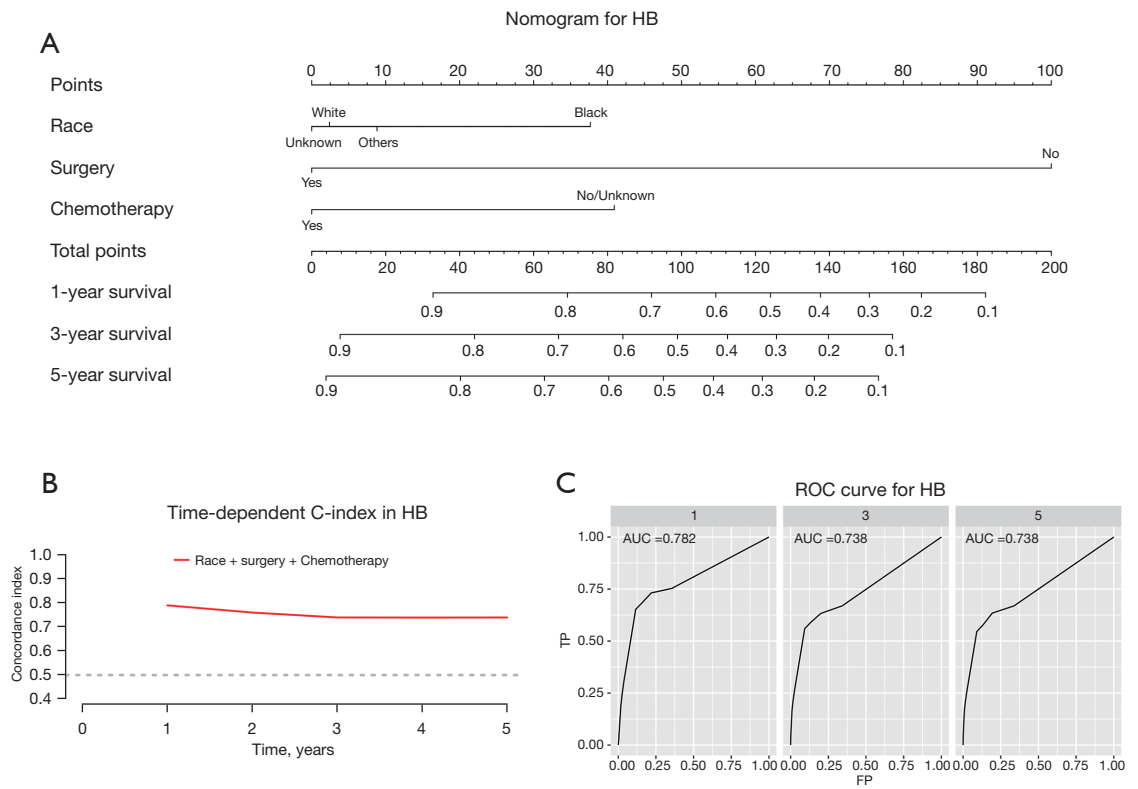

Figure 6 HB survival nomogram, C-index, and ROC curves. (A) Prognostic nomogram integrating the independent prognostic factors for predicting overall survival (OS), (B) C-index curves, and (C) ROC curves for predicting patient survival at 1, 3, and 5 years in all hepatoblastoma patients. HB, hepatoblastoma; C-index, concordance index; ROC, receiver operating characteristic; AUC, Area Under Curve; TP, true positive; FP, false positive.

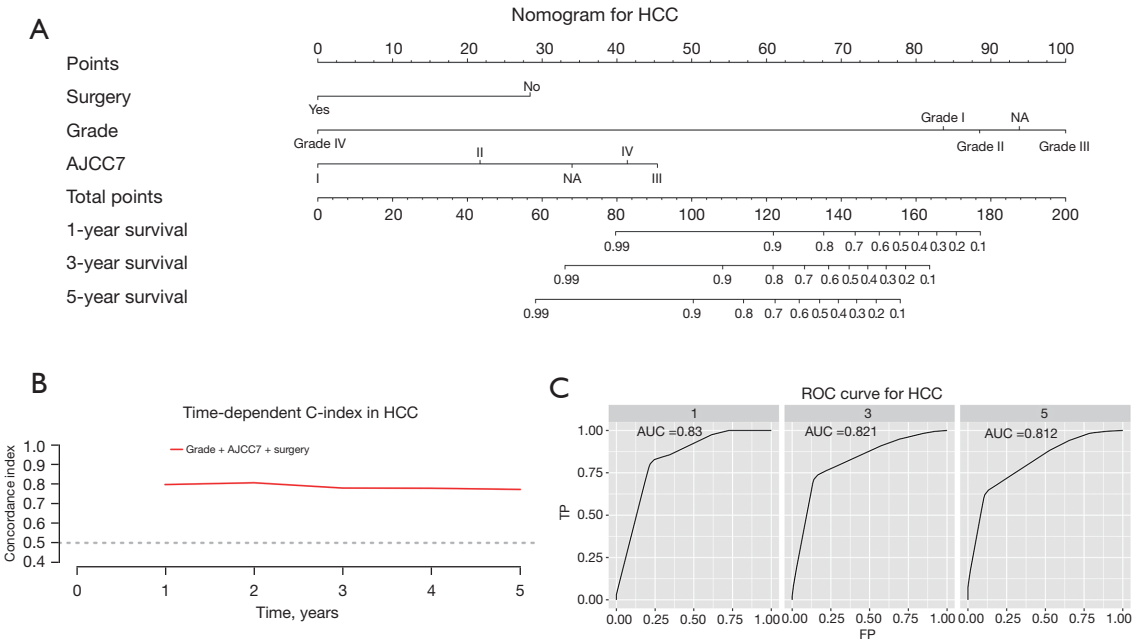

Figure 7 HCC survival nomogram, C-index, and ROC curves. (A) Prognostic nomogram integrating the independent prognostic factors for predicting OS, (B) C-index curves, and (C) ROC curves for predicting patient survival at 1, 3, and 5 years in all hepatocellular carcinoma patients. HCC, hepatocellular carcinoma; AJCC, American Joint Cancer Committee; C-index, concordance index; ROC, receiver operating characteristic; AUC, area under curve; TP, true positive; FP, false positive; OS, overall survival.

cancers, and platinum-based chemotherapy has provided a foundation for the current management of HB (15). A study has applied a policy of selective preoperative chemotherapy, and 90% of HB are resectable (16).

HCC is the seventh most frequent cancer among men and women (17) and the second most common malignant liver tumor in children. The spectrum of background liver disease predisposing to HCC in children is different from that in adults; tyrosinemia and perinatally acquired hepatitis B virus (HBV) infection are two major prognostic factors for HCC in children (2). Meanwhile, cirrhosis is one of the most important pathologies of HCC in adults but is absent in 26–62% of childhood cases (18). Surgery is an effective treatment for HCC; a previous report demonstrated that the resection rates in pediatric HCC have improved to 40%, with a median survival time of more than 30 months (19). Liver transplantation is a promising clinical treatment, with a 5-year OS rate of 72–83% (20). Histological grade is a significant predictor of survival in the prognostic evaluation of HCC patients treated with liver translation and liver resection (21). There are significant differences in terms of the histological grades, with a higher histological grade signifying a better OS. It is well known that staging influences mortality but there is currently no uniformly accepted staging system for HCC in children, despite the Barcelona Clinic Liver Cancer score and the tumor node metastasis (TNM) staging system being the main staging systems in HCC.

ES is the third most common type of malignant liver tumor in children and adolescents, which is a rare neoplasm that accounts for 9–15% of pediatric liver malignancies (3). Shi *et al.* reported an OS of 86% in ES; however, for patients who had undergone surgical resection alone, this rate was 100%, which is a promising approach for ES patients (22). An increasing number of scholars have reported that household income is an independent prognostic factor in various tumors in children and adolescents (23-25). To our knowledge, this study is the first to demonstrate that household income is an independent prognostic factor in patients with ES.

We then integrated the prognostic factors into a nomogram to predict the 1, 3, and 5 years OS. Nomograms are effective and convenient statistical tools that incorporate all prognostic variables and have been generated for a variety of cancer types (26-28). Our nomogram performed well according to the C-index and time-dependent ROC-

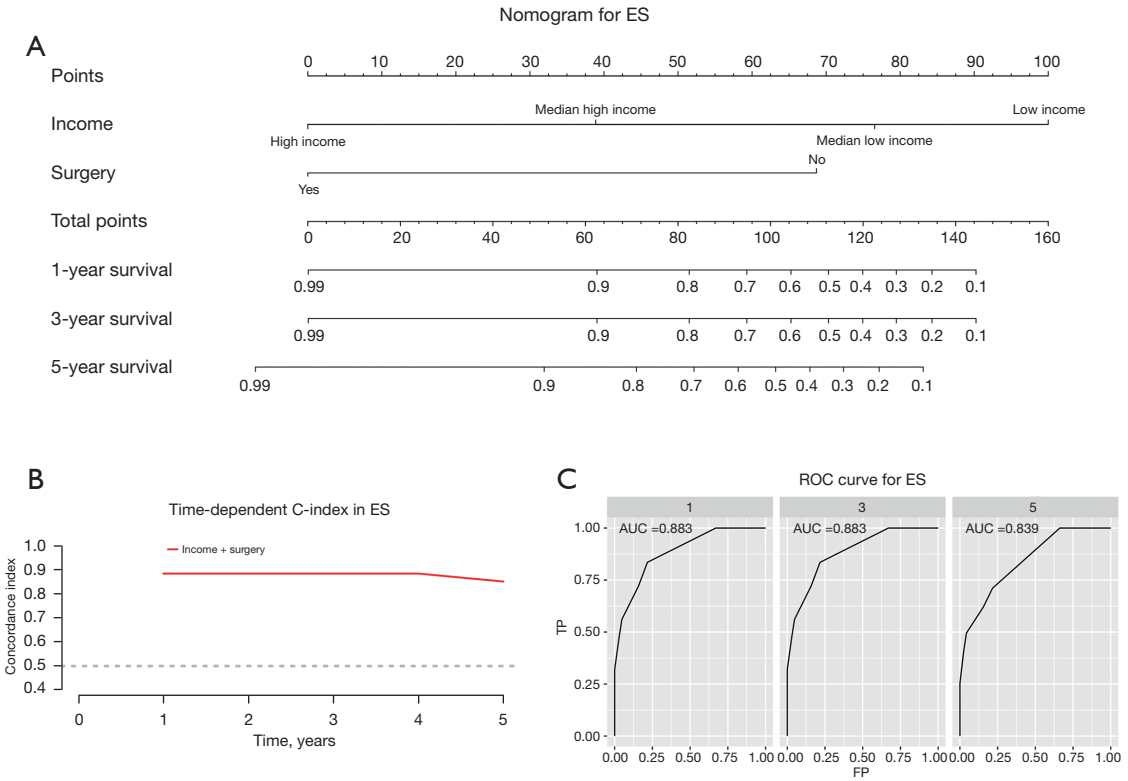

Figure 8 ES survival nomogram, C-index and ROC curves. (A) Prognostic nomogram integrating the independent prognostic factors for predicting OS, (B) C-index curves, and (C) ROC curves for predicting patient survival at 1, 3, and 5 years in all embryonal sarcoma patients. ES, embryonal sarcoma; C-index, concordance index; ROC, receiver operating characteristic; AUC, area under curve; TP, true positive; FP, false positive; OS, overall survival.

AUCs. Also, the calibration curves were closely matched to the ideal standard line, which indicated that the nomogram had high predictive power. The main reason for this is that the accuracy of prognostic prediction decreased regardless of the patient's background and other clinical pathological characteristics (29).

There are several limitations in this study that should be noted. Firstly, this study is a retrospective analysis; therefore, the applicability of the nomogram has not been validated in a separate cohort or at others institutions. Secondly, the critical inclusion and exclusion criteria may have resulted in significant amounts of valuable data being missed. Also, as has been demonstrated in previous studies, the SEER dataset excludes a considerable amount of data relating to several important clinical variables, which contributes to the absence of several important variables in the system, introducing considerable bias (30). For example, it is well known that the American Joint Cancer Committee (AJCC) tumor-node-metastasis (TNM) staging system is commonly used for tumor classification. However, PRETEXT is the only staging system that allows for surgical planning at the time of presentation for HB (31). Finally, multicenter prospective studies are needed to confirm or improve the accuracy of our nomogram.

Conclusions

In summary, this comprehensive analysis of liver tumors in children and adolescents from 2000 to 2019 based on the SEER cancer database showed a continued overall plateau in the incidence of the three main types of malignant liver tumors among children and adolescents. Race, household income, surgery, histological grade, staging, and chemotherapy are independent prognostic factors for the OS of liver tumors patients. Despite the limitations of this study, the nomogram based on these factors presented superior accuracy and applicability in predicting the clinical outcomes of HB, HCC, and ES patients, which could assist

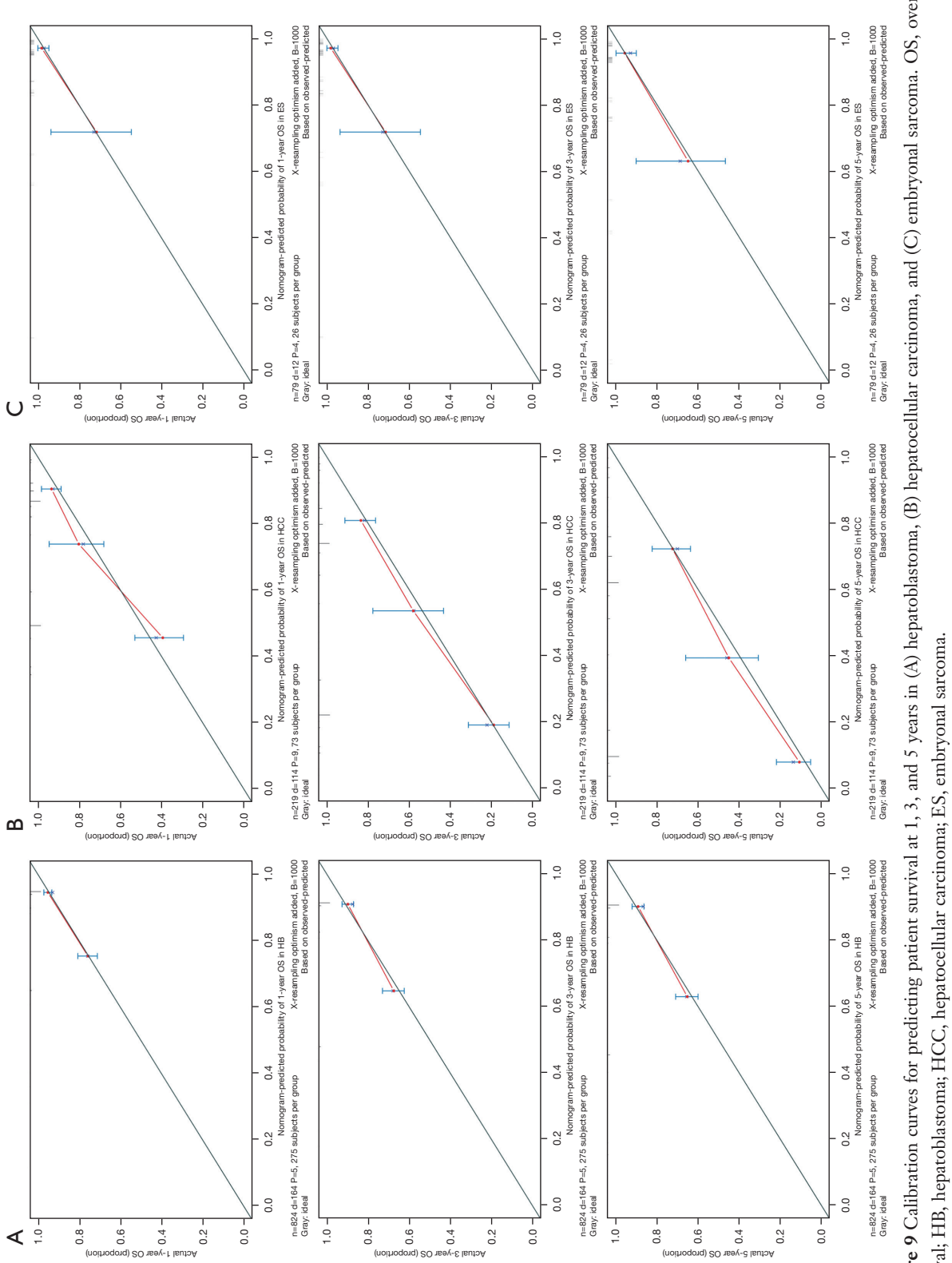

Figure 9 Calibration curves for predicting patient survival at 1, 3, and 5 years in (A) hepatoblastoma, (B) hepatocellular carcinoma, and (C) embryonal sarcoma. OS, overall survival; HB, hepatoblastoma; HCC, hepatocellular carcinoma; ES, embryonal sarcoma.

in the optimization of clinical decision-making.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Characteristics of the hepatoblastoma cohort

Characteristics	Level	Alive	Dead	P
n		660	164	
Age, mean (SD)		1.63 (2.29)	2.30 (2.98)	0.002
Tumor size (mm), median [IQR]		100.00 [70.00, 116.50]	110.00 [77.50, 130.00]	0.021
Sex (%)	Female	258 (39.1)	57 (34.8)	0.351
	Male	402 (60.9)	107 (65.2)	
Race (%)	Black	46 (7.0)	25 (15.2)	0.009
	Other (American Indian/AK Native, Asian/Pacific Islander)	103 (15.6)	22 (13.4)	
	Unknown	9 (1.4)	2 (1.2)	
	White	502 (76.1)	115 (70.1)	
Grade (%)	Grade I	25 (3.8)	3 (1.8)	0.543
	Grade II	3 (0.5)	2 (1.2)	
	Grade III	5 (0.8)	2 (1.2)	
	Grade IV	12 (1.8)	3 (1.8)	
	NA	615 (93.2)	154 (93.9)	
AFP (%)	NA	226 (34.2)	83 (50.6)	0.001
	Negative	9 (1.4)	2 (1.2)	
	Positive	425 (64.4)	79 (48.2)	
Fibrosis score (%)	Moderate fibrosis	28 (4.2)	8 (4.9)	0.907
	NA	629 (95.3)	155 (94.5)	
	Severe fibrosis	3 (0.5)	1 (0.6)	
AJCC7 (%)	Blank(s)	418 (100.0)	122 (100.0)	NA
Lymph nodes surgery (%)	NA	80 (12.1)	44 (26.8)	<0.001
	None	374 (56.7)	99 (60.4)	
	Yes	206 (31.2)	21 (12.8)	
Radiotherapy (%)	No	658 (99.7)	164 (100.0)	1
	Yes	2 (0.3)	0 (0.0)	
Chemotherapy (%)	No/Unknown	37 (5.6)	28 (17.1)	<0.001
	Yes	623 (94.4)	136 (82.9)	
Systemic therapy (%)	NA	165 (25.0)	74 (45.1)	<0.001
	No	60 (9.1)	51 (31.1)	
	Yes	435 (65.9)	39 (23.8)	
Income (%)	High income	267 (40.5)	56 (34.1)	0.368
	Low income	17 (2.6)	6 (3.7)	
	Median high income	280 (42.4)	72 (43.9)	
	Median low income	96 (14.5)	30 (18.3)	
Survival months, median [IQR]		88.00 [41.00, 145.00]	9.00 [3.00, 19.00]	<0.001
Surgery (%)	No	56 (8.5)	89 (54.3)	<0.001
	Yes	604 (91.5)	75 (45.7)	
Status (%)	Alive	660 (100.0)	0 (0.0)	<0.001
	Dead	0 (0.0)	164 (100.0)	

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Table S2 Characteristics of the hepatocellular carcinoma cohort

Characteristics	Level	Alive	Dead	P
n		105	114	
Age, mean (SD)		11.58 (5.40)	13.49 (3.96)	0.003
Tumor size (mm), median [IQR]		81.00 [31.50, 140.00]	124.50 [88.00, 150.00]	0.01
Sex (%)	Female	40 (38.1)	49 (43.0)	0.55
	Male	65 (61.9)	65 (57.0)	
Race (%)	Black	7 (6.7)	11 (9.6)	0.399
	Other (American Indian/AK Native, Asian/Pacific Islander)	15 (14.3)	16 (14.0)	
	Unknown	6 (5.7)	2 (1.8)	
	White	77 (73.3)	85 (74.6)	
Grade (%)	Grade I	22 (21.0)	10 (8.8)	0.007
	Grade II	24 (22.9)	19 (16.7)	
	Grade III	6 (5.7)	12 (10.5)	
	Grade IV	3 (2.9)	0 (0.0)	
	NA	50 (47.6)	73 (64.0)	
AFP (%)	NA	45 (42.9)	48 (42.1)	0.819
	Negative	26 (24.8)	25 (21.9)	
	Positive	34 (32.4)	41 (36.0)	
Fibrosis score (%)	Moderate fibrosis	12 (11.4)	7 (6.1)	0.119
	NA	86 (81.9)	104 (91.2)	
	Severe fibrosis	7 (6.7)	3 (2.6)	
AJCC7 (%)	I	16 (15.2)	1 (0.9)	<0.001
	II	6 (5.7)	3 (2.6)	
	III	2 (1.9)	8 (7.0)	
	IV	6 (5.7)	18 (15.8)	
	NA	75 (71.4)	84 (73.7)	
Lymph nodes surgery (%)	NA	7 (6.7)	24 (21.1)	<0.001
	None	56 (53.3)	67 (58.8)	
	Yes	42 (40.0)	23 (20.2)	
Radiotherapy (%)	No	100 (95.2)	103 (90.4)	0.259
	Yes	5 (4.8)	11 (9.6)	
Chemotherapy (%)	No/Unknown	57 (54.3)	30 (26.3)	<0.001
	Yes	48 (45.7)	84 (73.7)	
Systemic therapy (%)	NA	20 (19.0)	41 (36.0)	0.02
	No	58 (55.2)	49 (43.0)	
	Yes	27 (25.7)	24 (21.1)	
Income (%)	High income	44 (41.9)	50 (43.9)	0.575
	Low income	2 (1.9)	5 (4.4)	
	Median high income	45 (42.9)	41 (36.0)	
	Median low income	14 (13.3)	18 (15.8)	
Survival months, median [IQR]		78.00 [25.00, 148.00]	14.00 [4.25, 36.75]	<0.001
Surgery (%)	No	16 (15.2)	70 (61.4)	<0.001
	Yes	89 (84.8)	44 (38.6)	
Status (%)	Alive	105 (100.0)	0 (0.0)	<0.001
	Dead	0 (0.0)	114 (100.0)	

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Table S3 Characteristics of the embryonal sarcoma cohort

Characteristics	Level	Alive	Dead	P
n		67	12	
Age, mean (SD)		8.72 (3.70)	8.42 (4.76)	0.805
Tumor size (mm), median [IQR]		140.00 [108.50, 172.50]	188.50 [177.00, 194.00]	0.047
Sex (%)	Female	35 (52.2)	8 (66.7)	0.542
	Male	32 (47.8)	4 (33.3)	
Race (%)	Black	4 (6.0)	3 (25.0)	0.121
	Other (American Indian/AK Native, Asian/Pacific Islander)	7 (10.4)	0 (0.0)	
	Unknown	2 (3.0)	0 (0.0)	
	White	54 (80.6)	9 (75.0)	
Grade (%)	Grade III	0 (0.0)	1 (8.3)	0.01
	Grade IV	49 (73.1)	11 (91.7)	
	NA	18 (26.9)	0 (0.0)	
AFP (%)	NA	37 (55.2)	5 (41.7)	0.528
	Negative	28 (41.8)	6 (50.0)	
	Positive	2 (3.0)	1 (8.3)	
Fibrosis score (%)	Moderate fibrosis	8 (11.9)	0 (0.0)	0.457
	NA	59 (88.1)	12 (100.0)	
AJCC7 (%)	Blank(s)	46 (100.0)	9 (100.0)	NA
Lymph nodes surgery (%)	NA	7 (10.4)	4 (33.3)	0.091
	None	38 (56.7)	6 (50.0)	
	Yes	22 (32.8)	2 (16.7)	
Radiotherapy (%)	No	60 (89.6)	9 (75.0)	0.355
	Yes	7 (10.4)	3 (25.0)	
Chemotherapy (%)	No/Unknown	3 (4.5)	2 (16.7)	0.34
	Yes	64 (95.5)	10 (83.3)	
Systemic therapy (%)	NA	20 (29.9)	6 (50.0)	0.032
	No	2 (3.0)	2 (16.7)	
	Yes	45 (67.2)	4 (33.3)	
Income (%)	High income	27 (40.3)	2 (16.7)	0.062
	Low income	1 (1.5)	1 (8.3)	
	Median high income	32 (47.8)	5 (41.7)	
	Median low income	7 (10.4)	4 (33.3)	
Survival months, median [IQR]		103.00 [32.50, 159.00]	6.50 [0.00, 62.75]	<0.001
Surgery (%)	No	5 (7.5)	5 (41.7)	0.005
	Yes	62 (92.5)	7 (58.3)	
Status (%)	Alive	67 (100.0)	0 (0.0)	<0.001
	Dead	0 (0.0)	12 (100.0)	

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