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Original Article

Incidence trends and predictive model of hepatic malignant tumors in children: a population-based study

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Abstract: Objective: To analyze the incidence trend and establish a model to predict the prognosis of hepatic malignant tumors in children (CHMTs). Methods: We analyzed the incidence data of CHMTs from 1975 to 2018 from the Surveillance, Epidemiology, and End Results (SEER) database, and evaluated the incidence trends based on different demographic and pathological features. We also analyzed clinicopathologic data from 2000 to 2018 from the SEER database. Univariate and multivariate Cox regression analyses were performed to explore prognostic factors related to overall survival (OS). Then, we established nomograms based on independent predictors and verified them using receiver operating characteristic curves, calibration plots, and decision curve analysis plots. Results: The incidence of CHMTs increased significantly, from 0.1 per 100,000 in 1975 to 0.4 per 100,000 in 2018. Incidences among different races and genders were increasing and converging. The incidence of hepatoblastoma (HB) increased, while that of hepatocellular carcinoma (HCC) was relatively stable. The 1-, 3-, 5-, and 10-year OS rates were 86.2%, 77.5%, 74.2%, and 70.2%, respectively. Being Spanish-Hispanic-Latino, HB, surgery, and systemic therapy were independent predictors of longer OS, whereas regional and distant stages were independent predictors of shorter OS. Nomograms with good predictive ability and clinical utility were established to evaluate the prognosis of children with HB or HCC. Conclusion: The incidence of CHMTs is increasing, especially for HB and in younger children. This study identified independent predictors and developed nomograms that could provide a personalized and accurate prognosis for CHMTs.

Keywords: Incidence, nomogram, prognosis, hepatic malignant tumors, children

Introduction

Primary liver tumors in children are rare, accounting for approximately 1% of children's tumors and 5%~6% of abdominal tumors, but most of them are malignant (about 50%~60%) [1-3]. There are many kinds of primary hepatic malignant tumors in children (CHMTs), among which the most common are hepatoblastoma (HB) and hepatocellular carcinoma (HCC) [3-5]. HB is the third most common abdominal tumor in children after nephroblastoma and neuroblastoma. The incidence of HB is about 1 to 1.5 per million per year, with an increasing trend in many countries, which may be related to the increasing cohort of preterm birth and low-birth-weight survivors [6]. Fewer than 1% of HCC cases occur in people under the age of 20 [2]. HCC is the second most common CHMT, and the most common malignant liver tumor in adolescence, for which the prognosis is worse than that of HB [3, 4]. However, there is a lack of systematic research to clarify the incidence rate of CHMTs.

In the current era of individualized medicine, a more effective model for disease prognosis could reduce excessive intervention. Compared to conventional staging methods, nomograms can realize rapid calculation and are more individualized, accurate, and easy to understand, so they have been widely used as prognostic tools [7-10]. However, there is a lack of models to predict the prognosis of CHMTs, and there are few nomograms for prognosis of HB and HCC in children [11, 12]. In addition, the accuracy of the nomogram can be affected by sample size and source [13]. However, there are

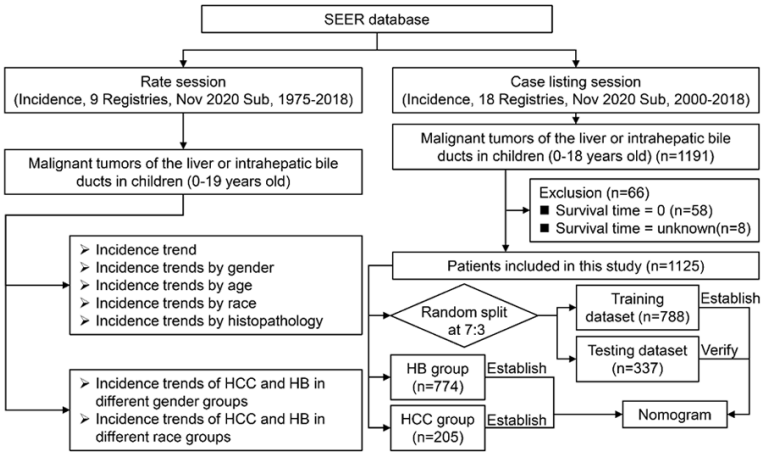

Figure 1. Flowchart of this study in the Surveillance, Epidemiology, and End Results (SEER) database. Note: HB: hepatoblastoma. HCC: hepatocellular carcinoma.

fewer patients with CHMTs, and there is a lack of large-scale and multicenter research on CHMTs. The Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov) has the advantages of a long-time span and large population coverage, which may be the key for medical research about rare diseases, such as CHMTs.

In this study, we analyzed the incidence trends and explored the prognostic factors of CHMTs based on the SEER database, and further established and verified a nomogram to assess their prognosis.

Patients and methods

Data source and patients

We obtained the incidence data of CHMTs from 1975 to 2018 online from the Rate Session of SEER*Stat software (version 8.3.9.2, https://seer.cancer.gov/). Because the Rate Session of the SEER database had specific age interval division rules, patients aged 0 to 19 represented children and were included in this section. The clinicopathologic data of patients aged 0 to 18 with CHMTs from 2000 to 2018 were downloaded online from the Case Listing Session of the above software, including age at diagnosis, gender, race, origin, alpha-fetoprotein (AFP), tumor size, tumor type, grade, stage, surgery, radiation, chemotherapy, survival status, and survival time. Then, we excluded patients with a survival time of 0 or unknown. The screening process in this study is shown in **Figure 1**. Data in the SEER database were public and anonymous, so this study did not require ethical approval or informed consent from patients.

Definition of variables

Age was classified into four groups: infancy (< 1 year old), infancy (1 to 2 years old), preschool & school period (male aged 3 to 11, female aged 3 to 9), and puberty (male aged 12 to 18, female aged 10 to 18). Tumor size was also classified into < 50 mm, ≥ 50 mm, and unknown. AFP status was also classified into positive, negative, and unknown. Grade was generally not used for HB, so this factor was not included in Cox analysis of the HB group (**Tables 1** and **4**). Patients with grade IV (n=3), American Indian & Alaska Native (n=1) and surgery of unknown (n=1) of HCC group were too few to analyze, so the above patients were not included in the Cox analysis of the HCC group (**Tables 1** and **5**; **Figure 1**). Because the American Joint Committee on Cancer tumor-node-metastasis staging system is not used for HB patients, we used localized, regional, distant, and unstaged (including unknown) to describe tumor staging. The therapies were categorized as none or unknown, only surgery, only adjuvant therapy (chemotherapy and/or radiotherapy), and systemic therapy (surgery combined with chemotherapy and/or radiotherapy). However, because there were too many missing values of AFP and radiotherapy variables (91.8% and 96.7%), the above variables were not included in the Cox analysis (**Tables 1**-**5**). Overall survival (OS) was defined as the period from diagnosis to death from any cause. Survival time in months was defined as the interval measured between diagnosis and death or the last follow-up.

Statistical design and analysis

The age-adjusted incidence trends of CHMTs according to the 2000 United States standard population (19 age groups: Census P25-1130) were obtained from the Rate Session in the SEER database, and the rates were per

Table 1. Clinicopathological factors of all patients, the HB group, and the HCC group

	Overall (n=1125)	HB (n=774)	HCC (n=210)	*p* value
Age at Diagnosis				
Infancy (< 1 years old)	268 (23.8%)	239 (30.9%)	6 (2.9%)	< 0.001
Infancy (1-2 years old)	391 (34.8%)	368 (47.5%)	8 (3.8%)	
Preschool & school period	256 (22.8%)	151 (19.5%)	43 (20.5%)	
Puberty	210 (18.7%)	16 (2.1%)	153 (72.9%)	
Race				
White	856 (76.1%)	592 (76.5%)	156 (74.3%)	0.307
Black	96 (8.5%)	63 (8.1%)	20 (9.5%)	
Asian & Pacific Islander	138 (12.3%)	94 (12.1%)	28 (13.3%)	
American Indian & Alaska Native	19 (1.7%)	16 (2.1%)	1 (0.5%)	
Unknown & Others	16 (1.4%)	9 (1.2%)	5 (2.4%)	
Origin				
Non-Spanish-Hispanic-Latino	752 (66.8%)	507 (65.5%)	153 (72.9%)	0.054
Spanish-Hispanic-Latino	373 (33.2%)	267 (34.5%)	57 (27.1%)	
Gender				
Male	670 (59.6%)	476 (61.5%)	126 (60.0%)	0.752
Female	455 (40.4%)	298 (38.5%)	84 (40.0%)	
AFP				
Negative	41 (3.6%)	0 (0.0%)	40 (19.0%)	< 0.001
Positive	51 (4.5%)	0 (0.0%)	49 (23.3%)	
Unknown	1033 (91.8%)	774 (100.0%)	121 (57.6%)	
Tumor Size				
< 50 mm	128 (11.4%)	84 (10.9%)	37 (17.6%)	0.015
≥ 50 mm	830 (73.8%)	584 (75.5%)	140 (66.7%)	
Unknown	167 (14.8%)	106 (13.7%)	33 (15.7%)	
Tumor Type				
HCC	210 (18.7%)	0 (0.0%)	210 (100.0%)	/
HB	774 (68.8%)	774 (100.0%)	0 (0.0%)	
Others	141 (12.5%)	0 (0.0%)	0 (0.0%)	
Grade				
Grade I	67 (6.0%)	29 (3.7%)	38 (18.1%)	< 0.001
Grade II	56 (5.0%)	5 (0.6%)	47 (22.4%)	
Grade III	38 (3.4%)	8 (1.0%)	18 (8.6%)	
Grade IV	90 (8.0%)	17 (2.2%)	3 (1.4%)	
Unknown	874 (77.7%)	715 (92.4%)	104 (49.5%)	
Stage				
Localized	511 (45.4%)	369 (47.7%)	74 (35.2%)	0.002
Regional	320 (28.4%)	221 (28.6%)	68 (32.4%)	
Distant	254 (22.6%)	155 (20.0%)	63 (30.0%)	
Unknown & Unstaged	40 (3.6%)	369 (47.7%)	74 (35.2%)	
Surgery				
None	239 (21.2%)	124 (16.0%)	75 (35.7%)	< 0.001
Local tumor destruction & Segmental resection	216 (19.2%)	149 (19.3%)	36 (17.1%)	
Lobectomy	444 (39.5%)	335 (43.3%)	51 (24.3%)	
Hepatectomy & Transplantation	212 (18.8%)	156 (20.2%)	47 (22.4%)	
Unknown	14 (1.2%)	10 (1.3%)	1 (0.5%)	

Radiation				
None & Unknown	1088 (96.7%)	772 (99.7%)	195 (92.9%)	< 0.001
Radiation	37 (3.3%)	2 (0.3%)	15 (7.1%)	
Chemotherapy				
Chemotherapy	987 (87.7%)	731 (94.4%)	129 (61.4%)	< 0.001
None & Unknown	138 (12.3%)	43 (5.6%)	81 (38.6%)	
Therapy				
None & Unknown	34 (3.0%)	17 (2.2%)	9 (4.3%)	< 0.001
Only surgery	104 (9.2%)	28 (3.6%)	70 (33.3%)	
Only adjuvant therapy	197 (17.5%)	105 (13.6%)	61 (29.0%)	
Systemic therapy	790 (70.2%)	624 (80.6%)	70 (33.3%)	

Note: HB: hepatoblastoma. HCC: hepatocellular carcinoma. AFP: alpha-fetoprotein. Chi-square was used for statistical analysis, $P < 0.05$ was considered significant.

Table 2. Comparison of demographic and clinical characteristics between training and testing datasets

	Training Dataset (n=788)	Testing Dataset (n=337)	*p* value
Age at Diagnosis			
Infancy (< 1 years old)	200 (25.4%)	68 (20.2%)	0.307
Infancy (1-2 years old)	270 (34.3%)	121 (35.9%)	
Preschool & school period	174 (22.1%)	82 (24.3%)	
Puberty	144 (18.3%)	66 (19.6%)	
Race			
White	605 (76.8%)	251 (74.5%)	0.651
Black	69 (8.8%)	27 (8.0%)	
Asian & Pacific Islander	90 (11.4%)	48 (14.2%)	
American Indian & Alaska Native	12 (1.5%)	7 (2.1%)	
Unknown & Others	12 (1.5%)	4 (1.2%)	
Origin			
Non-Spanish-Hispanic-Latino	530 (67.3%)	222 (65.9%)	0.702
Spanish-Hispanic-Latino	258 (32.7%)	115 (34.1%)	
Gender			
Male	476 (60.4%)	194 (57.6%)	0.411
Female	312 (39.6%)	143 (42.4%)	
Tumor Size			
< 50 mm	92 (11.7%)	36 (10.7%)	0.886
≥ 50 mm	580 (73.6%)	250 (74.2%)	
Unknown	116 (14.7%)	51 (15.1%)	
Tumor Type			
HCC	140 (17.8%)	70 (20.8%)	0.488
HB	549 (69.7%)	225 (66.8%)	
Others	99 (12.6%)	42 (12.5%)	
Stage			
Localized	367 (46.6%)	144 (42.7%)	0.559
Regional	224 (28.4%)	96 (28.5%)	
Distant	170 (21.6%)	84 (24.9%)	
Unknown & Unstaged	27 (3.4%)	13 (3.9%)	

Therapy			
None & Unknown	24 (3.0%)	10 (3.0%)	0.917
Only surgery	71 (9.0%)	33 (9.8%)	
Only adjuvant therapy	135 (17.1%)	62 (18.4%)	
Systemic therapy	558 (70.8%)	232 (68.8%)	

Note: HB: hepatoblastoma. HCC: hepatocellular carcinoma. Chi-square was used for statistical analysis; two-sided P < 0.05 was considered significant.

Table 3. Univariate and multivariate regression analysis in the training database

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at Diagnosis				
Infancy (< 1 years old)	1.000 [Reference]	-	1.000 [Reference]	-
Infancy (1-2 years old)	0.808 [0.526, 1.240]	0.329	0.685 [0.436, 1.076]	0.100
Preschool & school period	1.413 [0.928, 2.152]	0.107	1.041 [0.673, 1.609]	0.857
Puberty	2.453 [1.649, 3.650]	9.57e-06	0.943 [0.553, 1.606]	0.828
Race				
White	1.000 [Reference]	-	-	-
Black	1.768 [1.164, 2.685]	0.075	-	-
Asian & Pacific Islander	1.159 [0.752, 1.786]	0.504	-	-
American Indian & Alaska Native	0.960 [0.306, 3.012]	0.944	-	-
Unknown & Others	0.779 [0.193, 3.144]	0.725	-	-
Origin				
Non-Spanish-Hispanic-Latino	1.000 [Reference]	-	1.000 [Reference]	-
Spanish-Hispanic-Latino	0.604 [0.435, 0.837]	0.003	0.693 [0.497, 0.967]	0.031
Gender				
Male	1.000 [Reference]	-	-	-
Female	0.844 [0.632, 1.126]	0.248	-	-
Tumor Size				
< 50 mm	1.000 [Reference]	-	1.000 [Reference]	-
≥ 50 mm	1.746 [1.008, 3.023]	0.046	1.509 [0.857, 2.658]	0.154
Unknown	3.039 [1.662, 5.557]	3.05e-04	1.249 [0.660, 2.365]	0.494
Tumor Type				
HCC	1.000 [Reference]	-	1.000 [Reference]	-
HB	0.320 [0.235, 0.436]	4.84e-13	0.449 [0.270, 0.748]	0.002
Others	0.603 [0.393, 0.928]	0.021	0.763 [0.457, 1.276]	0.302
Stage				
Localized	1.000 [Reference]	-	1.000 [Reference]	-
Regional	1.887 [1.298, 2.743]	8.89e-04	1.487 [1.014, 2.182]	0.042
Distant	4.266 [3.007, 6.053]	4.29e-16	2.864 [1.950, 4.207]	8.21e-08
Unknown & Unstaged	2.312 [1.09, 4.866]	0.027	0.889 [0.395, 1.999]	0.775
Therapy				
None & Unknown	1.000 [Reference]	-	1.000 [Reference]	-
Only surgery	0.123 [0.056, 0.268]	1.36e-07	0.110 [0.047, 0.254]	2.72e-07
Only adjuvant therapy	0.794 [0.459, 1.373]	0.408	0.673 [0.373, 1.214]	0.188
Systemic therapy	0.112 [0.0646, 0.195]	8.51e-15	0.120 [0.065, 0.221]	1.03e-11

Note: HR: Hazard ratio. CI: confidence interval. HB: hepatoblastoma. HCC: hepatocellular carcinoma.

Table 4. Univariate and multivariate regression analysis in the HB group

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at Diagnosis				
Infancy (< 1 years old)	1.000 [Reference]	-	1.000 [Reference]	-
Infancy (1-2 years old)	1.336 [0.856, 2.083]	0.202	0.849 [0.532, 1.354]	0.491
Preschool & school period	2.297 [1.428, 3.696]	6.10e-04	1.710 [1.048, 2.790]	0.032
Puberty	3.912 [1.713, 8.933]	0.001	2.806 [1.218, 6.467]	0.015
Race				
White	1.000 [Reference]	-	1.000 [Reference]	-
Black	2.194 [1.356, 3.548]	0.001	2.541 [1.550, 4.168]	2.21e-04
Asian & Pacific Islander	0.819 [0.459, 1.460]	0.498	0.927 [0.513, 1.676]	0.801
American Indian & Alaska Native	0.771 [0.190, 3.125]	0.715	1.223 [0.298, 5.026]	0.780
Unknown & Others	1.824 [0.450, 7.398]	0.400	1.538 [0.371, 6.367]	0.553
Origin				
Non-Spanish-Hispanic-Latino	1.000 [Reference]	-	-	-
Spanish-Hispanic-Latino	0.859 [0.597, 1.236]	0.414	-	-
Gender				
Male	1.000 [Reference]	-	-	-
Female	0.816 [0.573, 1.162]	0.260	-	-
Tumor Size				
< 50 mm	1.000 [Reference]	-	1.000 [Reference]	-
≥ 50 mm	1.579 [0.797, 3.130]	0.190	1.323 [0.660, 2.651]	0.430
Unknown	3.503 [1.676, 7.323]	8.62e-04	1.476 [0.681, 3.197]	0.323
Stage				
Localized	1.000 [Reference]	-	1.000 [Reference]	-
Regional	2.010 [1.276, 3.167]	0.003	1.605 [0.994, 2.592]	0.053
Distant	4.056 [2.628, 6.262]	2.59e-10	2.417 [1.505, 3.879]	2.58e-04
Unknown & Unstaged	4.206 [2.078, 8.514]	6.54e-05	1.677 [0.783, 3.590]	0.184
Surgery				
None	1.000 [Reference]	-	1.000 [Reference]	-
Local tumor destruction & Segmental resection	0.141 [0.081, 0.242]	1.74e-12	0.178 [0.100, 0.315]	3.28e-09
Lobectomy	0.113 [0.073, 0.175]	< 2e-16	0.151 [0.094, 0.242]	3.42e-15
Hepatectomy & Transplantation	0.146 [0.087, 0.246]	4.18e-13	0.152 [0.089, 0.261]	7.68e-12
Unknown	0.830 [0.335, 2.059]	0.688	1.120 [0.444, 2.824]	0.810
Chemotherapy				
None & Unknown	1.000 [Reference]	-	-	-
Chemotherapy	1.602 [0.841, 3.05]	0.152	-	-

Note: HB: hepatoblastoma. HR: Hazard ratios. CI: confidence interval.

100,000. The annual percentage changes (APCs) were calculated using the weighted least squares method. The APC is significantly different from zero ($P < 0.05$). We assessed the incidence of CHMTs, stratified by gender, age at diagnosis, race, and tumor type. We evaluated incidence based on tumor types in different gender and race groups. We plotted incidence trends and performed linear fitting, using the ggplot2 package in R software (version 4.0.2, https://www.r-project.org).

Categorical variables were expressed as numbers (percentage). For statistical comparison of the baseline characteristics between groups, the chi-Square test was used for categorical variables. We used the Kaplan-Meier method to plot survival curves and calculate 1-, 3-, and 5-year survival rates. The log-rank test was used to compare the survival differences of patients. We analyzed the prognostic factors using univariate and multivariate Cox regression analyses. Variables ($P < 0.05$) in the multivariate analysis were regarded as independent factors, and were used to establish a nomogram. Moreover, we used the area under the curve (AUC) of receiver operating characteristic

Table 5. Univariate and multivariate regression analysis in the HCC group

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at Diagnosis				
Infancy (< 1 years old)	1.000 [Reference]	-	-	-
Infancy (1-2 years old)	8.130e-08 [0.00, Inf]	0.994	-	-
Preschool & school period	2.432 [0.571, 10.360]	0.229	-	-
Puberty	2.175 [0.534, 8.86]	0.278	-	-
Race				
White	1.000 [Reference]	-	-	-
Black	1.100 [0.585, 2.069]	0.768	-	-
Asian & Pacific Islander	1.216 [0.699, 2.115]	0.489	-	-
Unknown & Others	0.498 [0.0692, 3.580]	0.488	-	-
Origin				
Non-Spanish-Hispanic-Latino	1.000 [Reference]	-	-	-
Spanish-Hispanic-Latino	0.956 [0.620, 1.473]	0.837	-	-
Gender				
Male	1.000 [Reference]	-	-	-
Female	1.304 [0.886, 1.917]	0.178	-	-
Tumor Size				
< 50 mm	1.000 [Reference]	-	1.000 [Reference]	-
≥ 50 mm	3.074 [1.483, 6.371]	0.003	1.780 [0.791, 4.006]	0.164
Unknown	4.514 [1.997, 10.201]	2.910e-04	1.363 [0.541, 3.434]	0.512
Grade				
Grade I	1.000 [Reference]	-	1.000 [Reference]	-
Grade II	2.251 [1.024, 4.948]	0.043	1.268 [0.546, 2.949]	0.581
Grade III	4.067 [1.710, 9.675]	0.002	2.565 [1.017, 6.473]	0.046
Unknown	3.711 [11.845, 7.463]	2.35e-04	1.459 [0.685, 3.110]	0.328
Stage				
Localized	1.000 [Reference]	-	1.000 [Reference]	-
Regional	2.438 [1.405, 4.230]	0.002	1.511 [0.826, 2.765]	0.180
Distant	5.957 [3.505, 10.124]	4.26e-11	2.682 [1.457, 4.935]	0.002
Unknown & Unstaged	0.805 [0.108, 5.998]	0.832	0.584 [0.076, 4.511]	0.606
Surgery				
None	1.000 [Reference]	-	1.000 [Reference]	-
Local tumor destruction & Segmental resection	0.164 [0.086, 0.314]	4.95e-08	0.219 [0.106, 0.449]	3.52e-05
Lobectomy	0.225 [0.137, 0.370]	4.13e-09	0.271 [0.150, 0.488]	1.36e-05
Hepatectomy & Transplantation	0.120 [0.063, 0.231]	2.04e-10	0.211 [0.103, 0.432]	2.10e-05
Chemotherapy				
None & Unknown	1.000 [Reference]	-	1.000 [Reference]	-
Chemotherapy	0.335 [0.209, 0.537]	5.42e-06	0.865 [0.510, 1.467]	0.590

Note: HCC: hepatocellular carcinoma. HR: Hazard ratios. CI: confidence interval.

(ROC) curves to evaluate the discrimination of the nomogram, used calibration plots to evaluate the calibration of the nomogram, and used decision curve analysis (DCA) plots to evaluate clinical utility of the nomogram in the testing dataset [14]. Due to the small number of patients in the HB group and HCC group, we conducted only internal verification. Two-sided $P < 0.05$ was considered statistically significant. All analyses were performed using the caret, survival, tableone, rms, timeROC, pec, foreign, ggDCA and stdca.R packages in R software.

Results

Clinicopathological features

From 2000 to 2018, there were 1191 children with hepatic malignant tumors (including liver

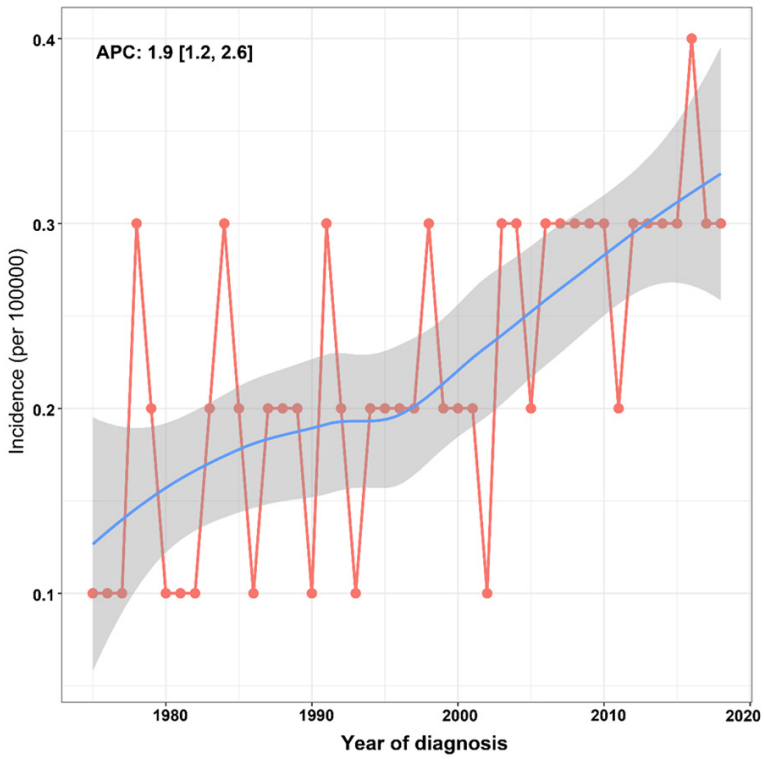

Figure 2. Incidence trend of hepatic malignant tumors in children (CHMTs). Note: APC: annual percentage changes.

and intrahepatic bile duct) in the SEER database. 66 patients with a survival time of 0 or unknown were excluded. Finally, 1125 patients were included in this study. Most of them were infants (< 2 years old, 58.6%), male (59.6%), white (76.1%) and non-Spanish-Hispanic-Latino (66.8%). Most patients had tumor lesions larger than 50 mm (73.8%). Most patients had HB (68.8%) or HCC (18.7%). About half the patients had localized lesions (45.4%). Most patients received surgery (77.5%) or chemotherapy (87.7%), and only a few received radiotherapy (3.3%). Demographics and clinicopathologic characteristics are shown in **Table 1**.

We compared the demographic and clinicopathologic characteristics of the HB and HCC groups (**Table 1**). HB occurred more frequently in infants (78.4% vs. 6.7%), but HCC tended to occur in puberty (72.9% vs. 2.1%), and the difference was significant ($P < 0.05$). Most of HB and HCC lesions were larger than 50 mm (75.5% and 66.7%). More patients with HB had localized staging (47.7% vs. 35.2%), while most patients with HCC had regional or distant stage (48.6% vs. 62.4%). In addition, more patients with HB received hepatectomy and chemotherapy (43.3% vs. 24.3%, 94.4% vs. 61.4%), while more patients with HCC received no surgery and radiotherapy (35.7% vs. 16.0%, 7.1% vs. 0.3%). In short, more patients with HB received systemic treatment (80.6% vs. 33.3%, $P < 0.05$).

Incidence trends

The incidence of CHMTs increased from 0.1 per 100,000 in 1975 to 0.3 per 100,000 in 2018, and the APC was 1.9% with a 95% confidence interval (CI) of 1.2%-2.6%. According to the fitting curve, the incidence rate of CHMTs increased (**Figure 2**). We found that the incidence rate in males was usually higher than that in females, but the gap gradually narrowed (**Figure 3A**). The incidence rate of infancy was significantly higher than that of other age groups, and those of people aged over 5 remained low (**Figure 3B**). Incidence rates of different races were also getting closer, and that of black had increased significantly in recent years (**Figure 3C**). The incidence rate of HB was significantly higher than that of HCC, and the gap was increasing (**Figure 3D**). In addition, we found that the incidence rates of HB or HCC in male and female groups were similar and both increased (**Figure 3E**). HB incidences of different races were increasing (**Figure 3F**).

Survival analysis

The patients included in this study were followed up for 1 to 227 months, of which 286 patients died (25.4%), and the 1-, 3-, 5-, and 10-year OS rates were 86.2%, 77.5%, 74.2%, and 70.2% respectively (**Figure 4**). The 1-, 3-, and 5-year OS rates of HB were significantly higher than those of HCC in children (90.0% vs. 78.4%, 82.9% vs. 61.3%, and 81.8% vs. 50.3%) (**Figure 5F**).

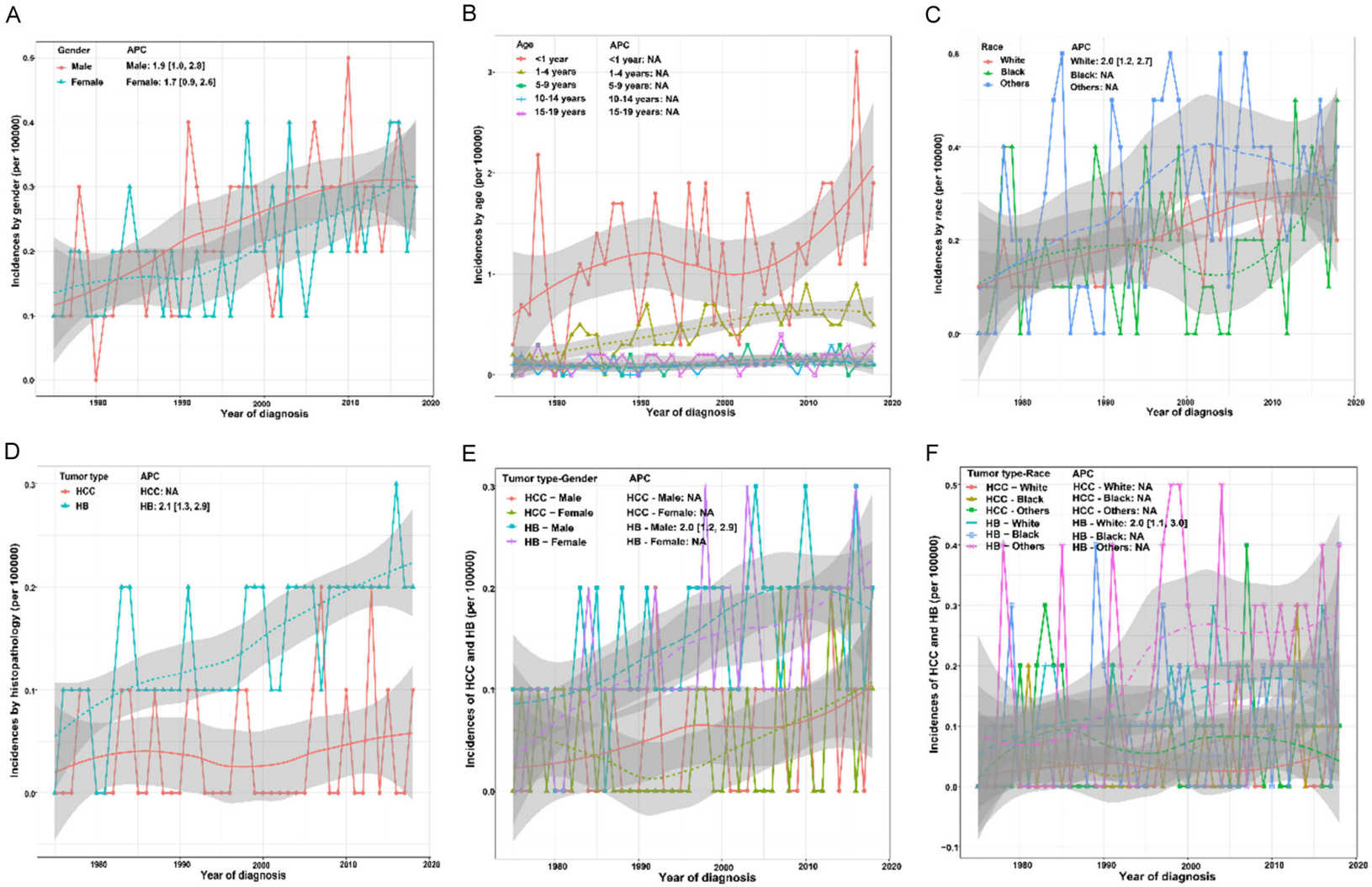

Figure 3. Incidence trend of hepatic malignant tumors in children (CHMTs) in different clinicopathologic groups. A: Gender. B: Age. C: Race. D: Tumor type. E, F: Incidence trends of hepatocellular carcinoma (HCC) and hepatoblastoma (HB) in different gender and race groups. Note: APC: annual percentage changes.

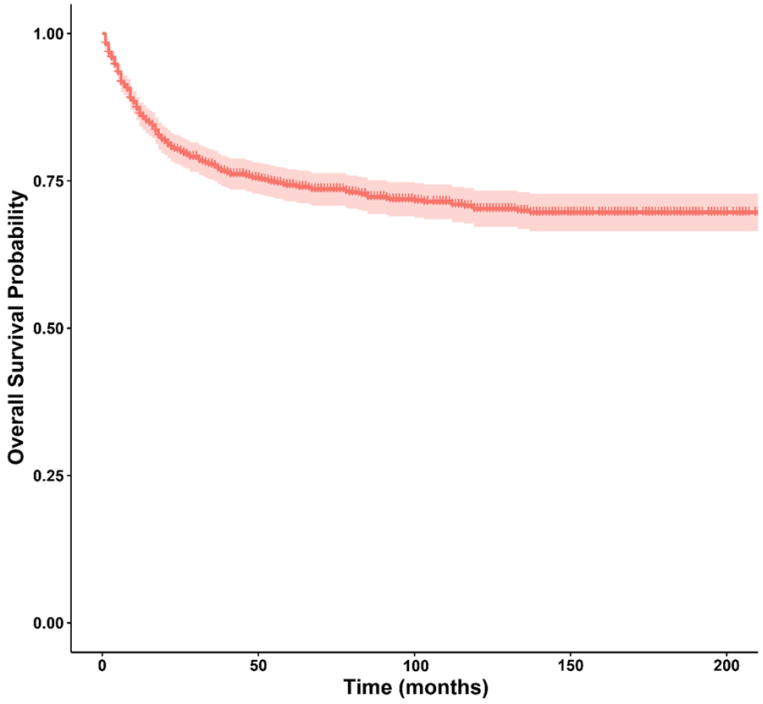

Figure 4. Survival curve of hepatic malignant tumors in children (CHMTs).

The patients included in this study were randomly divided into the training dataset (n=788) and testing dataset (n=337) at a ratio of 7:3 (**Figure 1**). There was no significant difference in baseline data between the training and testing datasets (**Table 2**). In the training dataset, we plotted survival curves of patients with different gender, age, race, origin, tumor size, pathological type, stage, and therapy groups (**Figure 5A-H**). The results of univariate Cox regression analysis showed that age, origin, tumor size, stage and therapy significantly affected the prognosis of patients ($P < 0.05$, **Table 3**). Multivariate Cox regression analysis showed that Spanish-Hispanic-Latino, HB, surgery, and systemic therapy were independent predictors of longer OS, whereas regional and distant stages were independent predictors of shorter OS (**Figure 6**). However, age and tumor size were not independent factors for OS (**Table 3**).

In addition, we evaluated the prognostic factors in the HB and HCC groups. We found that age, race, tumor size, stage and surgery significantly affected the prognosis of children with HB ($P < 0.05$, **Figure 7A-E**), and multivariate Cox regression analysis showed that surgery was an independent predictor of longer OS, whereas preschool & school period, puberty, black and distant stage were independent predictors of shorter OS (**Figure 8**; **Table 4**). We found that grade, tumor size, stage, surgery, and chemotherapy significantly affected the prognosis of children with HCC ($P < 0.05$, **Figure 9A-E**), and multivariate Cox regression analysis showed that surgery was an independent predictor of longer OS, whereas grade III and distant stage were independent predictors of shorter OS (**Figure 10**; **Table 5**).

Nomogram construction and validation

We established a nomogram using the above independent predictors. Each factor is listed separately with a corresponding point, and then the total points of all variables are matched to the probability of 1-, 3- and 5-year OS (**Figures 11-13**). Therapy was the most important predictor as shown in our nomograms.

Moreover, the AUCs of the 1-, 3-, and 5-year OS in the training and testing datasets, and the HCC and HB groups were good, all over 0.750 (**Figures 14A**, **14B**, **15A**, and **16A**). According to the nomogram, every patient enrolled in our studies could obtain a risk score. We plotted the survival curves between different risk score levels in the training and testing datasets, and the HB and HCC groups (**Figures 14C**, **14D**, **15B**, and **16B**). Therefore, our nomogram had good discriminative ability. Calibration plots in the training and testing datasets, and the HB and HCC groups indicated that the prediction of our nomogram approximated the actual outcome, and our nomogram had good calibration power (**Figures 14E**, **14F**, **15C**, and **16C**). DCA plots showed that our nomogram performed well in terms of clinical utility, and patients could benefit greatly from our model (**Figures 14G**, **14H**, **15D-F**, and **16D-F**).

Online publication of the prediction tool

Based on our nomogram, we published an online, free, public, and registration-free, pre-

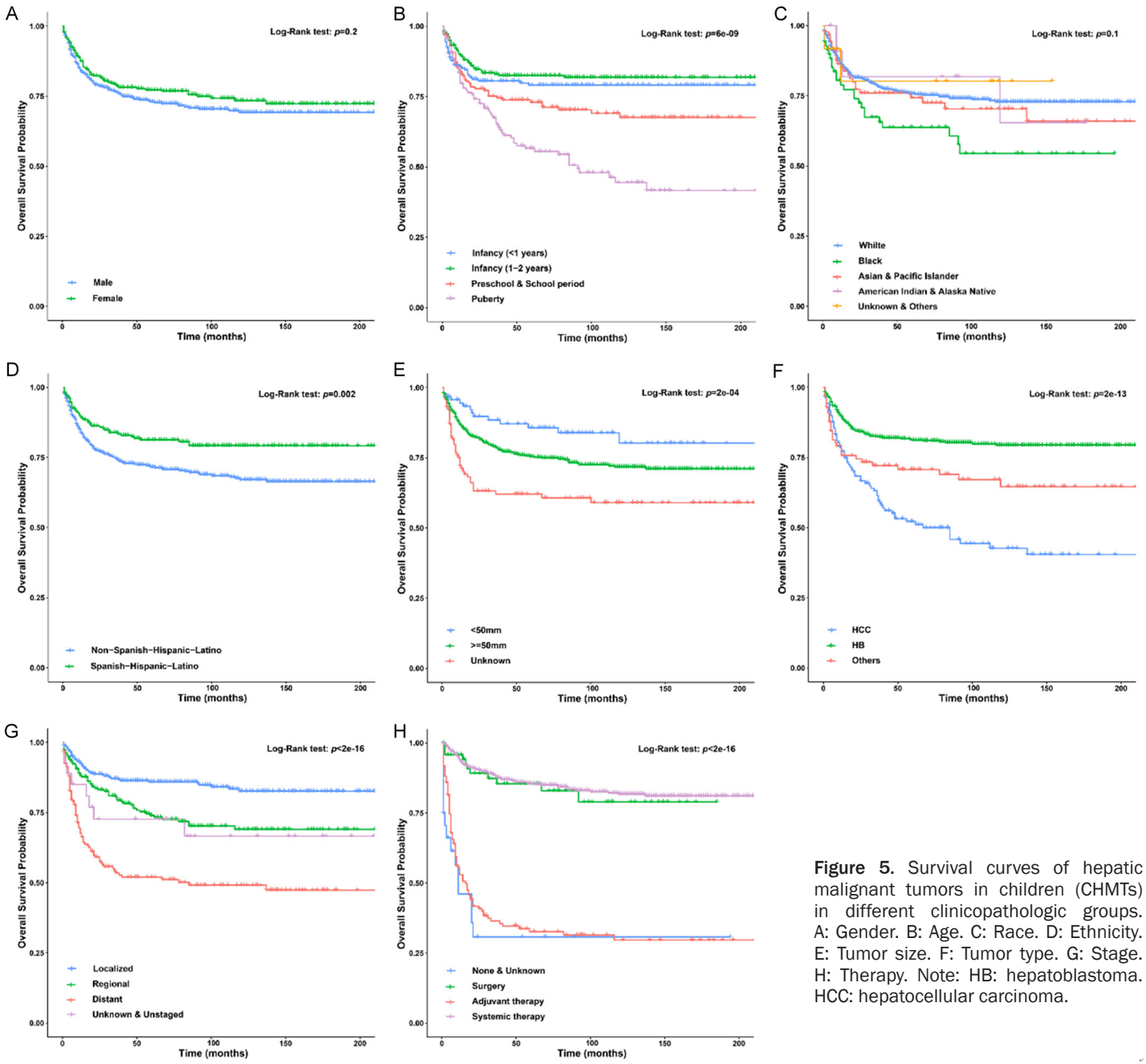

Figure 5. Survival curves of hepatic malignant tumors in children (CHMTs) in different clinicopathologic groups. A: Gender. B: Age. C: Race. D: Ethnicity. E: Tumor size. F: Tumor type. G: Stage. H: Therapy. Note: HB: hepatoblastoma. HCC: hepatocellular carcinoma.

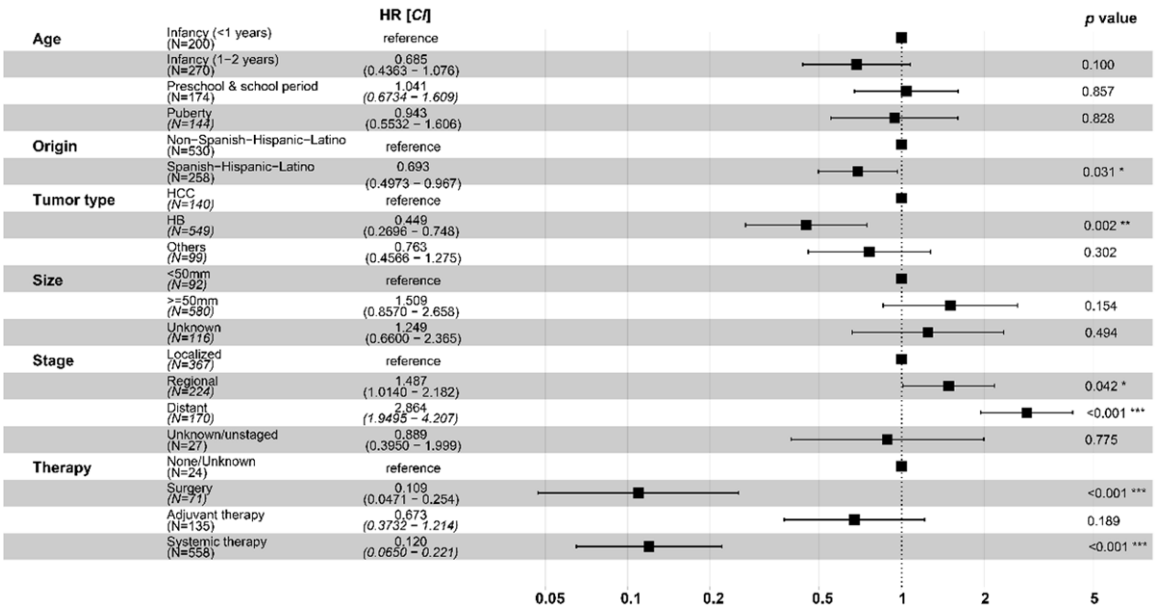

Figure 6. Forest plot of multivariate Cox regression analysis in hepatic malignant tumors in children (CHMTs). Notes: *p* value Significance Codes: 0 ≤ *** < 0.001 ≤ ** < 0.01 ≤ * < 0.05. HB: hepatoblastoma. HCC: hepatocellular carcinoma. HR: Hazard ratios. CI: confidence interval.

diction tool (https://clinical-prediction-model.shinyapps.io/DynNomapp/), which could benefit clinicians and patients in a straightforward manner. Users could open the above website, enter the clinicopathologic features of the patient, and then click the "Predict" button to obtain the prognosis of the patient.

Discussion

In this population-based study, we found that the age-adjusted incidence of CHMTs was significantly increasing with an APC of 1.9%, especially in infants and for HB. We found that although there were more males than females, the incidence in the white group was higher than that of the other racial groups, but the incidences in different gender and racial groups were getting closer. In addition, the incidences of HCC and the adolescent population remained lower and relatively stable. Then, we found that origin, tumor type, stage, and therapy were independent predictors for OS, while age and tumor size were relatively less valuable in predicting the OS of CHMTs. Surgery was an independent predictor of longer OS and that distant stage was an independent predictor of shorter OS for both the HB and HCC groups. We also established nomograms for children with HCC or HB, which had great prediction ability, with all AUCs greater than 0.750. Moreover, patients could benefit greatly through our prediction model.

Although CHMTs, mainly including HB and HCC, are one of the most common malignant tumors in the abdomen, their incidences are low. A population-based study in Taiwan showed that the crude incidence rate and the age-standardized incidence rate of HB were 0.52 and 0.76 per million persons per year, respectively, and the highest age-standardized incidence rate was in the 0 to 14-year-old group (2.67 per million per year), and more patients were male [15]. Another population-based study in South Africa showed that the incidences of HB and HCC were 0.61 and 0.37 per million children per year, respectively [16]. However, single-center, single-disease or short-term studies are not able to accurately assess the incidence trend. The SEER database has been widely used in cancer epidemiology research, such as pancreatic cancer, breast cancer, non-small cell lung cancer, and thyroid cancer [17-20]. Feng et al. reported that the incidence of HB increased significantly, from 1.89 per million in 2000 to 2.16 per million in 2015 based on the SEER database [12]. Previous studies based on the SEER database showed that the incidences of HCC in children were 0.5 per million in 2009,

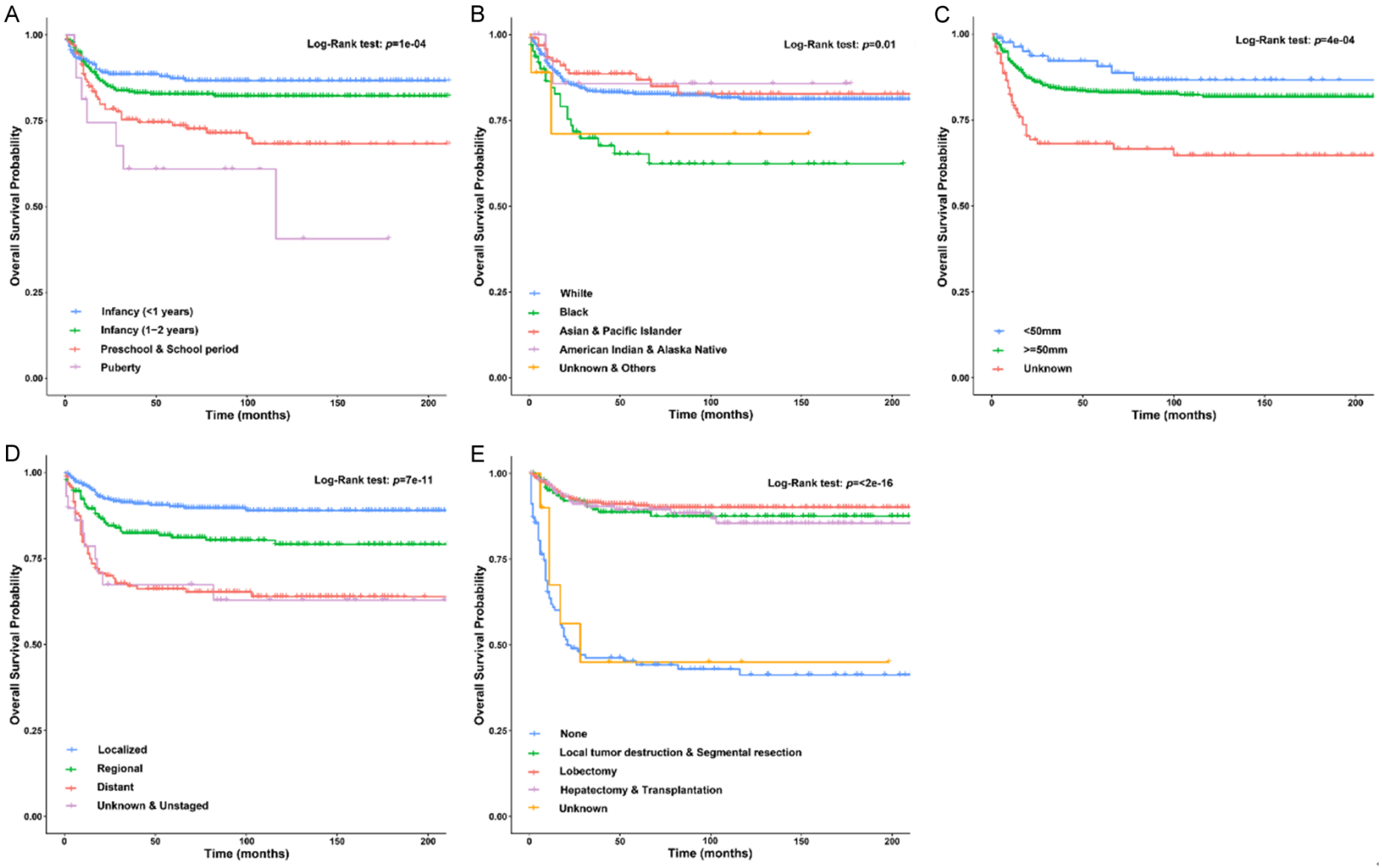

Figure 7. Survival curves of children with hepatoblastoma (HB) in different clinicopathologic groups. A: Age. B: Race. C: Tumor size. D: Stage. E: Surgery.

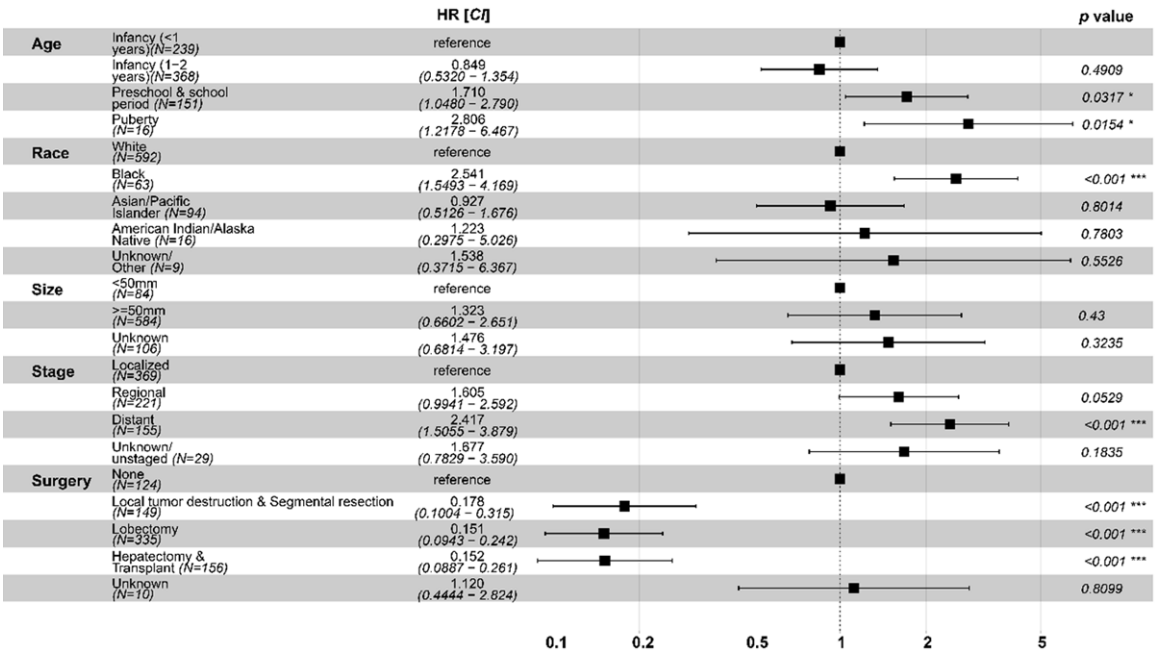

Figure 8. Forest plot of multivariate Cox regression analysis in the hepatoblastoma (HB) group. Notes: *p* value Significant Codes: 0 ≤ *** < 0.001 ≤ ** < 0.01 ≤ * < 0.05. HR: Hazard ratios. CI: confidence interval.

and 0.59 per million in 2013, respectively [21, 22]. Darbari et al. analyzed the epidemiology of primary CHMTs from 1973 to 1997 based on the SEER database and found that age-adjusted incidences of HB and HCC were 1.09 and 0.41 per million per year, respectively, and more HB patients were white and under 5 years old [23]. However, there is currently a lack of systematic research on the incidence trend of CHMTs, and the incidences of HB and HCC in children should be updated. In this study, we demonstrated the up-to-date incidence trend of CHMTs from 1975 to 2018. We found that the incidence of CHMTs increased significantly, especially in infants, white individuals, and HB patients. Interestingly, the incidences of different gender and race groups were approaching. In addition, the incidence in puberty was low and relatively stable, probably because HCC was the most common malignant tumor of the liver in adolescence and its incidence was low and relatively stable.

With the increasing survival rate of preterm infants and low-birth-weight neonates, the incidence of HB is increasing [6]. The incidence of HCC in children has been controlled by measures such as the extensive application of hepatitis B vaccine [24]. However, the prognosis of CHMTs is still poor. A study based on the SEER database from 1979 to 1996 showed that the 5-year survival rate of HB was 52.4%, while that of HCC in children was only 18.0% [23]. A study showed that from 1985 to 2013, the 5-year survival rates of CHMTs were 70.1% in Ontario, Canada, 68.5% in the United States and 75.9% in Australia [25]. Our study showed that the 1-, 3-, 5-, and 10-year OS rates were 86.2%, 77.5%, 74.2%, and 70.2% respectively, and the 1-, 3-, and 5-year OS rates of HB and HCC in children were 90.0%, 82.9%, and 81.8%, 78.4%, 61.3%, and 50.3% respectively, which might indicate that the prognosis of CHMTs has improved recently. Di Giuseppe et al. reported that the prognosis of CHMTs was related to age, year of diagnosis, stage and tumor type, but the study did not further analyze independent prognostic factors [25]. Nautsch et al. reported that the therapy, age, tumor type, and year of diagnosis could be associated with the prognosis of CHMTs [26]. We found that Spanish-Hispanic-Latino, HB, surgery, and systemic therapy were independent predictors of longer OS, whereas regional and distant stages were independent predictors of shorter OS. The prognosis of HB was significantly better than that of HCC in children, and systematic therapy including surgery, radiotherapy, and chemotherapy might be the

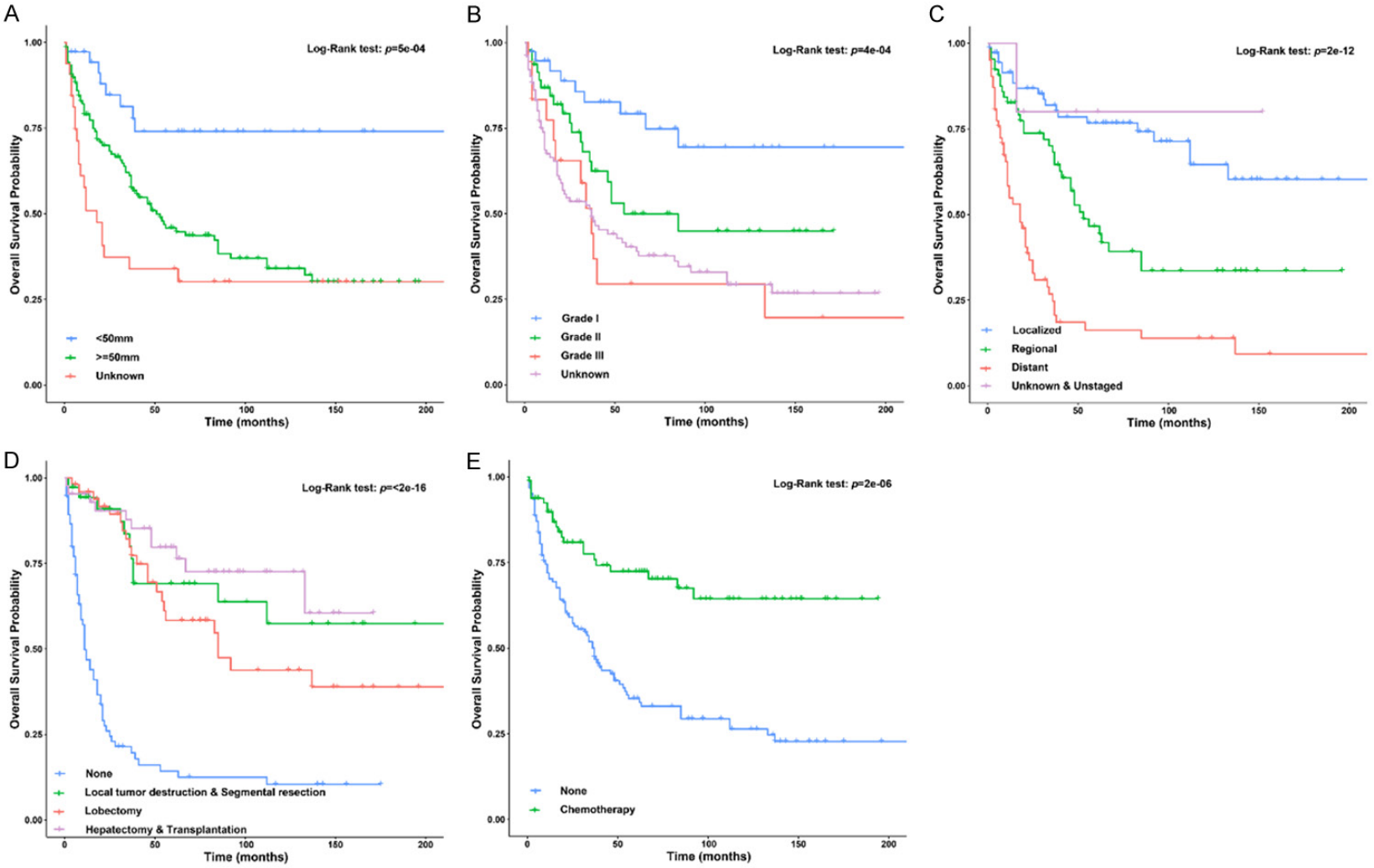

Figure 9. Survival curves of children with hepatocellular carcinoma (HCC) in different clinicopathologic groups. A: Tumor size. B: Grade. C: Stage. D: Surgery. E: Chemotherapy.

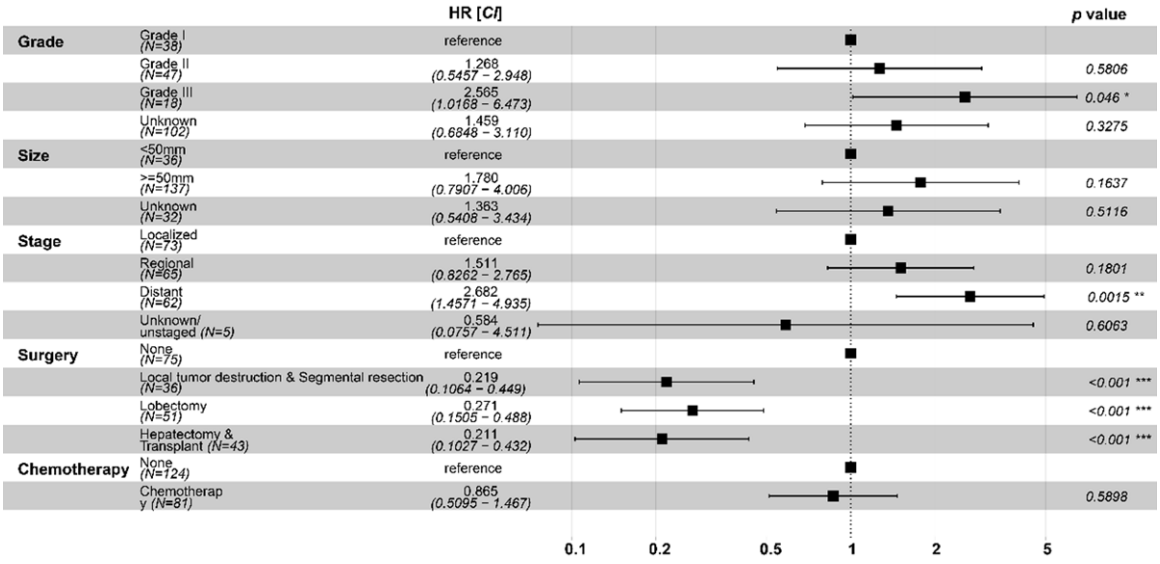

Figure 10. Forest plot of multivariate Cox regression analysis in the hepatocellular carcinoma (HCC) group. Notes: *p* value Significant Codes: 0 ≤ *** < 0.001 ≤ ** < 0.01 ≤ * < 0.05. HR: Hazard ratios. CI: confidence interval.

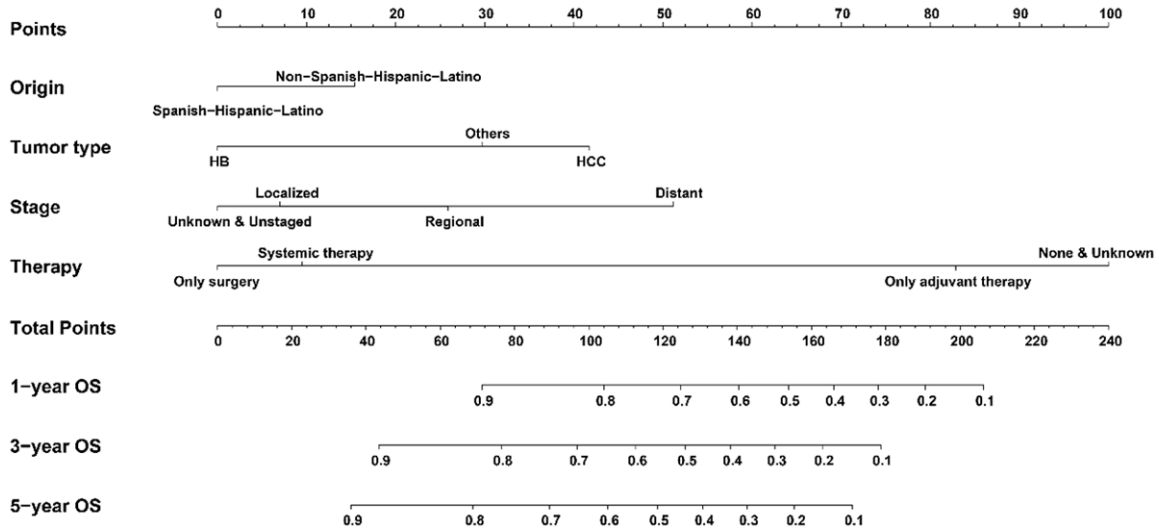

Figure 11. Nomogram for predicting overall survival (OS) of hepatic malignant tumors in children (CHMTs). Note: HB: hepatoblastoma. HCC: hepatocellular carcinoma.

key to improving the prognosis of HB. At present, different standardized chemotherapy schemes have been proposed for different stages of HB, which has effectively improved the prognosis [27-30]. However, the effect of chemotherapy on HCC is not ideal, and whether the focus could be resected completely may be the key to improving the prognosis [22, 31]. We found that age, race, stage, and surgery were independent predictors of OS for children with HB, and grade, stage, and surgery were independent predictors of OS for children with HCC, which showed that early detection and early surgical treatment may be the key to improving the prognosis of patients with HB or HCC.

In recent years, many studies have analyzed the prognosis of HB and HCC in children, but most of them were small sample, single-disease and single-center studies [32-36]. In addition, there were only two prediction models for HB in PubMed (https://pubmed.ncbi.nlm.nih.

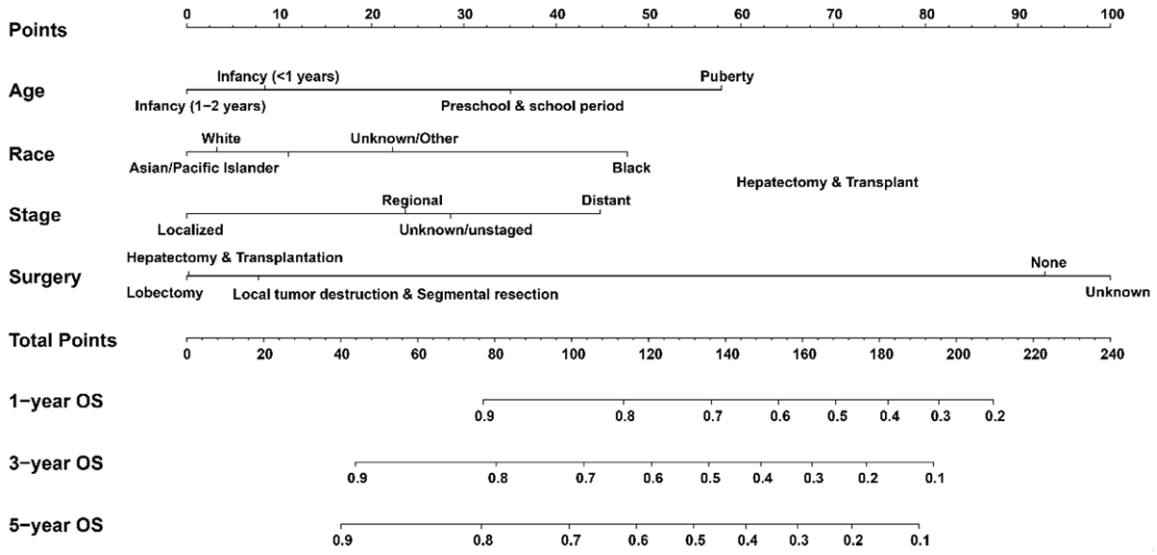

Figure 12. Nomogram for predicting overall survival (OS) of children with hepatoblastoma (HB).

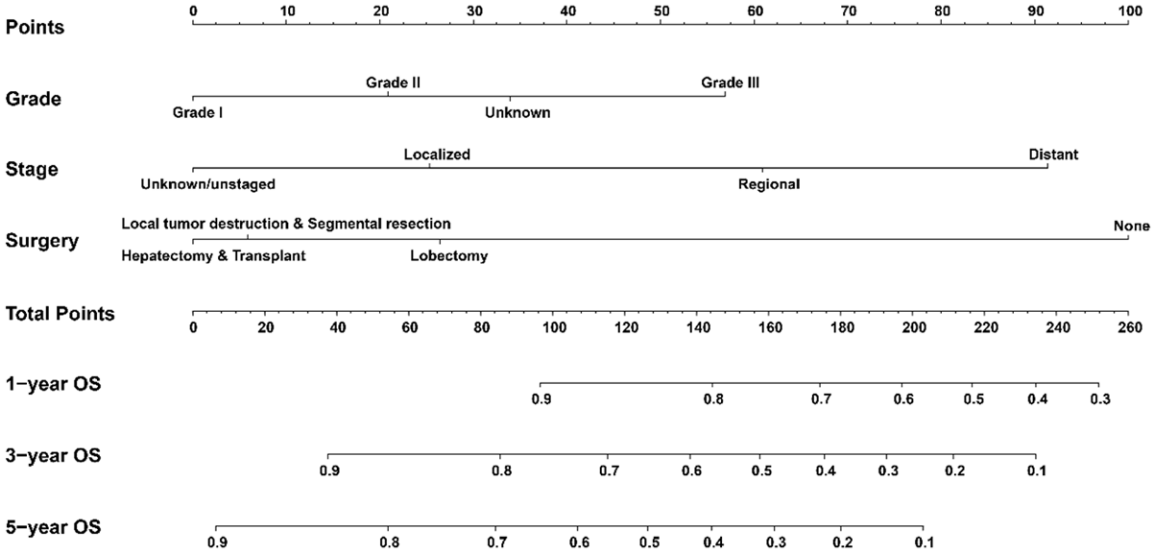

Figure 13. Nomogram for predicting overall survival (OS) of children with hepatocellular carcinoma (HCC).

gov/), but there was no prediction model for HCC in children. Feng et al. established a nomogram to predict the prognosis of children with HB based on SEER data from 2004 to 2015, with a concordance index (C-index) of 0.79 [12]. Jiang et al. established a nomogram for predicting the prognosis of children with HB based on preoperative CT and clinicopathological data of 88 patients, with a C-index of 0.88 [11]. Our prediction models based on the latest SEER data enrolled larger sample sizes, and could be applied to CHMTs, HB or HCC. Through internal and external validation, it was confirmed that our prediction models performed well in discrimination ability and clinical practicability. Moreover, we also published an online computing tool for clinical application. Therefore, our models might be closer to the real world and provide a good prognostic prediction tool for patients after treatment.

Nonetheless, this study had several weaknesses. First, because the data in the SEER database are incomplete, there are no data on com-

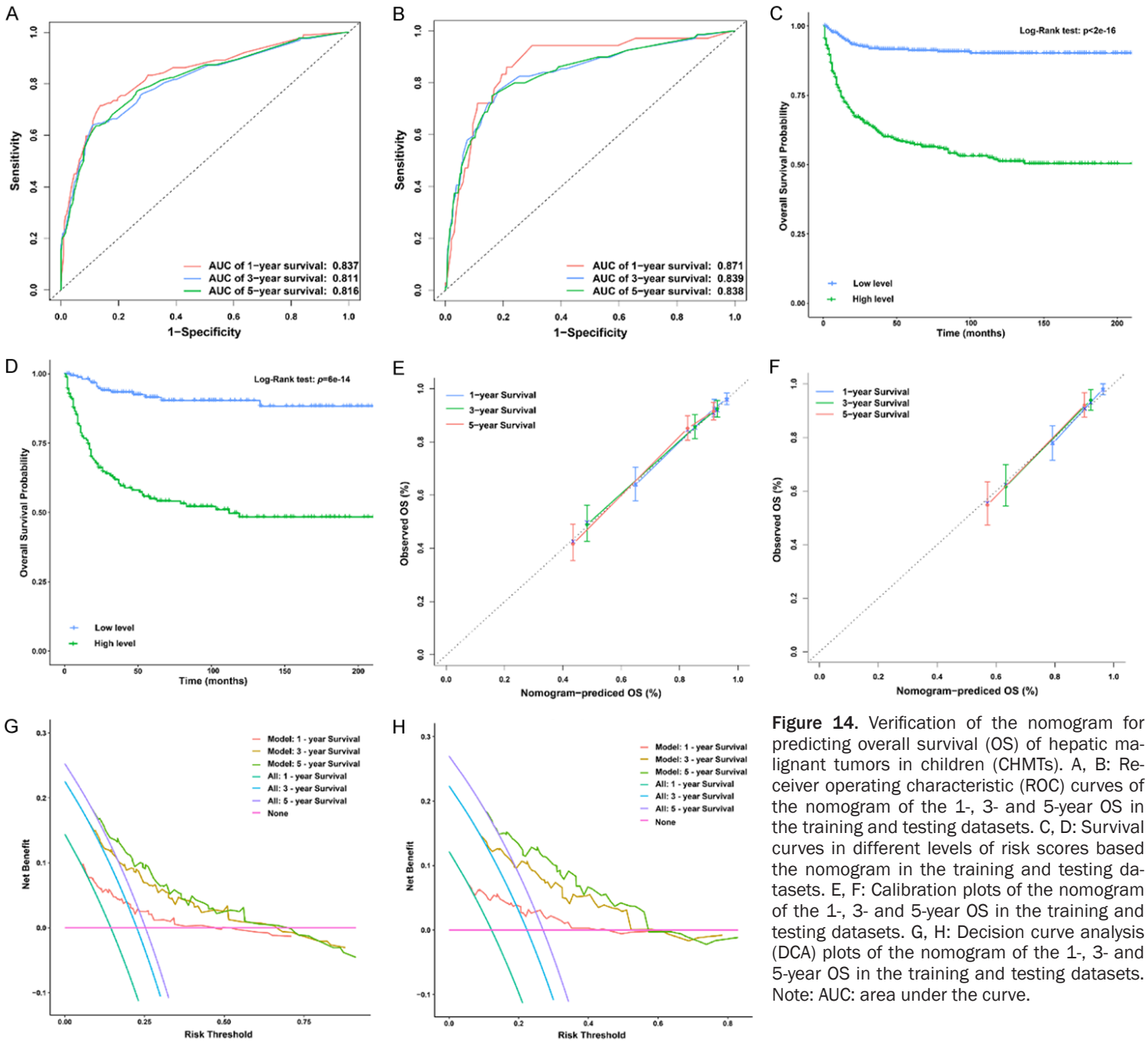

Figure 14. Verification of the nomogram for predicting overall survival (OS) of hepatic malignant tumors in children (CHMTs). A, B: Receiver operating characteristic (ROC) curves of the nomogram of the 1-, 3- and 5-year OS in the training and testing datasets. C, D: Survival curves in different levels of risk scores based the nomogram in the training and testing datasets. E, F: Calibration plots of the nomogram of the 1-, 3- and 5-year OS in the training and testing datasets. G, H: Decision curve analysis (DCA) plots of the nomogram of the 1-, 3- and 5-year OS in the training and testing datasets. Note: AUC: area under the curve.

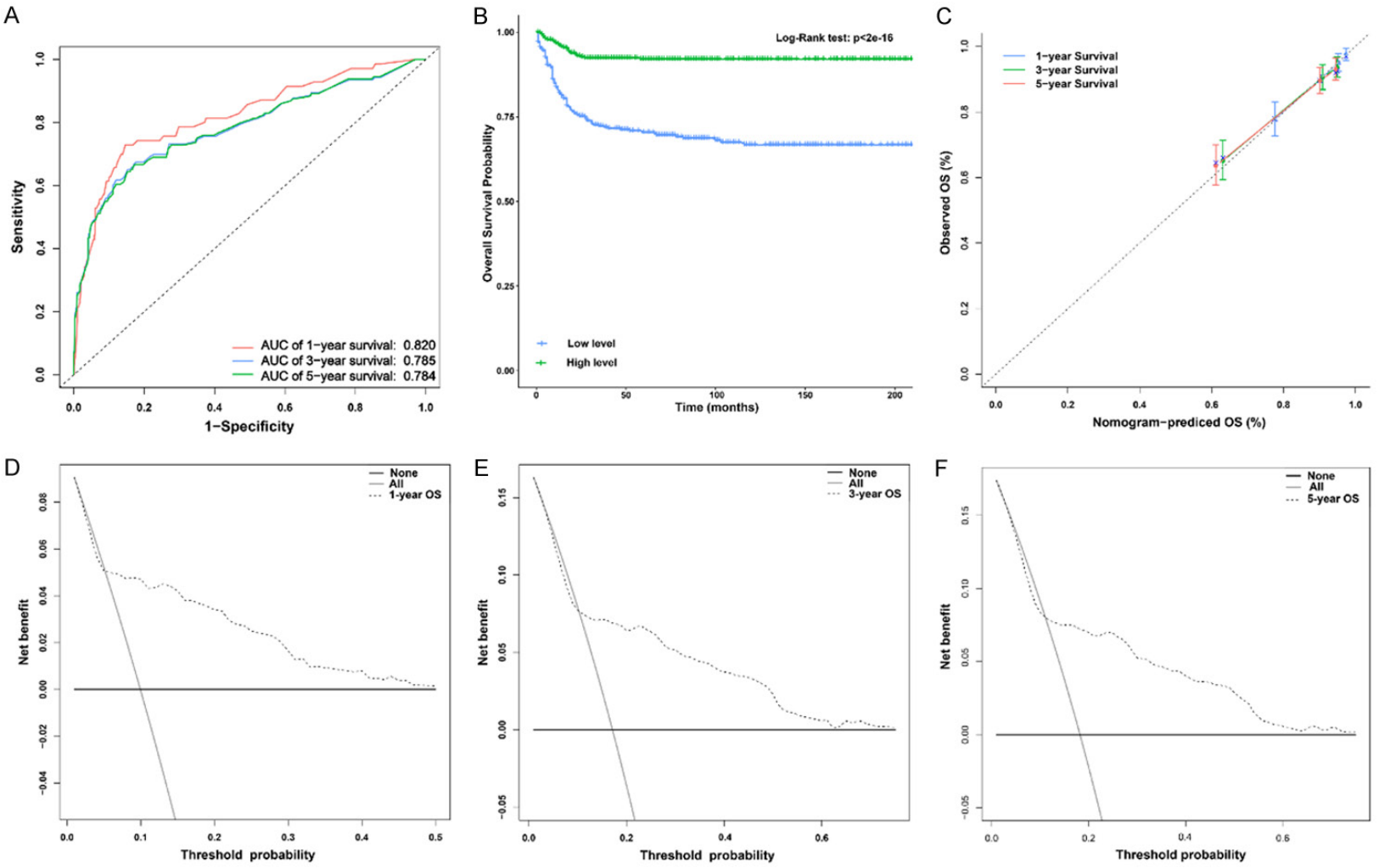

Figure 15. Verification of the nomogram for predicting overall survival (OS) of children with hepatoblastoma (HB). A: Receiver operating characteristic (ROC) curves of the nomogram of the 1-, 3- and 5-year OS. B: Survival curves in different levels of risk scores based the nomogram. C: Calibration plots of the nomogram of the 1-, 3- and 5-year OS. D-F: Decision curve analysis (DCA) plots of the nomogram of the 1-, 3- and 5-year OS. Note: AUC: area under the curve.

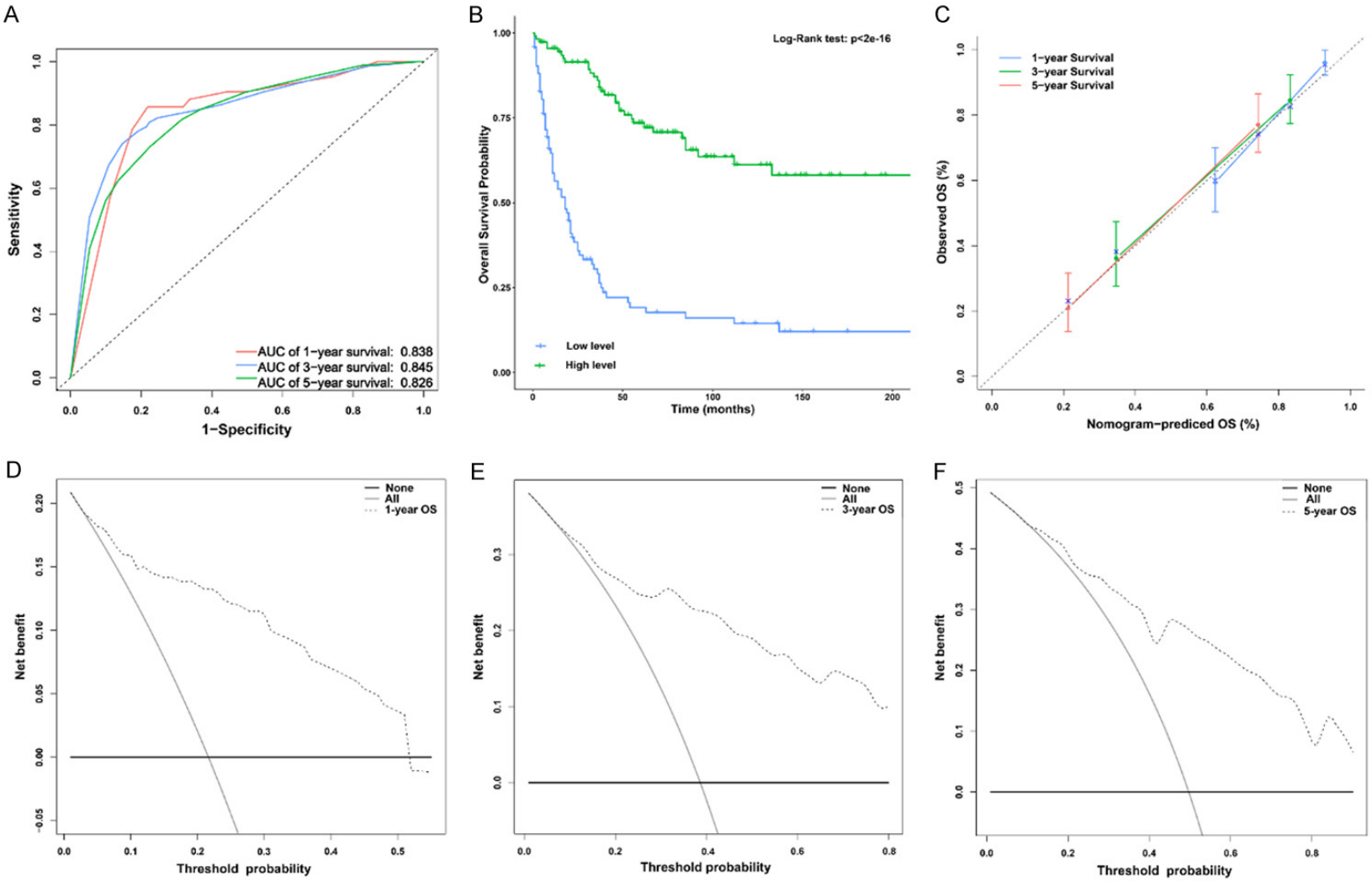

Figure 16. Verification of the nomogram for predicting overall survival (OS) of children with hepatocellular carcinoma (HCC). A: Receiver operating characteristic (ROC) curves of the nomogram of the 1-, 3- and 5-year OS. B: Survival curves in different levels of risk scores based the nomogram. C: Calibration plots of the nomogram of the 1-, 3- and 5-year OS. D-F: Decision curve analysis (DCA) plots of the nomogram of the 1-, 3- and 5-year OS. Note: AUC: area under the curve.

bined diseases, chemotherapy regimen, reasons for not receiving treatment, or birth information, such as duration of pregnancy and birth weight. Therefore, there may be bias in the selection of patients and variables. In addition, this study is a retrospective study that has inherent defects such as selection bias. Third, we did not use external, prospective data to validate our prediction models, which limited their application scope. In the future, we will analyze CHMT data in China and externally verify our models.

Conclusion

This study showed the incidence trends of CHMTs, analyzed the prognostic factors, and developed and published a nomogram for predicting prognosis. Our nomograms had good predictive ability and clinical utility and might more accurately estimate the prognosis of CHMTs.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

CHMTs, hepatic malignant tumors in children; SEER, Surveillance, Epidemiology, and End Results; OS, overall survival; HB, hepatoblastoma; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; APC, annual percentage changes; AUC, area under the curve; ROC, receiver operating characteristic; DCA, decision curve analysis; HR, Hazard ratios; CI, confidence intervals; C-index, concordance index.

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References

[1] Darbari A, Sabin K, Shapiro C and Schwarz K. Epidemiology of primary hepatic malignancies in U.S. children. Hepatology 2003; 38: 560-566.

[2] Ng K and Mogul D. Pediatric liver tumors. Clin Liver Dis 2018; 22: 753-772.

[3] Lucas B, Ravishankar S and Pateva I. Pediatric primary hepatic tumors: diagnostic considerations. Diagnostics (Basel) 2021; 11: 333.

[4] Finegold M, Egler R, Goss J, Guillerman R, Karpen S, Krishnamurthy R and O'Mahony C. Liver tumors: pediatric population. Liver Transpl 2008; 14: 1545-1556.

[5] Board WCoTE. WHO Classification of Tumours of Digestive System Tumours. US: WHO; 2019.

[6] Spector L and Birch J. The epidemiology of hepatoblastoma. Pediatr Blood Cancer 2012; 59: 776-779.

[7] Balachandran V, Gonen M, Smith J and DeMatteo R. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015; 16: e173-180.

[8] Cheng E, Ou F, Ma C, Spiegelman D, Zhang S, Zhou X, Bainter T, Saltz L, Niedzwiecki D, Mayer R, Whittom R, Hantel A, Benson A, Atienza D, Messino M, Kindler H, Giovannucci E, Van Blarigan E, Brown J, Ng K, Gross C, Meyerhardt J and Fuchs C. Diet- and lifestyle-based prediction models to estimate cancer recurrence and death in patients with stage III colon cancer (CALGB 89803/Alliance). J Clin Oncol 2022; 40: 740-751.

[9] Gafita A, Calais J, Grogan T, Hadaschik B, Wang H, Weber M, Sandhu S, Kratochwil C, Esfandiari R, Tauber R, Zeldin A, Rathke H, Armstrong W, Robertson A, Thin P, D'Alessandria C, Rettig M, Delpassand E, Haberkorn U, Elashoff D, Herrmann K, Czernin J, Hofman M, Fendler W and Eiber M. Nomograms to predict outcomes after Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study. Lancet Oncol 2021; 22: 1115-1125.

[10] Serenari M, Han K, Ravaioli F, Kim S, Cucchetti A, Han D, Odaldi F, Ravaioli M, Festi D, Pinna A and Cescon M. A nomogram based on liver stiffness predicts postoperative complications in patients with hepatocellular carcinoma. J Hepatol 2020; 73: 855-862.

[11] Jiang Y, Sun J, Xia Y, Cheng Y, Xie L, Guo X and Guo Y. Preoperative assessment for event-free survival with hepatoblastoma in pediatric patients by developing a CT-based radiomics model. Front Oncol 2021; 11: 644994.

[12] Feng J, Polychronidis G, Heger U, Frongia G, Mehrabi A and Hoffmann K. Incidence trends and survival prediction of hepatoblastoma in children: a population-based study. Cancer Commun (Lond) 2019; 39: 62.

[13] Iasonos A, Schrag D, Raj G and Panageas K. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol 2008; 26: 1364-1370.

[14] Collins G, Reitsma J, Altman D and Moons K. Transparent reporting of a multivariable pre-

diction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015; 350: g7594.
[15] Hung G, Lin L, Yu T, Lee C, Yen H and Horng J. Hepatoblastoma incidence in Taiwan: a population-based study. J Chin Med Assoc 2018; 81: 541-547.
[16] Moore S, Millar A, Hadley G, Ionescu G, Kruger M, Poole J, Stones D, Wainwright L, Chitnis M and Wessels G. Hepatocellular carcinoma and liver tumors in South African children: a case for increased prevalence. Cancer 2004; 101: 642-649.
[17] Ellington T, Miller J, Henley S, Wilson R, Wu M and Richardson L. Trends in breast cancer incidence, by race, ethnicity, and age among women aged ≥ 20 years - United States, 1999-2018. MMWR Morb Mortal Wkly Rep 2022; 71: 43-47.
[18] Ganti A, Klein A, Cotarla I, Seal B and Chou E. Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US. JAMA Oncol 2021; 7: 1824-1832.
[19] Davis Lynn B, Chernyavskiy P, Gierach G and Rosenberg P. Decreasing incidence of estrogen receptor-negative breast cancer in the United States: trends by race and region. J Natl Cancer Inst 2022; 114: 263-270.
[20] Powers A, Marcadis A, Lee M, Morris L and Marti J. Changes in trends in thyroid cancer incidence in the United States, 1992 to 2016. JAMA 2019; 322: 2440-2441.
[21] Allan B, Wang B, Davis J, Parikh P, Perez E, Neville H and Sola J. A review of 218 pediatric cases of hepatocellular carcinoma. J Pediatr Surg 2014; 49: 166-171.
[22] Khanna R and Verma S. Pediatric hepatocellular carcinoma. World J Gastroenterol 2018; 24: 3980-3999.
[23] Darbari A, Sabin K, Shapiro C and Schwarz K. Epidemiology of primary hepatic malignancies in U.S. children. Hepatology 2003; 38: 560-566.
[24] Chang M. Decreasing incidence of hepatocellular carcinoma among children following universal hepatitis B immunization. Liver Int 2003; 23: 309-314.
[25] Di Giuseppe G, Youlden D, Aitken J and Pole J. Pediatric hepatic cancer incidence and survival: 30-year trends in Ontario, Canada; the United States; and Australia. Cancer 2021; 127: 769-776.
[26] Nautsch F, Ludwig J, Xing M, Johnson K and Kim H. Racial disparities and sociodemographic differences in incidence and survival among pediatric patients in the united states with primary liver cancer: a Surveillance, Epidemiology, and End Results (SEER) population study. J Clin Gastroenterol 2018; 52: 262-267.
[27] Perilongo G, Maibach R, Shafford E, Brugieres L, Brock P, Morland B, de Camargo B, Zsiros J, Roebuck D, Zimmermann A, Aronson D, Childs M, Widing E, Laithier V, Plaschkes J, Pritchard J, Scopinaro M, MacKinlay G and Czauderna P. Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med 2009; 361: 1662-1670.
[28] Zsíros J, Maibach R, Shafford E, Brugieres L, Brock P, Czauderna P, Roebuck D, Childs M, Zimmermann A, Laithier V, Otte J, de Camargo B, MacKinlay G, Scopinaro M, Aronson D, Plaschkes J and Perilongo G. Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. J Clin Oncol 2010; 28: 2584-2590.
[29] Zsiros J, Brugieres L, Brock P, Roebuck D, Maibach R, Zimmermann A, Childs M, Pariente D, Laithier V, Otte J, Branchereau S, Aronson D, Rangaswami A, Ronghe M, Casanova M, Sullivan M, Morland B, Czauderna P and Perilongo G. Dose-dense cisplatin-based chemotherapy and surgery for children with high-risk hepatoblastoma (SIOPEL-4): a prospective, single-arm, feasibility study. Lancet Oncol 2013; 14: 834-842.
[30] Katzenstein H, Furman W, Malogolowkin M, Krailo M, McCarville M, Towbin A, Tiao G, Finegold M, Ranganathan S, Dunn S, Langham M, McGahren E, Rodriguez-Galindo C and Meyers R. Upfront window vincristine/irinotecan treatment of high-risk hepatoblastoma: a report from the Children's Oncology Group AHEP0731 study committee. Cancer 2017; 123: 2360-2367.
[31] Sindhi R, Rohan V, Bukowinski A, Tadros S, de Ville de Goyet J, Rapkin L and Ranganathan S. Liver transplantation for pediatric liver cancer. Cancers (Basel) 2020; 12: 720.
[32] Wang J, Mao Y, Liu Y, Chen Z, Chen M, Lao X and Li S. Hepatocellular carcinoma in children and adolescents: clinical characteristics and treatment. J Gastrointest Surg 2017; 21: 1128-1135.
[33] Yu S, Kim H, Eo H, Won J, Jung S, Park K and Kim W. Clinical characteristics and prognosis of pediatric hepatocellular carcinoma. World J Surg 2006; 30: 43-50.
[34] Zhang Y, Zhang W, Tang S, Chen L, Yi Y, Zhang P, Liu A, Zhi T and Huang D. A single-center retrospective study of pediatric hepatoblastoma. Oncol Lett 2016; 12: 3919-3925.
[35] Yu W, Liu X, Li J, Xi Z, Jin J, Huang H, Ge Y and Xia Q. A single-center retrospective analysis of childhood hepatoblastoma in China. Gland Surg 2020; 9: 1502-1512.
[36] Liu J, Wu X, Li T, Hao X, Duan Y, Zhao J, Zhu C, Wei B and Dong Q. Analysis of survival rates and prognosis of hepatoblastoma in children: a retrospective study from a single center in China. Pediatr Hematol Oncol 2021; 38: 319-330.