European Review for Medical and Pharmacological Sciences 2023; 27: 10553-10562

2 years is a reasonable age cut-off level for prognostic assessment of children with hepatoblastoma

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Abstract. – OBJECTIVE: We aimed to elucidate the prognostic significance of age in hepatoblastoma patients.

PATIENTS AND METHODS: Data from 783 patients with hepatoblastoma were obtained from the Surveillance, Epidemiology and End Results database (2000-2018). The best age cut-off level was determined by X-tile, and the Kaplan-Meier method was used to estimate overall survival (OS) and cancer-specific survival (CSS). The results of the X-tile were verified by selecting the appropriate cut-off value to maximize the difference in survival outcomes at intervals of 1 year. The Cox regression model was used to determine the prognostic impact of risk factors and age.

RESULTS: X-tile analysis determined that 2 years was the best cut-off age for OS and CSS. The overall prognosis in the ≥ 2 years group was worse than that in the < 2 years group (OS: $p = 0.00017$; CSS: $p < 0.0001$). In Cox univariate analysis, when 2 years was used as the standard group, the numbers of patients in the two groups were similar, with high hazard ratio (HR) value and narrow 95% confidence interval (CI) (OS: HR, 1.834; 95% CI, 1.329 – 2.532; $p < 0.001$; CSS: HR, 1.988; 95% CI, 1.410 – 2.801; $p < 0.001$), which was consistent with the age cut-off point determined by X-tile. Cox multivariate analysis showed that age ≥ 2 years, black ethnicity, no surgery, no chemotherapy, distant metastasis, and tumor size ≥ 5 cm were independent predictors of poor OS and CSS. On subgroup analysis, patients aged ≥ 2 years had worse survival if they were Caucasian, had elevated alpha-fetoprotein, tumor size ≥ 5 cm, or distant metastasis.

CONCLUSIONS: Age is an important prognostic factor for hepatoblastoma. Age ≥ 2 years at diagnosis may predict poor prognosis and more active treatment measures can be implemented.

Key Words:
Hepatoblastoma, Age, Overall Survival, Cancer-specific survival, SEER.

Introduction

Hepatoblastoma is the most common malignant neoplasm of the liver in children, accounting for approximately two-thirds of all malignant liver tumors in children[1]. The estimated annual incidence of hepatoblastoma is 1.5 cases/year/million[2,3]. The disease most commonly presents within the first three years of life[4]. With the continuous advances in chemotherapy regimens, complete tumor resection, and liver transplantation, the overall survival (OS) rate has improved significantly, and the reported 3-year event-free survival (EFS) rate is > 80%[5]. However, there are limited treatment options for clinically advanced tumors and the prognosis is poor (3-year EFS rate: 34%)[6].

The International Cooperation Organization for Childhood Liver Cancer (CHIC) recently established a new risk-stratification system for the prognostic assessment of patients with hepatoblastoma. The stratification system is based on the summary data of 1,605 patients treated by four research groups [International Childhood Liver Tumor Strategy Group (SIOPEL), Children's Cancer Group (COG), German Society for Pediatric Oncology and Haematology (GPOH), and the Japanese Study Group for Pediatric Liver Tumors (JOLT)] over a period of 25 years[2]. The risk level of hepatoblastoma is comprehensively judged according to clinical and biological indicators, which helps inform clinical decision-making[7,8]. Except for age, the factors used in the new risk stratification represent all aspects of tumor load and anatomical structure. Age has been widely reported as a prognostic factor in patients with gastric cancer[9], hepatocellular carcinoma[10], and lung cancer[11], which indicates

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that age at diagnosis is a key determinant of patient prognosis. Few studies in the literature have investigated the prognostic value of age in the context of hepatoblastoma, and the reported age cut-off levels have shown much variability. Therefore, it is not clear whether age is an independent prognostic factor for the OS of patients with hepatoblastoma. In addition, the optimal age cutoff level, and the differences in clinical characteristics among different age groups are not well characterized.

In the present study, we used the Surveillance, Epidemiology, and End Results (SEER) database to analyze the impact of age at diagnosis on the OS and cancer-specific survival (CSS) of patients with hepatoblastoma, and to determine the optimal cut-off level of age to identify patients with poor prognosis.

Patients and Methods

Patients and Ethics

We used the SEER database and SEER-stat software version 8.3.9 (National Cancer Institute, Calverton, MD, US) to identify and collect the data of patients aged ≤ 18 years with a confirmed diagnosis of hepatoblastoma between 2000 and 2018 according to the International Classification of Diseases for Oncology (ICD-O-3). Data pertaining to the following variables were extracted: age, sex, ethnicity, survival time, tumor size, chemotherapy, surgery, and cause of death.

The inclusion criteria were: 1) patients diagnosed with hepatoblastoma according to the International Classification of Tumor Diseases, Third Edition [(ICD-O-3); code 8,970/3; 2]. Hepatoblastoma was the primary tumor. The exclusion criteria were: 1) lack of follow-up data; 2) diagnosis not confirmed by pathological examination; 3) age > 18 years.

A total of 783 patients qualified for the selection criteria and were included in the analysis (Figure 1). The median duration of follow-up in our cohort was 86 months (range 0 – 227). The data used in this study were obtained from the open-source SEER database. All data in the database are anonymized in terms of personal information; therefore, ethical approval was not required for this study.

Definition of Variables

Patients were divided into 2 groups-based X-tile: < 2 and ≥ 2 years. Sex was classified as male or female. Ethnicity was classified into three categories: Caucasian, black, and other/unknown. Surgery type (no surgery, liver resection, liver transplantation, and unknown), chemotherapy status (yes and no), and the presence or absence of distant metastasis (yes, no, and unknown) were

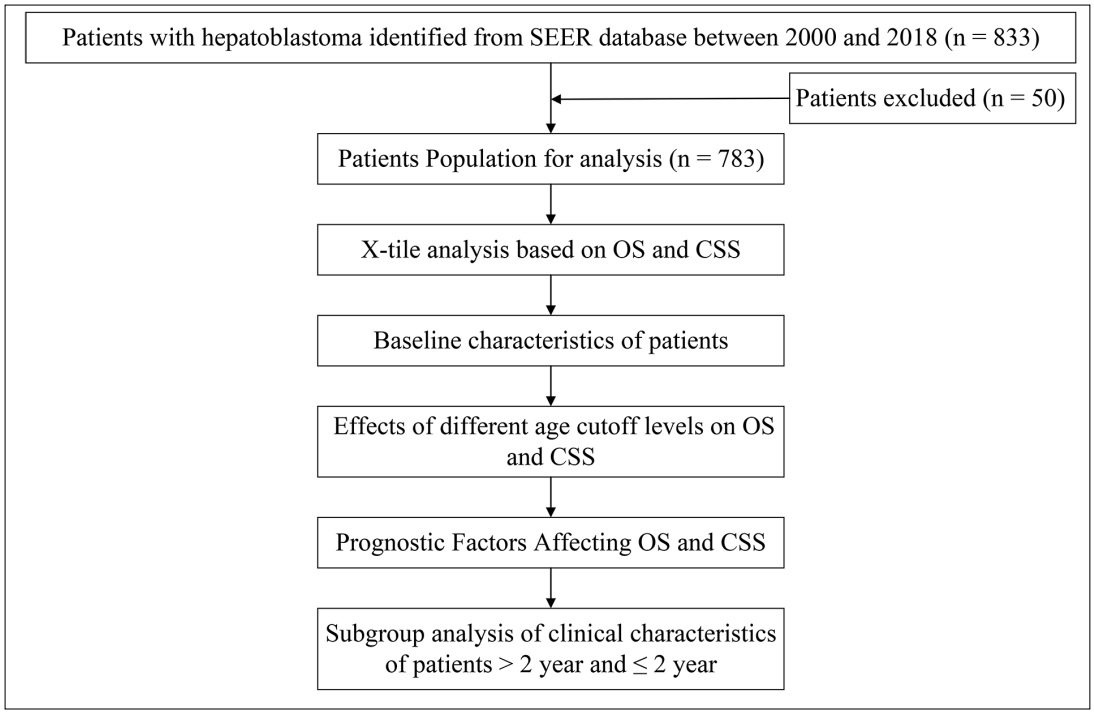

Figure 1. Flow chart of the overall study design.

recorded. Tumor size was classified into three categories: < 5 cm, ≥ 5 cm, and unknown[4,12]. Serum alpha-fetoprotein (AFP) levels were divided into three categories: elevated, normal, and unknown.

Statistical Analysis

The X-tile software version 3.6.1 (Yale University School of Medicine, New Haven, CT, US) was used to determine the optimal cut-off point for age by comparing the survival rate, according to age, and generating the minimum *p*-value. According to the optimal cut-off value of X-tile, the best cut-off ages for predicting OS and CSS were determined, respectively.

Survival curves were generated using the Kaplan-Meier method and between-group differences were assessed using the log-rank test. Multivariate Cox regression models were utilized to determine prognostic factors. Univariate Cox analysis was performed to identify factors ($p<0.05$) for inclusion in the multivariate Cox regression models.

Data analysis was performed with SPSS 26.0 for Windows (IBM Corp., Armonk, NY, USA) and R software (version 3.6.3, Vienna, Austria) utilizing the 'survival' and 'ggplot2' packages. *p*-values <0.05 were considered indicative of statistical significance.

Results

X-Tile Analysis Based on OS and CSS

The X-tile was used to determine the optimal cut-off level of age at the time of diagnosis that may most significantly affect OS and CSS. The optimal cut-off level for age was identified as 2 years based on OS and CSS status (Figure 2). 498 (63.6%) patients were in the < 2 years group, while 285 (36.4%) patients were in the ≥ 2 years group, based on age at diagnosis. Kaplan-Meier curve showed that the OS and CSS of patients aged ≥ 2 years were worse than those of children aged < 2 years (OS: $p = 0.00017$; CSS: $p < 0.0001$). As shown in Figures 3A and 3B, the 1-, 3- and 5-year OS rates in the < 2 years group and ≥ 2 years group were 97.4% and 96.8%, 95.4% and 92.5%, 92.9% and 85.8%, respectively, and the 1-, 3- and 5-year CSS rates were 98.2% and 97.5%, 96.1% and 93.5%, 93.8% and 87.4%, respectively ($p < 0.05$ for all).

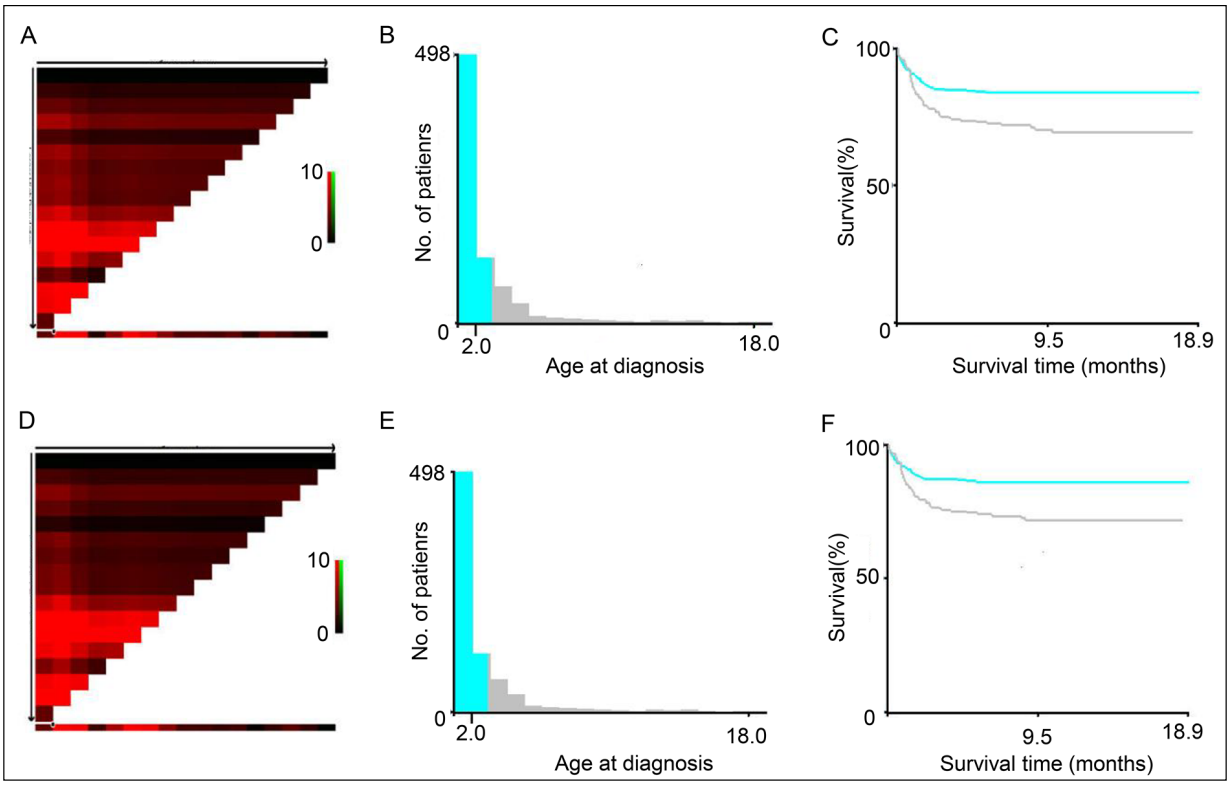

Figure 2. X-tile analysis of survival data from the SEER registry. The optimal cut-off level for tumor size was obtained based on the OS (**A-C**) and CSS (**D-F**) of patients. Each graph contains the X-tile plot, a histogram, and the data related to the optimal cut-off level. OS: overall survival; CSS: cancer-specific survival.

Clinical Features of Different-Age Patients with Hepatoblastoma

A total of 783 patients, 480 males (61.3%) and 303 females (38.7%), were enrolled in the study. The mean age at diagnosis was 1 year [interquartile range (IQR), 0-18 years]. The approximate ratio of patients aged < 2 years and ≥ 2 years was 5:3. As shown in Table I, the comparison of clinical features between < 2 years and ≥ 2 years groups did not show any significant difference, except for distant metastasis, which was higher in the ≥ 2 years group ($p = 0.005$).

Effects of Different Age Cutoff Levels on OS and CSS

Cox regression results showed that there was a significant difference when the dividing line was set at 2-3 years old and 5-8 years old ($p < 0.05$ for all, Table II). When the patients were divided into two groups with the age of 5 years as the boundary, the hazard ratio (HR) value was the largest (OS: HR = 1.768; CSS: HR = 1.910); however, only 6.1% (n = 48) of patients in our cohort were older than 5 years and the 95% CI was wide. Similar phenomena were observed at the age of 6 years or 7 years. When taking two years as the standard group, the number of patients aged ≥ 2 years [n = 285 (36.3%)] and < 2 years [n = 498 (63.6%)] was relatively close, and the HR value was high with a narrow 95% CI. Based on the above considerations, the final cut-off point was ≥ 2 years.

Prognostic Factors Affecting OS and CSS

Prognostic factors associated with OS and CSS were analyzed by univariate and multivariate Cox regressions. Univariate analysis showed that age ≥ 2 years, black, no surgery, no chemotherapy, presence of distant metastasis, tumor size ≥ 5 cm, and AFP status were the risk factors of prognosis ($p < 0.05$ for all) (Table III). In Cox multivariate analysis, age ≥ 2 years, black, no surgery, no chemotherapy, presence of distant metastasis, and tumor size ≥ 5 cm were associated with poor OS and CSS ($p < 0.05$ for all) (Table IV).

Subgroup Analysis

The OS and CSS of subgroup analysis are shown in Figures 4A and 4B. In most sub-

Table I. Characteristics of hepatoblastoma patients.

Variable	Overall	< 2 years	≥ 2 years	*p*-value
Total	783 (100.0)	498 (100.0)	285 (100.0)	
Sex				0.206
Female	303 (38.7)	201 (40.4)	102 (35.8)	
Male	480 (61.3)	297 (59.6)	183 (64.2)	
Ethnicity				0.665
Black	67 (8.6)	44 (8.8)	23 (8.1)	
Caucasian	593 (75.7)	372 (74.7)	221 (77.5)	
Others/Unknown	123 (15.7)	82 (16.5)	41 (14.4)	
Surgical therapy				0.146
None	130 (16.6)	82 (16.5)	48 (16.8)	
Liver resection	514 (65.6)	339 (68.1)	175 (61.4)	
Liver transplantation	129 (16.5)	71 (14.3)	58 (20.4)	
Unknown	10 (1.3)	6 (1.2)	4 (1.4)	
Chemotherapy				0.145
No	55 (7.0)	40 (8.0)	15 (5.3)	
Yes	728 (93.0)	458 (92.0)	270 (94.7)	
Distant metastasis				0.005
No	396 (50.6)	264 (53.0)	132 (46.3)	
Yes	122 (15.6)	62 (12.4)	60 (21.1)	
Unknown	265 (33.8)	172 (34.5)	93 (32.6)	
Tumor size (cm)				0.388
< 5	167 (21.3)	113 (22.7)	54 (18.9)	
≥ 5	404 (51.6)	256 (51.4)	148 (51.9)	
Unknown	212 (27.1)	129 (25.9)	83 (29.1)	
AFP				0.311
Elevated	505 (64.5)	317 (63.7)	188 (66.0)	
Normal	11 (1.4)	5 (1.0)	6 (2.1)	
Unknown	267 (34.1)	176 (35.3)	91 (31.9)	

AFP: Alpha-fetoprotein.

Table II. Univariate Cox proportional hazards regression model with different age cutoff values in patients with hepatoblastoma.

Age	N	OS Hazard ratio (95% CI)	*p*-value	CSS Hazard ratio (95% CI)	*p*-value
≥ 2	285	1.834 (1.329-2.532)	< 0.001	1.988 (1.410-2.801)	< 0.001
≥ 3	164	1.743 (1.233-2.463)	0.002	1.766 (1.223-2.549)	0.002
≥ 4	96	1.312 (0.847-2.031)	0.224	1.439 (0.918-2.258)	0.113
≥ 5	60	1.768 (1.092-2.862)	0.020	1.910 (1.161-3.141)	0.011
≥ 6	48	2.297 (1.419-3.719)	0.001	2.483 (1.510-4.085)	< 0.001
≥ 7	39	2.184 (1.280-3.726)	0.004	2.315 (1.330-4.031)	0.003
≥ 8	31	2.029 (1.098-3.751)	0.024	2.087 (1.095-3.978)	0.025
≥ 9	24	1.877 (0.920-3.827)	0.083	1.850 (0.864-3.962)	0.113
≥ 10	19	1.992 (0.932-4.255)	0.075	1.921 (0.847-4.359)	0.118
≥ 11	16	2.017 (0.891-4.565)	0.092	1.892 (0.774-4.626)	0.162
≥ 12	15	2.173 (0.960-4.918)	0.063	2.040 (0.834-4.986)	0.118

CI: Confidence interval; OS: Overall survival; CSS: Cancer-specific survival; N: Number.

Table III. Univariate Cox proportional hazard regression model of OS and CSS.

Age	OS Univariable analysis Hazard ratio (95% CI)	*p*-value	CSS Univariable analysis Hazard ratio (95% CI)	*p*-value
Age (year)				
< 2	Reference	—	Reference	—
≥ 2	1.834 (1.329-2.532)	< 0.001	1.988 (1.410-2.801)	< 0.001
Sex				
Female	Reference	—	—	—
Male	1.163 (0.831-1.628)	0.378	1.329 (0.923-1.914)	0.126
Ethnicity		0.001		< 0.001
Black	Reference	—	Reference	—
Caucasian	0.421 (0.270-0.656)	< 0.001	0.392 (0.246-0.625)	< 0.001
Others/Unknown	0.385 (0.211-0.702)	0.002	0.418 (0.226-0.773)	0.005
Surgical therapy		< 0.001		< 0.001
None	Reference	—	Reference	—
Liver resection	0.120 (0.084-0.171)	< 0.001	0.117 (0.080-0.170)	< 0.001
Liver transplantation	0.129 (0.074-0.226)	< 0.001	0.135 (0.076-0.241)	< 0.001
Unknown	0.584 (0.214-1.598)	0.295	0.661 (0.241-1.814)	0.422
Chemotherapy				
No	Reference	—	Reference	—
Yes	0.287 (0.182-0.452)	< 0.001	0.333 (0.200-0.555)	< 0.001
Distant metastasis		< 0.001		< 0.001
No	Reference	—	Reference	—
Yes	3.235 (2.126-4.925)	< 0.001	3.805 (2.433-5.951)	< 0.001
Unknown	2.334 (1.595-3.416)	< 0.001	2.617 (1.732-3.956)	< 0.001
Tumor size (cm)		< 0.001		< 0.001
< 5	Reference	—	Reference	—
≥ 5	2.151 (1.106-4.184)	0.024	2.349 (1.121-4.919)	0.024
Unknown	4.868 (2.509-9.447)	< 0.001	5.479 (2.625-11.436)	< 0.001
AFP		< 0.001		0.001
Elevated	Reference	—		
Normal	1.163 (0.285-4.736)	0.833	1.262 (0.309-5.149)	0.746
Unknown	2.096 (1.514-2.902)	< 0.001	1.944 (1.375-2.749)	< 0.001

CI: confidence interval; AFP: Alpha fetoprotein; OS: Overall survival; CSS: Cancer-specific survival.

groups, the prognosis of patients aged ≥ 2 years group was worse than that of the < 2 years group. Two-year-old patients with Caucasian ethnicity, elevated AFP level, tumor size ≥ 5 cm, or distant metastasis showed worse survival. For such patients, the curative effect was still not ideal, even with the use of a combination of surgery and chemotherapy.

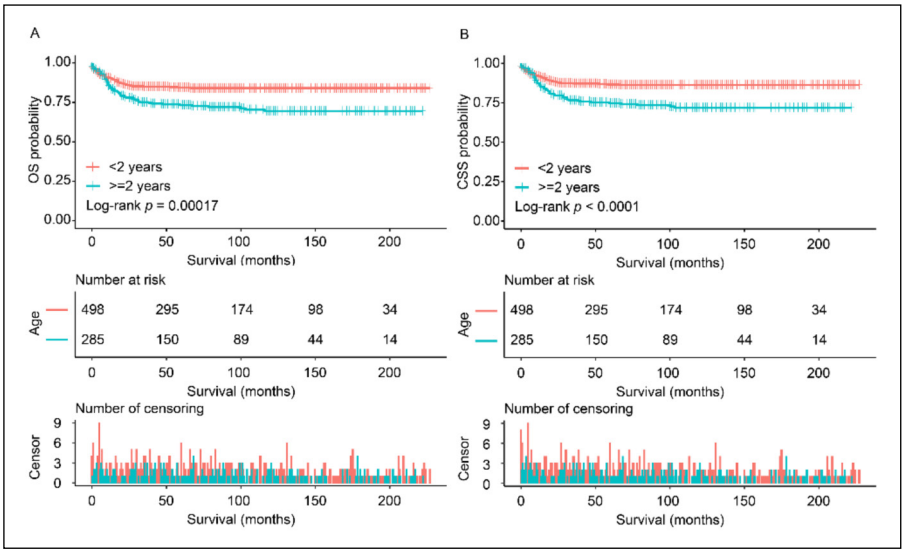

Figure 3. Kaplan-Meier curves for OS (**A**) and CSS (**B**) of patients of different age with hepatoblastoma. OS: overall survival; CSS: cancer-specific survival.

Discussion

In this study, we employed the X-tile procedure to determine the optimal cut-off age level at 2 years. Compared with patients aged ≥ 2 years at diagnosis, patients aged < 2 years at diagnosis had better OS and CSS ($p < 0.001$), and these patients had distinct clinical characteristics. Our findings may enable clinicians to identify children with hepatoblastoma with poor prognosis better. Age should be carefully

Table IV. Multivariate Cox proportional hazard regression model of OS and CSS.

Age	OS Univariable analysis Hazard ratio (95% CI)	*p*-value	CSS Univariable analysis Hazard ratio (95% CI)	*p*-value
Age (year)				
< 2	Reference	—	Reference	—
≥ 2	2.067 (1.469-2.908)	< 0.001	2.124 (1.479-3.051)	< 0.001
Ethnicity		0.002		< 0.001
Black	Reference	—	Reference	—
Caucasian	0.441 (0.278-0.699)	0.001	0.379 (0.233-0.617)	< 0.001
Others/Unknown	0.428 (0.232-0.789)	0.007	0.454 (0.243-0.849)	0.013
Surgical therapy		< 0.001		< 0.001
None	Reference	—	Reference	—
Liver resection	0.169 (0.114-0.251)	< 0.001	0.170 (0.112-0.259)	< 0.001
Liver transplantation	0.187 (0.104-0.337)	< 0.001	0.196 (0.107-0.360)	< 0.001
Unknown	0.807 (0.287-2.264)	0.683	1.036 (0.366-2.930)	0.947
Chemotherapy				
No	Reference	—	Reference	—
Yes	0.305 (0.186-0.500)	< 0.001	0.350 (0.201-0.609)	< 0.001
Distant metastasis		0.031		0.007
No	Reference	—	Reference	—
Yes	1.849 (1.170-2.921)	0.008	2.188 (1.344-3.563)	0.002
Unknown	1.384 (0.738-2.596)	0.311	1.854 (0.923-3.726)	0.083
Tumor size (cm)		0.024		0.012
< 5	Reference	—	Reference	—
≥ 5	2.464 (1.195-5.081)	0.015	2.843 (1.261-6.409)	0.012
Unknown	2.732 (1.280-5.829)	0.009	3.497 (1.515-8.076)	0.003
AFP		0.864		0.858
Elevated	Reference	—	Reference	—
Normal	0.934 (0.226-3.865)	0.925	1.060 (0.255-4.411)	0.936
Unknown	1.149 (0.682-1.935)	0.601	0.851 (0.475-1.526)	0.589

CI: Confidence interval; AFP: Alpha fetoprotein; OS: Overall survival; CSS: Cancer-specific survival.

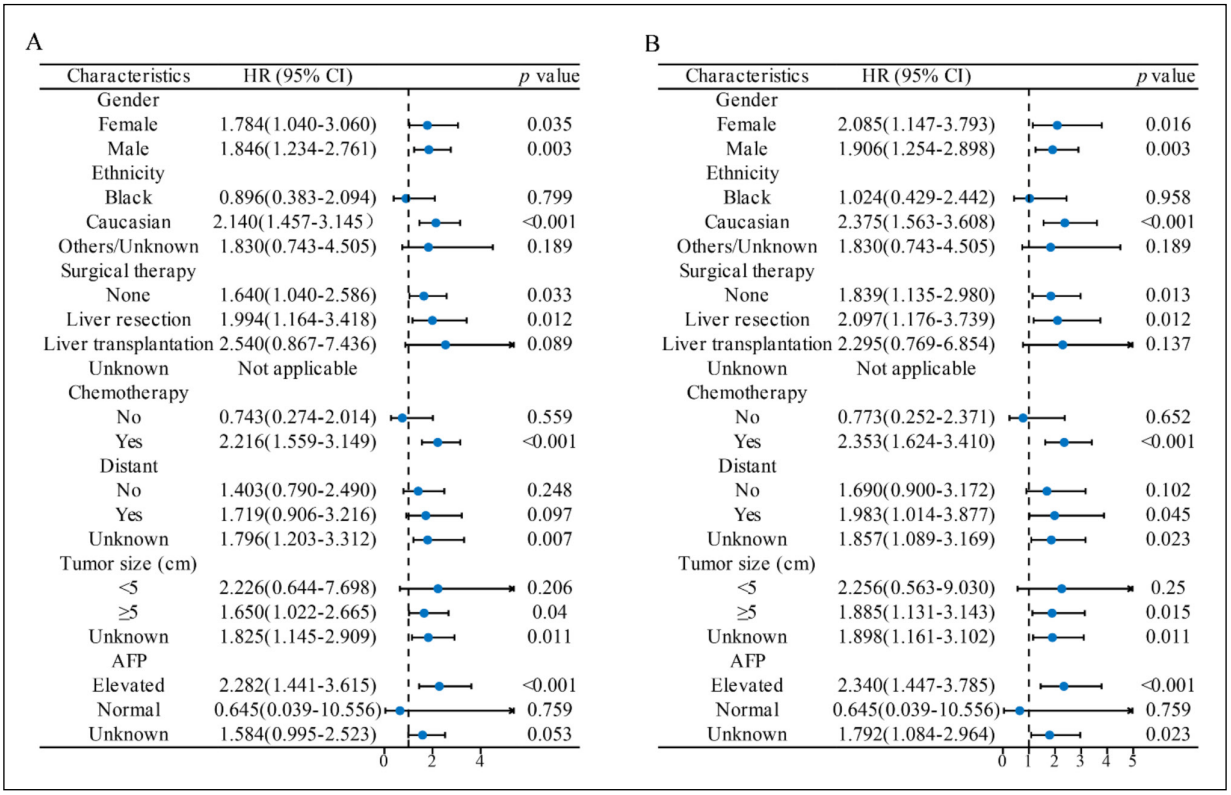

Figure 4. Subgroup analysis of OS (**A**) and CSS (**B**) according to age at diagnosis of hepatoblastoma (< 2 years and ≥ 2 years). OS: overall survival; CSS: cancer-specific survival; CI: confidence interval; HR: hazard ratio; AFP: Alpha-fetoprotein.

considered during individual treatment planning. For children with hepatoblastoma ≥ 2 years, in addition to striving for complete resection of the tumor, combined targeted or immunotherapy based on chemotherapy can be considered.

Due to the clinical heterogeneity of hepatoblastoma, risk stratification of patients can enable individualization of treatment plans. The age limit in CHIC risk stratification is 8 years[7]; however, the 0-5-year age group has the highest incidence of hepatoblastoma. We found only 24 cases over eight years old, accounting for 3% in this study. Therefore, the applicability of the age limit of 8 years needs to be further verified. Moreover, the tumor mutation load has been shown to increase with the age of children[13-15]. Age may be a marker of tumor biological and histopathological heterogeneity. This was also the purpose of this study to explore the role of the optimal age cut-off point on prognosis, which is helpful in identifying high-risk children better and seeking more active treatment.

In a study by Nautsch et al[16], age < 2 years was identified as a favorable prognostic factor. Zhi et al[17] found that children with hepatoblastoma aged < 1 year have better prognosis and survival rate. In the study by Wang et al[18], age < 5 years was identified as an independent predictor of the survival rate of patients with hepatoblastoma. Although previous studies in the literature have reported that 2 years may be the cut-off value that affects the prognosis of hepatoblastoma, there was no detailed comparison of the impact of different age cut-off points on prognosis and the relationship between different age cut-off points and clinical characteristics. At present, there is still no unified conclusion on the reasonable age cut-off level for prognosis evaluation of children with hepatoblastoma internationally. In this study, we used the X-tile diagram to evaluate all possible age thresholds and finally chose 2 years as the age cut-off. Compared to children aged < 2 years, children aged ≥ 2 years had worse OS and CSS. The risk of OS increased by 1.067 times, and the risk of CSS increased by 1.124 times. The HR, 95% CI, and related *p*-values of patients at different ages were compared. Considering comprehensively, 2 years is the best cut-off point, which is consistent with the prediction results of X-tile. More importantly, in subgroup analysis, patients aged ≥ 2 years had worse survival if they were Caucasian, had elevated AFP level, tumor size ≥ 5 cm, or had

distant metastasis. This may be related to different tumor biological behaviors and different responses to standard treatment. Therefore, in clinical decision-making, patients aged ≥ 2 years require more attention and better treatment options.

For children with hepatoblastoma aged ≥ 2 years, combined targeted or immunotherapy may be required in addition to surgery and chemotherapy. Recent gains in knowledge of the genomic and transcriptomic landscape of hepatoblastoma have deepened our understanding of its biological information, and our understanding of its biological behavior has been enriched. Genome sequencing revealed that up to 89% of patients were found to have mutations in the *CTNNB1* gene, leading to constitutive activation of the Wnt pathway[19]. Chemical inhibitor screening showed that trametinib, a mitogen-activated protein kinase kinase (MEK) inhibitor, buparlisib (NVP-BKM120), a PI3 kinase inhibitor, could inhibit the growth of hepatoblastoma[20]. In the model of hepatoblastoma induced by the activation of β-catenin and Yes-associated protein (YAP), inhibition of the mechanistic target of rapamycin (mTOR) pathway with rapamycin can reduce tumor growth[21]. In addition to targeted therapeutic drugs, immunotherapy will also become a new direction for future treatment of hepatoblastoma. Currently, chimeric antigen receptor T (CAR-T) cells to glypican-3 (GPC3)[22], a cell surface protein upregulated in hepatoblastoma, and CAR-T cells targeting AFP treatment have been in clinical trial stage[23]; Pembrolizumab, an antibody targeting PD-1, can successfully treat relapsed hepatoblastoma with high tumor mutation burden[24]. These new treatments may bring better benefits for the long-term survival of ≥ 2 years children with hepatoblastoma.

In addition, we observed that distant metastasis at diagnosis was a poor prognostic factor for OS and CSS. At present, there are different views on the effect of distant metastasis on the prognosis of hepatoblastoma. According to previous studies[25], distant metastasis represents a risk factor associated with a poor overall prognosis. However, several studies[12,26,27] have found that if the tumor is sensitive to chemotherapy, the presence or absence of distant metastasis has no significant effect on the prognosis of hepatoblastoma. This phenomenon may be attributable to the ability of neoadjuvant chemotherapy to clear metastases. Therefore, more research is required to determine whether distant metastasis can be used to predict the prognosis of hepatoblastoma.

Consistent with most research results, surgery and chemotherapy are the main treatment modalities for hepatoblastoma, which can significantly improve the prognosis of children. However, there was no significant difference in survival outcomes after liver tumor resection or liver transplantation. This may be attributable to the fact that both surgical techniques lead to complete tumor resection. Liver transplantation will never be performed in patients with distant metastases unless they have been surgically removed prior to transplantation[28-30]. In addition, in our cohort, Caucasian patients appeared to have better outcomes than black patients, which may be related to many factors such as genetic differences, access to medical care, and financial conditions.

Limitations

Some limitations of this study should be acknowledged. First, missing data in samples inevitably introduces an element of selection bias. Second, the age unit in the SEER database is the year, which is less accurate than the month for purposes of risk stratification. In addition, there is a lack of detailed information on chemotherapy regimen, tumor recurrence, specific value of AFP, histological sub-type (fetal *vs.* embryonal), and spontaneous rupture. 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. Lastly, this was a retrospective study, and further prospective, multicenter and large-scale studies are required to verify our findings.

Conclusions

The study determined that age is a key prognostic factor in patients with hepatoblastoma, and age ≥ 2 years may predict a poor prognosis. Therefore, we recommend targeted or immunotherapy may be added to the combination of surgery and chemotherapy for patients with hepatoblastoma aged ≥ 2 years to improve the overall prognosis of hepatoblastoma.

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgements

The authors sincerely thank the Surveillance, Epidemiology and End Results (SEER) program for providing the researchers with open resources.

Authors' Contributions

L.Y.B. and H.S.H. conceived and designed the study. L.Y.B. collected the data. H.S.H. analyzed the data. L.S. supervised the study. H.S.H. and L.Y. B. wrote the manuscript. L.S. prepared figures 1-4. All authors read and approved the final manuscript prior to submission.

Availability of Data and Materials

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.

Ethics Approval

Since the SEER database is public, the approval of the Ethics Committee is not required. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

The SEER database has hidden the patient's identity information, so the patient's informed consent is not applicable.

Funding

This study was supported by the Fujian Province Natural Science Foundation (grant number 2022J0112) and Subsidy Funds for the Medical Double-high project of Fujian province (grant number ETK2022002).

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