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The importance of age as prognostic factor for the outcome of patients with hepatoblastoma: Analysis from the Children's Hepatic tumors International Collaboration (CHIC) database

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Abbreviations: AFP, alpha-fetoprotein; CHIC, Children's Hepatic tumors International Collaboration; CI, confidence interval; COG, Children's Oncology Group; E, extrahepatic tumor; EFS, event-free survival; F, multifocal tumor; GPOH, German Society for Pediatric Oncology and Hematology; HB, hepatoblastoma; HcN-NOS, hepatocellular neoplasms not otherwise specified; HR, hazard ratio; JCCG, Japan Children's Cancer Group; JPLT, Japanese Study Group for Pediatric Liver Tumors; M, metastatic disease; P, Involvement of both right and left portal veins; PHITT, Pediatric Hepatic International Tumors Trial; PRETEXT, pretreatment extent of disease; R, tumor rupture; SEER, Surveillance, Epidemiology, and End Results; SIOPEL, International Childhood Liver Tumor Strategy Group; V, involvement of the vena cava or all three hepatic veins; VC, vena cava.

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Abstract

Purpose: Treatment outcomes for hepatoblastoma have improved markedly in the contemporary treatment era, principally due to therapy intensification, with overall survival increasing from 35% in the 1970s to 90% at present. Unfortunately, these advancements are accompanied by an increased incidence of toxicities. A detailed analysis of age as a prognostic factor may support individualized risk-based therapy stratification.

Methods: We evaluated 1605 patients with hepatoblastoma included in the CHIC database to assess the relationship between event-free survival (EFS) and age at diagnosis. Further analysis included the age distribution of additional risk factors and the interaction of age with other known prognostic factors.

Results: Risk for an event increases progressively with increasing age at diagnosis. This pattern could not be attributed to the differential distribution of other known risk factors across age. Newborns and infants are not at increased risk of treatment failure. The interaction between age and other adverse risk factors demonstrates an attenuation of prognostic relevance with increasing age in the following categories: metastatic disease, AFP < 100 ng/mL, and tumor rupture.

Conclusion: Risk for an event increased with advancing age at diagnosis. Increased age attenuates the prognostic influence of metastatic disease, low AFP, and tumor rupture. Age could be used to modify recommended chemotherapy intensity.

KEYWORDS

age, CHIC, hepatoblastoma, pediatric liver tumor, prognostic factor

1 | INTRODUCTION

For children with hepatoblastoma, overall survival rates have increased, from 35% in the 1970s to 90% at present.[1-3] Contemporary studies have focused upon therapy reduction for lower risk patients and treatment intensification for higher risk patients. Four major research groups—the International Childhood Liver Tumor Strategy Group (SIOPEL), the Children's Oncology Group (COG), the German Society for Pediatric Oncology and Hematology (GPOH), and the Japanese Study Group for Pediatric Liver Tumors (JPLT, now a subsidiary of the Japan Children's Cancer Group, JCCG)—have separately undertaken trials attempting to improve the outcomes by developing risk stratified treatment protocols.[4-12]

The Children's Hepatic tumor International Collaboration (CHIC) was established in 2011 as a cooperative effort between these multicenter trial groups to further refine the risk stratification. Analysis of 1605 patients with HB included in the CHIC common database led to the establishment of a new global risk stratification.[13,14] Except for age, the factors used in the new risk stratification represent aspects of tumor burden or anatomy. Although age at diagnosis has been identified as a prognostic factor in other pediatric embryonal neoplasms, its biological impact in HB has been less clear, likely due to the relatively small sample sizes of patients in individual trials of this rare tumor. This report is an in-depth investigation of the role played by age as a prognostic variable in the CHIC HB data set. We further describe the influence of increasing age upon the risk conferred by other known adverse prognostic variables.[13]

2 | METHODS

All 1605 patients included in the CHIC collaborative database were enrolled and treated on one of eight prospective multicenter cooperative group trials: SIOPEL-2, SIOPEL-3, COG-INT0098, COG-P9645, GPOH-HB89, GPOH-HB99, JPLT1, and JPLT2. As previously reported, analysis of each trial by outcome demonstrated no statistically significant difference in EFS.[14]

All 1605 patients were diagnosed as HB by the treating institution; 496 of these patients had central pathology review as part of their initial treatment trial. As part of the CHIC effort, an additional retrospective histological review was done for all patients with available liver tumor slides from all cooperative groups (n = 599 patients; 1456 slides). This review was performed by a group of international expert pediatric pathologists using the more contemporary consensus HB histologic subtype classification.[15,16] Seven pathologists blinded to clinical findings individually classified the material and, in case of discordant results, came to an agreement in a subsequent consensus group review.

All patients received adjuvant and/or neoadjuvant cisplatin-based chemotherapy and, when possible, complete tumor resection including orthotopic liver transplantation for unresectable tumors.[1,5-7,17-24] Cisplatin-based chemotherapy regimens were variously augmented by carboplatin, doxorubicin, pirarubicin, 5-fluorouracil, vincristine, and/or etoposide per individual trial and treatment arm. Initial univariate analysis demonstrated the most powerful prognostic indicators to be PRETEXT group (I/II, III, IV), low AFP (< 100, and 100-1000 ng/mL),
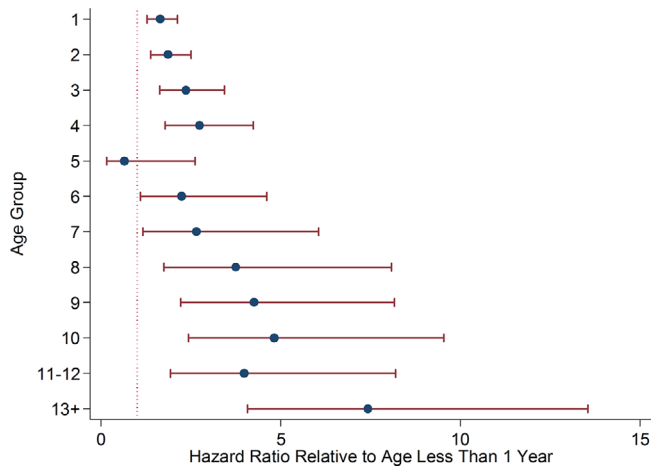
FIGURE 1 HR of EFS for age relative to age less than one year

PRETEXT annotation factors V (all three hepatic veins or IVC involvement), P (both right and left portal vein involvement), E (contiguous extrahepatic tumor), F (multifocality), R (rupture prior to diagnosis), M (metastatic disease), and age as published previously (Supporting Information Figure S1).[13] A detailed discussion of contemporary definitions of PRETEXT groups and annotations factors was published by Towbin et al.[25] We analyzed EFS for age by year and within the below one-year age group. The age distribution for each above mentioned risk factor and the interaction between the risk factors and age was assessed.

2.1 | Methods for statistical analysis

EFS was calculated from the date of trial enrollment until disease relapse or progression, date of a second malignant neoplasm, date of death or date of last follow-up, whichever occurred first. Patients who experienced disease progression or relapse, diagnosis of a second malignancy, or death were considered to have experienced an event. In all other cases, patients were considered censored at last patient contact. All analyses relating patient characteristics to risk of EFS event were conducted using the proportional hazards regression model.[26]

2.1.1 | Risk of EFS event according to age in whole years at enrollment

In order to assess the prognostic significance of young age at diagnosis with respect to risk for EFS event, patients were classified into one of 13 categories of whole years of age at diagnosis (Figure 1 and Table 1). A relative hazard regression model of EFS on these 13 categories was fitted to the data.

2.1.2 | Risk of EFS event for patients less than one year of age

In order to assess the prognostic significance of age at diagnosis among patients less than one year of age with respect to risk for EFS event, patients were classified into one of four age categories: (1) less than or equal to 28 days, (2) 29-92 days, (3) 93-183 days, and 184-365 days

TABLE 1 Age distribution and HR of EFS for age relative to age less than one year

Age (years)	Number of patients	HR	CI	P value
<1	551 (34.3%)	1		
1	524 (32.6%)	1.6	1.28-2.12	< 0.0001
2	243 (15.1%)	1.8	1.37-2.49	< 0.0001
3	104 (6.5%)	2.4	1.64-3.44	< 0.0001
4	61 (3.8%)	2.7	1.77-4.20	< 0.0001
5	16 (1.0%)	0.6	0.16-2.60	0.5
6	24 (1.5%)	2.2	1.08-4.57	0.03
7	13 (0.8%)	2.6	1.15-5.98	0.022
8	12 (0.8%)	3.7	1.73-8.01	0.001
9	14 (0.9%)	4.2	2.20-8.08	< 0.0001
10	14 (0.9%)	4.8	2.40-9.42	< 0.0001
11-12	14 (0.9%)	3.9	1.92-8.12	< 0.0001
13+	15 (0.9%)	7.3	4.02-13.35	< 0.0001
Total	1605 (100 %)			

TABLE 2 Age distribution and HR among patients < 1 year of age (reference group = age < 28 days)

Age (days)	Number of patients	HR	CI	P value
<29	26 (4.7%)	1		
29-92	53 (9.6%)	0.97	0.29-3.2	0.9
93-183	136 (24.7%)	1.2	0.43-3.6	0.7
184-365	336 (61.0%)	1.2	0.43-3.2	0.8
Total	551 (100%)			

(Table 2). The relative hazard regression model of EFS on indicator variables for the age groups was fitted.

2.1.3 | Modifying effect of age at diagnosis on other risk factors

To assess whether age at diagnosis modified the prognostic significance of the other factors used in the construction of risk categories from Meyers et al. in 2017,[14] the relative hazards regression model of EFS on age (in years), the chosen risk factor individually, and an interaction term between age and the risk factor were fitted to the data.[13,14] The hypothesis of no interaction was tested using the partial likelihood ratio test. A P value of 0.10 or less was considered significant for this exploratory analysis. If the test was considered significant, the hazard ratios were estimated from the model above. If the interaction test was considered not significant, the hazard ratios were estimated from the model that did not include the interaction term.

The assessment of the interaction between age and each risk factor was done individually to explore the modification of the factor's effect as the patient's age increased; multivariable modeling of all risk factors, age, and the associated interactions was not done for this

analysis. Because of this, the analysis of interaction for each risk factor only excluded cases where that particular risk factor was not reported.

3 | RESULTS

The detailed tumor and patient characteristics of the 1605 patients in the CHIC database have been published previously and are shown in Supporting Information Table S1.[13] The age distribution showed the expected pattern with most patients diagnosed under the age of three years ($n = 1318$, 82%). The median age at diagnosis was 16 months with a range of 0-185 months. Of the 1605 patients, 106 (6.6%) were six years or older at diagnosis, and 69 (4.2%) were eight years or older at diagnosis.

The univariable results demonstrate a rising hazard ratio (HR) by incrementally increasing whole-year age groups. The HRs for each whole-year-of-age cohort are shown in a forest plot in Figure 1. Younger age at diagnosis appears to confer a superior prognosis; conversely, the risk for adverse prognostic events rises continuously with increasing age. These data are presented in a more granular tabular format in Table 1. The distribution of age is weighted toward the younger age group (median age 1.4 years; range, 0-15.5 years); therefore, the HR confidence interval is larger in the higher age groups where there are fewer patients (Table 1). For children under one year at diagnosis ($n = 551$, 34%), there was no risk gradient between the four subgroups analyzed (≤ 28 days; 29-92 days; 93-183 days; and 184-365 days) with hazard ratios relative to those less than or equal to 28 days of age as shown in Table 2. Although children younger than 28 days have the same prognosis as all other children under one year at diagnosis, the entire less-than-one-year cohort has a better prognosis than all of the older age cohorts studied.

Table 3 shows the median age and age range for the other known HB risk factors as PRETEXT groups, PRETEXT annotation factors (VPEFRM), and AFP categories. Our analysis shows a balanced distribution of age across the other prognostic variables.

The comparison of the groups of patients with and without central confirmation of histology as part of the trial in which they were enrolled showed that the EFS was 75% in each of the groups, with a HR of 0.99 (95% CI, 0.81-1.21; $P = 0.94$) (Supporting Information Figure S2).

In the expert pathologist consensus review of histological material from the 599 patients with available slides, there was a consensus diagnosis of hepatoblastoma in 570 patients (95.2%); for 29 patients (4.8%), the consensus was a nonhepatoblastoma entity (10 rhabdoid tumors, 7 malignant hepatocellular neoplasms not otherwise specified [HcN-NOS], 12 others). It should be noted that the HcN-NOS subtype did not exist at the time of most of these trials, and in the current international PHITT trial is treated as a subgroup of HB. No glass slides were available for histological review for the remaining 1006 patients. In those retrospectively reviewed, five of seven HcN-NOS were found in patients with age above eight years, and two of seven in patients below three years of age. In these 570 patients, age above eight years conferred a significantly elevated EFS HR of 4.56 (95% CI, 2.39-8.71) when

compared with age < 1 year, thus confirming results seen in the complete population of 1605 patients (Table 1). Most importantly for the age analysis, the age distribution of the 570 patients with HB on retrospective CHIC histology review was virtually identical to the distribution of those in the remainder of the database (Supporting Information Table S2). Other clinical factors, such as PRETEXT group, or PRETEXT annotation factors were also distributed identically.

The proportional hazards regression model for EFS demonstrates interaction between age at diagnosis and low AFP level, metastatic disease M, PRETEXT annotation factors P, F, R, and their combination (identification of at least one of the annotation factors VPEFR). The interaction was significant between age and low AFP, M, the combination of PRETEXT annotation factors, and R. Specifically, the influence of these factors on outcome is attenuated with increasing patient age as shown in Table 4. For example, the presence of metastatic disease increases the overall risk of an event significantly (HR = 4.87); the overall influence of age consists in a risk increase of HR = 1.12 for each additional year; and with each additional year, the influence of metastatic disease is attenuated by a factor of HR = 0.87, resulting in a HR by metastatic disease of $4.87 \times 0.87 = 4.24$ between one and two years, $4.24 \times 0.87 = 3.69$ between two and three years, etc. (Supporting Information Figure S3). This means that in the youngest patients, metastatic disease confers an increased risk; as age increases, EFS deteriorates and metastatic disease confers less added risk. In the highest age cohorts, outcomes were so poor that the added effect of metastases was negligible (Supporting Information Figure S4 for patients above age 8). The analysis for the combination of annotation factors showed that the risk of having an EFS event in the presence of one or more annotation factors also diminished with age. Supporting Information Figure 5S demonstrates that for age above eight years, the presence of one or more annotation factors no longer correlates with EFS. There was no evidence of interaction between age at diagnosis and PRETEXT group nor PRETEXT annotation factors V and E. Accordingly, the effect of these risk factors was not modified significantly by increasing age at diagnosis, and interactions are not included where P values were not significant in the interaction test as shown in Table 4.

4 | DISCUSSION

Our analysis demonstrates that the risk of an event for patients with hepatoblastoma increases continuously with increasing age at diagnosis and that this is true even for younger patients. Although the negative impact of increased age on outcome has been previously postulated, to our knowledge, this is the first in-depth analysis that clearly demonstrates increasing age to continuously raise the risk of an event that adversely impacts EFS. In very early work, Brown et al. analyzed three age cohorts in SIOPEL 1 (< 6 months, 6-48 months, > 48 months) and showed no significant difference in univariate analysis.[27] Maibach et al, in an analysis of SIOPEL 2 and 3, reported a significantly increased HR with age greater than 60 months; no significant age effect was demonstrated in younger children.[12] From the SEER database, Allan et al. reported a worse prognosis for children over five years of age.[28]

TABLE 3 Age across risk factors (median age for each risk factor)

	Category	Age (years)			
		Number	Median	Minimum	Maximum
M	Absent	1320	1.3	0.01	15.5
	Present	277	1.8	0.22	15.3
	Not available	8	1.9	0.56	10.1
AFP Category	< 100	65	1.1	0.07	10.6
	100-999	110	1.9	0.07	14.7
	1000-1 M	971	1.4	0.01	15.3
	> 1 M	140	1.2	0.15	14.1
	Not available	319	1.5	0.03	15.5
PRETEXT Group	I	97	1.6	0.04	13.6
	II	529	1.4	0.02	14.8
	III	621	1.3	0.01	15.5
	IV	297	1.6	0.01	14.4
	Not available	61	1.7	0.04	13.0
V	Absent	1386	1.4	0.01	15.3
	Present	147	1.5	0.01	15.5
	Not available	72	1.2	0.02	11.4
P	Absent	1387	1.4	0.01	15.3
	Present	146	1.9	0.06	15.5
	Not available	72	1.2	0.02	11.4
E	Absent	1529	1.4	0.01	15.5
	Present	71	1.7	0.04	14.4
	Not available	5	1.9	1.11	13.5
F	Absent	1295	1.3	0.01	15.5
	Present	280	1.9	0.01	14.7
	Not available	30	1.2	0.22	9.8
R	Absent	1440	1.4	0.01	15.5
	Present	69	2.0	0.01	14.8
	Not available	96	1.3	0.01	11.4
Combined PRETXT annotation factor	Absent	993	1.3	0.01	15.3
	Present	533	1.7	0.01	15.5
	Not available	79	1.2	0.02	11.4

Abbreviations: AFP, alphafeto-protein; cava or liver veins; E, extrahepatic tumor; F, multifocal tumor; M, metastatic disease; P, portal venous involvement; PRETEXT group, pretreatment extent of disease; R, preoperative rupture, combined PRETXT annotation factor: one or more of VPEFR; V, venous involvement of the V.

Von Schweinitz et al. in the GPOH and Hishiki et al. in JPLT showed a trend toward improved outcomes for patients under one year.[7] One prior study by Amman reported increased risk for infants under 28 days of life.[29] Our analysis does not confirm Amman's finding and is more consistent with the findings of Dall'Igna and Trobaugh-Lotrario, which showed no increased risk for this patient group.[30,31] Although some of these prior studies suggested a trend toward decreased outcome with advancing age, their relatively small cohorts limited the analytic power in regard to age as a prognostic variable. Even with the large size of this collaborative data set, the authors recognize that sample size remains a limitation in certain age groups. We theorize that this may explain the nonlinear effect on HR observed at the 5- and 11-12-year age time points. With the inclusion of additional legacy group data sets as well as the data from the recently opened international Pediatric Hepatic International Tumors Trial (PHITT), we anticipate the opportunity to validate this finding further.

The increased risk associated with higher age was not due to an increasing incidence of other known risk factors with age. In fact, the age distribution across other risk factors was balanced. Indeed each of the risk models that included age, as well as the univariate analysis of risk factors described by Czauderna,[13] demonstrate that their effect remains significant after inclusion of continuous age. Our interaction analysis demonstrates that the adverse effect of certain risk factors decreased with rising age. This attenuation was most significant for the

TABLE 4 Interaction between rising age and other risk factors

Patient characteristic	Category	HR	HR per year of age at diagnosis	P value for the test of no interaction between age and patient characteristic	Change in HR associated with the characteristic per year of age at diagnosis
M	Absent (RC)	1.0	1.12	<0.001	
	Present	4.87			0.87
AFP at diagnosis	1000-1 000 000 (RC)	1.0	1.17	<0.001	
	> 1 000 000	1.46			1.03
	100-999	1.86			0.91
	<100	6.71			0.79
PRETEXT group	I (RC)	1.0	1.13	0.46	
	II	1.51			
	III	2.58			
	IV	4.75			
V	Absent (RC)	1.0	1.15	0.97	
	Present	2.24			
P	Absent (RC)	1.0	1.15	0.056	
	Present	2.56			0.93
E	Absent (RC)	1.0	1.14	0.16	
	Present	1.75			
F	Absent (RC)	1.0	1.15	0.062	
	Present	2.48			0.94
R	Absent (RC)	1.0	1.16	0.0016	
	Present	2.47			0.88
Combined PRETEXT annotation factor					
	Absent (RC)	1.0	1.19	0.0003	
	Present	3.01			0.90

Abbreviations: AFP, alphafeto-protein; Cava or liver veins; E, extrahepatic tumor; F, multifocal tumor; M, metastatic disease; P, portal venous involvement; PRETEXT group, pretreatment extent of disease; R, preoperative rupture, combined PRETEXT annotation factor: one or more of VPEFR; RC, reference category; V, venous involvement of the V.

PRETEXT annotation factors M and R, and for low serum AFP at diagnosis. The influence of these other factors on prognosis significantly diminished with age and was negligible in patients over eight years. The cases being analyzed here derive from clinical trials spanning over two decades, when central histological review was not being consistently performed across all trial groups. Hence, in some patients, histologic confirmation of HB relied on the treating institution. The review of 599 patients out of the CHIC data set through a panel of expert pathologists showed that in 96% the diagnosis of hepatoblastoma was confirmed; therefore, the few cases of nonhepatoblastoma histology could not explain the observed correlation of EFS with age. In the group above eight years of age, five patients had evidence of the recently recognized hepatocellular neoplasm not otherwise specified (HcN-NOS) histologic subtype, which is being investigated in more detail in the current PHITT trial.[15,16] They are currently regarded as HB with variable associated HCC features and are treated on the HB treatment strata in PHITT with a collaborative international effort to better characterize their biology.

Tumor mutational burden is known to be low in children compared with adults and increases with age in many tumor types.[32,33] Work by Buendia and others has shown that the genetic instability and preponderance of mutations in liver tumors increases with age and in the HcN-NOS subgroup.[2,32] Recent work by Sumazin, Kappler, and others has shown a higher incidence of potentially relevant mutations in aggressive HBs and older children.[34,35] Age might be a marker for increasingly heterogeneous tumor biology and histopathology. Prospective molecular and genomic profiling will be essential for understanding these observations.

Until the interaction between age and biology is better characterized and accessible, age might be used as a surrogate for underlying biological features. Our analysis makes a strong case that age may be regarded as a readily accessible and effective substitute for some biological factors and may facilitate adaption of treatment via risk stratification and therapeutic approach. Age as a factor in HB risk stratification is currently being prospectively interrogated in the international collaborative PHITT trial.[14]

5 | SUMMARY

- The risk of an event in patients with HB progressively increased with higher age at diagnosis.

- This pattern could not be attributed to variations in the distribution of other known risk factors across age.

- After accounting for other known risk factors in the published risk stratification, the significant deleterious effect of increasing age remained and the influence of some risk factors (metastases, AFP below 100 ng/mL, tumor rupture, and presence of at least one annotation factor) was attenuated in older patients.

- Newborns and infants were not at an increased risk for treatment failure.

CONFLICTS OF INTEREST

We declare no conflict of interest.

AUTHOR CONTRIBUTION

All the authors have contributed to the manuscript in significant ways, have reviewed, and agreed upon the manuscript content.

DECLARATION OF INTERESTS

We declare no competing interests.

DATA ACCESSIBILITY STATEMENT

Data subject to third-party restrictions: The collection and the use of the data from the original trials in the CHIC database is regulated with a "memorandum of understanding" signed by the involved groups (COG JCCG SIOPEL and GPOH).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.