



Original Article

Retrospective Analysis of Childhood Hepatoblastoma in a Single Centre in China



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Abstract

Aims: To investigate the protocol efficacy and prognostic factors for paediatric hepatoblastoma in a multidisciplinary model in our centre.

Materials and methods: Consecutive hepatoblastoma patients (<18 years old) treated at Shanghai Children's Medical Center in China from August 2011 to October 2017 were analysed retrospectively for clinical features, chemotherapy courses, surgical treatment and outcomes.

Results: One hundred and four cases of paediatric hepatoblastoma (64 males, 40 females; median age at diagnosis 1.64 years) had a median follow-up of 30.68 months (range 8.3–73.3 months). First complete remission was achieved in 95 cases, 85 of which achieved continuous complete remission. Another three cases were lost to follow-up after a median of 24.73 months in complete remission. Seven cases relapsed later, with two achieving a second complete remission and four deaths. Nine cases did not achieve complete remission and five of them died. In general, the 5-year overall survival rate and 5-year event-free survival (EFS) rate were $86.3 \pm 5.0\%$ and $81.8 \pm 4.3\%$, respectively. Thirty-two cases were classified as standard risk and 72 as high risk with 5-year EFS of $96.8 \pm 3.2\%$ and $75.7 \pm 5.7\%$ ($P = 0.029$) and 5-year overall survival of 100% and $80.5 \pm 7.0\%$, respectively. The mean platelet count ($P = 0.0036$), lactate dehydrogenase ($P = 0.0443$) and ferritin level ($P = 0.0006$) at diagnosis were much higher in the high-risk group than in the standard-risk group. Univariate analysis showed that patients <5 years of age ($P = 0.018$), with higher α -fetoprotein (AFP) level (> 100 ng/ml, $P = 0.008$), without metastases at diagnosis ($P = 0.001$) and postoperative AFP recovery after no more than three chemocycles ($P = 0.014$) had better overall survival. In addition, the above factors, except metastases at diagnosis and risk group, were associated with prognosis in the multivariate analysis.

Conclusions: The result of this protocol had similar overall survival and EFS rates compared with those in developed countries. Normal postoperative AFP levels after three chemocycles has prognostic value.

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Key words: α -fetoprotein; child; hepatoblastoma; multidisciplinary

Introduction

Hepatoblastoma is a rare paediatric solid tumour representing 1% of all paediatric malignancies, but it is the

most common primary malignant liver neoplasm in children, with an increasing annual incidence of 1.2–1.5/million population/year [1]. Some multicentre cooperative study groups under multidisciplinary teams, which include surgeons, oncologists, radiologists and pathologists, have made significant contributions to improving the treatment and outcomes for patients with hepatoblastoma, with the survival rate reaching 80% [2]. In recent years, the Children's Hepatic Tumors International Collaboration (CHIC), a novel international group, identified that advanced PRETEXT, low α -fetoprotein

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(AFP; <100 ng/ml) and metastatic disease are associated with worse outcome [3]. However, few reports have been published on large samples regarding the survival of paediatric hepatoblastoma patients in China. The purpose of the present study was to investigate the protocol efficacy and prognostic factors for paediatric hepatoblastoma in a multidisciplinary model in our centre.

Materials and Methods

Inclusion and Exclusion Criteria

All patients newly diagnosed between August 2011 and October 2017 with pathological examination and clinical findings, including age, clinical history, physical examination, serum AFP level, lactate dehydrogenase (LDH), ferritin and computed tomography (CT) scan or magnetic resonance imaging (MRI), were considered for the study. The inclusion criteria were <18 years old and hepatoblastoma diagnosis confirmed by pathology, biopsy or surgical resection. Patients who underwent treatment for less than three cycles of chemotherapy, dropping out of the treatment without progressive disease, were excluded from this study.

Medical Data Collection

The medical records of all enrolled cases were reviewed retrospectively and their information, including physical examinations, CT/MRI images, serum AFP, LDH, ferritin, chemotherapy regimens, surgery and outcome, collected. Consent for treatment was obtained from each patient's parents or legal guardians before treatment. The Hematology/Oncology Ethics Committee of Shanghai Children's Medical Center approved this study.

Pathology, Staging and Risk Group

Based on World Health Organization pathological diagnostic criteria, patients were divided into pure fetal, combined fetal and embryonal epithelial, and mixed epithelial and mesenchymal subtypes. The pathology was confirmed by two senior pathologists.

Hepatic hepatoblastoma staging was according to the PRETEXT system [4] and Children's Oncology Group (Evans) staging system [5]. Standard-risk hepatoblastoma is entirely limited to the liver (PRETEXT 1–2 tumours) and resectable with AFP levels >100 ng/ml. High-risk hepatoblastoma is metastatic or PRETEXT 3–4 tumours, extrahepatic/vascular extension or low AFP (≤ 100 ng/ml).

Treatment Schema and Follow-up

Surgical tumour resection was recommended for standard-risk patients, followed by four to six courses of C5V chemotherapy depending on AFP level. C5V consists of cisplatin (90 mg/m²/day) administered over 6 h on day 1, 5-fluorouracil (600 mg/m²/day) on day 2 and vincristine (1.5

mg/m²/day) on days 2, 9 and 16. There was a 21-day interval between two courses.

High-risk patients were usually biopsied first and then received two to four courses of chemotherapy, which included C5V and doxorubicin (D; 30 mg/m²/day on days 1 and 2) after pathology-based diagnosis. The AFP measurement and type-B ultrasound and/or CT/MRI were repeated every two courses of chemotherapy to evaluate the possibility of surgery by multidisciplinary team members. Four total courses of C5VD were followed by two to four courses of ICE, which consisted of ifosfamide (1.5 mg/m²/day) on days 1–5, carboplatin (450 mg/m²/day) on day 1 and etoposide (100 mg/m²/day) on days 1–3. Patients would drop off the protocol when the disease progressed or did not respond to [AQ2]C5AD and received an individual treatment plan. Table 1 shows the treatment procedures and chemotherapeutic regimens. Liver transplantation was not included in our treatment routine during this period.

After completing therapy, the AFP level was checked monthly, and abdominal ultrasound and chest X-ray were repeated every 2 months in the first year of follow-up, then every 3 months in the second and third years, and then every 6 months in the fourth and fifth years.

Statistical Analysis

Complete remission was defined as no evidence of tumour on CT and/or MRI and serum AFP level returned to normal for at least 4 weeks. Progressive disease referred to an increase in the size of any new lesion of at least 25%. Relapse referred to a new lesion in any location. Increasing AFP was closely watched until the decision with or without progress/relapse was made. The decision was confirmed by pathology if progression and relapse were not clear clinically.

Overall survival was defined as the time from diagnosis to death. Event-free survival (EFS) was defined as the time from diagnosis to the date of event, including progress, relapse or death. Loss to follow-up was defined as losing contact after complete therapy for more than 6 months. Patients lost to follow-up were censored at the time of last

Table 1
Treatment procedures and chemotherapeutic regimens

Low-risk group	High-risk group
Surgical resection	Biopsy or partial resection
C5V	C5VD
C5V	C5VD
C5V	Surgical resection, if feasible
C5V	C5VD
C5V	C5VD
Follow-up	Surgical resection, if feasible
	ICE
	ICE
	ICE
	ICE
	Follow-up

C5V, cisplatin (90 mg/m²)/5-fluorouracil/vincristine; C5VD, cisplatin (90 mg/m²)/5-fluorouracil/vincristine/doxorubicin; ICE, ifosfamide/carboplatin/etoposide.

contact. The Kaplan–Meier method was used to generate survival curves. Proportions were compared between groups using the chi-squared test. The clinical characteristic analysis was estimated by the Log-rank test. Cox proportional hazard models were used for multivariate analyses. All statistical calculations were carried out in R statistical software version 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria; <https://www.r-project.org/>). A two-tailed P -value < 0.05 was considered significant.

Results

Patient Characteristics

In total, 108 cases of paediatric hepatoblastoma were admitted to Shanghai Children's Medical Center from August 2011 to October 2017. Four patients were excluded, including two who dropped out of the regimen in complete remission after two courses of chemotherapy and lost contact. Thus, 104 patients were enrolled in this study, with a male to female ratio of 1.6:1 (64 males and 40 females). The median age at diagnosis was 1.64 years (range 0.05–14.6 years). According to the World Health Organization pathological criteria, seven patients were classified as the pure fetal subtype, 29 cases as the combined fetal and embryonal epithelial subtype and 32 cases as the mixed epithelial and mesenchymal subtype.

Total tumour resection with possible expended margin was carried out in 102 cases, 44 cases before chemotherapy

and 58 cases after two to eight courses of chemotherapy (median three courses) and two cases did not undergo resection because of disease progression. Between two and 10 courses (median five courses) were given for the standard-risk group, but one pure fetal hepatoblastoma case did not receive chemotherapy after tumour resection. The high-risk group received five to 11 courses (median eight courses), with one case receiving only one course and dropping out because of disease progression. The demographic and clinical characteristics of 104 hepatoblastoma patients are given in Table 2.

At diagnosis, the mean platelet counts of the high-risk and standard-risk groups were $646.7 \times 10^9/l$ and $470.5 \times 10^9/l$ ($P = 0.0036$). The mean serum LDH levels of the high-risk and standard-risk groups were 1160 U/l and 844.2 U/l ($P = 0.0443$). The mean serum ferritin levels of the high-risk and standard-risk groups were 186.1 ng/ml and 74.52 ng/ml, respectively ($P = 0.0006$; Figure 1).

Outcomes and Survival Analysis

Until the end of October 2018, the median follow-up was 30.68 months (range 8.3–73.3 months). Ninety-five cases achieved first complete remission, 85 of whom achieved continuous complete remission and another three cases were lost after a median 24.73 months in complete remission. Seven cases relapsed; two of them achieved second complete remission, four of them died and one was lost to follow-up with disease. Nine cases did not achieve complete

Table 2
Clinical characteristics and univariate survival outcomes of hepatoblastoma patients

Characteristic	Case number, n (%)	5-year overall survival (\pm standard error)	P -value	5-year event-free survival (\pm standard error)	P -value
All	104	86.3 \pm 5.0%		81.8 \pm 4.3%	
Gender			0.078		0.023
Male	64 (61.5)	79.8 \pm 7.3%		73.8 \pm 6.3%	
Female	40 (38.5)	97.1 \pm 2.9%		94.6 \pm 3.7%	
Age			0.018		0.028
<1 year old	37 (35.6)	97.3 \pm 2.7%		94.5 \pm 3.8%	
1–5 years old	58 (55.8)	83.6 \pm 7.9%		80.6 \pm 5.6%	
>5 years old	9 (9.7)	66.7 \pm 15.7%		50.0 \pm 18.6%	
Pathological subtypes			0.639		0.488
Pure fetal pattern	7 (6.7)	100%		68.6 \pm 18.6%	
Fetal and embryonal	29 (27.9)	85.9 \pm 8.1%		89.4 \pm 5.8%	
Epithelial and mesenchymal	32 (30.8)	91.6 \pm 5.8%		85.0 \pm 7.0%	
No specific classification	36 (34.6)	82.8 \pm 8.0%		77.2 \pm 7.8%	
Serum α -fetoprotein level at diagnosis			0.008		0.001
≤ 100 ng/ml	3 (2.9)	66.7 \pm 27.2%		33.3 \pm 27.2%	
>100 ng/ml	101 (97.1)	87.1 \pm 5.0%		83.3 \pm 4.2%	
Risk group			0.044		0.029
Standard risk	32 (30.8)	100%		96.8 \pm 3.2%	
High risk	72 (69.2)	80.5 \pm 7.0%		75.7 \pm 5.7%	
Metastasis at the onset			0.001		0.007
Yes	14 (13.5)	63.5 \pm 15.3%		63.5 \pm 13.1%	
No	90 (86.5)	89.3 \pm 5.3%		84.7 \pm 4.4%	
Post-surgical α -fetoprotein recovery			0.014		0.011
≤ 3 chemocycles	64 (64.6)	90.2 \pm 7.5%		91.3 \pm 4.4%	
>3 chemocycles	35 (35.4)	78.0 \pm 8.0%		73.4 \pm 8.2%	

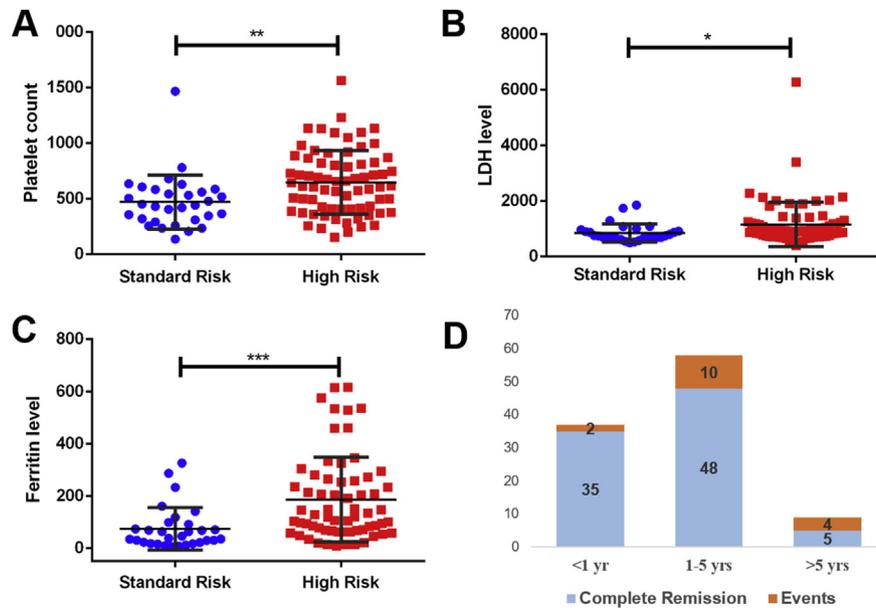


Fig 1. The platelet count (A), lactate dehydrogenase (LDH; B) and ferritin levels (C) at diagnosis of hepatoblastoma patients in different risk groups. (D) Patients in complete remission and events in different age groups.

remission; five of them died, three lost contact and one had stable disease (Figure 2). There were no chemotherapy-related deaths.

The 5-year overall survival and 5-year EFS rates were $86.3 \pm 5.0\%$ and $81.8 \pm 4.3\%$, respectively, for all groups (Figure 3). Fifty-eight cases (55.8%) were 1–5 years old, 37 were <1 year old and nine cases were >5 years old. The 5-year EFS rates were $80.6 \pm 5.6\%$, $94.5 \pm 3.8\%$ and $50.0 \pm 18.6\%$, respectively ($P = 0.028$; Figure 4B). Thirty-two cases were classified as standard risk and 72 as high risk and the 5-year EFS rates were $96.8 \pm 3.2\%$ and $75.7 \pm 5.7\%$ ($P = 0.029$), respectively (Figure 4A).

Three cases had lower serum AFP levels (<100 ng/ml) at diagnosis and their 5-year EFS rate was $33.3 \pm 27.2\%$, which was much lower than that of patients with higher AFP levels at onset (Figure 4E). In particular, the AFP level was quickly back to normal after no more than three chemocycles after complete resection in 64 patients, but in 35 patients it was not; their 5-year EFS rates were $91.3 \pm 4.4\%$ and $73.4 \pm 8.2\%$ ($P = 0.01$), respectively (Figure 4F).

In total, 14 patients had metastasis at first presentation, 13 (92.9%) had lung or pleural metastases another one had celiac metastases. No patient underwent pulmonary metastectomy during this period. The 5-year EFS rates with and without metastases were $63.5 \pm 13.1\%$ and $84.7 \pm 4.4\%$ ($P = 0.001$), respectively (Figure 4C). The 5-year EFS rates with and without metastases in the high-risk group were $63.5 \pm 13.1\%$ and $78.7 \pm 6.2\%$ ($P = 0.053$), respectively (Figure 4D). Table 2 shows the clinical characteristics and univariable survival outcomes.

In addition, seven cases experienced relapse, five of which had liver relapse, one had liver and lung relapse and one had liver and bladder relapse; they were all in the high-risk group and two had pure fetal subtype hepatoblastoma. Two of seven survived in second complete

remission. The 5-year overall survival rate was $21.4 \pm 18.8\%$ for the relapsed group.

In summary, the univariate analysis showed that patients younger than 5 years of age with higher AFP levels, without metastases at diagnosis and post-resection AFP recovery after no more than three chemocycles had better prognosis (Figure 4). All of the above factors were drawn into a multivariate Cox proportional hazards regression model, which indicated that older age, lower AFP level and post-resection AFP recovery after more than three chemocycles were risk factors contributing to poorer prognosis (Table 3).

Discussion

Limited reports on large samples have been published on the survival of paediatric hepatoblastoma patients in China. Some co-operative multicentre study groups have made significant contributions to improving the treatment and outcomes for patients with hepatoblastoma and the survival rate of children with hepatoblastoma is reaching 80% [2,6]. Chemotherapy is an important part of the treatment for hepatoblastoma patients. For patients with standard risk, the SIOPEL group (Société Internationale d'Oncologie Pédiatrique Epithelial Liver Tumor Study Group; SIOPEL-2) showed in a randomised trial that patients with hepatoblastoma treated with six courses of cis-platinum (CDDP) alone had equivalent outcomes as those treated with CDDP and doxorubicin, with a cumulative dose of cisplatin of 480 mg/m² [7]. In the COG study AHEP 0731, very low-risk patients (stage I, Pure Fetal Histology) did not receive any chemotherapy; low-risk patients received only two courses of C5V postoperatively to reduce toxicity, with the 3-year EFS > 90%. Intermediate-risk patients received neoadjuvant chemotherapy with two to four courses C5V plus

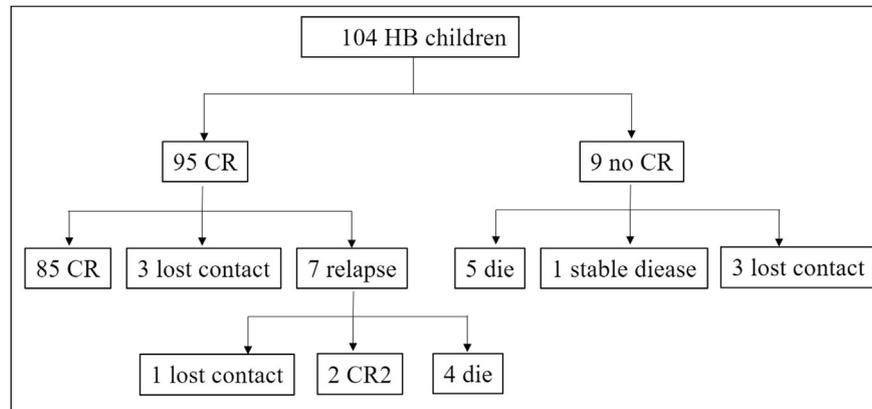


Fig 2. Flow diagram of paediatric hepatoblastoma patients.

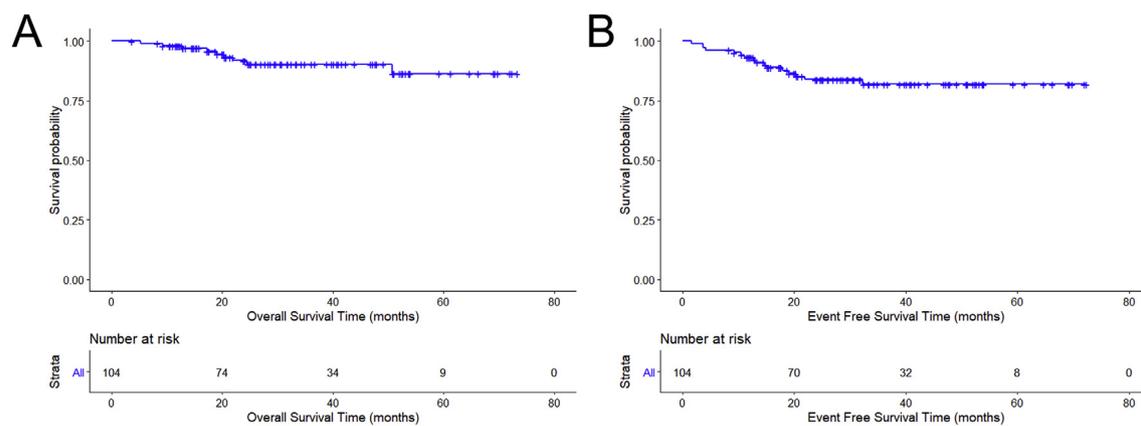


Fig 3. Overall survival (A) and event-free survival (B) curves for 104 patients with hepatoblastoma.

doxorubicin (30 mg/m²) and two additional courses after resection or orthotopic liver transplantation, with 3-year EFS of 87%. In high-risk patients, an upfront window therapy with two courses of vincristine (1.5 g/m²) and irinotecan (50 mg/m²) is applied, and in the case of a response is followed by six courses of C5VD with one course of vincristine and irinotecan between each two-course block, whereas in non-responders only six courses of C5VD are given and tumour resection or orthotopic liver transplantation is carried out after four courses of C5VD with a 3-year EFS of 49% [8]. SIOPEL-4 established a new treatment regimen consisting of dose-dense cisplatin-based (570 mg/m²) and doxorubicin (180 mg/m²) chemotherapy in children with high-risk (PRETEXT-IV and AFP <100 ng/ml) hepatoblastoma; after surgery, chemotherapy consisting of doxorubicin (120 mg/m²) and carboplatin was given, with the final analysis showing 3-year EFS and overall survival of 76% and 83%, respectively, in the high-risk group [9]. Focus is needed on the side-effects of therapy, such as ototoxicity [10], derived from cisplatin because the severity of ototoxicity may be inversely related to age at the time of exposure, with very young patients exhibiting higher grades of hearing loss [11]. Recently, a randomised, controlled trial by SIOPEL-6 provided compelling evidence that sodium thiosulfate administered 6 h after cisplatin chemotherapy

results in a lower incidence of cisplatin-induced hearing loss among children with standard-risk hepatoblastoma, without jeopardising overall survival or EFS [12]. Our regimen used a slightly different treatment strategy and incorporated ifosfamide, vincristine and etoposide to decrease the cumulative dose of cisplatin and doxorubicin (Tables 1 and 4), but the increase in ifosfamide and etoposide still needs to be explored. Because of its retrospective nature, it was too difficult to obtain an accurate record of toxicity. However, because of imprecise information on PRETEXT staging of hepatoblastoma patients at our centre, we only defined the PRETEXT I–II and III–IV groups. Our risk stratification included hepatic and extrahepatic/vascular extension or metastasis and AFP level onset, but more precise risk stratification may be needed. In this study, we did not detect any very low-risk patients from the standard-risk group who might receive unnecessary chemotherapy. This should be revised in the next protocol. The 5-year EFS rate for the standard-risk and high-risk groups were 96.9% and 75.7% ($P = 0.027$), respectively, even though longer follow-ups are needed; whether standard-risk patients are overtreated needs to be explored.

Serum AFP is a sensitive marker of active and viable hepatoblastoma. Most children with hepatoblastoma have markedly elevated AFP levels at presentation, although

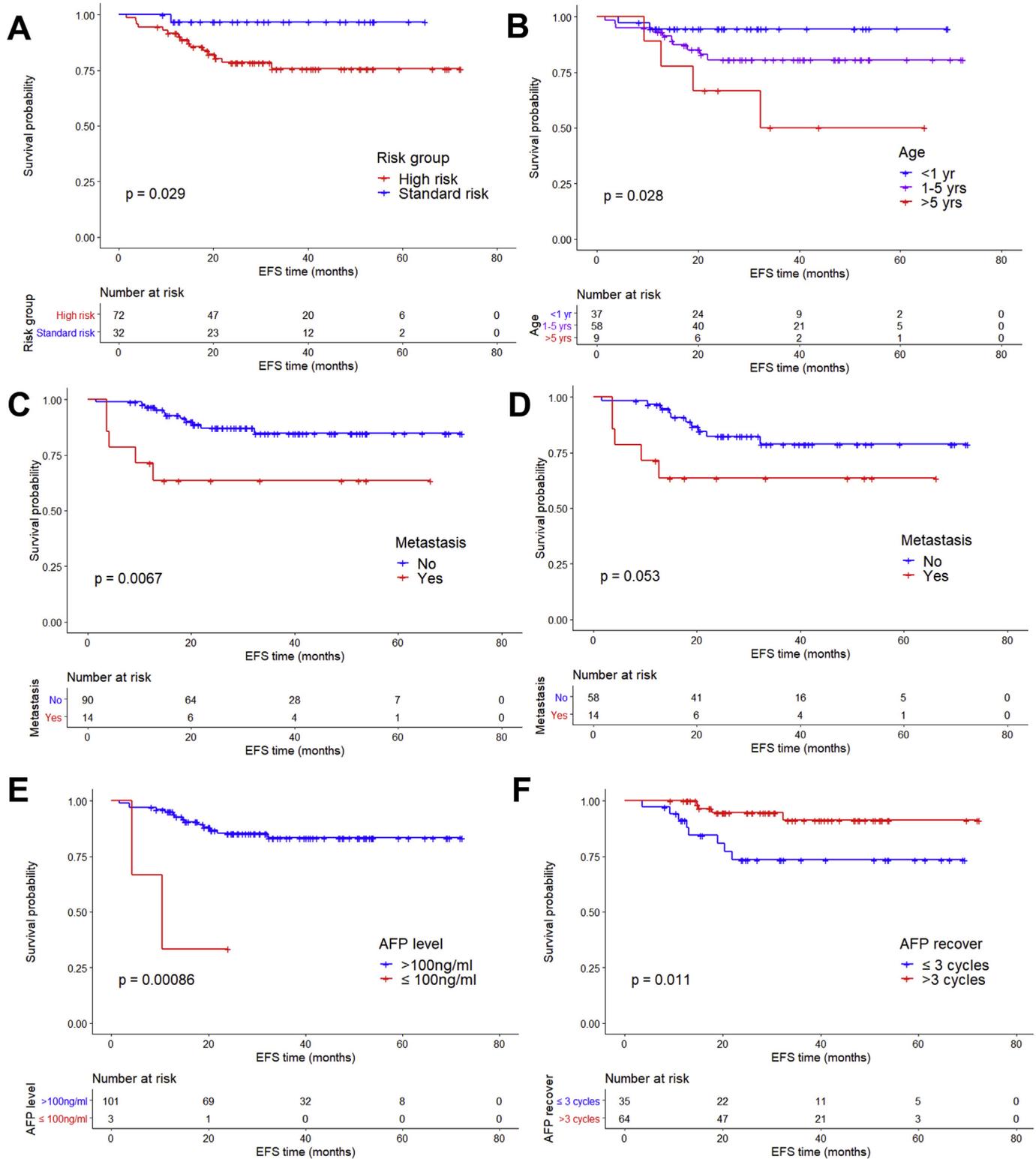


Fig 4. Event-free survival (EFS) curves for different groups: (A) risk groups; (B) age groups; (C) with or without metastasis at diagnosis; (D) with or without metastasis at diagnosis in the high-risk group; (E) different serum α -fetoprotein (AFP) levels at diagnosis; (F) AFP recovery after three post-resection chemocycles.

5–10% have unexpectedly low or even normal AFP levels [15]. On the one hand, AFP levels at diagnosis or other times during treatment are related to tumour burden or the biological nature of the tumour and can be evaluated to predict

outcomes; on the other hand, a decrease in AFP may be indicative of tumour responsiveness to therapy [16] and relapse surveillance [17]. AFP could also be a prognostic indicator in children with hepatoblastoma. AFP levels <100

Table 3
Multivariate analysis with Cox regression

Factors		Hazard ratio	95% confidence interval	P-value
Age	<1 year old	1		
	>5 years old	6.75	1.05–43.04	0.043
	1–5 years old	5.56	1.14–27.00	0.033
Risk group	Standard risk	1		
	High risk	5.11	0.64–41.02	0.125
α -fetoprotein level	>100 ng/ml	1		
	\leq 100 ng/ml	14.82	1.77–123.96	0.013
Metastasis at the onset	No	1		
	Yes	1.65	0.52–5.23	0.395
Post-resection α -fetoprotein recovery	\leq 3 cycles	1		
	>3 cycles	6.83	2.03–22.99	0.002

Table 4
Cumulative dose of chemotherapeutic regimens by risk group according to treatment regimen

	Our regimen		COG (AHEP0731) [13]			SIOPEL-2 [14]	SIOPEL-4
	Standard risk	High risk	Low risk	Intermediate risk	High risk	Standard risk	High risk
Percentage	30.8%	69.2%	21.5%	45.6%	29.4%	57%	/
3-year event-free survival	96.8%	75.7%	>90%	87%	49%	89%	76%
Cisplatin (mg/m ²)	450	360	200	600	600	480	570
5-fluorouracil (mg/m ²)	3000	2400	1200	3600	3600		
Vincristine (mg/m ²)	22.5	18	9	9	39		
Doxorubicin (mg/m ²)		240		180	360		400
Carboplatin (mg/m ²)		1800					1188~1272*
Ifosfamide (g/m ²)		30					
Etoposide (mg/m ²)		1200					
Irinotecan (mg/m ²)					1000		

ng/ml [15] and >1 000 000 ng/ml have been associated with poor outcome. One study found that an initially favourable AFP response, defined as >1 log decline in serum AFP after the first cycle of chemotherapy, better predicts postoperative outcome after chemotherapy compared with the magnitude of AFP decline during preoperative chemotherapy, which is significantly associated with survival outcomes [16]. In our study, three cases had lower serum AFP levels (<100 ng/ml) at diagnosis, including one patient with normal AFP but higher CA199. The 5-year EFS rate was $33.3 \pm 27.2\%$, which was much lower than patients with a higher AFP level at onset. Notably, hepatoblastoma patients with low or normal AFP should have other tumour-associated indices tested to indicate the treatment response. Particularly, the AFP level of 66 patients recovered quickly to normal after three chemocycles after complete resection and but in 35 patients did not. Their 5-year EFS rates were 89.9% and 73.4% ($P = 0.023$), respectively (Figure 4F). We think that monitoring the decrease in AFP levels between each post-surgical chemocycle is more simple and effective than the logarithmic method.

Although the highest incidence of hepatoblastoma occurs in children younger than 5 years old, hepatoblastoma cases have been published in older children [18]. The influence of age at diagnosis on prognosis has not been well studied. However, the 5-year EFS of patients older than 5 years was only 51.4% at our centre, which is much poorer than in

younger patients. These results are similar to those from the CHIC [3], SIOPEL [19] and Wuhan Protocol [20], but the reason is not entirely clear. It is possible that this is associated with different tumour biologies, as well as the different responses to standard therapy. The mean platelet count, LDH and ferritin levels at diagnosis were much higher for the high-risk group than for the standard-risk group. One study indicated that thrombocytosis is significantly associated with better survival outcomes [16], but we did not find a significant association with survival outcomes.

Approximately one-fifth of patients have metastases at diagnosis, which most frequently occur in the lung [21]. It is recommended that lung disease is treated with chemotherapy first and residual cases after chemotherapy would be candidates for pulmonary metastasectomy [22,23]. Patients with lung metastases in this study did not undergo resection, because most lung lesions (9/13) could be responsive to chemotherapy and disappear or not be resectable (4/13).

The treatment of hepatoblastoma has been making great progress in the past few years. The outcomes at Shanghai Children's Medical Center showed similar overall survival and EFS rates with some different drug accumulations and fewer side-effects compared with those in developed countries. Previous co-operative group studies have identified variables such as PRETEXT, presence of metastatic disease and very low serum AFP (<100 ng/ml) as poor prognostic factors [24,25]. We also found that whether AFP

level recovers to normal early after complete tumour resection is associated with prognosis. However, the treatment of hepatoblastoma needs to be explored further and optimised for our study, especially for very high-risk patients with metastasis, progressed disease and relapse, and very low-risk patients.

Conflict of interest

The authors declare no conflicts of interest.

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