

# Prognosis Factors of Young Patients Undergoing Curative Resection for Hepatitis B Virus-Related Hepatocellular Carcinoma: A Multicenter Study

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**Background:** The prognosis of young and older patients with hepatocellular carcinoma (HCC) is controversial. We aim to compare the clinicopathological features and prognosis of young (age  $\leq 40$  years) versus older patients (aged  $>40$  years) with hepatitis B virus (HBV)-related HCC after curative resection.

**Methods:** A total of 4504 patients with HBV-related HCC who underwent curative resection were included in this study and divided into young group (n=699) and older group (n=3805). Subgroup analyses were conducted to compare. Independent risk factors were identified by Cox regression analysis.

**Results:** Young patients had better ALBI grade, lower rates of liver cirrhosis, higher rates of elevated serum AFP levels, larger tumor size, higher rates of microvascular invasion and macrovascular invasion, higher rates of Edmondson grade III–IV, lower rates of tumor capsular, more advanced AJCC TNM stages and more advanced BCLC stages than older patients (All  $p < 0.05$ ). Meanwhile, young patients had a worse overall survival (OS) rate ( $p = 0.0091$ ) and a worse recurrence-free survival (RFS) rate ( $p = 0.045$ ) than older patients. Multivariate analysis revealed that AFP, resection margin, tumor size, tumor capsular, and macrovascular invasion were associated with OS. The independent risk factors associated with RFS were ALB, tumor size, microvascular invasion, and macrovascular invasion.

**Conclusion:** Young patients had better liver function, more aggressive tumor characteristics, and worse prognosis than older patients. A tumor size of  $\geq 5$  cm and macrovascular invasion were associated with poor OS and RFS in young patients. If tumors could be detected at the early stage by more frequent surveillance, long-term survival can be expected in the young patients.

**Keywords:** hepatocellular carcinoma, young, older, hepatectomy, prognosis

## Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.<sup>1</sup> Patients with hepatitis B virus (HBV) infection are one of the major risk factors for the development of HCC, particularly those with chronic liver disease and cirrhosis.<sup>2</sup> It is associated with 70–90% of patients with HCC in the highly endemic Asia-Pacific region, particularly in China.<sup>3</sup> There are various kinds of treatments for HBV-related HCC, such as liver resection, liver transplantation, transarterial chemoembolization, radiofrequency ablation, etc.<sup>4</sup> Liver resection is a mainstay of treatment for HBV-related HCC patients.<sup>5</sup>

With the development of modern medical technology and screening programs, HBV-related HCC is detected to be getting younger.<sup>2,6,7</sup> However, a limited number

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of studies have reported the prognosis of young HBV-related HCC patients and the conclusions are variable. Some authors have found that young patients have better long-term outcomes,<sup>8–10</sup> whereas others have reported that young patients have advanced tumor factors, thereby indicating a poor prognosis.<sup>11,12</sup> Several studies have demonstrated that the long-term outcomes after HCC resection are similar between young and older groups.<sup>13–15</sup> Most of these studies enrolled less than 100 patients investigated the prognosis of young HCC patients. Hence, it remains controversial whether the prognosis of HCC in young patients is different from that in older patients.

To address this issue, we conducted a large multicenter study to compare the clinicopathological features and the prognosis of young patients (age  $\leq 40$  years) versus older patients (aged  $>40$  years) with HBV-related HCC after curative resection.

## Methods

### Patients and Study Design

This study was approved by the institutional ethics committee of Mengchao Hepatobiliary Hospital of Fujian Medical University (NO.:2019\_069\_01). Informed consent was obtained from each patient for their data to be used for research purposes. HBV-related HCC patients who underwent liver resection between January 2008 and December 2015 were extracted from primary liver cancer big data by an IT engineer, and then were verified by two researchers (Dr. Jianxing Zeng and Dr. Kongying Lin) in this study.

The inclusion criteria included: (1) 0 to 1 score of performance status,<sup>16</sup> (2) positive hepatitis B surface antigen (HBsAg) and negative hepatitis C antibody, (3) no evidence of extrahepatic metastasis, (4) no history of pre-operative anticancer treatment, (5) no history of other malignancies, and (6) curative resection with tumor-negative resection margins (R0 resection).<sup>17</sup> Patients who received palliative tumor resection, received recurrent tumor resection, had incomplete clinical data, died of severe surgical complications, and lost to follow-up within 60 days after discharge were excluded.

All patients received routine serological examination including white blood cell, platelet count, total bilirubin, albumin, alpha-fetoprotein (AFP), hepatitis B virus and hepatitis C virus immunology, and HBV deoxyribonucleic acid (HBV-DNA) load. Imaging studies included chest radiography, abdominal ultrasonography, and contrast-

enhanced computed tomography (CT)/magnetic resonance imaging (MRI) of the abdomen.

Histopathological study of the resected specimens was performed independently by three pathologists who came to a consensus by discussion if there was any controversy. Histologic grading of HCC was based on the Edmondson-Steiner classification.<sup>18</sup> The criterion of the American Association for the Study of Liver Diseases was used for pre-operative clinical diagnosis of HCC.<sup>19</sup> All patients were staged using the American Joint Committee on Cancer (AJCC) staging system and Barcelona Clinic Liver Cancer (BCLC) staging system.<sup>20,21</sup>

### Follow-Up

Patients were followed up once every 3 months for the first 2 years after discharge from hospitals and every 3–6 months in subsequent years. The follow-up program included liver function, AFP level, and abdominal ultrasound. Contrast-enhanced CT or MRI was performed when tumor recurrence was clinically suspected. The diagnostic criteria for tumor recurrence were the same as for the initial diagnosis. The follow-up was censored on 31st October 2018.

The end-points of the study were overall survival (OS) and recurrence-free survival (RFS). OS was defined as the interval between the date of surgery and the date of patient death or the date of last follow-up. RFS was the interval between the date of surgery and the date when tumor recurrence was diagnosed or the date of patient death or the date of last follow-up.

### Statistical Analysis

The age cut-off of 40 years was based on previous studies.<sup>2,12,13,22–25</sup> We defined young patients as aged  $\leq 40$  years and older patients as aged  $>40$  years. The clinicopathological features and the prognosis in young patients were compared with those in older patients.

Categorical variables were grouped on the basis of a normal reference value or clinical judgment. The albumin-bilirubin (ALBI) grade was calculated by the formula,  $0.66 \times \log_{10}(\text{bilirubin, } \mu\text{mol/L}) - 0.085 \times (\text{albumin, g/l})$ .<sup>26</sup> According to previously described cut-off resulting in 2 grades: ALBI grade 1 ( $\leq -2.60$ ), grade 2 ( $> -2.60$  to  $-1.39$ ) and grade 3 ( $> -1.39$ ). ALBI grade 2 and ALBI grade 3 were group together due to the low sample size in the latter. The results were compared using the chi-square test or Fisher exact test. Continuous variables were compared using the Student's *t*-test or Mann-Whitney *U*-test for variables with an abnormal distribution.

Kaplan-Meier method was used to estimate OS and RFS rates, and the difference between the two groups was analyzed by the Log rank test. Univariate and multivariate Cox proportional hazard regression was performed to detect the independent factors of OS and RFS. Subgroup analysis was conducted based on the univariate Cox model and the forest plot of subgroup analysis was depicted with each estimated HRs and 95% CI. All statistical tests were 2-tailed and a p-value of less than 0.05 was considered statistically significant. All statistical analysis was performed with R version 3.5.2 (<http://www.r-project.org/>).

## Results

### Comparison of Clinicopathological Features Between Young and Older HBV-Related HCC Patients

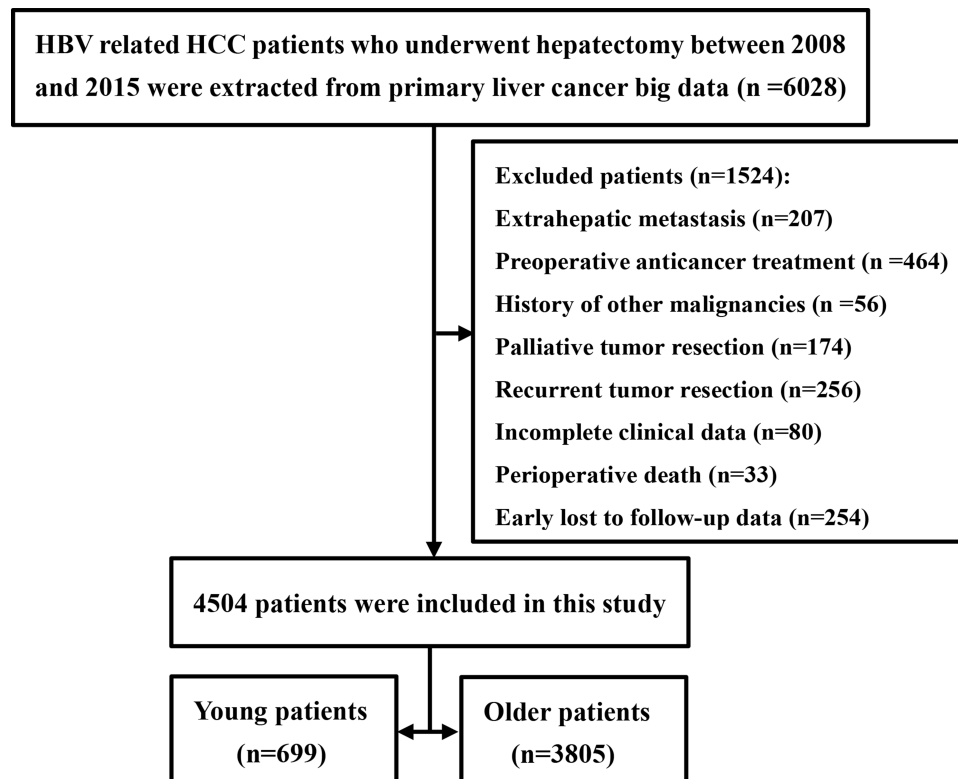
During the study period, there were a total of 6028 patients with HBV-related HCC who received curative resection. 1524 patients were excluded because of extrahepatic metastasis (n=207), preoperative anticancer treatment (n=464), history of other malignancies (n=56), palliative tumor resection (n=174), recurrent tumor resection (n=256), incomplete

clinical data (n=80), perioperative death (n=33), and early lost to follow-up after discharge (n=254). Finally, the study consisted of 4504 patients, which comprises 699 young HCC patients and 3805 older HCC patients. The flow chart of this patient selection is shown in Figure 1.

As summarized in Table 1, young patients had higher serum albumin levels (p<0.001), higher platelet counts (p<0.001), better ALBI grade (p<0.001), and lower rates of liver cirrhosis (p=0.001) than older patients. Considering tumor factors, young patients had higher rates of elevated serum AFP levels (p<0.001), larger tumor size (p<0.001), higher rates of microvascular invasion (p<0.001) and macrovascular invasion (p<0.001), higher rates of Edmondson grade III–IV (p=0.01), lower rates of tumor capsular (p=0.025), more advanced AJCC TNM stages (p<0.001) and more advanced BCLC stages (p<0.001) than older patients.

### Comparison of Prognosis Between Young and Older HBV-Related HCC Patients

The prognosis after liver resection for HBV-related HCC between young and older patients is shown in Figure 2. The overall survival rates at 1, 3, 5 years were 81.2%,



**Figure 1** The flow chart of selected patients.

**Abbreviations:** HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

**Table 1** Comparison of Clinicopathological Features Between Young and Older HBV-Related HCC Patients

Variables	Young HCC	Older HCC	p-value
	(n=699)	(n=3805)	
<b>Age, years, Median [IQR]</b>	36.0 [32.0, 39.0]	53.0 [47.0, 60.0]	<0.001
<b>Gender</b>			
Female	84 (12.0%)	519 (13.6%)	0.272
Male	615 (88.0%)	3286 (86.4%)	
<b>AFP</b>			
<10ng/mL	141 (20.2%)	1153 (30.3%)	<0.001
≥10ng/mL	558 (79.8%)	2652 (69.7%)	
<b>HBV-DNA</b>			
<1000IU/L	79 (11.3%)	512 (13.5%)	0.136
≥1000IU/L	620 (88.7%)	3293 (86.5%)	
<b>WBC, 10<sup>9</sup>/L, Mean (SD)</b>	5.60 (1.69)	5.33 (1.79)	<0.001
<b>PLT, 10<sup>9</sup>/L, Mean (SD)</b>	182 (70.4)	157 (66.8)	<0.001
<b>ALB, g/L, Mean (SD)</b>	43.2 (3.76)	41.8 (3.61)	<0.001
<b>TBIL, μmol/L, Median [IQR]</b>	13.4 [10.5, 17.4]	13.5 [10.7, 17.0]	0.349
<b>ALBI grade</b>			
Grade 1	597 (85.4%)	2851 (74.9%)	<0.001
Grade 2	102 (14.6%)	954 (25.1%)	
<b>Resection margin width</b>			
<1cm	544 (77.8%)	3082 (81.0%)	0.0582
≥1cm	155 (22.2%)	723 (19.0%)	
<b>Blood transfusion</b>			
No	625 (89.4%)	3423 (90.0%)	0.709
Yes	74 (10.6%)	382 (10.0%)	
<b>Operative bleeding loss</b>			
<800mL	643 (92.0%)	3500 (92.0%)	1.000
≥800mL	56 (8.0%)	305 (8.0%)	
<b>Tumor size, cm Median [IQR]</b>	5.80 [3.70, 9.20]	5.00 [3.30, 8.00]	<0.001
<b>Tumor number</b>			
Solitary	565 (80.8%)	3067 (80.6%)	0.931
Multiple	134 (19.2%)	738 (19.4%)	
<b>Microvascular invasion</b>			
No	374 (53.5%)	2423 (63.7%)	<0.001
Yes	325 (46.5%)	1382 (36.3%)	
<b>Macrovascular invasion</b>			
No	568 (81.3%)	3329 (87.5%)	<0.001
Yes	131 (18.7%)	476 (12.5%)	
<b>Edmondson grade</b>			
I-II	65 (9.3%)	490 (12.9%)	0.010
III-IV	634 (90.7%)	3315 (87.1%)	
<b>Tumor capsular</b>			
No	163 (23.3%)	743 (19.5%)	0.025
Yes	536 (76.7%)	3062 (80.5%)	

(Continued)

**Table 1** (Continued).

Variables	Young HCC	Older HCC	p-value
	(n=699)	(n=3805)	
<b>Satellite nodules</b>			
No	395 (56.5%)	2258 (59.3%)	0.175
Yes	304 (43.5%)	1547 (40.7%)	
<b>Liver cirrhosis</b>			
No	344 (49.2%)	1616 (42.5%)	0.001
Yes	355 (50.8%)	2189 (57.5%)	
<b>BCLC stage</b>			
0/A	487 (69.7%)	2827 (74.3%)	<0.001
B	81 (11.6%)	502 (13.2%)	
C	131 (18.7%)	476 (12.5%)	
<b>AJCC TNM stage (8th)</b>			
I	323 (46.2%)	2057 (54.1%)	<0.001
II	188 (26.9%)	971 (25.5%)	
IIIA	57 (8.2%)	301 (7.9%)	
IIIB	131 (18.7%)	476 (12.5%)	

**Notes:** Categorical variables are presented as no. (%). Mean (standard deviation) presented for normally distributed continuous variables, while median (interquartile range) was given to those with non-normally distributed continuous variables.

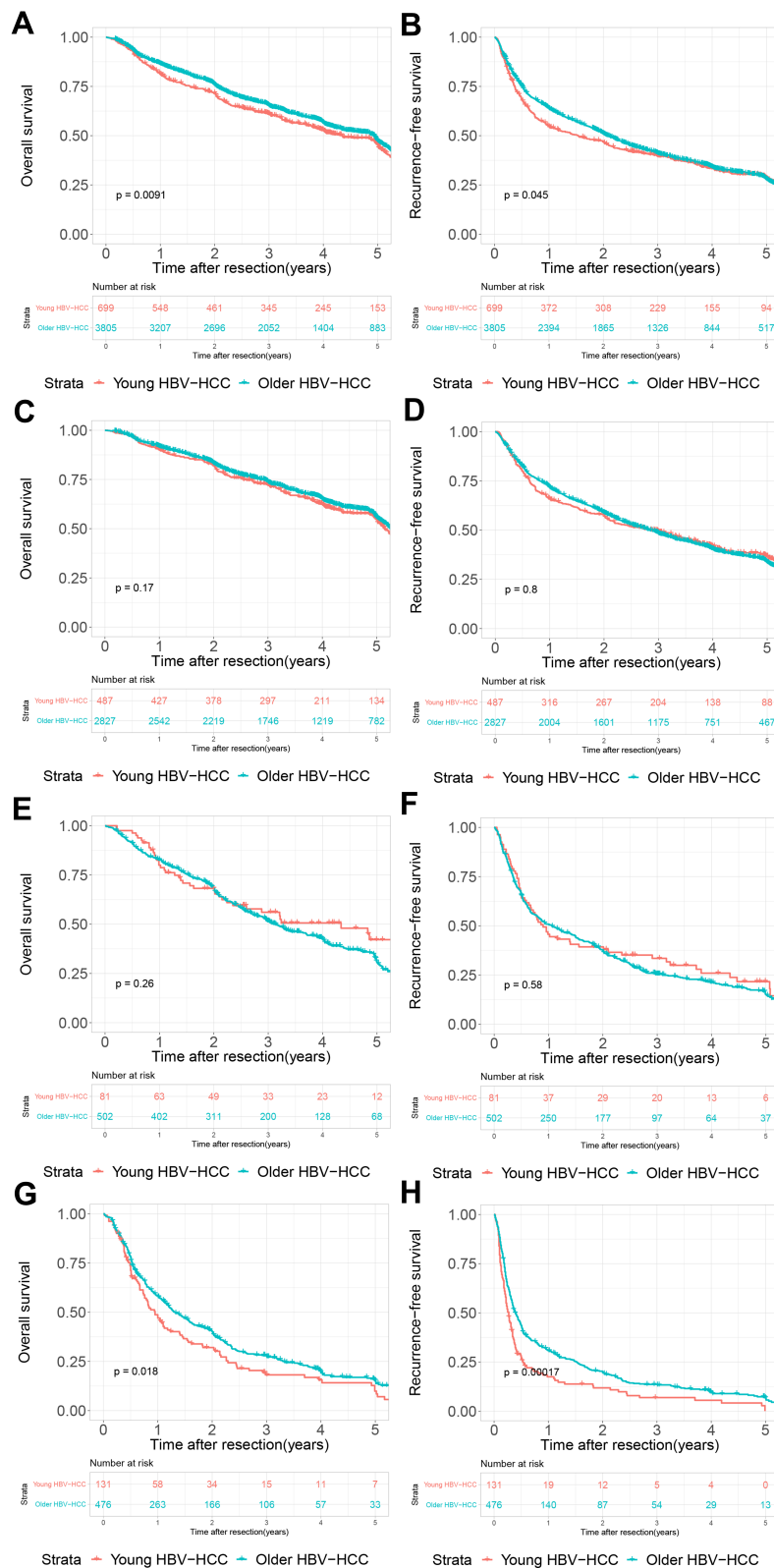
**Abbreviations:** HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; WBC, white blood cell; PLT, platelet count; ALB, albumin; TBIL, total bilirubin; ALBI grade, albumin-bilirubin grade; BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; TNM, tumor, node, metastases; SD, standard deviation; IQR, interquartile range.

61%, and 45.3%, respectively, in young patients with HCC and 86.4%, 65.3%, and 47.7%, respectively, in the older patients with HCC ( $p=0.0091$ , Figure 2A). The recurrence-free survival rates at 1, 3, 5 years were 54.7%, 39.7%, and 28.2%, respectively, in young group and 63.8%, 41.1%, and 28%, respectively, in the older group ( $p=0.045$ , Figure 2B).

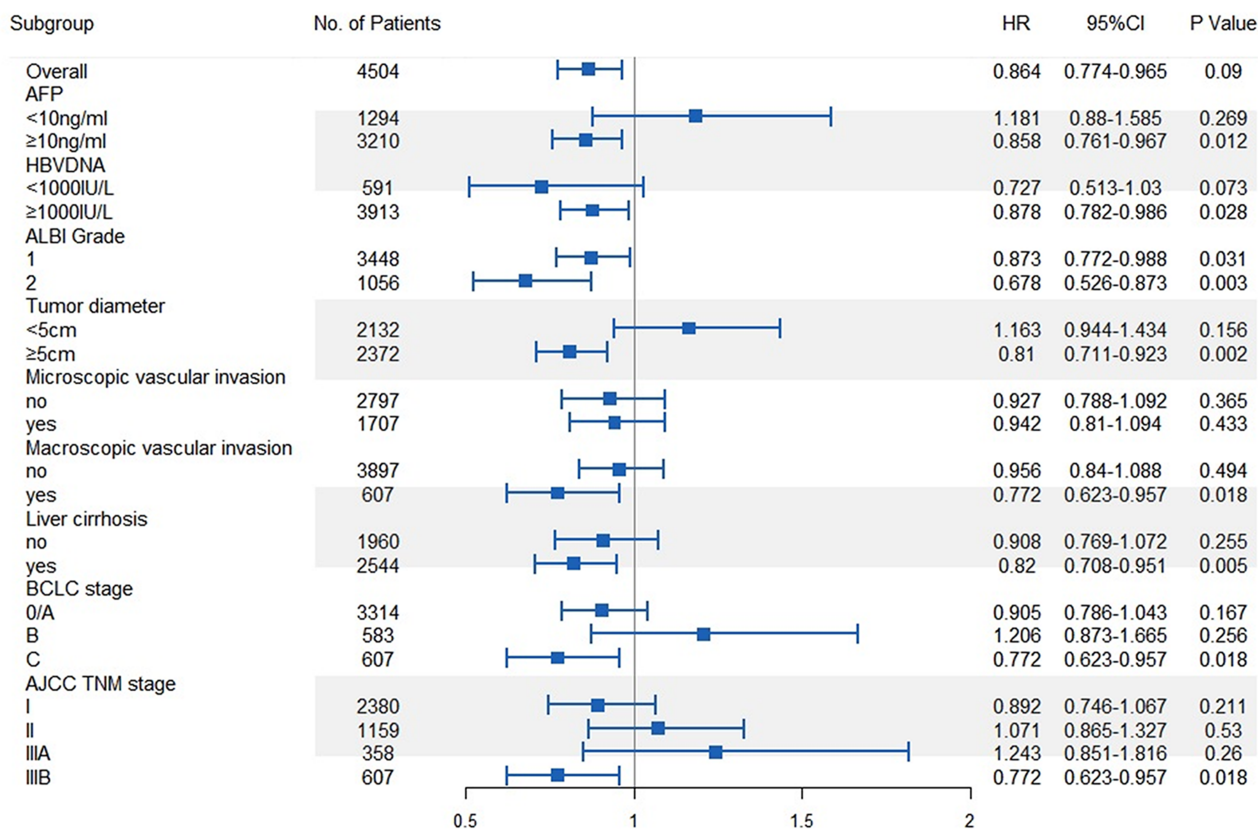
To stratify by tumor factors and liver functional reserve, we performed several subgroup analyses of OS and RFS (Figures 3 and 4, respectively). After stratification by the BCLC staging system, there were no significant differences in OS and RFS between young and older groups in BCLC 0/A staging ( $p=0.17$ ;  $p=0.8$ ) and BCLC B staging ( $p=0.26$ ;  $p=0.58$ ) (Figure 2C–F). In BCLC C staging, young HCC patients had a significantly worse prognosis than older HCC patients ( $p=0.018$ ;  $p=0.00017$ ) (Figure 2G and H).

## Risk Factors Associated with OS and RFS in Young HBV-Related HCC Patients

The univariate and multivariate Cox analysis for determining the risk factors associated with OS and RFS in young HBV-related HCC patients are shown in Table 2.



**Figure 2** Comparison of prognosis between young and older groups. **(A)** OS in the entire patients; **(B)** RFS in the entire patients; **(C)** OS in BCLC 0/A staging; **(D)** RFS in BCLC 0/A staging; **(E)** OS in BCLC B staging; **(F)** RFS in BCLC B staging; **(G)** OS in BCLC C staging; **(H)** RFS in BCLC C staging. **Abbreviations:** OS, overall survival; RFS, recurrence-free survival; BCLC, Barcelona Clinic Liver Cancer.



**Figure 3** Subgroup analysis of overall survival between young and older groups.

**Abbreviations:** AFP, alpha-fetoprotein; ALBI grade, albumin-bilirubin grade; BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; TNM, tumor, node, metastases; HR, hazard ratio; CI, confidence interval.

Multivariate analysis revealed that a serum AFP levels of  $\geq 10\text{ng/mL}$ , a resection margin width of  $< 1\text{cm}$ , a tumor size of  $\geq 5\text{cm}$ , the absence of tumor capsular, and the presence of macrovascular invasion were the independent risk factors associated with mortality (Table 2). A serum ALB level of  $< 35\text{g/L}$ , a tumor size of  $\geq 5\text{cm}$ , the presence of microvascular invasion, and macrovascular invasion were the independent risk factors associated with tumor recurrence by multivariate analysis (Table 2).

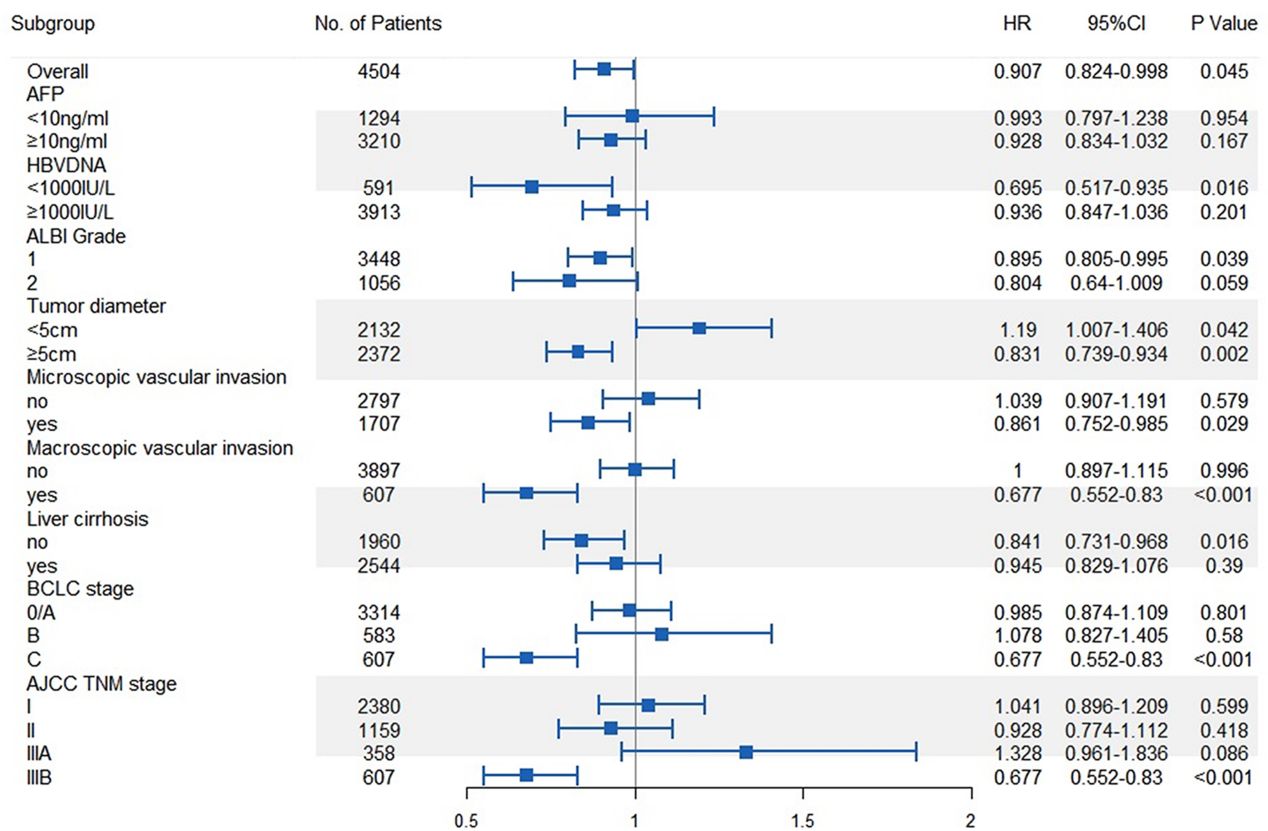
## Discussion

Generally, Hepatocellular carcinoma (HCC) usually occurs in middle-aged and elderly individuals. The age distribution of HCC varies according to geographical location and etiology.<sup>27</sup> In areas where hepatitis B infection is endemic, screening programs for HCC in high-risk populations are important to increase the rate of early diagnosis and improve treatment outcome.<sup>2</sup> Nonetheless, the prevalence of HBV-related HCC in young patients, especially in high-risk populations, has increased.<sup>3</sup> However, the prognosis of young patients with HBV-related HCC is controversial.

Some authors have found that young patients have better long-term outcomes,<sup>8-10</sup> whereas others have reported that young patients have advanced tumor factors, thereby indicating a poor prognosis.<sup>11,12</sup> Several studies have demonstrated that the long-term outcomes after HCC resection are similar between the two groups.<sup>13-15</sup>

The variable conclusions may be attributed to the following two aspects. Firstly, the number of young and older patients with HCC was too small for accurate analysis in these studies.<sup>12,22-24</sup> The present study focused on a relatively small proportion of young and older patients with HBV-related HCC in China, and this population was further restricted to patients who intended to curative hepatic resection with good liver functional reserve. Such strict patient selection could be fully compared the clinical characteristics, outcome, and prognostic factors after hepatectomy of young HCC patients with older HCC patients.

Secondly, the lack of standardization of what cut-off age constituted “young and older HCC”. In some studies, the cut-off was defined as 30 or 40 years, whereas in others below 55 years.<sup>2,10,15,28</sup> The determination of the



**Figure 4** Subgroup analysis of recurrence-free survival between young and older groups.

**Abbreviations:** AFP, alpha-fetoprotein; ALBI grade, albumin-bilirubin grade; BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; TNM, tumor, node, metastases; HR, hazard ratio; CI, confidence interval.

cut-off age for older HCC patients has also varied in the literature.<sup>28–32</sup> We defined young patients as aged ≤40 years and older patients as aged >40 years. The age cut-off of 40 years was based on previous studies.<sup>2,10,11,20–23</sup>

We believe this allows for more meaningful comparisons with other studies. Besides, the Chinese guidelines for the management of HCC recommend screening of males beginning at age 40.<sup>33</sup> Hence, we were interested in

**Table 2** Univariate and Multivariate Cox Regression for OS and RFS in Young HBV Related HCC Patients

Variables	OS				RFS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender (Female as ref)								
Male	1.24 (0.90–1.70)	0.19			1.01 (0.99–1.03)	0.37		
AFP (<10ng/mL as ref)								
≥10ng/mL	2.15 (1.59–2.90)	<0.01	1.48 (1.09–2.02)	0.01	1.56 (1.24–1.97)	<0.01		
HBV-DNA (<1000IU/L as ref)								
≥1000IU/L	0.84 (0.59–1.18)	0.30			0.94 (0.70–1.25)	0.65		
WBC (<4×10 <sup>9</sup> /L as ref)								
≥4×10 <sup>9</sup> /L	1.20 (0.90–1.59)	0.22			1.35 (1.05–1.74)	0.02		

(Continued)

Table 2 (Continued).

Variables	OS				RFS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
PLT (<100×10 <sup>9</sup> /L as ref)								
≥100×10 <sup>9</sup> /L	1.29 (0.91–1.83)	0.15			1.54 (1.12–2.12)	<0.01		
ALB (<35g/L as ref)								
≥35g/L	0.62 (0.30–1.26)	0.18			0.45 (0.25–0.83)	0.01	0.39 (0.20–0.75)	<0.01
TBIL (<17.1μmol/L as ref)								
≥17.1μmol/L	1.24 (0.99–1.54)	0.06			1.13 (0.93–1.38)	0.21		
ALBI grade (Grade I as ref)								
Grade 2	1.63 (1.25–2.12)	<0.01			1.41 (1.11–1.78)	<0.01		
Resection margin width (<1cm as ref)								
≥1cm	0.56 (0.43–0.72)	<0.01	0.66 (0.50–0.87)	<0.01	0.69 (0.55–0.85)	<0.01		
Blood transfusion (no as ref)								
Yes	2.67 (2.02–3.53)	<0.01			2.24 (1.73–2.90)	<0.01		
Operative bleeding loss (<800mL as ref)								
≥800mL	2.41 (1.77–3.29)	<0.01			1.74 (1.29–2.35)	<0.01		
Tumor size (<5cm as ref)								
≥5cm	3.08 (2.44–3.87)	<0.01	2.10 (1.63–2.70)	<0.01	2.64 (2.18–3.20)	<0.01	2.04 (1.65–2.50)	<0.01
Tumor number (Solitary as ref)								
Multiple	1.55 (1.21–1.97)	<0.01			1.59 (1.28–1.97)	<0.01		
Microvascular invasion (no as ref)								
Yes	2.21 (1.80–2.71)	<0.01			2.25 (1.88–2.69)	<0.01	1.50 (1.22–1.84)	<0.01
Macrovascular invasion (no as ref)								
Yes	4.28 (3.40–5.38)	<0.01	2.29 (1.75–3.00)	<0.01	4.35 (3.51–5.40)	<0.01	2.77 (2.15–3.58)	<0.01
Edmondson grade (I–II as ref)								
III–IV	2.86 (1.78–4.59)	<0.01			2.19 (1.53–3.14)	<0.01		
Tumor capsular (no as ref)								
Yes	0.51 (0.41–0.64)	<0.01	0.69 (0.55–0.87)	<0.01	0.60 (0.49–0.73)	<0.01		
Satellite nodules (no as ref)								
Yes	1.76 (1.44–2.16)	<0.01			1.52 (1.27–1.81)	<0.01		
Liver cirrhosis (no as ref)								
Yes	1.20 (0.98–1.47)	0.08			1.08 (0.91–1.29)	0.38		

**Abbreviations:** OS, overall survival; RFS, recurrence-free survival; AFP, alpha-fetoprotein; WBC, white blood cell; PLT, platelet count; ALB, albumin; TBIL, total bilirubin; ALBI grade, albumin-bilirubin grade; HR, hazard ratio; CI, confidence interval; Ref, reference.



evaluating the prognosis in HBV-related HCC patients below this age threshold.

In the present study, the results demonstrated that young patients had higher serum AFP levels, larger tumor size, higher rates of microvascular invasion and macrovascular invasion, higher rates of Edmondson grade III–IV, lower rates of tumor capsular, more advanced AJCC TNM stages, and more advanced BCLC stages than older patients. Meanwhile, young patients also had worse OS and RFS rate than older patients, which is consistent with previous study.<sup>11,12</sup>

Multivariate analysis revealed that a tumor size of  $\geq 5$  cm and macrovascular invasion were associated with OS and RFS in young patients, so aggressive tumor factors lead to poor prognosis in young patients. Previous studies have shown young patients diagnosed with HCC more often had symptomatic presentations and were less likely to be identified by surveillance.<sup>2,14</sup> It implies that if tumors could be detected at the early stage by more frequent surveillance and radical treatment is performed, long-term survival can be expected in the young patients.

## Conclusions

This multicenter study indicated that young patients had better liver function, more aggressive tumor characteristics, and worse prognosis than older patients. A tumor size of  $\geq 5$  cm and macrovascular invasion lead to poor prognosis in young patients.

## Abbreviations

HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; HBV, hepatitis B virus; WBC, white blood cell; PLT, platelet count; ALB, albumin; TBIL, total bilirubin; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; TNM, tumor, node, metastases; SD, standard deviation; IQR, interquartile range.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

This study was approved by the institutional ethics committee of Mengchao Hepatobiliary Hospital of Fujian

Medical University. Informed consent was obtained from each patient for their data to be used for research purposes.

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## Disclosure

The authors declare no conflicts of interest.

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