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ORIGINAL RESEARCH ARTICLE

The status of compensated cirrhosis might be negatively associated with the tumor size in patients with hepatitis B virus-related hepatocellular carcinoma

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Abstract

Liver cirrhosis has been a well-known risk factor for the development of hepatocellular carcinoma (HCC). However, this view has recently been challenged. This study aimed to investigate the potential association of cirrhosis with hepatitis B virus (HBV)-related HCC. In this study, two independent multicenter clinical cohorts that included 1,431 HCC patients with chronic HBV infection were retrospectively studied. The first cohort consisted of 334 HCC patients undergoing curative resection and cirrhosis, who have been pathologically diagnosed. The second cohort consisted of 1,087 HCC patients, who have been diagnosed for the presence of cirrhosis based on clinical evidence. Patients of each cohort were further divided into different subgroups according to the presence of cirrhosis and the severity of the cirrhosis. In both cohorts, patients with cirrhosis had smaller tumor size compared to those without cirrhosis ($P < 0.05$) and a relatively lower proportion of large tumor, defined as tumor size > 5 cm in diameter ($P < 0.05$). Patients with decompensated cirrhosis had the highest rate of vascular invasion and/or extrahepatic metastases compared with compensated cirrhosis and non-cirrhosis (53.0% vs. 24.8% vs. 26.9%, $P < 0.001$). In the first cohort, globulin (odds ratio [OR] = 1.096, $P = 0.001$) and vascular invasion (OR = 4.013, $P = 0.013$) were independent risk predictors of HCC tumor size >5 cm, while cirrhosis stage Laennec 4B/C was a protective factor (OR = 0.372, $P = 0.002$). Similar results were observed in the second cohort. In conclusion, this study implied that HCC patients with compensated cirrhosis tend to harbor smaller tumor, but severe cirrhosis favors tumor vascular invasion and metastasis.

Keywords: Liver cirrhosis; Hepatocellular carcinoma; Hepatitis B virus; Neoplasm metastasis; Vascular invasion

1. Introduction

Hepatocellular carcinoma (HCC) is a primary liver cancer with an estimated 906,000 newly diagnosed cases and 830,000 deaths yearly, and is ranked the top six most common cancers and the third leading cause of cancer death worldwide in 2020[1]. Liver fibrosis is strongly associated with HCC, while 90% of HCC cases arising in cirrhotic livers[2]. For hepatitis B and C virus infection, the presence of fibrosis and cirrhosis has been identified as risk factors for HCC; and the cancer risk is positively correlated with the fibrosis severity[3,4]. HCC development has also been shown to be linked to alcoholic cirrhosis, nonalcoholic steatohepatitis, and hemochromatosis, with a yearly HCC incidence of 1.7% and 2.6% in alcoholic cirrhosis and non-alcoholic steatohepatitis cirrhosis, respectively[5]. It has been reported that cirrhosis, as a late-stage form of fibrosis, contributes to an over 30-fold increase in HCC risk[6]. Approximately 80% of hepatitis B and C patients presented with HCC are already cirrhotic[7], and liver cirrhosis occurs in about 80% of HCC patients, indicating that liver cirrhosis is the major risk factor for the development of HCC[8].

Recently, there has been emerging opinions suggesting that regenerative nodules (RNs) and fibrosis either exert physical forces to spatially restrict malignant hepatocytes or activate immunosurveillance to suppress the development of HCC[9] and "premalignant mutations" found in the RNs were independent of carcinogenesis associated with HCC development. As RNs are surrounded by fibrotic septa, the fibrosis is postulated to act as a mechanical "fence" to constrain the transformation or spatially limit the spread of cancer cells[10]. Apparently, such a novel view on the cirrhosis as a liver-protective response to various injuries, rather than a risk factor for HCC[9], has challenged the conventional view.

Few studies have been carried out to clarify the controversies on the role of cirrhosis in HCC development. Herein, this study aimed to investigate the potential association of cirrhosis with hepatitis B virus (HBV)-related HCC in two independent cohorts.

2. Materials and methods

2.1. Study subjects

Two retrospective cohorts were used in this study. The first cohort consisted of adult patients with HCC undergoing curative resection in the Fifth Medical Center of Chinese PLA General Hospital (Beijing, China) between 2015 and 2017. The inclusion criteria were: (i) Age ≥18 years; (ii) positive for hepatitis B surface antigen for at least 6 months; (iii) having complete information on laboratory data and clinical characteristics of the tumors; and (iv) pathologically confirmed for HCC and liver cirrhosis. Meanwhile, the exclusion criteria were: (i) liver disease due to co-infection with hepatitis C virus or other hepatitis, genetic and autoimmune disorders, primary biliary cirrhosis, and sclerosing cholangitis; (ii) had prior treatment for HCC or have had anti-HBV treatment within 6 months before prior to HCC diagnosis; (iii) having other malignant tumors; and (iv) being pregnant. In the first cohort, the METAVIR scoring system was used to evaluate the hepatic fibrosis stage, and the severity of liver cirrhosis was histologically staged as 4A, 4B, and 4C using the Laennec staging system, according to the size of regenerated nodules and the width of fibrous septa.

To further validate the association of the severity of liver cirrhosis with the tumor size, we included another independent cohort, in which the study subjects were recruited from four university hospitals (The Fifth Medical Center of Chinese PLA General Hospital, Beijing; The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou; Peking University Shenzhen Hospital, Shenzhen; The Third Hospital of Hebei Medical University, Shijiazhuang) in China from 2010 to 2018. The subjects in this cohort were recruited using the above-mentioned inclusion and exclusion criteria. In this cohort, HCC were histopathologically and/or clinically diagnosed, while cirrhosis was diagnosed by a combination of clinical, laboratory, and imaging approaches. This study was approved by the ethics committee of Peking University Health Science Center (IRB00001052-19081) and conducted according to the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.2. Statistical analysis

Statistical analysis was performed by SPSS 24.0 software (IBM SPSS Statistics, New York, USA). Continuous variables are expressed as mean ± standard deviation or median and interquartile range, and qualitative variables are expressed as number and percentage (%). The *t*-test, Mann-Whitney *U* test, one-way analysis of variance, or Chi-square test were used to evaluate the differences between groups, as appropriate. Factors that are possibly associated with the tumor size were analyzed using logistic regression analysis. A forward selection method was used in the multivariate analysis. $P < 0.05$ is considered statistically significant.

3. Results

3.1. Patient characteristics

A total number of 1431 patients diagnosed with HCC were included in this study, with 334 and 1087 patients from the

first and second cohorts, respectively. In the first cohort, the mean age of the patients was 51.40 ± 9.62 years, with 283 (84.7%) males and 51 females (15.3%), and 276 (82.6%) patients had compensated cirrhosis, while the rest of the patients did not show the presence of cirrhosis. In the second cohort, there were 946 male and 141 female patients, the mean age of the patients was 51.81 ± 11.04, and 80.5% (n = 894) patients showed the presence of cirrhosis. The baseline characteristics of the two cohorts are summarized in Table 1 and 2, respectively, and the study enrollment and analysis flow chart are shown in Figure 1.

3.2. Tumor size in patients with different severity of cirrhosis

In the first cohort, patients with cirrhosis had smaller tumor size compared to those without cirrhosis (4.5 cm vs. 5.8 cm, P = 0.015). In addition, a decline trend in tumor size was observed as the severity of cirrhosis increased from no cirrhosis to Laennec stage 4A and 4B/C (5.8 cm vs. 5.0 cm vs. 4.5 cm, P = 0.020). The proportions of patients with tumor size >5 cm among the three subgroups, that is, HCC without cirrhosis, HCC with Laennec stage 4A, and HCC with Laennec stage 4B/C were 58.6%, 46.3%, and 38.8%, respectively (P = 0.025) (Table 1).

The tumor characteristics were analyzed in the second cohorts in patients with different severity of cirrhosis. The results showed that patients with cirrhosis had smaller tumor size, compared to those without cirrhosis (5.9 cm vs. 7.9 cm, P < 0.001). Besides, they had a relatively lower proportion of large tumor, which was defined as tumor size >5 cm in diameter (493/894 [54.9%] vs. 122/193 [63.2%], P = 0.035). Patients with cirrhosis were further categorized into compensated and decompensated cirrhosis groups. Among the three subgroups (non-cirrhosis, compensated cirrhosis, and decompensated cirrhosis), patients with compensated cirrhosis had the smallest tumor size (5.4 cm), and the proportion of patients with tumor size >5 cm were 286 over 524 (54.6%, P < 0.001), while patients without cirrhosis had the largest tumor size (7.9 cm), and the proportion of patients with tumor >5 cm were 122 over 193 (63.2%, P < 0.001) (Table 3).

Table 1. Comparison of the characteristics of tumor in different pathological stages of cirrhosis

Variables	HCC without cirrhosis (n=58)	HCC with Laennec 4A (n=80)	HCC with Laennec 4B/C (n=196)	P-value
Age (year)	51.71±9.68	51.21±10.12	51.39±9.43	0.956
Male, n (%)	50 (86.2)	66 (82.5)	167 (85.2)	0.803
Alanine transaminase (U/L)	34.0 (21.0, 48.0)	33.0 (21.0, 48.0)	37.0 (25.3, 58.5)	0.067
Aspartate aminotransferase (U/L)	36.9 (26.0, 56.3)	35.1 (26.3, 44.8)	34.7 (28.0, 54.0)	0.927
Albumin (g/L)	40.0 (38.0, 43.0)	39.0 (37.3, 42.0)	39.0 (36.0, 42.0)	0.022
Globulin (g/L)	27.0 (24.8, 30.0)	28.0 (25.0, 31.0)	28.0 (25.0, 31.0)	0.391
Total Bilirubin (umol/L)	13.3 (10.7, 17.8)	12.3 (9.5, 16.7)	14.6 (11.3, 18.4)	0.038
Tumor size* (cm)	5.8 (3.5, 10.0)	5.0 (3.0, 8.0)	4.5 (3.0, 6.5)	0.020
Distribution of tumor size*, n (%)				0.025
≤5 cm	24 (41.4)	43 (53.8)	120 (61.2)	-
>5 cm	34 (58.6)	37 (46.3)	76 (38.8)	-
Number of tumors, n (%)				0.397
1	53 (91.4)	73 (91.3)	169 (86.2)	
2 – 3	5 (8.6)	4 (5.0)	19 (9.7)	
>3	0	3 (3.8)	8 (4.1)	
Vascular invasion, n (%)				0.112
Yes	3 (5.2)	1 (1.3)	15 (7.7)	-
No	55 (94.8)	79 (98.8)	181 (92.3)	-
Degree of pathological differentiation, n (%)				0.566
High	2 (3.4)	0 (0)	3 (1.5)	-
Middle	54 (93.1)	78 (97.5)	186 (94.9)	-
Poor	2 (3.4)	2 (2.5)	7 (3.6)	-

Age is expressed as mean±standard deviation, and tumor size is expressed as median and interquartile range. *Tumor size indicates the maximum diameter of the tumor. HCC: Hepatocellular carcinoma

Table 2. Comparison of the characteristics of tumor between HCC patients with and without cirrhosis

Variables	HCC without cirrhosis (n=193)	HCC with cirrhosis (n=894)	*P*-value
Age (year)	50.35±12.39	52.12±10.70	0.066
Male, *n* (%)	170 (88.1)	776 (86.8)	0.631
Alanine transaminase (U/L)	39.0 (26.0, 65.5)	44.0 (30.0, 72.0)	0.003
Aspartate aminotransferase (U/L)	47.0 (29.0, 81.7)	54.0 (35.0, 95.0)	0.015
Albumin (g/L)	39.0 (35.0, 42.1)	37.0 (32.2, 40.0)	<0.001
Globulin (g/L)	28.7 (26.0, 32.7)	30.0 (26.0, 34.0)	0.159
Total Bilirubin (umol/L)	15.9 (11.7, 20.4)	18.4 (12.9, 28.9)	<0.001
Tumor size* (cm)	7.9 (4.0, 11.9)	5.9 (3.0, 10.0)	<0.001
Distribution of tumor size*, *n* (%)			0.035
≤5 cm	71 (36.8)	403 (45.1)	-
>5 cm	122 (63.2)	491 (54.9)	-
Number of tumors, *n* (%)			0.195
1	143 (74.1)	646 (72.3)	-
2 – 3	12 (6.2)	92 (10.3)	-
>3	38 (19.7)	156 (17.4)	-
Vascular invasion, *n* (%)			0.004
Yes	45 (23.3)	305 (34.1)	-
No	148 (76.7)	589 (65.9)	-
Vascular invasion or extrahepatic metastases, *n* (%)			0.012
Yes	52 (26.9)	326 (36.5)	-
No	141 (73.1)	568 (63.5)	-

Age is expressed as mean±standard deviation, and tumor size is expressed as median and interquartile range. *Tumor size indicates the maximum diameter of the tumor. HCC: Hepatocellular carcinoma

3.3. Vascular invasion and extrahepatic metastases in patients with different severity of cirrhosis

We also analyzed the rate of vascular invasion and extrahepatic metastases in these patients. As a result, in the first cohort, there were no differences in the rate of tumor vascular invasion among HCC patients without cirrhosis, with cirrhosis + Laennec stage 4A, and with cirrhosis + Laennec stage 4B/C (5.2% vs. 1.3% vs. 7.7%, $P = 0.112$). In the second cohort, a significantly higher rate of vascular invasion of HCC (34.1% vs. 23.3%, $P = 0.004$), and vascular invasion and/or extrahepatic metastases (36.5% vs. 26.9%, $P = 0.012$) were observed in HCC patients with cirrhosis compared to those without cirrhosis (Table 2). Specifically, patients with decompensated cirrhosis had the highest rate of vascular invasion and/or extrahepatic metastases (53.0%, 196/370), followed by patients with non-cirrhosis patients (26.9%, 52/193) and compensated cirrhosis (24.8%, 130/524) ($P < 0.001$) (Table 3).

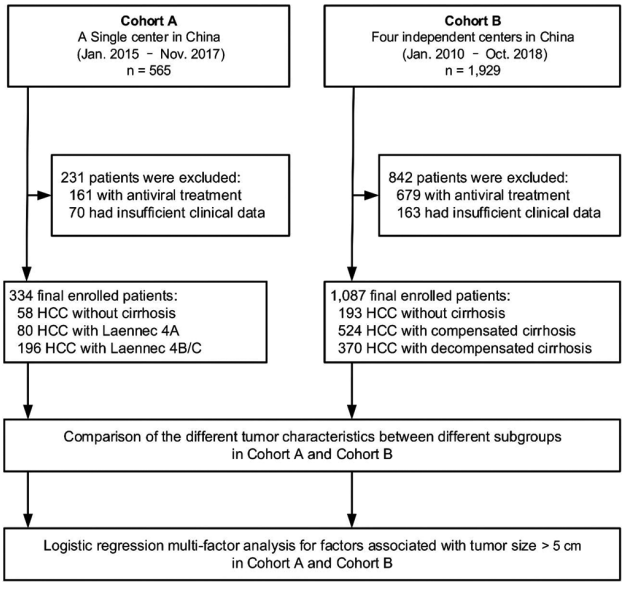

Figure 1. Study subjects enrollment and analysis flow chart.

Table 3. Comparison of the characteristics of tumor among the three subgroups

Variables	HCC without cirrhosis (n=193)	HCC with compensated cirrhosis (n=524)	HCC with decompensated cirrhosis (n=370)	P-value
Age (year)	50.35±12.39	51.01±10.57	53.71±10.70	<0.001
Male, *n* (%)	170 (88.1)	454 (86.6)	322 (87.0)	0.878
Alanine transaminase (U/L)	39.0 (26.0, 65.5)	40.5 (27.0, 65.0)	53.0 (34.0, 84.3)	<0.001
Aspartate aminotransferase (U/L)	47.0 (29.0, 81.7)	42.6 (30.0, 72.0)	80.0 (48.8, 138.0)	<0.001
Albumin (g/L)	39.0 (35.0, 42.1)	38.0 (35.0, 41.0)	34.0 (30.2, 38.0)	<0.001
Globulin (g/L)	28.7 (26.0, 32.7)	29.0 (25.6, 32.0)	32.0 (27.2, 36.4)	<0.001
Total Bilirubin (umol/L)	15.9 (11.7, 20.4)	15.7 (11.6, 21.4)	25.6 (17.7, 42.9)	<0.001
Tumor size*(cm)	7.9 (4.0, 11.9)	5.4 (3.0, 9.2)	6.5 (3.1, 11.0)	<0.001
Distribution of tumor size*, *n* (%)				0.003
≤5 cm	71 (36.8)	256 (48.9)	147 (39.7)	-
>5 cm	122 (63.2)	268 (51.1)	223 (60.3)	-
Number of tumors, *n* (%)				0.130
1	143 (74.1)	379 (72.3)	267 (72.2)	
2–3	12 (6.2)	61 (11.6)	31 (8.4)	
>3	38 (19.7)	84 (16.0)	72 (19.5)	
Vascular invasion, *n* (%)				<0.001
Yes	45 (23.3)	115 (21.9)	190 (51.4)	
No	148 (76.7)	409 (78.1)	180 (48.6)	
Vascular invasion or extrahepatic metastases, *n* (%)				<0.001
Yes	52 (26.9)	130 (24.8)	196 (53.0)	-
No	141 (73.1)	394 (75.2)	174 (47.0)	-

Age is expressed as mean±standard deviation, and tumor size is expressed as median and interquartile range, * Tumor size indicates the maximum diameter of the tumor. HCC: Hepatocellular carcinoma

3.4. Factors associated with HCC tumor size

Univariate and multivariate logistic regression analyses were conducted to analyze the possible factors which are associated with tumor size (Table 4). In the first cohort, results of univariate analysis showed that globulin (P = 0.010), vascular invasion (P = 0.012), and Laennec 4B/C (P = 0.008) were significantly associated with HCC tumor size >5 cm. On the other hand, multivariate analysis revealed that globulin (odds ratio [OR]: 1.096; 95% CI: 1.037 – 1.158; P = 0.001) and vascular invasion (OR: 4.013; 95% CI: 1.342 – 11.996; P = 0.013) were independent risk predictors of HCC tumor size >5 cm; however, cirrhosis stage Laennec 4B/C was a protective factor (OR: 0.372; 95% CI: 0.200 – 0.693; P = 0.002). As for the second cohort, univariate analysis results revealed that age (P = 0.004), alanine transaminase (P = 0.047), aspartate aminotransferase (P < 0.001), albumin (P = 0.002), globulin (P < 0.001), number of tumor (P < 0.001), vascular invasion (P < 0.001), and compensated cirrhosis (P = 0.004) were significantly related to HCC tumor size >5 cm. While using multivariate analysis, number of tumor (OR: 1.731; 95% CI: 1.364 – 2.196; P < 0.001) and vascular invasion (OR: 7.065; 95% CI: 4.238 – 11.775; P < 0.001) were identified as independent risk predictors of HCC tumor size >5 cm, while age (OR: 0.977; 95% CI: 0.962 – 0.992; P = 0.003), albumin (OR: 0.949; 95% CI: 0.916 – 0.98; P = 0.003), and compensated cirrhosis (OR: 0.551; 95% CI: 0.379 – 0.801; P = 0.002) were found to be protective factors. As vascular invasion had the largest OR values associated with tumor size >5 cm, the occurrence of vascular invasion in patients with different tumor size was compared as shown in Table 5. In short, patients with larger tumor size tend to have higher rates of vascular invasion, confirmed by the multivariate logistic regression analysis.

4. Discussion

Tumor size has been considered one of the prognostic factors for HCC[11,12]. This study demonstrated that the presence of liver cirrhosis, especially compensated cirrhosis, could be an important factor that is negatively associated with the tumor size in HBV-related HCC. Conversely, the vascular invasion showed a positive

Table 4. Univariate and multivariate logistic analysis of tumor size>5 cm and associated factors in hepatocellular carcinoma patients

First cohort	Univariate	*P*-value	Multivariate	*P*-value
	OR (95%CI)		OR (95%CI)	
Age (year)	0.994 (0.972, 1.017)	0.618		
Gender (Male)	1.528 (0.840, 2.780)	0.165		
Alanine transaminase (U/L)	1.000 (0.996, 1.003)	0.768		
Aspartate aminotransferase (U/L)	1.001 (0.998, 1.004)	0.543		
Albumin (g/L)	0.955 (0.906, 1.008)	0.094		
Globulin (g/L)	1.062 (1.015, 1.111)	0.010	1.096 (1.037, 1.158)	0.001
Total Bilirubin (umol/L)	0.992 (0.975, 1.009)	0.354		
Number of tumor (1/2–3/>3)	1.283 (0.786, 2.095)	0.319		
Vascular invasion	3.832 (1.347, 10.90)	0.012	4.013 (1.342, 11.996)	0.013
Degree of pathological differentiation (Poor/Middle/High)	1.096 (0.407, 2.949)	0.856		
Cirrhosis				
No (reference)	-	-	-	-
Laennec 4A	0.607 (0.307, 1.202)	0.152	-	-
Laennec 4B/C	0.447 (0.246, 0.812)	0.008	0.372 (0.200, 0.693)	0.002
Second cohort	**Univariate**	***P*-value**	**Multivariate**	***P*-value**
	OR (95%CI)		**OR (95%CI)**	
Age (year)	0.980 (0.967, 0.994)	0.004	0.977 (0.962, 0.992)	0.003
Gender (Male)	0.758 (0.490, 1.173)	0.214		
Alanine transaminase (U/L)	1.001 (1.000, 1.002)	0.047		
Aspartate aminotransferase (U/L)	1.003 (1.002, 1.005)	<0.001		
Albumin (g/L)	0.967 (0.946, 0.988)	0.002	0.949 (0.916, 0.983)	0.003
Globulin (g/L)	1.038 (1.017, 1.060)	<0.001		
Total Bilirubin (umol/L)	1.001 (0.999, 1.003)	0.192		
Number of tumor (1/2–3/>3)	1.751 (1.475, 2.078)	<0.001	1.731 (1.364, 2.196)	<0.001
Vascular invasion	10.056 (7.07, 14.287)	<0.001	7.065 (4.238, 11.775)	<0.001
Cirrhosis				
No (reference)	-	-	-	-
Compensated cirrhosis	0.609 (0.434, 0.855)	0.004	0.551 (0.379, 0.801)	0.002
Decompensated cirrhosis	0.883 (0.616, 1.264)	0.496		

association with the tumor size. Furthermore, it is also suggested that decompensated cirrhosis favors vascular invasion and metastasis of HCC relative to non-cirrhosis and compensated cirrhosis. Nevertheless, it should be emphasized that the association of cirrhosis with HCC is only restricted to the size of tumor but not the vascular invasion or metastasis, and to the HCC patients with compensated cirrhosis, since this stage favors other tumor biological behaviors, such as tumorigenesis, vascular invasion, metastasis, and differentiation of tumor[13]. All these results imply that compared to those without cirrhosis, HCC patients with cirrhosis tend to harbor smaller tumor, and this is consistent with the physical and mechanical constraint of tumor transformation in patients with cirrhosis[10].

The main finding of this study was that compensated cirrhosis might be a protective factor against tumor growth, and this may be counterintuitive to the clinician's perspective. However, this idea is supported by the fact that liver responds to acute injury through tissue repair, which leads to synthesis, deposition, and accumulation of extracellular matrix[14]. In addition, other previously published experimental evidence also showed that liver

Table 5. Occurrence of vascular invasion in patients with different tumor size

First cohort	Tumor size				*P*-value
	≤2cm (*n*=34)	>2 and≤5cm (*n*=153)	>5 and≤10cm (*n*=106)	>10 cm (*n*=41)	
Vascular invasion					<0.001
Yes	1 (2.9)	4 (2.6)	6 (5.7)	8 (19.5)	
No	33 (97.1)	149 (97.4)	100 (94.3)	33 (80.5)	
Second cohort	**Tumor size**				***P*-value**
	≤2cm (*n*=128)	>2 and≤5cm (*n*=346)	>5 and≤10cm (*n*=339)	>10 cm (*n*=274)	
Vascular invasion					<0.001
Yes	8 (6.2)	35 (10.1)	131 (38.6)	176 (64.2)	
No	120 (93.8)	311 (89.9)	208 (61.4)	98 (35.8)	

fibrosis may play a protective role[15-17]. Further, a recent study showed that the value of liver stiffness measurement inside the tumor and in the peri-tumoral tissue was negatively correlated with serum alpha-fetoprotein ($P < 0.05$)[18], which to some extent supports the above idea that cirrhosis is an important factor which is negatively associated with the tumor size, since the value of liver stiffness measurement would reflect the severity of cirrhosis and the alpha-fetoprotein level is strongly correlated with the tumor size[19]. Besides, the importance of fibrosis as an activator of the immune system against cancer has been previously shown in pancreatic cancers[20,21], where fibrosis development and cirrhosis-induced inflammation might prime the immune system and ensure a better response against malignant cells present in the liver[9]. However, it should be emphasized that this process is harmful in the long term, as indicated by our results that patients with decompensated cirrhosis had larger tumor size (a higher proportion of patients had tumor >5 cm) and a significantly higher rate of vascular invasion and extrahepatic metastasis than those with compensated cirrhosis and non-cirrhosis. When cirrhosis progresses to decompensated cirrhosis, immune dysfunction in HCC patients with severely decompensated cirrhosis would result in significant tumor growth and metastasis[13]. Decreased efficiency of cell durotaxis and increased level of stiffness from soft matrix to rigid matrix has been reported previously[22], which may explain the limitation on HCC tumor margins as seen in the patients with cirrhosis. However, many studies have shown that tumor cells would spread better and migrate faster in the rigid matrix than in the soft matrix[23-25]. These studies may also explain why vascular invasion occurred more frequently in HCC patients with cirrhosis, especially in patients with decompensated cirrhosis. In addition, changes of vascular permeability in these patients may also lead to a higher probability of vascular invasion and extrahepatic metastases.

The present study also showed that globulin is a risk factor for HCC tumor growth, while albumin is a protective factor. This result is justifiable since the albumin levels reflect the nutrition status of patients, and numerous studies have shown that malnourished patients with HCC with low serum albumin levels have poor overall survival and high recurrence rate[26]. In contrast, high levels of globulin indicate a systematic inflammatory response, which plays an important role in proliferation, progression, development, and metastasis of tumor cells[26-28].

The current study is restrained by several limitations. Although we had excluded the patients having anti-HBV treatment within 6 months before prior to HCC diagnosis, to reduce the potential influence of different screening frequency between patients with and without cirrhosis, some bias may still exist because of the retrospective and cross-sectional nature of this study. In addition, the disease background of both cohorts was not exactly the same; therefore, similar results observed from the two cohorts might verify its reliability only to some extent but could not be compared directly with each other. Further, only HBV-infected patients were investigated in this study; therefore, future studies including patients with other etiological factors of HCC are warranted.

5. Conclusion

In summary, this retrospective multicenter study demonstrated that HCC patients with compensated cirrhosis tend to harbor smaller tumor but severe cirrhosis favors tumor vascular invasion and metastasis, which affect tumor recurrence and survival of the patients. This further reminds us that for patients with cirrhosis, especially those with decompensated cirrhosis, risk of

vascular invasion and/or extrahepatic metastases should be given more attention. These observations may reconcile current controversies regarding the role of liver cirrhosis in HCC and may raise more heated discussions on this topic. Prospective and mechanism-related studies are needed to further clarify the effects of fibrosis and cirrhosis on HCC development and progression as these aspects would provide valuable insights into the development of anti-fibrotic therapy as HCC treatment.

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Conflict of interest

The authors declared no conflict of interest related to this article.

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