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ORIGINAL RESEARCH

Comparison of Clinical Manifestations and Related Factors of Hepatocellular Carcinoma with Chronic Hepatitis B

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Background: The aim of this study was to describe the demographic and clinical characteristics of hepatitis B virus (HBV) associated hepatocellular carcinoma (HCC), analyse the risk factors associated with HBV-associated HCC, and to provide some references to the diagnosis and treatment of HCC.

Methods: This study retrospectively enrolled 730 patients, including 390 patients with chronic hepatitis B (CHB) as controls, and 340 patients with CHB complicated with HCC as patients. Relevant information and medical records of these participants were collected, including age, sex, cigarette smoking, alcoholism, diabetes mellitus (DM), hypertension, coronary heart disease (CHD), cirrhosis, occupation, ascites, HBV-DNA load, the qualitative analysis of HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb serological markers, and levels of alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), gamma-glutamyltransferase (GGT), TNM stage, tumor size and tumor number. The *T* test, Chi-square test, non-parametric rank-sum test, logistic regression analyses were used to explore the influencing factors and their degree of association with HCC in patients with HBV.

Results: The proportion of smoking, alcoholism, married status, DM, hypertension, and the rate of HBV-DNA with a viral load of ≥500 copies/mL were significantly higher in the HCC group than in the controls (all $p<0.05$). Cirrhosis was more common among patients with CHB+HCC than in controls ($p=0.013$). The proportion of patients with HBsAg, HBeAb, and HBcAb positive was greater in CHB+HCC group than that in CHB group. Logistic regression analysis indicated that age ≥60 years (OR: 1.835, 95% CI: 1.020–3.302, $p=0.043$), HBeAb positive (OR: 9.105, 95% CI: 4.796–17.288, $p<0.001$), antiviral treatment with entecavir (OR: 2.209, 95% CI: 1.106–4.409, $p=0.025$), and GGT (OR: 1.004, 95% CI: 1.001–1.007, $p=0.002$) were risk factors for HCC in patients with CHB.

Conclusion: Advanced age, HBeAb positive, antiviral treatment with entecavir, and GGT were independent risk factors for HCC in HBV patients.

Keywords: chronic hepatitis B, hepatocellular carcinoma, cirrhosis, hepatitis B virus

Introduction

Hepatitis B virus (HBV) is a DNA virus that causes acute and chronic hepatitis, cirrhosis, severe liver failure and even death.[1,2] Approximately 250 million people are estimated to be infected with the HBV all over the world.[3] The prevalence of HBV infection in the general Chinese population was approximately 6.5% in 2018.[4] Chronic Hepatitis B (CHB) infection can promote mutations in liver cells and cause premature death from uncompensated liver cirrhosis and hepatocellular carcinoma (HCC).[5] Approximately 10%-25% of HBV-infected individuals will develop HCC during their lifetime.[6] HCC is the main type of liver cancers and accounts for 90% of primary liver cancers.[7] As one of the most common malignancies and the leading cause of death in 2020, HCC is the sixth most commonly diagnosed cancer and

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the third most common cause of cancer-related deaths worldwide, accounting for 8.3% of all cancers.[8,9] In particular, China alone accounted for 45.3% of liver cancer cases and 47.1% of liver cancer deaths.[10]

Chronic HBV infection can also cause hepatic cirrhosis, which is an important risk factor for HCC and the with an incidence rate of 3.78/100 person year.[11–13] Cirrhotic decompensation together with tumour recurrence, contributes to long-term mortality, even when curative treatment for early HCC is achieved. The prognosis of patients with HCC and cirrhotic is relatively poor, with a 5-year survival rate of < 20%.[14,15] The annual incidence of primary hepatocellular carcinoma (PHC) in non-cirrhotic HBV-infected patients is 0.5–1.0%, while that of PHC in HBV patients with cirrhosis is 3%-6%.[16] However, HCC in patients without liver cirrhosis should not be ignored. In addition, there is not doubt that even though there is an effective vaccine available to combat HBV infection, it remains a global public health problem. Over the past 30 years, antiviral drugs, nucleos(t)ide analog and/or interferon have been used in active chronic HBV carriers as antiviral treatment to delay and reduce the occurrence and development of hepatitis B-related events.[17] However, antiviral therapy cannot completely block the progression of hepatitis B infection to HCC. At present, survival rates for HCC are still poor.[18,19] Therefore, significant efforts in early diagnosis and better treatment are certainly needed.

The risk factors for the HCC related to HBV include age, sex, ethnicity,[10,20] socioeconomic status,[21] metabolic syndrome, cigarette,[22] alcohol consumption,[23] and so on.[11,24] Whether diabetes mellitus (DM) increases the risk of progression to HCC progression in patients with CHB remains unclear. Iliana Doycheva et al considered that DM did not increase the HCC risk in patients with CHB or primary biliary cholangitis,[25] while Abu Baker F et al showed that DM in patients with CHB was significantly and independently associated with cirrhosis and possibly with an increased risk of HCC.[26] Variations in the age-, sex-, and race-specific rates of HCC rates in different geographic regions are likely to be related to differences in the prevalence of HBV in these populations. The prevalence of HBV is uneven in different regions of China, to be specific, high in some southern provinces (>8%) and low in some western provinces (4–6%).[27]

Meizhou is a city located in the northeast of Guangdong Province, where the majority of residents are Hakka. However, information on the incidence of HBV-related cirrhosis and HCC is still lacking, and the risk factors need to be further investigated. In the present study, the comparison of clinical manifestations and related factors of HCC and cirrhotic patients with CHB was analyzed among Hakka people in southern China to increase our understanding of HCC prevalence and help to provide HCC prevention and control strategies.

Materials and Methods

Subjects

From December 2021 to December 2022, 730 patients diagnosed with CHB who underwent hematological testing and imaging analysis were recruited from the Meizhou People's Hospital, Guangdong province, China. There were 340 CHB-related HCC patients and 390 CHB individuals as controls.

HBV infection was diagnosed based on a periodical or consistently high alanine transaminase (ALT) level (≥ twice the upper limit of normal), and the presence of serum HBsAg and HBV DNA for more than six months.[28,29] HCC was diagnosed via liver biopsy and histology using computed tomography (CT) and magnetic resonance imaging, which also included a portal venous contrast-enhanced scan showing increased arterial vascularization within the tumor. Liver cirrhosis was diagnosed based on liver biopsy.[30] The exclusion criteria were co-infection with human immunodeficiency virus or hepatitis C virus, a history of any other malignancy, and a history or signs of infection or other causes of liver disease.

Data Collection

Clinical and laboratory parameters of patients were recorded and analyzed for the following variables: sex, age, the presence of cirrhosis, cigarette smoking, marital status, the presence of ascites, the history of DM, hypertension, coronary heart disease (CHD), levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), gamma-glutamyltransferase (GGT), international standardized ratio (INR), HBV DNA, the qualitative and quantitative analysis of HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb serological markers, and tumor number, tumor size, and tumor-node-metastasis (TNM) stage. Tumor size was measured as the longest diameter of the

tumor lesion(s) in at least one dimension, using liver dynamic computed tomographic findings.[31] This study was performed in accordance with the ethical standards of the Declaration of Helsinki and approved by the Human Ethics Committees of Meizhou People's Hospital.

Statistical Analysis

The data were analyzed using the SPSS software 26.0. The measurement data that met the normal distribution were expressed as means ± standard deviations using the *t*-test; the data not meeting the normal distribution were expressed as medians (25th and 75th percentiles) using the nonparametric test. Categorical variables were expressed as numbers and percentages and analyzed by the Chi-square test. Multivariate logistic regression analysis was used to account for possible confounding variables, and adjusted odds ratios (OR) were obtained with 95% confidence intervals (CI). All tests were two-tailed, with $p<0.05$ indicating statistical significance.

Results

Patient Demographic and Clinical Data

This study included 730 CHB patients, including 340 patients with HCC (296 males and 44 females) and 390 individuals without HCC (289 males and 101 females) as controls. The clinical characteristics of the CHB patients with and without HCC are summarized in Table 1. Among the 340 patients with HCC, the average age was 56.84±11.77 years, and 87.1% were men. Among the 390 patients without HCC, the average age was 47.64±12.95 years, and 74.1% were men. Compared with the control group, the HCC group was significantly older and had a higher proportion of male patients ($p<0.001$). The proportion of married status ($p<0.001$), cigarette smoking ($p<0.001$), alcoholism ($p=0.021$), DM ($p=0.004$), hypertension ($p<0.001$), and the proportion of HBV DNA with a viral load of ≥500 copies/mL ($p<0.001$) were significantly higher in the HCC group than in the control group. With regard to HBV status, the proportion of HBsAg positive ($p=0.005$), HBeAg positive ($p<0.001$), and HBeAb positive ($p<0.001$) were lower in the CHB+HCC group than those in the CHB group. Cirrhosis was more common among patients with CHB+HCC (60.0%) than in

Table 1 Demographic and Clinical Characteristics of CHB Patients with and without HCC

Characteristic	Total (n=730)	CHB Group (n=390)	CHB+HCC Group (n=340)	*p* values
Age, years	51.92±13.23	47.64±12.95	56.84±11.77	<0.001
Gender				<0.001
Male, *n*(%)	585 (80.1)	289 (74.1)	296 (87.1)	
Female, *n*(%)	145 (19.9)	101 (25.9)	44 (12.9)	
Married, *n*(%)	471 (64.5)	178 (45.6)	293 (86.2)	<0.001
Cigarette smoking, *n*(%)	59 (8.1)	15 (3.8)	44 (12.9)	<0.001
Alcoholism, *n*(%)	24 (3.3)	7 (1.8)	17 (5.0)	0.021
Diabetes mellitus, *n*(%)	42 (5.7)	13 (3.3)	29 (8.5)	0.004
Hypertension, *n*(%)	43 (5.8)	11 (2.8)	32 (9.4)	<0.001
CHD, *n*(%)	8 (1.1)	4 (1.0)	4 (1.2)	1.000
Cirrhosis, *n*(%)	399 (54.7)	195 (50.0)	204 (60.0)	0.013
Occupation, *n*(%)				<0.001
Unemployed	107 (14.7)	39 (10.0)	68 (20.0)	
Farmer	54 (7.4)	21 (5.4)	33 (9.7)	
Freelance	229 (31.4)	96 (24.6)	133 (39.1)	
Civil	2 (0.3)	2 (0.5)	0 (0)	
Self-employed	7 (1.0)	1 (0.3)	6 (1.8)	
Worker	16 (2.2)	10 (2.6)	6 (1.8)	
Other	69 (9.5)	23 (5.9)	46 (13.5)	
Unknown	246 (33.7)	198 (50.8)	48 (14.1)	

(*Continued*)

Table 1 (Continued).

Characteristic	Total (n=730)	CHB Group (n=390)	CHB+HCC Group (n=340)	*p* values
Ascites, *n*(%)	175 (24.0)	70 (17.9)	105 (30.9)	<0.001
HBV-DNA (copies/mL), n(%)				
<500	529(72.5)	309(79.2)	220(64.7)	<0.001
≥500	200(27.4)	81(20.8)	119(35.0)	
Unknown	1 (0.1)	0(0)	1 (0.3)	
HBV status				
HBsAg(+), *n*(%)	664(91.0)	364(93.3)	300(88.2)	0.005
HBsAb(+), *n*(%)	42(5.8)	16(4.1)	26(7.6)	0.128
HBeAg(+), *n*(%)	204(27.9)	140(35.9)	64(18.8)	<0.001
HBeAb(+), *n*(%)	191(26.2)	32(8.2)	159(46.8)	<0.001
HBcAb (+), *n*(%)	703(96.3)	375(96.2)	328(96.5)	0.847
Antiviral medication usage				
Entecavir	472(64.7)	218(55.9)	254(74.7)	<0.001
Tenofovir disoproxil tablets	100(13.7)	78(20.0)	22(6.5)	
Others	28(3.8)	23(5.9)	5(1.5)	
Unknown	130(17.8)	71(18.2)	59(17.4)	
ALT (IU/L)	39.00 (24.00, 101.00)	36.00 (23.00, 111.00)	41.00 (27.00, 99.00)	0.104
AST (IU/L)	43.00 (27.00, 106.00)	35.00 (24.00, 85.00)	54.00 (32.00, 123.00)	<0.001
TBIL(μmol/L)	18.20 (12.00, 33.00)	17.30 (10.80, 32.90)	19.45 (13.30, 33.58)	0.016
DBIL(μmol/L)	4.70 (2.70, 13.30)	3.80 (2.50, 11.70)	6.05 (3.10, 14.30)	<0.001
GGT (U/L)	58.00 (28.00, 127.00)	38.00 (23.00, 85.00)	94.00 (44.00, 168.75)	<0.001

Notes: Values for age expressed as mean±SD; Other nonparametric data are expressed as the median (25th and 75th percentiles). $p < 0.05$ was considered statistically significant.

Abbreviations: CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; CHD, coronary heart disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; GGT, gamma-glutamyltransferase.

controls (50.0%) (p=0.013). AST (p<0.001), TBIL (p=0.016), DBIL (p<0.001), and GGT (p<0.001) levels were significantly higher in patients with HCC than in controls without HCC. No statistically significant differences were observed between the groups in CHD (p=1.000). In terms of antiviral drug usage, the proportion of entecavir treatment in CHB+HCC group was significantly higher than that in CHB group (74.7% vs 55.9%, p<0.001).

Distribution Characteristics of HBV Serologic Positive Markers

According to Table 2, ① was regarded as HBsAg positive; ② anti-HBs-positive, ③ HBeAg positive, ④ anti-HBe positive, and ⑤ anti-HBc positive. There were 12 types of HBV status, of which the ①⑤, ①③⑤, and ①④⑤ types were the most common in patients with CHB. The numbers of ①⑤, ①③⑤ types in the CHB group without HCC were higher than those in the CHB group with HCC, while ①④⑤ was greater in the CHB+HCC group than in the CHB group. All CHB patients tested positive for anti-HBc antibodies.

General Characteristics of HCC Patients with and without Cirrhosis

Among patients with HCC, we studied the clinical characteristics of the cirrhosis and control groups (Table 3). In HCC patients, there was no significant difference between cirrhosis patients and the control group in TNM stage (p=0.640), tumor number (p=0.101), tumor size (p=0.054), positive rate of HBV status (all p>0.05), and ALT (p=0.998) level. In addition, a viral load of HBV-DNA <500 copies/mL was more common with or without cirrhosis, the proportion of HBV DNA with a viral load of ≥500 copies/mL was more common in HCC patients with cirrhosis than in the control group (40.7% vs 22.9%, p=0.002). AST (p=0.047), GGT (p=0.005), TBIL (p<0.001), and DBIL (p=0.001) levels were significantly higher than those in patients without cirrhosis. The proportion of entecavir treatment in cirrhosis group

Table 2 Serological Pattern Distribution of the Five HBV Markers Associated with HCC in Patients with CHB

HBV Serological Mode	Total (n=730)	CHB Group (n=390)	CHB+HCC Group (n=340)	*p* values
①⑤	288(39.5)	192(49.2)	96(28.2)	<0.001
①③⑤	185(25.3)	134(34.4)	51(15.0)	<0.001
①④⑤	164(22.5)	29(7.4)	135(39.7)	<0.001
②⑤	16(2.2)	7(1.8)	9(2.6)	0.458
①②③⑤	10(1.4)	4(1.0)	6(1.8)	0.527
④⑤	9(1.2)	0(0.0)	9(2.6)	0.001
②④⑤	8(1.1)	2(0.5)	6(1.8)	0.155
①③④⑤	8(1.1)	1(0.3)	7(2.1)	0.028
⑤	6(0.8)	2(0.5)	4(1.2)	0.425
①②⑤	5(0.7)	3(0.8)	2(0.6)	1.000
①②④⑤	2(0.3)	0(0.0)	2(0.6)	0.217
①②③④⑤	1(0.1)	0(0.0)	1(0.3)	0.466
Unknown	27(3.7)	15(3.8)	12(3.5)	–

Notes: $p< 0.05$ was considered statistically significant. ①, HBsAg positive; ②, Anti-HBs positive; ③, HBeAg positive; ④, Anti-HBe positive; ⑤, Anti-HBc positive.
Abbreviations: CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; Null, not available.

Table 3 Comparison of the Clinical Characteristics of HCC Patients with and without Cirrhosis

Characteristic	Total (n=309)	Control Group (n=105)	Cirrhosis Group (n=204)	*p* values
TNM stage				0.640
I-II	30(9.7)	8(7.6)	22(10.8)	
III-IV	68(22.0)	22(21.0)	46(22.5)	
Tumor number, *n*(%)				0.101
1	26(8.4)	13(12.4)	13(6.4)	
>1	14(4.5)	3(2.9)	11(5.4)	
Tumor size, *n*(%)				0.054
<5	131(42.4)	62(59.0)	69(33.8)	
≥5	91(29.4)	31(29.5)	60(29.4)	
HBV-DNA (copies/mL), n(%)				0.002
<500	201(65.0)	81(77.1)	120(58.8)	
≥500	107(34.6)	24(22.9)	83(40.7)	
HBV status				
HBsAg(+), *n*(%)	286(92.6)	93(88.6)	193(94.6)	0.059
HBsAb(+), *n*(%)	22(7.1)	11(10.5)	11(5.4)	0.224
HBeAg(+), *n*(%)	62(20.1)	27(25.7)	35(17.2)	0.125
HBeAb(+), *n*(%)	150(48.5)	45(42.9)	105(51.5)	0.211
HBcAb (+), *n*(%)	308(99.7)	105(100.0)	203(99.5)	1.000
Antiviral medication usage				0.002
Entecavir	239(77.3)	70(66.7)	169(82.8)	
Tenofovir disoproxil tablets	21(6.8)	14(13.3)	7(3.4)	
Others	5(1.6)	1(1.0)	4(2.0)	
ALT (IU/L)	41.00 (27.00, 99.00)	38.00 (23.00, 159.25)	42.00 (28.00, 83.00)	0.998
AST (IU/L)	54.00 (32.00, 123.00)	42.00 (28.00, 164.50)	58.00 (37.00, 122.00)	0.047
TBIL(μmol/L)	19.70 (13.30, 33.60)	16.30 (10.90, 26.73)	22.20 (14.40, 38.60)	<0.001
DBIL(μmol/L)	6.10 (3.10, 14.80)	4.55 (2.60, 9.70)	6.80 (3.70, 17.20)	0.001
GGT (U/L)	94.00 (44.00, 161.00)	70.50 (31.50, 137.00)	104.00 (48.00, 178.00)	0.005
Ascites, n(%)	103 (33.3)	14 (13.3)	89 (43.6)	<0.001

Notes: Nonparametric data are expressed as the median (25th and 75th percentiles). Categorical variables are expressed as numbers and percentages. TNM stage: American Joint Committee on Cancer-Tumor Node Metastasis staging. $p< 0.05$ was considered statistically significant.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; GGT, gamma-glutamyltransferase.

was significantly higher than that in control group (82.8% vs 66.7%, p=0.002). The proportion of ascites is higher in patients with HCC and cirrhosis than that in the control group (p<0.001).

Factors Associated with HCC in Patients with CHB

Logistic regression analysis was used to evaluate the independent predictors of HCC in patients with HBV infection. Univariate regression analysis was performed to obtain the unadjusted OR, and multiple logistic regression analysis was performed to obtain the adjusted OR. The Results of univariate regression analysis showed that there was a significantly higher risk of HCC in aged ≥60 years (p<0.001), males (p<0.001), the presence of smoking (p=0.013) and hypertension (p=0.035), serum HBV DNA load ≥500 copies/mL (p<0.001), HBeAb positive (p<0.001), antiviral treatment with entecavir (p<0.001), and cirrhosis (p=0.003). After adjusting for confounding factors using multiple logistic regression analysis, age ≥60 years (OR: 1.835, 95% CI: 1.020–3.302, p=0.043), HBeAb positive (OR: 9.105, 95% CI: 4.796–17.288, p<0.001), antiviral treatment with entecavir (OR: 2.209, 95% CI: 1.106–4.409, p=0.025), and GGT (OR: 1.004, 95% CI: 1.001–1.007, p=0.002) were risk factors for HCC. However, we found that cirrhosis was not an independent risk factor for HCC in multivariate logistic regression analysis (OR: 1.412, 95% CI: 0.779–2.559, p=0.255) (Table 4).

Discussion

HBV infection is a major risk factor for the development of HCC.[6] The proportion of HCC cases associated with HBV infection in China is as high as 84%.[32] Studies have shown that age, male gender,[33] tobacco exposure,[34] DM,[35,36] obesity,[37] HBV viral load,[38] ALT and AST,[39] TBIL,[40] GGT[41] are the independent risk factors for HCC in patients with HBV. As well as a risk factor for HCC, HBV viral load is also associated with HCC prognosis.[42] However, the HCC incidence rate varies not only among geographical locations but also among different populations inhabiting the same area.[43] Patients with HCC in China have their own special features in etiology, demographic features (risk factors, age of onset, gender distribution time trend of incidence), biological behavior, clinical manifestation, treatment strategy and prognosis.[44] Therefore, screening and identifying the high-risk groups of CHB patients with HCC is of great significance for the clinical diagnosis and treatment of these patients.

In this present study, the average age were 56.84±11.77 and 47.64±12.95 in the CHB+HCC group and CHB group, respectively. Corresponding to previous researches, some studies have shown that the mean age of HCC patients was 53 years.[45,46] Our study found that age ≥60 years was an independent risk factor for HCC progression in patients with HBV

Table 4 Logistic Regression Analysis of Risk Factors Associated with HCC in Patients with CHB

Variables	Unadjusted values		Adjusted values	
	OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values
Age (≥60/<60, years)	4.177(2.956–5.901)	<0.001	1.835(1.020–3.302)	0.043
Gender (Male/Female)	2.351(1.593–3.470)	<0.001	1.811(0.956–3.431)	0.069
Smoking (Yes/No)	2.023(1.158–3.535)	0.013	2.103(0.941–4.701)	0.070
Alcoholism (Yes/No)	0.985(0.500–1.939)	0.965	0.397(0.141–1.119)	0.081
Hypertension (Yes/No)	2.146(1.053–4.372)	0.035	1.527(0.591–3.948)	0.382
Cirrhosis (Yes/No)	1.604(1.171–2.197)	0.003	1.412(0.779–2.559)	0.255
HBV-DNA (≥500/<500, copies/mL)	2.063(1.482–2.873)	<0.001	0.944(0.547–1.631)	0.837
HBsAg (±)	0.324(0.159–0.661)	0.002	0.252(0.032–1.998)	0.192
HBeAb (±)	10.115(6.631–15.429)	<0.001	9.105(4.796–17.288)	<0.001
Antiviral medication usage (Entecavir/Antiviral drugs other than entecavir)	4.358(2.747–6.915)	<0.001	2.209(1.106–4.409)	0.025
AST	1.000(1.000–1.001)	0.204	1.000(0.999–1.001)	0.913
TBIL	1.001(0.998–1.003)	0.626	1.011(0.990–1.033)	0.312
DBIL	1.001(0.997–1.004)	0.613	0.979(0.951–1.008)	0.153
GGT	1.005(1.004–1.007)	<0.001	1.004(1.001–1.007)	0.002

Notes: p< 0.05 was considered statistically significant.

Abbreviations: CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; GGT, gamma-glutamyltransferase. OR, odds ratio; CI, confidence interval.

infection. CHB patients aged ≥60 years were more than 1.8 times more likely to develop HCC than those aged < 60 years. Previous studies have confirmed that poor lifestyle habits are associated with a high incidence of HCC. Tobacco smoke contains more than 7000 toxic substances, 60 of which are active carcinogens. In a 2010 meta-analysis of 16 studies, the risk of HCC increased from 15.8 to 21.6% in HBV-positive individuals who smoked.[47] Our results revealed that smoking to be an risk factor of HCC progression before adjustment, however, no significant difference was found after adjusting for confounding factors. It has been shown that around 591,000 male patients were found in a large study involving 854,000 patients with HCC worldwide in 2015, accounting for 69.20% in the HCC individuals.[48] This study found that the prevalence of HCC was higher in men than in women in southern China, which is in accordance with the above-mentioned study. The incidence of HCC is associated with metabolic diseases including DM and hypertension. Our study revealed that the DM and hypertension were more common in the CHB individuals with HCC ($p<0.05$), although there were not the independent risk factors for HCC progression.

In addition, married, unemployed, and freelancers are more likely to develop HCC. Marriage may be more strenuous and more likely to exacerbate disease progression, and jobless and freelancers are under greater employment pressure, which is more likely to trigger adverse emotions such as depression, which promotes the development of HCC.[49] The high HBV viral load (>500 copies/mL) was significantly different between the HBV and CHB+HCC groups, and the proportions of HBsAg positive and HBeAg positive were higher in CHB group while HBeAb positive was more greater in the CHB+HCC group. The levels of ALT, AST, TBIL, DBIL, and GGT were also likely to affect the development of HCC, but only HBeAb positive and GGT level were the independent risk factors for HCC progression in patients with HBV. CHD and ascites did not appear to affect the incidence of HCC, which may be because of the small size of the study sample.

Following HBV infection, a series of consistent antigens and antibodies is released into the serum, and their levels have a continuous process of change.[50,51] Therefore, the examination of the combination pattern of HBV serological markers is not only advantageous in detecting the immune status of the population against HBV, but also in estimating the therapeutic effect and prognostic outcomes of HBV-infected patients.[52,53] In this study, the top three serological combination patterns of patients with HBV infection were HBsAg-HBcAb positive, HBsAg-HBeAg-HBcAb positive and HBsAg-HBeAb-HBcAb positive. It was still noteworthy that the HBcAb was presented in all patients with HBV, with or without HCC. The patterns of HBsAg-HBcAb positive and HBsAg-HBeAg-HBcAb positive were more common in the HBV group, and HBsAg-HBeAb-HBcAb positive were more obvious in patients with HBV and HCC, indicating that the acute phase may exacerbate inflammation while, whereas, the chronic phase may promote cancer development. Individuals infected with HBV typically produce high level of HBcAb, which remain detectable for the duration of their lives; thus, the presence of HBcAb serves as a reliable indicator for evaluating the prevalence of HBV infection within a given population.[54,55]

Furthermore, cirrhosis was more common in the CHB patients with HCC, suggesting that cirrhosis may be an important cause of HCC development. Thus, our study analyzed the clinical manifestations of patients with HCC with or without cirrhosis. TNM stage, tumor number, tumor size, HBeAb positive, and ALT did not appear to affect the cirrhosis in patients with HCC. HBV-DNA load ≥500 copies/mL and antiviral treatment with entecavir were more common in the HCC patients who had cirrhosis. And the levels of AST, TBIL, DBIL, and GGT were higher in HCC patients with cirrhosis than those in HCC patients without cirrhosis (all $p<0.05$). The results indicated that cirrhosis was not strongly associated with the tumour characteristics of HCC, it did not influence the tumour stage or tumour size. In addition, some studies suggested that tenofovir disoproxil fumarate treatment was associated with a significantly lower risk of HCC than entecavir treatment in patients with CHB.[56–58] However, there are also some studies suggested that the difference in efficacy of different antiviral therapies in preventing HCC in CHB patients is unclear.[59–62] So more clinical studies are needed to determine this relationship.

The results of this study will provide a valuable reference for screening and identifying high-risk groups of CHB patients with HCC, and have important implications for clinical diagnosis and treatment of these patients. Specifically, imaging surveillance of the liver should be enhanced in CHB patients with ≥60 years old, HBeAb positive, and antiviral treatment with entecavir. It allows for early diagnosis and treatment of patients who develop HCC. This study has some limitations. First of all, this was a retrospective study, and there may have been selection bias because the patients were selected from one medical institution. Secondly, we analyzed the relationship between demographic and clinical characteristics, and HCC in patients with HBV infection; however, the data were still incomplete for a variety of reasons.

Thirdly, the region of the Subjects in this study was relatively limited, therefore, there may be some deviations in the results. It is necessary to increase the sample region and size for this study, which will be the focus of our future work.

Conclusion

In the present study, among patients with HBV infection, advanced age, HBeAb positive, antiviral treatment with entecavir, and GGT were independent risk factors for HCC. Our results need to be confirmed in future studies with larger sample size. The results should provide valuable information for the diagnosis and treatment of HCC.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital. All participants signed informed consent in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

References

1. Guvenir M, Arikan A. Hepatitis B virus: from diagnosis to treatment. *Pol J Microbiol*. 2020;69(4):391–399. doi:10.33073/pjm-2020-044
2. Odenwald MA, Paul S. Viral hepatitis: past, present, and future. *World J Gastroenterol*. 2022;28(14):1405–1429. doi:10.3748/wjg.v28.i14.1405
3. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ, Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet (London, England)*. 2015; 386(10003):1546–1555doi:10.1016/S0140-6736(15)61412-X
4. Wang H, Men P, Xiao Y, et al. Hepatitis B infection in the general population of China: a systematic review and meta-analysis. *BMC Infect Dis*. 2019;19(1):811. doi:10.1186/s12879-019-4428-y
5. Pisano MB, Giadans CG, Flichman DM, Ré VE, Preciado MV, Valva P. Viral hepatitis update: progress and perspectives. *World J Gastroenterol*. 2021;27(26):4018–4044. doi:10.3748/wjg.v27.i26.4018
6. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. *Hepatology*. 2021;1(Suppl 1):4–13. doi:10.1002/hep.31288
7. Péneau C, Imbeaud S, La Bella T. Hepatitis B virus integrations promote local and distant oncogenic driver alterations in hepatocellular carcinoma. *Gut*. 2022;71(3):616–626. doi:10.1136/gutjnl-2020-323153
8. Rizzo GEM, Cabibbo G, Craxì A, Hepatitis B. Virus-associated hepatocellular carcinoma. *Viruses*. 2022;14(5):986. doi:10.3390/v14050986
9. Sung H, Ferlay J, Siegel RL. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
10. Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. *J Hepatol*. 2022;77(6):1598–1606. doi:10.1016/j.jhep.2022.08.021
11. Petruzziello A. Epidemiology of hepatitis B Virus (HBV) and hepatitis C virus (HCV) related hepatocellular carcinoma. *Open Virol J*. 2018;12:26–32. doi:10.2174/1874357901812010026
12. Orci LA, Sanduzzi-Zamparelli M, Caballol B, et al. Incidence of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. *Clin Gastroenterol Hepatol*. 2022;20(2):283–292.e210. doi:10.1016/j.cgh.2021.05.002

13. Tan YW. Risk stratification of primary liver cancer. *World J Clin Cases*. 2022;10(26):9545–9549. doi:10.12998/wjcc.v10.i26.9545
14. Brar G, Greten TF, Graubard BI. Hepatocellular carcinoma survival by etiology: a SEER-medicare database analysis. *Hepatol Commun*. 2020;4 (10):1541–1551. doi:10.1002/hep4.1564
15. De Flora S, Crocetti E, Bonanni P, Ferro A, Vitale F.Incidence of infection-associated cancers in Italy and prevention strategies. *Epidemiol Prev*. 2015;39(4 Suppl 1):14–20.
16. Hou JL, Lai W. The guideline of prevention and treatment for chronic hepatitis B: a 2015 update. *Chin J Hepatol*. 2015;23(12):888–905. doi:10.3760/cma.j.issn.1007-3418.2015.12.002
17. Kruse RL, Kramer JR, Tyson GL, et al. Clinical outcomes of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients. *Hepatology*. 2014;60(6):1871–1878. doi:10.1002/hep.27337
18. Noh B, Park YM, Kwon Y, et al. Machine learning-based survival rate prediction of Korean hepatocellular carcinoma patients using multi-center data. *BMC Gastroenterol*. 2022;22(1):85. doi:10.1186/s12876-022-02182-4
19. Brown ZJ, Tsilimigras DI, Ruff SM, et al. Management of hepatocellular carcinoma: a review. *JAMA Surg*. 2023;158(4):410–420. doi:10.1001/jamasurg.2022.7989
20. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012;142(6):1264–1273.e1261. doi:10.1053/j.gastro.2011.12.061
21. Yun EH, Lim MK, Oh JK, et al. Combined effect of socioeconomic status, viral hepatitis, and lifestyles on hepatocelluar carcinoma risk in Korea. *Br J Cancer*. 2010;103(5):741–746. doi:10.1038/sj.bjc.6605803
22. Petrick JL, Campbell PT, Koshiol J, et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: the liver cancer pooling project. *Br J Cancer*. 2018;118(7):1005–1012. doi:10.1038/s41416-018-0007-z
23. Kimura T, Tanaka N, Fujimori N, et al. Mild drinking habit is a risk factor for hepatocarcinogenesis in non-alcoholic fatty liver disease with advanced fibrosis. *World J Gastroenterol*. 2018;24(13):1440–1450. doi:10.3748/wjg.v24.i13.1440
24. Pandyarajan V, Govalan R, Yang JD. Risk factors and biomarkers for chronic hepatitis b associated hepatocellular carcinoma. *Int J Mol Sci*. 2021;22(2):479. doi:10.3390/ijms22020479
25. Doycheva I, Zhang T, Amjad W, Thuluvath PJ. Diabetes and hepatocellular carcinoma: incidence trends and impact of liver disease etiology. *J Clin Exp Hepatol*. 2020;10(4):296–303. doi:10.1016/j.jceh.2019.11.004
26. Abu Baker F, Davidov Y, Israel A, et al. Chronic hepatitis B infection and diabetes mellitus: a double liver trouble? *Minerva Med*. 2023;114 (5):658–666. doi:10.23736/S0026-4806.23.08428-8
27. Wang Z, Huang Y, Wen S, Zhou B, Hou J. Hepatitis B virus genotypes and subgenotypes in China. *Hepatol Res*. 2007;37(s1):S36–41. doi:10.1111/j.1872-034X.2007.00102.x
28. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology*. 1996;111(4):1018–1022. doi:10.1016/s0016-5085(96)70070-7
29. Martin P, Lau DT, Nguyen MH, et al. A treatment algorithm for the management of chronic hepatitis b virus infection in the United States: 2015 update. *Clin Gastroenterol Hepatol*. 2015;13(12):2071–2087.e2016. doi:10.1016/j.cgh.2015.07.007
30. Di Lelio A, Cestari C, Lomazzi A, Beretta L. Cirrhosis: diagnosis with sonographic study of the liver surface. *Radiology*. 1989;172(2):389–392. doi:10.1148/radiology.172.2.2526349
31. Nijhara R, Jana SS, Goswami SK, et al. Sustained activation of mitogen-activated protein kinases and activator protein 1 by the hepatitis B virus X protein in mouse hepatocytes in vivo. *J Virol*. 2001;75(21):10348–10358. doi:10.1128/JVI.75.21.10348-10358.2001
32. Wang X, Lin SX, Tao J, et al. Study of liver cirrhosis over ten consecutive years in Southern China. *World J Gastroenterol*. 2014;20 (37):13546–13555. doi:10.3748/wjg.v20.i37.13546
33. Yip TC, Chan HL, Wong VW, Tse YK, Lam KL, Wong GL. Impact of age and gender on risk of hepatocellular carcinoma after hepatitis B surface antigen seroclearance. *J Hepatol*. 2017;67(5):902–908. doi:10.1016/j.jhep.2017.06.019
34. Purohit V, Rapaka R, Kwon OS, Song BJ. Roles of alcohol and tobacco exposure in the development of hepatocellular carcinoma. *Life Sci*. 2013;92 (1):3–9. doi:10.1016/j.lfs.2012.10.009
35. Li Q, Xu H, Sui C, Zhang H. Impact of metformin use on risk and mortality of hepatocellular carcinoma in diabetes mellitus. *Clin Res Hepatol Gastroenterol*. 2022;46(2):101781. doi:10.1016/j.clinre.2021.101781
36. Björkström K, Franzén S, Eliasson B, et al. Risk Factors for Severe Liver Disease in Patients With Type 2 Diabetes. *Clin Gastroenterol Hepatol*. 2019;17(13):2769–2775.e2764. doi:10.1016/j.cgh.2019.04.038
37. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. *J Clin Gastroenterol*. 2013;47(Suppl(0)):S2–6. doi:10.1097/MCG.0b013e3182872f29
38. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006;295 (1):65–73. doi:10.1001/jama.295.1.65
39. Ding Y, Liu K, Xu Y, et al. Combination of inflammatory score/liver function and AFP improves the diagnostic accuracy of HBV-related hepatocellular carcinoma. *Cancer Med*. 2020;9(9):3057–3069. doi:10.1002/cam4.2968
40. Kariyama K, Nouso K, Hiraoka A, et al. EZ-ALBI score for predicting hepatocellular carcinoma prognosis. *Liver Cancer*. 2020;9(6):734–743. doi:10.1159/000508971
41. De Jesus Brait B, Da silva lima SP, Aguiar FL, et al. Genetic polymorphisms related to the vitamin D pathway in patients with cirrhosis with or without hepatocellular carcinoma (HCC). *Ecancermedicalscience*. 2022;16:1383. doi:10.3332/ecancer.2022.1383
42. Chan HL, Tse CH, Mo F, et al. High viral load and hepatitis B virus subgenotype ce are associated with increased risk of hepatocellular carcinoma. *J Clin Oncol*. 2008;26(2):177–182. doi:10.1200/JCO.2007.13.2043
43. Liu M, Jiang L, Guan XY. The genetic and epigenetic alterations in human hepatocellular carcinoma: a recent update. *Protein Cell*. 2014;5 (9):673–691. doi:10.1007/s13238-014-0065-9
44. Wu Q, Qin SK. Features and treatment options of Chinese hepatocellular carcinoma. *Chin Clin Oncol*. 2013;2(4):38. doi:10.3978/j.issn.2304-3865.2013.09.07
45. Feng H, Kuai JH, Zhang MY, Wang GC, Shi YJ, Zhang JY. Tumor necrosis factor-alpha gene −308G > A polymorphism alters the risk of hepatocellular carcinoma in a Han Chinese population. *Diagn Pathol*. 2014;9(1):199. doi:10.1186/s13000-014-0199-3

46. Lu SN, Su WW, Yang SS, et al. Secular trends and geographic variations of hepatitis B virus and hepatitis C virus-associated hepatocellular carcinoma in Taiwan. *Int, J, Cancer*. 2006;119(8):1946–1952. doi:10.1002/ijc.22045
47. Chuang SC, Lee YC, Hashibe M, Dai M, Zheng T, Boffetta P. Interaction between cigarette smoking and hepatitis B and C virus infection on the risk of liver cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2010;19(5):1261–1268. doi:10.1158/1055-9965.EPI-09-1297
48. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: new trends. *J Hepatol*. 2020;72(2):250–261. doi:10.1016/j.jhep.2019.08.025
49. Pu C, Tian S, He S, et al. Depression and stress levels increase risk of liver cancer through epigenetic downregulation of hypocretin. *Genes Dis*. 2022;9(4):1024–1037. doi:10.1016/j.gendis.2020.11.013
50. Xiang KH, Michailidis E, Ding H, et al. Effects of amino acid substitutions in hepatitis B virus surface protein on virion secretion, antigenicity, HBsAg and viral DNA. *J Hepatol*. 2017;66(2):288–296. doi:10.1016/j.jhep.2016.09.005
51. Razavi-Shearer D, Child H, Razavi-Shearer K, Polaris Observatory Collaborators. Adjusted estimate of the prevalence of hepatitis delta virus in 25 countries and territories. *J Hepatol*. 2024;80(2):232–242. doi:10.1016/j.jhep.2023.10.043
52. Huang D, Wu D, Wang P, et al. End-of-treatment HBcrAg and HBsAb levels identify durable functional cure after Peg-IFN-based therapy in patients with CHB. *J Hepatol*. 2022;77(1):42–54. doi:10.1016/j.jhep.2022.01.021
53. Yin S, Wan Y, Issa R, et al. The presence of baseline HBsAb-Specific B cells can predict HBsAg or HBeAg seroconversion of chronic hepatitis B on treatment. *Emerg Microbes Infect*. 2023;12(2):2259003. doi:10.1080/22221751.2023.2259003
54. Kantar FU, Kahraman S, Ece G, Cagırgan S. Hepatitis B sero-prevalence among hematology patients: importance of Anti-HbcAb and efficiency of antiviral prophylaxis. *Afr Health Sci*. 2022;22(3):561–566. doi:10.4314/ahs.v22i3.60
55. Su S, Wong WC, Zou Z, et al. Cost-effectiveness of universal screening for chronic hepatitis B virus infection in China: an economic evaluation. *Lancet Glob Health*. 2022;10(2):e278–e287. doi:10.1016/S2214-109X(21)00517-9
56. Choi WM, Choi J, Lim YS. Effects of tenofovir vs entecavir on risk of hepatocellular carcinoma in patients with chronic HBV infection: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19(2):246–258.e249. doi:10.1016/j.cgh.2020.05.008
57. Yip TC, Wong VW, Chan HL, Tse YK, Lui GC, Wong GL. Tenofovir is associated with lower risk of hepatocellular carcinoma than entecavir in patients with chronic HBV infection in China. *Gastroenterology*. 2020;158(1):215–225.e216. doi:10.1053/j.gastro.2019.09.025
58. Liu H, Han CL, Tian BW, et al. Tenofovir versus entecavir on the prognosis of hepatitis B virus-related hepatocellular carcinoma: a systematic review and meta-analysis. *Expert Rev Gastroenterol Hepatol*. 2023;17(6):623–633. doi:10.1080/17474124.2023.2212161
59. Kim SK, Fujii T, Kim SR, et al. Hepatitis B virus treatment and hepatocellular carcinoma: controversies and approaches to consensus. *Liver Cancer*. 2022;11(6):497–510. doi:10.1159/000525518
60. Kim SU, Seo YS, Lee HA, et al. A multicenter study of entecavir vs. tenofovir on prognosis of treatment-naïve chronic hepatitis B in South Korea. *J Hepatol*. 2019;71(3):456–464. doi:10.1016/j.jhep.2019.03.028
61. Lee SW, Kwon JH, Lee HL. Comparison of tenofovir and entecavir on the risk of hepatocellular carcinoma and mortality in treatment-naïve patients with chronic hepatitis B in Korea: a large-scale, propensity score analysis. *Gut*. 2020;69(7):1301–1308. doi:10.1136/gutjnl-2019-318947
62. Oh H, Yoon EL, Jun DW, et al. No difference in incidence of hepatocellular carcinoma in patients with chronic hepatitis b virus infection treated with entecavir vs tenofovir. *Clin Gastroenterol Hepatol*. 2020;18(12):2793–2802.e2796. doi:10.1016/j.cgh.2020.02.046