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Original Article

Clinical characteristics and risk factors of hepatitis B virus-related cirrhosis/hepatocellular carcinoma: A single-center retrospective study☆

Feng Chen [a, b], Qianhui Li [a], Xiaomin Xu [a], Fei Wang [a, *]

[a] Division of Gastroenterology, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, Guangdong, China
[b] National Clinical Research Center for Infectious Diseases, The Third People's Hospital of Shenzhen, Shenzhen, Guangdong, China

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ABSTRACT

Background and aims: Hepatitis B virus (HBV) infection is a major global health problem which progresses to liver cirrhosis (LC) and hepatocellular carcinoma (HCC). Early prediction of disease changes and intervention are essential to slow disease progression and protect liver function. This study aimed to analyze the clinical characteristics of patients with HBV-related LC and HCC at different serum alanine aminotransferase (ALT) levels and explore the risk factors of HBV infection progressing to LC/HCC.

Methods: A total of 379 patients with HBV infection treated in The Third People's Hospital of Shenzhen between January 2014 and December 2016 without any antiviral drug therapy were enrolled. Patients were divided into the LC/HCC and non-LC/HCC groups based on clinical diagnosis, which was determined through imaging and expressions of pathological and laboratory test markers, and patients with LC/HCC were further divided into three groups according to the serum ALT levels. Differences in general information, clinical symptoms, and expression levels of serological indices of the above groups were compared and analyzed, logistic regression was used to analyze the risk factors for LC/HCC development, and the clinical diagnostic efficacy of indicators was judged by the receiver operator characteristic (ROC).

Results: LC/HCC mainly occurred in the ALT normal and mildly elevated groups, with 70.83% of patients with HCC having an LC background. In the comparison of different ALT level groups, the moderately−severely elevated group had the highest proportion of patients with skin jaundice, abdominal varices, rebound tenderness, higher white blood cell and neutrophil (NEUT) counts; and higher levels of aspartate aminotransferase, glutamyl transpeptidase, total bilirubin, and direct bilirubin. The LC/HCC group was older and had significantly higher proportions of male patients, alcohol consumption, and combined hypertension than the non-LC/HCC group (all $P < 0.05$). Logistic regression analysis showed that age, combined hypertension, abdominal varicose veins, subcostal palpation, and NEUT count were risk factors for LC/HCC development; and the area under the curve for this model on the ROC analysis was 0.935 (95% confidence interval 0.899−0.972) with specificity and sensitivity of 97.4% and 70.7%, respectively.

Conclusions: Advanced age, combined hypertension, abdominal varicose veins, subcostal palpation, and high NEUT count are risk factors for LC/HCC development in patients with untreated HBV infection.

1. Introduction

Hepatocellular carcinoma (HCC) has high morbidity and mortality rates in recent years because of its insidious onset, rapid progression, and high rates of recurrence and metastasis, with an overall 5-year survival rate of approximately 10%.[1] It is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide, accounting for more than 8% of all cancer-related deaths.[2] Viral hepatitis, particularly hepatitis B virus (HBV) infection, is the most common underlying liver disease leading to liver cirrhosis (LC) and HCC. Approximately 820,000 people die annually worldwide from HBV-related diseases, and HBV-related LC and HCC deaths account for 52% and 38%,

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* Corresponding author. Division of Gastroenterology, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, Guangdong, China.
E-mail address: wangf323@mail.sysu.edu.cn (Fei Wang).

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respectively.[3] In China, the proportion of HCC cases caused by HBV infection is as high as 84%.[3] Owing to the high prevalence of HBV infection and the seriousness of the resulting disease, it remains a serious threat to the health and safety of the population. Thus, in clinical practice, a careful understanding of the clinical course of patients with HBV infection diagnosed early and the risk factors that predict disease progression is an important reference for monitoring and guiding the treatment of patients.

Currently, recognized risk factors for liver cancer include HBV or hepatitis C virus infection, heavy alcohol consumption, obesity, aflatoxin exposure, and metabolic diseases such as diabetes.[4] Studies have identified LC as a major risk factor in HCC development.[5,6] HBV infection in patients with hepatitis B-related cirrhosis continues to exacerbate hepatic impairment and may eventually lead to HCC; however, a small proportion of patients with chronic hepatitis B (CHB) without cirrhosis may develop HCC directly, and up to one-third of patients with HBV infection leading to HCC do not have manifestations of cirrhosis.[7] In addition, LC is considered an independent risk factor for HCC-related death.[6] Timely identification and determination of the risk degree of patients developing LC/HCC and early intervention are key to determining patient outcomes. Clinical assessment of disease is usually based on the patient's pathology and imaging findings; however, pathology is invasive, patient compliance is poor, and diagnostic imaging is technically demanding and expensive. If markers with sensitive, specific, cost-effective, and reproducible tests could be identified to predict disease progression, the incidence of LC/HCC and mortality could be reduced. To thoroughly examine the clinical characteristics of HBV-related LC/HCC patients with different serum alanine aminotransferase (ALT) levels and explore the risk factors for LC/HCC progression, this study retrospectively analyzed relevant infection cases reported by The Third People's Hospital of Shenzhen to provide a reference basis for their clinical diagnosis and treatment.

2. Patients and methods

2.1. Ethical approval

All procedures were carried out according to the ethical standards of the institutional and/or national research committee, based on the 1975 Declaration of Helsinki. This retrospective study was approved by the Ethics Committee of The Third People's Hospital of Shenzhen (No. 2018–038). Written informed consent was obtained from each participant.

2.2. Patient selection and study design

In total, 379 patients with HBV infection who first visited The Third People's Hospital of Shenzhen between January 2014 and December 2016 and did not receive antiviral therapy were included. Patients who were eligible to be positive for hepatitis B surface antigen (HBsAg) and had complete medical history information and examination results were enrolled. Patients who had alcoholic liver disease, drug-related liver disease, autoimmune liver disease, hepatomegaly, other diseases that can affect liver function, thyroid disease and other autoimmune system diseases, other viral liver diseases (*e.g.*, hepatitis A, C, D, and E), and/or human immunodeficiency virus infection; previous anti-HBV treatment and/or immunomodulators; psychiatric illness, pregnancy, and breastfeeding; and other major organ damage diseases; and were participating in other interventional studies were excluded. According to the clinical diagnosis based on imaging, pathology, and expression of laboratory test markers, patients were divided into the LC/HCC group ($n = 55$) and the non-LC/HCC group ($n = 324$). In addition, according to serum ALT level, patients in the LC/HCC group were divided into the normal group (ALT <40 U/L, $n = 23$), mildly elevated group (40 U/L $\leq$ ALT <120 U/L, $n = 22$), and moderately–severely elevated group (120 U/L $\leq$ ALT <400 U/L, $n = 10$). A flow chart of the study design is presented in Fig. 1.

2.3. Research methods

By using a retrospective analysis method, clinical data of the enrolled patients were collected through the hospital's electronic medical record system, including general information such as sex, age, duration of HBV infection, family history of hepatitis B, marital history, smoking, alcohol consumption, and comorbidities. The presence of liver palms, spider nevus, scleral and skin jaundice, abdominal masses, abdominal varices, rebound tenderness, subcostal palpation, mobile turbid tones, and Kernig sign was recorded. The serological test indices of patients' first examination on admission were recorded, including routine blood count, hepatitis B markers, hepatic fibrosis, and liver function. Complications such as ascites, portal hypertension, and splenomegaly were recorded according to imaging and pathological findings. The clinical data of patients with different serum ALT levels and whether they have LC/HCC were compared and analyzed to explore the risk factors related to LC/HCC.

2.4. Statistical analysis

IBM SPSS Statistics version 26.0 (IBM Corp, Armonk, NY, USA) was used for data analysis. Quantitative data with normal distribution were expressed as mean ± standard deviation. Comparisons between multiple groups were first made by the one-way analysis of variance, and if differences between groups were statistically significant, further two-way comparisons were made using the LSD-*t* test. Quantitative data with non-normal distribution were represented by median and interquartile range as the central tendency, Kruskal–Wallis *H*-test and Dunnett's *t*-test for comparison between multiple groups, Wilcoxon rank sum test for comparison between two groups, and Chi-square test for comparison of categorical data. $P < 0.05$ was considered a statistically significant difference. Factors that were significant in the univariate analysis were included in the logistic regression analysis using the forward-biased likelihood ratio stepwise regression method, with the significance level of the included variables set at 0.05. Risk factors for LC/HCC development were screened, risk prediction models were constructed, and its differential diagnostic performance was evaluated by receiver operator characteristic (ROC) curves.

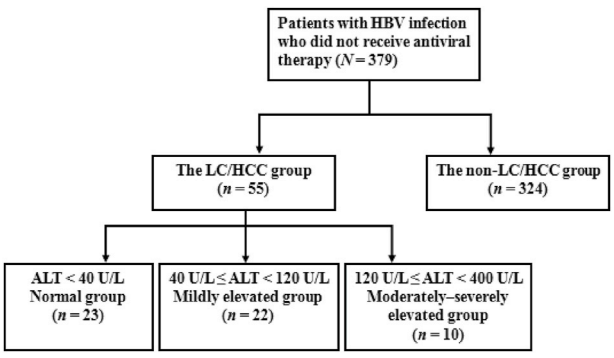

Fig. 1. Flow chart of the study design. Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LC, liver cirrhosis.

3. Results

3.1. Clinical characteristics of the LC/HCC group with different serum ALT levels

3.1.1. General information and clinical symptom analysis

A comparative analysis of general data and clinical symptoms of the LC/HCC group with different serum ALT levels at the first examination on admission (Table 1) revealed that LC/HCC mainly occurred in the normal and mildly elevated groups, with 70.8% of patients with HCC having a background of cirrhosis. Sex, age, marital status, smoking history, alcohol consumption, and comorbidities were not statistically significant when comparing groups by serum ALT levels (all $P > 0.05$). The proportion of patients with HBV family history was significantly higher in the moderately–severely elevated group than in the other two groups ($P < 0.05$). The duration of HBV positivity was longer in the moderately–severely elevated group (16.51 ± 11.79 years); however, no significant difference was observed in the comparison ($P > 0.05$). Our results also showed that the majority of patients with LC/HCC (39/55, 70.9%) were characterized by liver palms, with statistically significant differences (all $P < 0.05$) in the incidence of skin jaundice, abdominal varices, and rebound tenderness in patients with different ALT levels, and the rate was the highest in the moderately–severely elevated group. No significant differences in liver palms, spider nevus, scleral jaundice, abdominal masses, subcostal palpation, mobile turbid tones, ascites, portal hypertension, and splenomegaly were found among patients with different ALT levels (all $P > 0.05$).

3.1.2. Analysis of clinical parameters

After comparing and analyzing the laboratory results of the LC/HCC group by different serum ALT levels at the first examination on admission (Table 2), white blood cell (WBC) count, neutrophil (NEUT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), total protein (TP), total bilirubin (TBIL), and direct bilirubin (DBIL) showed significant differences among the groups (all $P < 0.05$) (Table 2). WBC, NEUT, AST, GGT, TBIL, and DBIL had the highest expression levels in the moderately–severely elevated group, followed by the mildly elevated group, which were significantly higher than those in the normal ALT group. In addition, the expression of TP was significantly lower in the moderately–severely elevated group than in the normal group, whereas no significant differences were observed in blood platelet (PLT) count, monocyte (MONO) ratio, HBV markers, carcinoma embryonic antigen (CEA), procollagen type III (PC-III), type IV collagen (IV-C), laminin (LN), hyaluronidase (HA), and indirect bilirubin (IBIL) among the groups (all $P > 0.05$) (Table 2).

3.2. Factors associated with the risk of LC/HCC development

3.2.1. General information and clinical symptom analysis

Among 55 patients with LC/HCC, the majority were male (44/55, 80.0%), the average age was 50.09 years, 90.9% were married, 30.9% had a family history of hepatitis B infection, the average time to detection of HBV positivity was 12.52 years, and 20.0% and 25.5% had a history of smoking and alcohol consumption, respectively (Table 3). The proportions of patients with combined hypertension, diabetes, and renal disease were 12.7%, 5.5%, and 1.8%, respectively. The LC/HCC group had significantly higher proportions of older patients, male patients, patients with a history of alcohol consumption, and patients with combined hypertension than the non-LC/HCC group (all $P < 0.05$) (Table 3). However, no significant differences were found in the number of married patients, duration of HBV positivity, family history of hepatitis B infection, smoking history, and combined diabetes and renal disease between the two groups (all $P > 0.05$) (Table 3). Furthermore, the LC/HCC group showed more pronounced clinical symptoms and had higher rates

Table 1
General information and clinical characteristics of patients with cirrhosis/hepatocellular carcinoma by different serum ALT levels.

Characteristics	ALT			F/χ^2-value	P- value
	Normal ($n = 23$)	Mildly elevated ($n = 22$)	Moderately– severely elevated ($n = 10$)		
General information					
Male, n (%)	17 (73.9)	18 (81.8)	9 (90.0)	$\chi^2 = 1.203$	0.548
Age (year)	50.35 ± 15.13	47.91 ± 14.48	54.30 ± 11.54	$F = 0.693$	0.505
Married, n (%)	21 (91.3)	20 (90.9)	9 (90.0)	$\chi^2 = 0.014$	0.993
Duration of HBV positivity (years)	10.85 ± 10.80	12.46 ± 7.06	16.51 ± 11.79	$F = 1.194$	0.311
Family history of HBV, n (%)	3 (13.0)	8 (36.4)	6 (60.0)	$\chi^2 = 7.707$	**0.021**
Smoking history, n (%)	5 (21.7)	3 (13.6)	3 (30.0)	$\chi^2 = 1.225$	0.542
Drinking history, n (%)	6 (26.1)	5 (22.7)	3 (30.0)	$\chi^2 = 0.200$	0.905
Comorbidities, n (%)					
Hypertension	3 (13.0)	2 (9.1)	2 (20.0)	$\chi^2 = 0.740$	0.691
Diabetes	2 (8.7)	0	1 (10.0)	$\chi^2 = 2.138$	0.343
Kidney disease	1 (4.3)	0	0	$\chi^2 = 1.417$	0.492
Clinical characteristics, n (%)					
Liver palms	16 (69.6)	14 (63.6)	9 (90.0)	$\chi^2 = 2.351$	0.309
Spider nevus	9 (39.1)	6 (27.3)	3 (30.0)	$\chi^2 = 0.759$	0.684
Scleral jaundice	5 (21.7)	6 (27.3)	6 (60.0)	$\chi^2 = 5.005$	0.082
Skin jaundice	5 (21.7)	7 (31.8)	7 (70.0)	$\chi^2 = 7.300$	**0.026**
Abdominal masses	0	2 (9.1)	0	$\chi^2 = 3.113$	0.211
Abdominal varices	4 (17.4)	1 (4.5)	4 (40.0)	$\chi^2 = 6.345$	**0.042**
Rebound tenderness	4 (17.4)	3 (13.6)	6 (60.0)	$\chi^2 = 9.042$	**0.011**
Subcostal palpation	5 (21.7)	7 (31.8)	6 (60.0)	$\chi^2 = 4.648$	0.098
Mobile turbid tones	9 (39.1)	8 (36.4)	5 (50.0)	$\chi^2 = 0.545$	0.761
Ascites	3 (13.0)	2 (9.1)	0	$\chi^2 = 1.435$	0.488
Portal hypertension	5 (21.7)	4 (18.2)	1 (10.0)	$\chi^2 = 0.646$	0.724
Splenomegaly	6 (26.1)	5 (22.7)	2 (20.0)	$\chi^2 = 0.160$	0.923
HCC, n (%)	8 (34.8)	10 (45.5)	6 (60.0)	$\chi^2 = 1.851$	0.396
HCC with cirrhosis background, n (%)	6/8 (75.0)	7/10 (70.0)	4/6 (66.7)	$\chi^2 = 0.121$	0.941

Data were expressed as mean ± standard deviation or n (%).
Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.
Bold indicates P values < 0.05.

Table 2
Clinical parameters of patients with cirrhosis/hepatocellular carcinoma by serum ALT levels.

Variable	ALT			*H*-value	*P*-value
	Normal ($n = 23$)	Mildly elevated ($n = 22$)	Moderately–severely elevated ($n = 10$)		
WBC ($\times 10^9$/L)	5.52 (4.72–6.70)	8.18 (4.65–13.24)[a]	10.83 (6.12–14.39)[a]	6.646	**0.036**
PLT ($\times 10^9$/L)	185.00 (95.50–237.00)	185.50 (116.00–294.25)	179.00 (121.00–308.00)	0.757	0.685
MONO (%)	6.05 (5.38–8.23)	5.25 (4.05–8.40)	6.25 (3.95–8.23)	1.078	0.583
NEUT (%)	63.00 (57.03–72.18)	74.75 (63.43–88.40)[a]	82.80 (65.10–89.53)[a]	6.689	**0.035**
HBsAg (IU/mL)	268.41 (0.02–1513.42)	329.55 (1.63–1564.72)	625.40 (40.64–2553.60)	1.350	0.509
HBsAb (mIU/mL)	0.34 (0.09–2.78)	0.18 (0–1.42)	0.55 (0–3.97)	0.767	0.681
HBeAg (S/CO)	0.39 (0.36–0.52)	0.36 (0.33–0.42)	0.36 (0.34–0.38)	2.914	0.233
HBeAb (S/CO)	0.250 (0.020–0.820)	0.055 (0.010–0.405)	0.020 (0.018–0.035)	2.668	0.263
HBcAb (S/CO)	10.38 (9.50–10.94)	10.77 (9.35–11.66)	10.02 (8.51–11.21)	1.187	0.552
CEA (μg/L)	1.87 (0.92–3.16)	1.74 (1.05–2.86)	1.90 (0.80–2.59)	0.071	0.965
PC-III (ng/mL)	40.60 (23.31–56.65)	60.25 (33.28–160.13)	63.30 (43.01–74.92)	5.508	0.064
IV-C (ng/mL)	40.41 (25.10–53.46)	58.68 (34.52–146.30)	55.10 (37.87–90.46)	5.697	0.058
LN (ng/mL)	64.13 (38.22–76.89)	66.83 (48.52–110.90)	73.61 (58.48–92.05)	2.163	0.339
HA (ng/mL)	243.57 (114.71–399.78)	361.72 (148.89–1267.38)	457.58 (313.45–1423.50)	5.107	0.078
AST (U/L)	36.00 (29.00–46.00)	108.50 (40.25–245.50)[a]	493.00 (156.25–627.50)[a,b]	26.377	**0.000**
GGT (U/L)	38.00 (20.00–79.00)	130.50 (52.50–361.75)[a]	327.50 (121.00–887.00)[a]	17.808	**0.000**
TP (g/L)	71.90 (68.40–77.80)	70.10 (60.73–75.93)	64.10 (60.15–69.55)[a]	7.244	**0.027**
TBIL (μmol/L)	10.30 (4.80–40.50)	21.90 (7.60–87.25)	51.70 (14.83–159.58)[a]	6.533	**0.038**
DBIL (μmol/L)	5.30 (3.80–14.30)	15.15 (5.70–106.00)[a]	33.75 (9.83–132.85)[a]	9.154	**0.010**
IBIL (μmol/L)	11.60 (7.90–25.20)	17.75 (9.93–43.75)	31.65 (17.65–63.68)	6.010	0.050

Data were expressed as median (interquartile range).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoma embryonic antigen; IV-C, type IV collagen; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; HA, hyaluronidase; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B envelope antibody; HBeAg, hepatitis B envelope antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; IBIL, indirect bilirubin; LN, laminin; MONO, monocyte; NEUT, neutrophil; PC-III, procollagen type III; PLT, platelet; S/CO, signal-to-cutoff; TBIL, total bilirubin; TP, total protein; WBC, white blood cell.
[a] Compared with the normal group, $P < 0.05$; [b] compared with the mildly elevated group, $P < 0.05$.
Bold indicates P values < 0.05.

Table 3
General information and clinical symptoms of patients with cirrhosis/hepatocellular carcinoma.

Characteristics	Cirrhosis/hepatocellular carcinoma		t/χ^2-value	*P*-value
	Yes ($n = 55$)	No ($n = 324$)		
General information				
Male, *n* (%)	44 (80.0)	202 (62.3)	$\chi^2 = 6.434$	**0.011**
Age (year)	50.09 ± 14.22	35.78 ± 10.65	$t = -8.781$	**0.000**
Married, *n* (%)	50 (90.9)	265 (81.8)	$\chi^2 = 2.786$	0.095
Duration of HBV positivity (year)	12.52 ± 9.71	10.93 ± 7.64	$t = -1.370$	0.172
Family history of HBV, *n* (%)	17 (30.9)	118 (36.4)	$\chi^2 = 0.623$	0.430
Smoking history, *n* (%)	11 (20.0)	45 (13.9)	$\chi^2 = 1.394$	0.238
Drinking history, *n* (%)	14 (25.5)	30 (9.3)	$\chi^2 = 12.018$	**0.001**
Comorbidities, *n* (%)				
Hypertension	7 (12.7)	11 (3.4)	$\chi^2 = 9.052$	**0.003**
Diabetes	3 (5.5)	7 (2.2)	$\chi^2 = 1.986$	0.159
Kidney disease	1 (1.8)	10 (3.1)	$\chi^2 = 0.268$	0.604
Clinical characteristics, *n* (%)				
Liver palms	39 (70.9)	146 (45.1)	$\chi^2 = 12.572$	**0.000**
Spider nevus	18 (32.7)	34 (10.5)	$\chi^2 = 19.634$	**0.000**
Scleral jaundice	17 (30.9)	68 (21.0)	$\chi^2 = 2.660$	0.103
Skin jaundice	19 (34.5)	75 (23.1)	$\chi^2 = 3.275$	0.070
Abdominal masses	2 (3.6)	0	$\chi^2 = 11.844$	**0.001**
Abdominal varices	9 (16.4)	4 (1.2)	$\chi^2 = 32.490$	**0.000**
Rebound tenderness	13 (23.6)	11 (3.4)	$\chi^2 = 32.478$	**0.000**
Subcostal palpation	18 (32.7)	12 (3.7)	$\chi^2 = 54.338$	**0.000**
Mobile turbid tones	22 (40.0)	4 (1.2)	$\chi^2 = 110.583$	**0.000**
Kernig sign	0	1 (0.3)	$\chi^2 = 0.170$	0.680
Ascites	5 (9.1)	2 (0.6)	$\chi^2 = 18.623$	**0.000**
Portal hypertension	10 (18.2)	0	$\chi^2 = 60.506$	**0.000**
Splenomegaly	13 (23.6)	0	$\chi^2 = 79.302$	**0.000**

Data were expressed as mean ± standard deviation or n (%).
Abbreviation: HBV, hepatitis B virus.
Bold indicates P values < 0.05.

of liver palms, spider nevus, scleral jaundice, skin jaundice, subcostal palpation, mobile turbid sounds, rebound tenderness, splenomegaly, abdominal varices, portal hypertension, ascites, and abdominal mass than the non-LC/HCC group. Except for scleral jaundice, skin jaundice, and Kernig sign, which were not significantly different in the comparison (all $P > 0.05$), all other symptoms were significantly different between the two groups (all $P < 0.01$) (Table 3).

3.2.2. Analysis of laboratory results

In the comparison of clinical parameters between the two groups at the first examination on admission, the levels of NEUT, CEA, PC-III, IV-C, LN, HA, GGT, TBIL, DBIL, and IBIL were significantly higher in the LC/HCC group than in the non-LC/HCC group (Table 4). Meanwhile, the levels of HBsAg, hepatitis B envelope antigen (HBeAg), hepatitis B envelope antibody (HBeAb), and ALT were significantly lower than those in the non-LC/HCC group, with statistical significance (all $P < 0.05$) (Table 4), whereas the other indicators such as WBC, PLT, MONO, hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), AST, and TP were not significantly different between the two groups (all $P > 0.05$) (Table 4).

3.3. Logistic regression analysis of the risk of cirrhosis/HCC

The indicators that were statistically significant in the above comparative analysis were further selected for the multifactor logistic regression analysis. Among the influencing factors that were entered in the final model, age, combined hypertension, abdominal varices, subcostal palpation, and NEUT count were positively associated with the risk of LC/HCC development (Table 5). The regression equation established by these combination factors to predict the LC/HCC risk was logit (P) = −11.306 + 0.081 × age + 2.121 × combined hypertension + 2.997 × abdominal varices + 2.299 × subcostal palpation + 0.084 × NEUT, and the diagnostic performance of the model was evaluated by ROC, which showed that area under the curve (AUC) was 0.935 (95% CI 0.899–0.972), with a sensitivity and specificity of prediction of 70.7% and 97.4% respectively, indicating a high diagnostic value (Fig. 2A). When they were analyzed as independent risk factors for predicting LC/HCC development, their respective ROC curves showed that AUCs corresponding to age, combined hypertension, abdominal varices, subcostal palpation, and NEUT count were 0.803 (95% CI 0.739–0.867), 0.546 (95% CI 0.458–0.634), 0.576 (95% CI 0.486–0.666), 0.646 (95% CI 0.555–0.737), and 0.752 (95% CI 0.671–0.832), respectively (Fig. 2B). The results of the ROC analysis with different combinations of multiple factors showed that the AUCs corresponding to age + NEUT (Fig. 2C), age + NEUT + subcostal palpation (Fig. 2D), age + NEUT + subcostal palpation + abdominal varices (Fig. 2E), and age + subcostal palpation + abdominal varices + combined hypertension (Fig. 2F) were 0.840 (95% CI 0.780–0.900), 0.865 (95% CI 0.809–0.920), 0.875 (95% CI 0.820–0.929), and 0.847 (95% CI 0.789–0.905), respectively, all of moderate diagnostic value.

4. Discussion

HBV infection causes a continuous recurrent process of hepatocellular and extracellular matrix damage, leading to progressive chronic liver disease damage, such as cirrhosis, with complex clinical manifestations and aggressive complications, which,

Table 4
Comparison of clinical parameters in patients with cirrhosis/hepatocellular carcinoma.

Variable	Cirrhosis/hepatocellular carcinoma		*Z*-value	*P*-value
	Yes ($n = 55$)	No ($n = 324$)		
WBC (× 10^9/L)	6.65 (4.79–12.36)	6.22 (5.12–7.48)	−1.220	0.223
PLT (× 10^9/L)	184.00 (111.25–268.25)	206.00 (164.00–246.00)	−1.700	0.089
MONO (%)	5.95 (4.43–8.18)	6.30 (4.90–7.80)	−0.588	0.556
NEUT (%)	69.85 (60.38–83.80)	56.60 (49.90–63.40)	−5.912	**0.000**
HBsAg (IU/mL)	354.95 (0.51–1579.74)	3299.59 (560.49–13636.83)	−6.090	**0.000**
HBsAb (mIU/mL)	0.33 (0–2.45)	0.32 (0.02–1.03)	−0.757	0.449
HBeAg (S/CO)	0.37 (0.34–0.45)	4.36 (0.38–870.74)	−5.777	**0.000**
HBeAb (S/CO)	0.04 (0.02–0.46)	1.18 (0.02–45.54)	−4.831	**0.000**
HBcAb (S/CO)	10.38 (9.39–11.19)	10.52 (9.31–11.61)	−1.049	0.294
CEA (μg/L)	1.81 (1.08–2.66)	1.00 (0.50–1.69)	−4.093	**0.000**
PC-III (ng/mL)	47.51 (34.13–79.37)	27.56 (19.82–44.26)	−4.657	**0.000**
IV-C (ng/mL)	46.26 (33.13–86.50)	27.12 (21.17–43.43)	−4.400	**0.000**
LN (ng/mL)	64.50 (51.53–84.02)	38.46 (30.31–64.50)	−5.154	**0.000**
HA (ng/mL)	313.21 (157.32–653.60)	119.56 (74.67–185.14)	−5.849	**0.000**
ALT (U/L)	51.00 (26.00–104.00)	120.50 (57.25–254.25)	−5.398	**0.000**
AST (U/L)	50.00 (35.00–187.00)	59.50 (35.25–113.75)	−0.391	0.696
GGT (U/L)	110.00 (37.00–311.00)	52.00 (28.00–116.00)	−2.594	**0.009**
TP (g/L)	70.60 (64.10–74.80)	70.25 (65.93–75.00)	−0.351	0.725
TBIL (μmol/L)	17.60 (7.70–59.10)	11.50 (5.10–35.10)	−2.137	**0.033**
DBIL (μmol/L)	10.60 (5.00–33.50)	5.60 (3.80–12.50)	−2.815	**0.005**
IBIL (μmol/L)	17.10 (9.10–32.70)	11.70 (7.73–18.40)	−2.617	**0.009**

Data were expressed as median (interquartile range).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoma embryonic antigen; IV-C, type IV collagen; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; HA, hyaluronidase; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B envelope antibody; HBeAg, hepatitis B envelope antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; IBIL, indirect bilirubin; LN, laminin; MONO, monocyte; NEUT, neutrophil; PC-III, procollagen type III; PLT, platelet; S/CO, signal-to-cutoff; TBIL, total bilirubin; TP, total protein; WBC, white blood cell.
Bold indicates *P* values < 0.05.

Table 5
Factors associated with the risk of cirrhosis/hepatocellular carcinoma.

Factors	B	SE	Wald χ^2	OR (95% CI)	*P*-value
Age	0.081	0.020	16.208	1.084 (1.043–1.128)	0.000
Combined hypertension	2.121	0.910	5.433	8.337 (1.401–49.593)	0.020
Abdominal varices	2.997	1.483	4.085	20.022 (1.095–366.151)	0.043
Subcostal palpation	2.299	0.904	6.462	9.966 (1.693–58.669)	0.011
NEUT	0.084	0.024	12.174	1.088 (1.037–1.140)	0.000

Abbreviations: CI, confidence interval; NEUT, neutrophil; OR, odds ratio; SE, standard error.

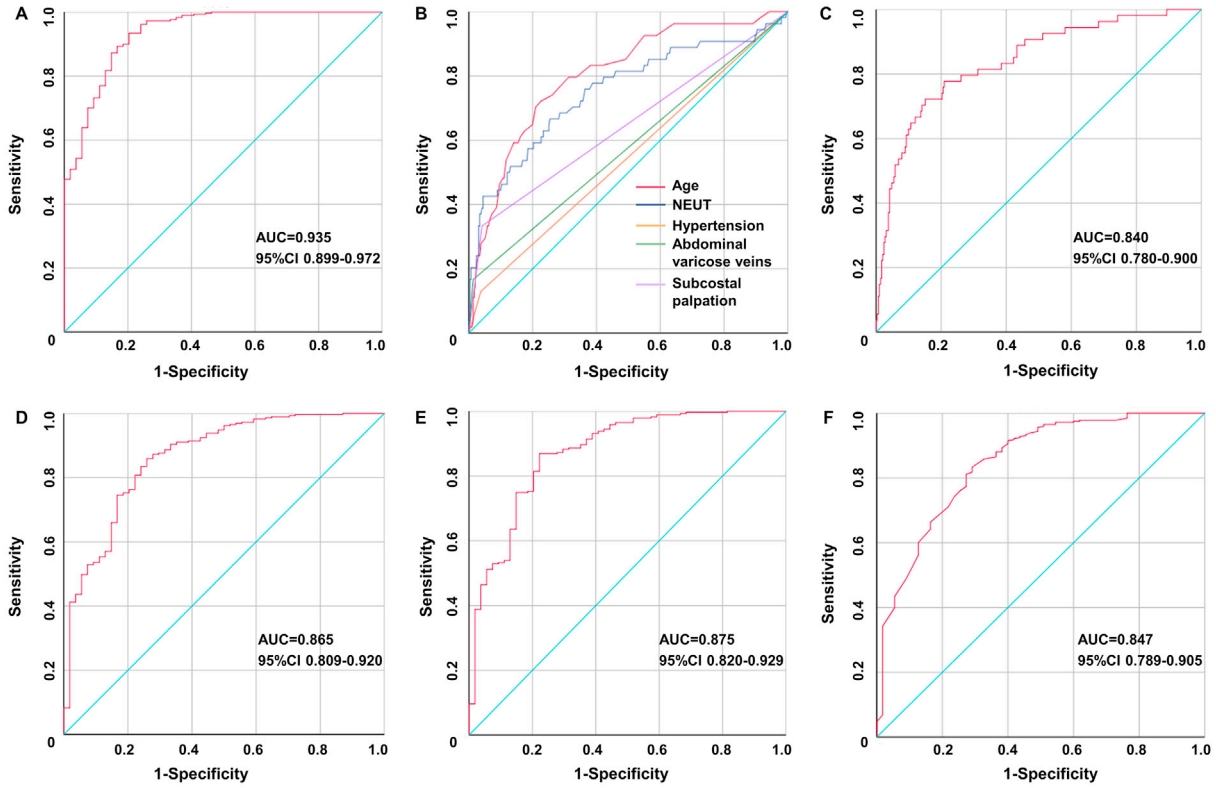

Fig. 2. ROC curve analysis of risk factors for cirrhosis/hepatocellular carcinoma development. **(A)** Combining these factors, including age, combined hypertension, abdominal varices, subcostal palpation, and NEUT count. **(B)** Age, NEUT count, combined hypertension, abdominal varices, and subcostal palpation as independent risk factors. ROC curves showed that AUCs corresponding to age, NEUT count, combined hypertension, abdominal varices, and subcostal palpation were 0.803 (95% CI 0.739–0.867), 0.752 (95% CI 0.671–0.832), 0.546 (95% CI 0.458–0.634), 0.576 (95% CI 0.486–0.666), and 0.646 (95% CI 0.555–0.737), respectively. Different combinations of multiple factors such as **(C)** age + NEUT count, **(D)** age + NEUT count + subcostal palpation, **(E)** age + NEUT count + subcostal palpation + abdominal varices, and (**F**) age + subcostal palpation + abdominal varices + combined hypertension. Abbreviations: AUC, area under the curve; CI, confidence interval; NEUT, neutrophil; ROC, receiver operator characteristic.

together with its complications such as hypersplenism, ascites, and carcinoma, are the main causes of death in patients with HBV infection.[8] In China, most patients with HCC have a background of chronic liver inflammation and cirrhosis, and more than half of these cases can be attributed to HBV infection. Despite the availability of vaccination prophylaxis and effective antiviral therapy, HBV infection remains the most common risk factor for LC/HCC because of the lack of early detection and late intervention in most patients, coupled with the poor prognosis and high mortality rate of HCC. If easy-to-operate screening markers with good sensitivity and specificity could be identified in the clinic for the prognosis of disease progression, early diagnosis and treatment of patients with LC/HCC would be possible,[9,10] reducing its incidence and mortality.

In this study, the clinical characteristics of patients with HBV-related LC/HCC with different serum ALT levels were initially compared and analyzed. The LC/HCC mainly occurred in patients in the normal and mildly elevated groups. Approximately 30% of patients with HCC did not have a cirrhosis background, which is slightly lower than previously reported proportions.[7] Signs of skin jaundice, abdominal varices and rebound tenderness, and abnormal expression levels of liver function markers were most pronounced in the moderately–severely elevated group, suggesting that among patients with untreated HBV infection, those with severe abnormalities in ALT levels have more intense liver inflammatory activity. At this stage, liver inflammation is still in a progressive state. Patients with normal ALT levels, although not showing significant abnormalities in liver function, should be informed of the severity of disease progression as age increases. Previous studies have shown that the incidence of HCC is positively correlated with age,[11] and the incidence of HCC in China increases significantly from the age of 25 years, peaking at the age of 60 years, with a linear increase in mortality from 45 to 85 years;[12] thus, older age is an independent predictor of the risk of cirrhosis and HCC in inactive HBV carriers.[13] Further comparisons of the clinical data of patients with or without LC/HCC in this study revealed that not only age but also the proportion of male participants, alcohol consumption, and combined hypertensions in the LC/HCC group were significantly higher than these in the non-LC/HCC group. The average age at diagnosis of HCC in China is 52 years old, more than 10 years younger than those in North America, Europe, and Japan.[14] Because some of the study participants had cirrhosis, a slightly lower average age than what is reported in the literature was noted. The incidence of HCC is 2–4 times higher in men than in women,[2] which may be related to the ability of androgens to directly bind to androgen response elements in the enhancer I region of the HBV genome, enhancing HBV gene replication and transcription, and consequently contributing to HCC development.[15] Meanwhile, men are exposed to more risk factors than women, such as smoking, alcohol consumption, and obesity. Excessive alcohol consumption is widely recognized as a risk factor for HCC development,[16] and a recent study showed that even mild-to-moderate alcohol intake was associated with higher all-cause mortality in patients with chronic viral hepatitis.[17] As the global prevalence of comorbidities such as diabetes, renal disease, hypertension, and coronary heart disease in patients with HBV infection continues to rise, these comorbidities are increasingly associated with HCC development. The European Association for the Study of the Liver identified diabetes as a risk factor for HCC in patients with CHB,[18] and the

results of another study suggested that in adults with HBV infection, diabetes is associated with progression to severe liver outcomes, including cirrhosis, HCC, and death.[19] However, whether comorbid hypertension is a risk factor for the progression of HBV infection to LC/HCC remains unclear.

The results of this study demonstrated that the LC/HCC group had more pronounced clinical symptoms, with signs mostly presenting as liver disease facies, commonly liver palms, spider nevi, scleral/skin jaundice, subcostal palpation, and mobile turbid tones; whereas abdominal varices, abdominal masses, and Kernig signs were rare; and complications included portal hypertension, ascites, splenomegaly, and higher expression levels of the liver fibrosis indicator and CEA than the non-LC/HCC group. The multifactor logistic regression analysis revealed that advanced age, combined hypertension, abdominal varices, subcostal palpation, and high NEUT count were risk factors for LC/HCC development in patients with HBV infection. The combined predictive model had an AUC of 0.935 with high sensitivity and specificity, indicating that the model has good diagnostic performance. Moreover, when the above factors were taken as independent risk factors for the ROC analysis, only age showed an AUC value > 0.800, indicating that advanced age alone also has a relatively good diagnostic value for predicting the risk of LC/HCC development, a finding that is consistent with the results of several studies.[20–22] The AUC values obtained by different combinations of the above factors slightly varied, ranging from 0.840 to 0.875, with somewhat poorer diagnostic performance than when the five factors were combined simultaneously.

A limitation of our study was the retrospective analysis, the small sample size of enrolled patients, the relatively short enrolment period, and the fact that it originated from a single hospital, which may lead to some bias and limitations in the results of the analysis, and prospective studies are needed to validate the reliability of the model constructed in this study.

5. Conclusions

In summary, our data suggested that in patients with HBV infection who are not on antiviral therapy, clinicians should be aware that the risk of progression to LC/HCC increases with age. The combination of advanced age, combined hypertension, abdominal varices, subcostal palpation, and NEUT count provides a good predictor of the risk of LC/HCC development in patients with HBV infection, and clinicians can improve patient prognosis by early detection and treatment of LC and HCC based on the expression of these factors.

Authors' contributions

Feng Chen and Fei Wang conceived and designed the study, analyzed data, and wrote the manuscript. Qianhui Li and Xiaomin Xu collected and analyzed the clinical data. All authors read and approved the final version of this manuscript.

Declaration of competing interest

The authors declare that there is no conflicts of interest.

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