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ABOUT COVER

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Retrospective Study

Hepatocellular carcinoma progression in hepatitis B virus-related cirrhosis patients receiving nucleoside (acid) analogs therapy: A retrospective cross-sectional study

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Abstract

BACKGROUND

Antiviral therapy cannot completely block the progression of hepatitis B to hepatocellular carcinoma (HCC). Furthermore, there are few predictors of early HCC progression and limited strategies to prevent progression in patients with HBV-related cirrhosis who receive nucleos(t)ide analog (NA) therapy.

AIM

The study aim was to clarify risk factors and the diagnostic value of alpha-fetoprotein (AFP) for HCC progression in NA-treated hepatitis B virus (HBV)-related cirrhosis patients.

METHODS

In this retrospective cross-sectional study, we analyzed the clinical data of 266 patients with HBV-related cirrhosis who received NA treatment between February 2014 and April 2020 at Zhejiang Provincial People's Hospital. The patients were divided into two groups, 145 who did not progress to HCC (No-HCC group), and 121 who progressed to HCC during NA treatment (HCC group). The logistic regression analysis was used to analyze the risk factors of HCC progression. The diagnostic value of AFP for HCC was evaluated by receiver operating characteristic (ROC) curve analysis.

RESULTS

Univariate analysis showed that age ≥ 60 years ($P = 0.001$), hepatitis B and alcoholic etiology ($P = 0.007$), smoking history ($P < 0.001$), family history of HBV-

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related HCC ($P = 0.002$), lamivudine resistance ($P = 0.011$), HBV DNA negative ($P = 0.023$), aspartate aminotransferase > 80 U/L ($P = 0.002$), gamma-glutamyl transpeptidase > 120 U/L ($P = 0.001$), alkaline phosphatase > 250 U/L ($P = 0.001$), fasting blood glucose (FBG) ≥ 6.16 (mmol/L) ($P = 0.001$) and Child-Pugh class C ($P = 0.005$) were correlated with HCC progression. In multivariate analysis, age ≥ 60 years [hazard ratio (HR) = 3.089, 95% confidence interval (CI): 1.437-6.631, $P = 0.004$], smoking history (HR = 4.001, 95%CI: 1.836-8.716, $P < 0.01$), family history of HBV-related HCC (HR = 6.763, 95%CI: 1.253-36.499, $P < 0.05$), lamivudine resistance (HR = 2.949, 95%CI: 1.207-7.208, $P = 0.018$), HBV DNA negative (HR = 0.026, 95%CI: 0.007-0.139, $P < 0.01$), FBG ≥ 6.16 mmol/L (HR = 7.219, 95%CI: 3.716-14.024, $P < 0.01$) were independent risk factors of HCC progression. ROC of AFP for diagnosis of HCC was 0.746 (95%CI: 0.674-0.818). A cutoff value of AFP of 9.00 ug/L had a sensitivity of 0.609, and specificity of 0.818 for diagnosing HCC.

CONCLUSION

Age ≥ 60 years, smoking history, family history of HCC, lamivudine resistance, HBV DNA negative, FBG ≥ 6.16 mmol/L were risk factors of HCC progression. Serum AFP had limited diagnostic value for HCC.

Key Words: Hepatitis B virus; Hepatocellular carcinoma; Cirrhosis; Risk factors; Nucleos(t)ide analogs; Progression

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Core Tip: This retrospective cross-sectional study analyzed risk factors of hepatocellular carcinoma (HCC) progression in hepatitis B virus-related cirrhosis patients receiving nucleoside acid analog therapy for at least 6 mo. We discuss the diagnostic value of serum alpha-fetoprotein level in these patients. The results of the present study increase our understanding of HCC pathogenesis and help to provide HCC prevention and control strategies.

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INTRODUCTION

Liver cancer has the third-highest cancer mortality rate worldwide[1]. Hepatocellular carcinoma (HCC) is one of the most common subtypes of liver cancer and is the sixth most prevalent cancer type. In most countries, the HCC mortality rates have increased in recent decades[2]. HCC is the fourth most common malignant tumor type in China, accounting for over 55% of the total number of HCC cases[3]. Infection with the hepatitis B virus (HBV) greatly increases the incidence of HCC because HBV causes chronic hepatitis B (CHB), liver cirrhosis, and ultimately HCC[4,5]. The estimated risk of developing HCC was observed to be 25 to 37-fold higher in hepatitis B surface antigen (HBsAg) carriers compared with noninfected patients HBV infection is one of the most important contributors to the pathogenesis of HCC[6-8]. Over the past 30 years, antiviral drugs, especially nucleos(t)ide analogs (NAs), have been widely used in clinical practice and have substantial long-term effects on the inhibition of HBV replication, namely, delaying and reducing the occurrence and development of hepatitis B-related events. Many studies have shown that antiviral therapy can considerably decrease the incidence of HCC, even for patients in whom CHB has progressed to cirrhosis[9,10]. However, antiviral therapy does not completely block the progression of CHB to liver cancer[11,12]. In the current study, we analyzed the risk factors of HCC progression in patients with HBV-related cirrhosis who received

NA therapy for at least 6 mo. The diagnostic value of the serum alpha-fetoprotein (AFP) level was evaluated in those patients by receiver operating characteristic (ROC) curve analysis. The study results increase our understanding of HCC pathogenesis and help to provide HCC prevention and control strategies.

MATERIALS AND METHODS

Patients and design

This cross-sectional study retrospectively enrolled 266 patients with HBV-related cirrhosis who were treated with NA antiviral therapy at Zhejiang Provincial People's Hospital between February 2014 and April 2020. The 266 patients were divided into two groups, 145 with cirrhosis who did not progress to HCC during the observation period (No-HCC group), and 121 with cirrhosis who progressed to HCC (HCC group). The inclusion criteria were: (1) Age ≥ 18 years; (2) Treatment with lamivudine (LAM), adefovir (ADV), telbivudine, entecavir (ENT), or tenofovir (TDF) nucleoside or NAs for at least 6 mo; (3) Diagnosis of cirrhosis established by either histology (progressive fibrosis, nodule formation, and loss of hepatic architecture) or clinical data (symptoms and signs of cirrhosis, abnormal liver function, and ultrasonic identification). Demographic, clinical, laboratory, imaging, and pathology data were collected during the patient's hospital stay. The severity of cirrhosis was classified by the Child-Pugh criteria. Patients with HBV-related cirrhosis were diagnosed in accord with the guidelines for the prevention and treatment of chronic hepatitis B formulated by the Hepatology Branch and the Infectious Diseases Branch of the Chinese Medical Association[13,14]; and (4) HCC and hepatitis diagnoses confirmed by clinical and serological characteristics, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), hepatic arteriography with digital subtraction angiography (DSA) and pathological examination consistent with the hepatitis and primary liver cancer clinical diagnosis criteria[15,16]. The exclusion criteria were: (1) Hepatitis C virus, hepatitis D virus, or human immunodeficiency virus coinfection; (2) Autoimmune hepatitis and drug hepatitis; and (3) Hepatocarcinoma prior to antiviral treatment or within 6 mo after antiviral treatment. The study received no support from any pharmaceutical company and was approved by the Ethics Committee of the Zhejiang Provincial People's Hospital (2020QT155), Hangzhou, Zhejiang Province, China.

Data collection and study design

The data collected from the electronic medical record system were age, sex, history of drinking and smoking, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), total bilirubin, fasting blood glucose (FBG), AFP, prothrombin time (PT), presence of ascites, hepatic encephalopathy, Child-Pugh score and classification, and family history of HBV, hepatitis B, and HCC. Serological markers of hepatitis B, serum content of HBV DNA, and history of NA treatment were reported by the patients or their families. All patients in the cohort were followed-up for 3 years or until death.

Serum liver function was tested by routine automated techniques using an Olympus AU5400 automated analyzer (Olympus, Tokyo, Japan). HBsAg, hepatitis B e-antigen (HBeAg), and hepatitis B e-antibody were assessed at baseline by chemiluminescence immunoassay (Abbott ARCHITECT i2000 SR analyzer; Abbott Diagnostics, Chicago, IL, United States). The serum HBV DNA load was assessed by RT-PCR using a LightCycler PCR system (Roche LightCycler480 II fluorescence quantitative PCR) in strict accordance with the instructions provided with the reagent kit (Shenzhen PG Biotech Co. Ltd, China). The detection limit was approximately 100 viral genome IU/mL. Genotypic resistance to LAM and ADV were determined at baseline by direct sequencing of the PCR amplification products. The serum AFP tumor marker was assayed by electrochemiluminescence. The study protocol conformed to the 1975 Declaration of Helsinki ethical guidelines for clinical studies.

Statistical analysis

Descriptive data were expressed as means \pm SD or n (%). Continuous variables were compared using Student's *t*-test. Skewness distribution data were reported as the median with the range and were analyzed using the Mann-Whitney *U* test. Categorical variables were analyzed using Fisher's exact test or Pearson's χ^2 test. A logistic regression model was used to analyze single factors, and multivariate analysis with stepwise regression was used to identify statistically significant variables in the

single-factor analysis. The diagnostic performance of the serum AFP level was evaluated using ROC curves. The cutoff value, which was the maximum area under the ROC curve (AUROC), and accuracy were calculated with 95% confidence intervals (CIs). A *P* value of less than 0.05 was determined to indicate statistical significance. The SPSS statistical package (version 22.0; SPSS, Chicago, IL, United States) was used for the statistical analysis.

RESULTS

Clinical characteristics of HBV-related cirrhosis patients receiving NA therapy

The clinical features of the No-HCC and the HCC group were compared. There were no significant differences between the two groups in the sex ratio, duration of NA therapy, HBsAg level, HBeAg positivity, jaundice index, Child-Pugh class B ratio, and PT level (*P* > 0.05). The HCC group included significantly more patients older than 60 years of age and patients with increased levels of ALT, AST, GGT, ALP, and FBG, and decreased levels of ALB than the No-HCC group. The HCC group also contained more patients with mixed etiology (alcohol + HBV), history of smoking, family history of HBV-related HCC, LAM resistance, Child-Pugh class C status, and an AFP > 20 µg/L and fewer HBV DNA-negative and Child-Pugh class A patients than the No-HCC group (Table 1).

Risk factors for HCC progression in HBV-related cirrhosis patients receiving NA therapy

We analyzed factors associated with HCC progression in HBV-related cirrhosis patients who received NA therapy. Univariate analysis found age ≥ 60 years (*P* = 0.002), HBV + alcohol mixed etiology (*P* = 0.007), smoking history (*P* < 0.001), family history of HBV-related HCC (*P* = 0.002), LAM resistance (*P* = 0.046), HBV DNA negativity (*P* = 0.023), AST > 80 U/L (*P* = 0.002), GGT > 120 U/L (*P* = 0.001), ALP > 250 U/L (*P* = 0.001), FBG ≥ 6.16 mmol/L (*P* = 0.001), and Child-Pugh class C (*P* = 0.005) to be significantly related to HCC (Table 2). Multivariate analysis showed that age ≥ 60 years [hazard ratio (HR) = 3.089, 95%CI: 1.437-6.631, *P* = 0.004], smoking history (HR = 4.001 95%CI: 1.836-8.716, *P* < 0.01), family history of HBV-related HCC (HR = 6.763, 95%CI: 1.253-36.499, *P* < 0.05), LAM resistance (HR = 2.949, 95%CI: 1.207-7.208, *P* = 0.018), HBV DNA negative (HR = 0.026, 95%CI: 0.007-0.139, *P* < 0.01), and FBG ≥ 6.16 mmol/L (HR = 7.219, 95%CI: 3.716-14.024, *P* < 0.01) independently predicted HCC progression in patients with HBV-related cirrhosis who received NAs therapy (Table 3).

Serum AFP levels in the No-HCC and HCC groups

In the HCC group, there were 56 patients with serum AFP levels > 20 µg/L, but that was seen in only 17 patients in the No-HCC group (*P* < 0.001). In the HCC group, 65 patients had AFP levels < 20 µg/L. The AFP levels of 37 patients in the HCC group were > 400 µg/L, but only two patients in the No-HCC group levels > 400 µg/L (*P* < 0.001, Table 4). The 17 patients in the No-HCC group with AFP levels > 20 µg/L were followed for 1 year. Their AFP level was determined every month and showed a dynamic decline, returning to normal within 1 year. All patients underwent enhanced MRI of imaging of the liver. We believe that hepatitis B activity, rather than HCC, led to the AFP abnormality. The AFP level distributions in the two groups are shown in Figures 1 and 2.

Serum AFP has limited ability to diagnose HBV-related HCC

We investigated the value of using serum AFP to diagnose HCC in patients who had HBV-related cirrhosis and were receiving NAs therapy. The AUROC of serum AFP for the diagnosis of HCC was 0.746 (95%CI: 0.674-0.818). The sensitivity of serum AFP in diagnosing HCC in those patients was 0.609, and the specificity was 0.818. The positive predictive value of HCC was 22.51%, the negative predictive value of HCC was 46.07%, the cutoff was 9.00, and the Youden index was 0.427 (Figure 3).

DISCUSSION

HBV infection remains a major risk factor for the development of cirrhosis and HCC[17]. Patients with chronic HBV are at risk of developing liver-related complica-

Table 1 Comparison of the clinical characteristics of patients with and without hepatocellular carcinoma

Characteristic	no-HCC group (n = 145)	HCC group (n = 121)	P value
Age ≥ 60 yr, n (%)	41 (28.3)	64 (52.9)	< 0.001
Male, n (%)	99 (68.3)	91 (75.2)	0.133
Etiology of liver cirrhosis, n (%)			
HBV	101 (60.7)	76 (62.8)	0.363
HBV + alcohol	31 (21.4)	45 (37.2)	0.006
HBV + HEV	1 (0.6)	0 (0.0)	-
HBV + schistosome	1 (0.6)	0 (0.0)	-
Smoking history, n (%)	21 (14.5)	51 (42.1)	< 0.001
Family history of HBV-related HCC, n (%)	10 (6.9)	23 (19.0)	0.004
Medication history			
Duration of NA treatment, yr, median (P ₂₅ , P ₇₅)	3.9 (2.1, 5.8)	5.4 (2.3, 6.9)	0.067
LAM resistance, n (%)	18 (12.4)	27 (22.3)	0.021
HBsAg level, IU/L, median (P ₂₅ , P ₇₅)	255.0 (56.0, 678.0)	269.0 (67.0, 656.0)	0.456
HBeAg positive, n (%)	37 (25.5)	21 (17.4)	0.136
HBV DNA negative, n (%)	67 (46.2)	39 (32.2)	0.033
ALB, U/L	36.29 ± 7.98	33.34 ± 6.62	0.002
ALT, U/L, median (P ₂₅ , P ₇₅)	27.00 (18.00, 37.00)	32.00 (21.27, 62.00)	0.006
AST, U/L, median (P ₂₅ , P ₇₅)	33.00 (23.00, 47.00)	44.50 (31.65, 96.85)	< 0.001
GGT, U/L, median (P ₂₅ , P ₇₅)	33.00 (20.00, 46.00)	61.50 (32.75, 160.75)	< 0.001
ALP, U/L, median (P ₂₅ , P ₇₅)	99.00 (73.00, 126.00)	134.50 (92.00, 198.85)	< 0.001
TB, μmol/L, median (P ₂₅ , P ₇₅)	20.41 (13.81, 44.60)	24.46 (16.60, 42.80)	0.192
FBS, mmol/L, median (P ₂₅ , P ₇₅)	5.17 ± 0.68	6.99 ± 1.31	0.025
Ascites, n (%)	33 (20.0)	43 (34.7)	0.022
Child-Pugh class, n (%)			
A	81 (55.9)	55 (45.5)	0.001
B	38 (26.2)	26 (21.5)	0.561
C	26 (17.9)	40 (33.1)	0.002
AFP ≥ 20 μg/L, n (%)	14 (9.7)	56 (46.3)	< 0.001
PT s, median (P ₂₅ , P ₇₅)	13.25 (11.80, 14.20)	13.51 (12.41, 15.02)	0.475

AFP: Alpha-fetoprotein; ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FBS: Fasting blood sugar; GGT: Glutamyl transpeptidase; HBeAb: Hepatitis B e-antibody; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; LAM: Lamivudine; PT: Prothrombin time; SD: Standard deviation; TB: Total bilirubin.

tions, namely, cirrhosis and HCC. In China, 77% of cirrhosis cases and 84% of HCC cases are caused by HBV infection[18]. Antiviral therapy can reduce but not eliminate the risk of developing HCC[19-21]. The annual incidence of HCC ranges from 0.01% to 5.4% in patients with CHB who are treated with ENT or TDF[19,22]. NAs antiviral treatments can markedly inhibit viral replication and improve liver necrosis, inflammation, and fibrosis. However, NAs cannot eliminate covalently closed template DNA (cccDNA) produced during hepatitis B viral replication or clear the integrated HBV genome; therefore, NAs cannot completely block hepatitis B cirrhosis from developing into HCC[12,21]. The persistence of cccDNA and an integrated HBV genome is the basis for hepatitis B cirrhosis progressing to primary liver cancer[23,24]. In this study, we investigated the clinical characteristics of HCC progression in patients with HBV-related cirrhosis who received antiviral therapy with NAs.

Table 2 Univariate logistic regression analysis of hepatitis B-related cirrhosis progressing to hepatocellular carcinoma in patients treated with nucleos(t)ide analogs

Characteristic	No-HCC group (n = 145)	HCC group (n = 121)	Univariate adjusted HR (95%CI)	P value
Age, yr				
≥ 60	40 (27.6)	65 (52.9)	2.664 (1.606-4.418)	0.001
< 60	105 (72.4)	56 (46.3)		
HBV + alcohol				
Yes	31 (21.4)	45 (37.2)	2.384 (1.271-4.473)	0.007
No				
Smoking history				
Yes	21 (14.5)	51 (42.1)	4.073 (2.281-7.273)	< 0.001
No				
Family history of HBV-related HCC				
Yes	10 (6.9)	23 (19.0)	3.546 (1.573-7.998)	0.002
No				
LAM resistance				
Yes	18 (12.4)	27 (22.3)	2.284 (1.214-4.297)	0.011
No				
HBV DNA negative				
Yes	67 (46.2)	39 (32.2)	0.559 (0.339-0.922)	0.023
No				
ALB (g/L)				
< 35	67(46.2)	62(51.2)	1.223 (0.754-1.984)	0.414
≥ 35	78 (53.8)	59 (48.8)		
ALT (U/L)				
50-100	13 (9.0)	15 (12.4)	1.324 (0.612-2.866)	0.476
> 100	10 (7.0)	14 (11.6)	1.138(0.482-2.688)	0.768
AST (U/L)				
40-80	32 (22.1)	24 (19.8)	0.919 (-0.713-0.514)	0.783
> 80	16 (10.3)	31 (29.8)	2.899 (0.436-1.767)	0.002
GGT (U/L)				
60-120	15 (10.3)	20 (16.5)	1.853 (0.892-3.847)	0.098
> 120	8 (5.1)	28 (23.1)	5.663 (1.075-2.573)	0.001
ALP (U/L)				
125-250	36(24.8)	45 (38.8)	1.609 (-0.062-1.028)	0.073
> 250	6 (1.4)	21 (17.4)	4.865 (0.667-2.993)	0.001
FBG (mmol/L)				
≥ 6.16	19 (13.1)	37 (30.6)	3.3179 (0.587-1.902)	0.001
< 6.16				
Ascites class				
Yes	33 (22.8)	43 (35.5)	0.834 (-0.412-0.060)	0.142
No				

Child-Pugh class				
A	81 (58.6)	55 (37.9)	0.658 (-0.938-0.064)	0.091
B	38 (26.2)	26 (21.5)	0.671 (-0.981-0.112)	0.165
C	26 (17.9)	40 (33.1)	2.260 (0.247-1.427)	0.005

Data are *n* (%) or mean \pm SD as shown. AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CI: Confidence interval; FBG: Fasting blood glucose; GGT: Glutaryl transpeptidase; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HR: Hazard ratio; LAM: Lamivudine. .

Table 3 Multivariate analysis of factors associated with hepatitis B-related cirrhosis progression to hepatocellular carcinoma in nucleos(t)ide analog-treated patients

Risk factor	β	SE	Wald	P value	OR (95%CI)
Age \geq 60 yr	1.127	0.390	8.347	0.004	3.089 (1.437-6.631)
Smoking history	1.387	0.397	12.180	< 0.01	4.001 (1.836-8.716)
Family history of HBV-related HCC	1.911	0.860	4.938	< 0.05	6.763 (1.253-36.499)
LAM resistance	1.082	0.456	5.638	0.018	2.949 (1.207-7.208)
HBV DNA negative	-3.479	0.816	19.427	< 0.01	0.026 (0.007-0.139)
FBG \geq 6.16 mmol/L	1.977	0.339	34.030	< 0.01	7.219 (3.716-14.024)

CI: Confidence interval; FBG: Fasting blood glucose; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; LAM: Lamivudine OR: Odds ratio;; SE: Standard error.

Table 4 Comparison of the alpha-fetoprotein level distributions in patients with and without hepatocellular carcinoma, *n* (%)

AFP (μ g/L)	No-HCC group (<i>n</i> = 145)	HCC group (<i>n</i> = 121)	P value
< 20	128 (88.27)	65 (53.72)	< 0.001
20-100	12 (8.27)	14 (11.57)	0.51
100-200	1 (0.69)	2 (2.17)	0.231
200-400	2 (1.38)	3 (2.48)	1
\geq 400	2 (1.38)	37 (30.58)	< 0.001

AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma.

Medical and healthcare progress, improved living standards, and decreased population fertility have led to population aging in China. Data from 22 tumor registration centers in China have shown that the average age of liver cancer onset increased from 58.80 to 62.35 years for men and from 64.02 to 68.99 years for women between 2000 and 2014[25]. Our study found that age \geq 60 years was an independent risk factor for the progression of hepatitis B-related cirrhosis to HCC while receiving NAs antiviral therapy. An aging population and the burden caused by HCC mortality could be a future challenge for China. Previous studies have confirmed that poor lifestyle habits are related to a high incidence of liver cancer; in particular, a history of smoking and drinking increases the risk of HCC[26,27]. Tobacco smoke contains various carcinogens, 11 of which are classified as International Agency for Research on Cancer Group 1 human carcinogens. Epidemiologic evidence from a recent meta-analysis showed a positive association between current tobacco smoking and liver cancer risk (risk ratio: 1.55, 95%CI: 1.46-1.65), suggesting a causal role of smoking in liver cancer development[28]. Liu *et al*[29] found that tobacco smoking and HBV infection positively interact in the development of liver cancer. Our results revealed smoking to be an independent risk factor of HCC progression (95%CI: 1.836-8.716, *P* < 0.01) even if the patients were receiving antiviral treatment. Studies have frequently reported that a family history of liver cancer increases HCC risk independent of

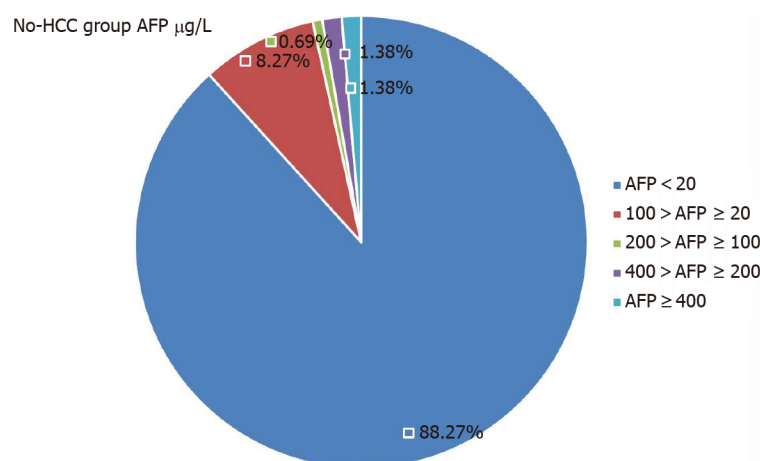


Figure 1 Distribution of alpha-fetoprotein levels in patients without hepatocellular carcinoma. AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma.

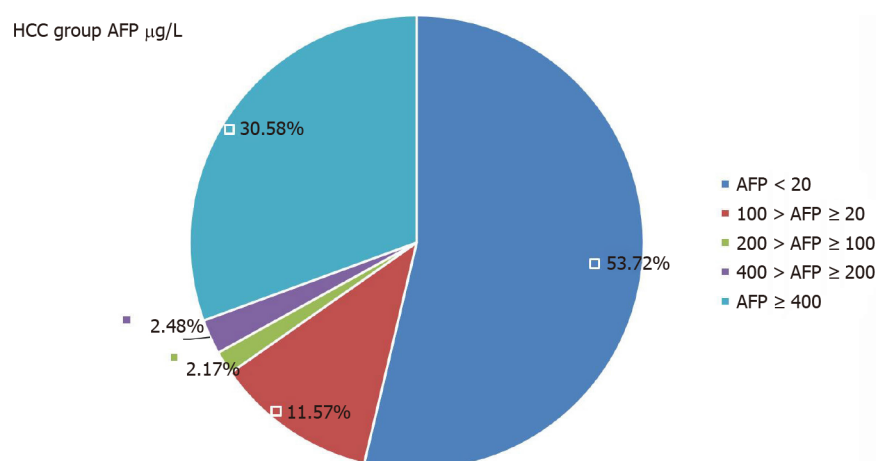


Figure 2 Distribution of alpha-fetoprotein level in patients with hepatocellular carcinoma. AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma.

hepatitis. The combination of a family history of liver cancer and hepatitis B serum markers is associated with a greater than 70-fold increase in HCC risk[30]. Super-additive and super-multiplicative interactions may exist between a family history of liver cancer and HBV infection that increase the risk of the development of liver cancer[31]. Our study found that a family history of HBV-related HCC is a risk factor of progression in cirrhotic patients receiving antiviral therapy (95%CI: 1.253-36.499, $P < 0.05$). Our results suggest that patients with HBV-related cirrhosis who smoke should quit smoking and cultivate a healthy lifestyle to reduce the risk of developing HCC[32,33]. Furthermore, close monitoring should be carried out if a patient's first-degree relative develops HBV-related HCC during antiviral treatment.

LAM has been used as an antiviral treatment for hepatitis B for the past 20 years in China. Some Chinese patients with hepatitis B-related cirrhosis have previously undergone primary LAM monotherapy. Studies have shown that long-term LAM antiviral therapy can delay disease progression, reduce liver function decompensation, and reduce the incidence of HCC[34,35]. The inflammation seen in liver histology can improve in patients with hepatitis B-related cirrhosis when they are treated with LAM, but with a prolonged treatment time, the incidence of drug-resistant viral mutation increases[34,36]. The clinical benefit of LAM is limited by the emergence of resistant mutant strains and viral breakthrough. Although some LAM-resistant CHB patients have received ADV combination therapy or sequential ENT or TDF monotherapy, some of these patients did not experience a beneficial treatment effect and still had continuous replication of HBV in the liver[37,38]. In patients with LAM resistance, those with cirrhosis had a higher HCC risk than non-cirrhotic patients. Rescue treatment with ADV in patients who developed viral breakthrough did not appear to reduce the risk of HCC compared with untreated patients without remission[11]. In

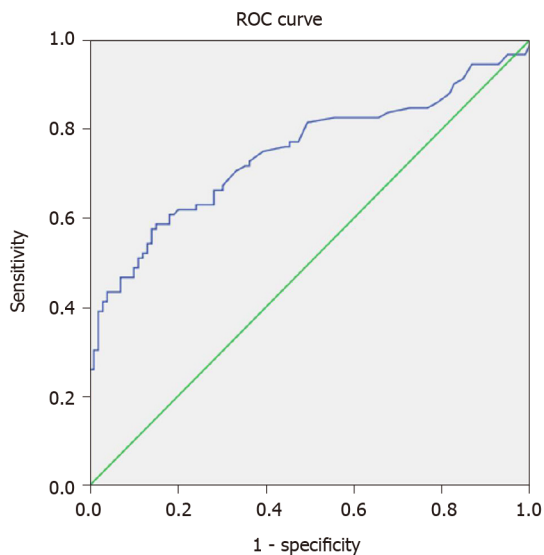


Figure 3 Receiver operating characteristic curve analysis of alpha-fetoprotein to diagnose hepatocellular carcinoma in patients with hepatitis B virus-related cirrhosis receiving nucleos(t)ide analog therapy. ROC: Receiver operating characteristic.

our study of patients treated with antiviral therapy for more than 6 mo, the number of HBV DNA-negative patients in the HCC group was lower than that in the No-HCC group. Many studies have found a correlation between serum HBV DNA levels and the occurrence of HCC in patients with hepatitis B. Kaneko *et al*[39] reported that detectable HBV DNA was significantly associated with a higher risk of HCC development compared with continuously undetectable HBV DNA. Chen *et al*[40] found that the incidence of HCC increased with serum HBV DNA level at study entry in a dose-response relationship ranging from 108/100,000 person-years for an HBV DNA level of < 300 copies/mL to 1152/100,000 person-years for an HBV DNA level of 1 million copies/mL or more. The corresponding cumulative incidence rates of HCC were 1.3% and 14.9%.

Even if the serum HBV DNA level in patients with hepatitis B-related cirrhosis is kept at a low level (< 2000 IU/mL), the risk of HCC is still high[41]. As shown in our study, HBV DNA negativity (HR = 0.026, 95%CI: 0.007-0.139, $P < 0.01$) independently predicted HCC progression in patients with HBV-related cirrhosis who received NAs therapy. Thus, to help avoid HCC progression, hepatitis B patients should continue to maintain an HBV DNA-negative status. Therefore, drugs with a high genetic barrier to resistance are suggested as first-line antiviral drugs for HBV therapy, and are recommended by current guidelines. Drugs such as ETV, TDF, and TDF alafenamide fumarate should be selected to generate a sustained antiviral treatment response and to reduce the occurrence of HBV resistance and the incidence of HCC[42,43].

As an important metabolic organ, the liver plays a key role in maintaining glucose homeostasis. Studies have found a positive relationship between liver cancer and diabetes mellitus[44,45]. Cell and animal experiments have shown that type 2 diabetes and male sex are associated with HCC development. Gao *et al*[46] demonstrated that heterozygous deletion of the *Ncoa5* gene caused spontaneous development of HCC exclusively in male mice, and NCOA5 deficiency increased susceptibility to both glucose intolerance and HCC. In a prospective cohort study, adjusted multivariable analysis showed that participants with $4.82 \text{ mmol/L} \leq \text{FBG} \leq 5.49 \text{ mmol/L}$ had a 47% increased risk of HCC, and those with an $\text{FBG} > 5.49 \text{ mmol/L}$ had a 69% increased risk[47]. In our study, the FBG level in the HCC group was higher than that in the No-HCC group (Table 1), and $\text{FBG} \geq 6.16 \text{ mmol/L}$ was an independent risk factor for the HCC progression in patients with hepatitis B-related cirrhosis receiving NA antiviral treatment. Controlling blood sugar concentrations might be a way to decrease the risk of HCC in the Chinese population.

AFP is a glycoprotein that exists in a variety of different glycotypes. AFP has been used in the screening, diagnosis, efficacy evaluation, and prognosis evaluation of HCC. AFP elevation is commonly seen in active hepatitis, pregnancy, liver cancer, and embryonic tumors[48,49]. Previous studies reported that there was a significant correlation between serum AFP levels and the tumor size in liver cancer, and that the sensitivity and specificity of AFP depended on the selected serum level threshold[20,50]. Liu *et al*[51] found that approximately one-third of patients with

HCC had normal serum AFP levels and that the level was related to the volume of liver cancer lesions, vascular invasion, and differentiation. In our study, we found 56 patients with a serum AFP > 20 µg/L, and 19 with serum AFP levels between 20 and 400 µg/L and with HCC confirmed by imaging and histopathological examination of liver masses. However, an AFP level of < 20 µg/L did not exclude the possibility of HCC. This study showed that 65 patients with a serum AFP of < 20 µg/L had space-occupying lesions that were confirmed as HCC by MRI enhancement, histopathology, and liver DSA examination. That indicates that more sensitive diagnostic markers of HCC must be developed. In addition, more sensitive serum tumor markers such as milk fat globule-EGF factor 8, osteopontin, miRNA classifier, glypican-3[52-54], and others should be actively investigated or combined to identify HCC at an early stage[55]. However, their clinical sensitivity and specificity must first be confirmed.

This study had some limitations. First, it was not prospective. The impact of antiviral treatment time and the amount of smoking and drinking on the development of HCC require confirmation in prospective studies with larger sample sizes. Second, longer follow-up and surveillance of HBV-related cirrhosis patients receiving NA therapy is necessary to observe whether they progress to HCC in their lifetime, even though the 145 cirrhotic patients with NA therapy did not progress to HCC during the observation period. Third, additional molecular markers should be assessed for their ability to provide an early diagnosis of HCC in patients with HBV-related cirrhosis. Some data indicate that the currently used potent NAs can reduce but not eliminate the risk of HCC. The inability to eliminate HCC risk might persist because of risk factors that are not amenable to change by antiviral therapy or because of events that may have taken place before treatment initiation.

CONCLUSION

In conclusion, age ≥ 60 years, a history of smoking, family history of HBV-related HCC, LAM resistance, HBV DNA negativity, and FBG ≥ 6.16 mmol/L were risk factors for HCC progression in patients with HBV-related cirrhosis who received NAs therapy. Patients with HBV-related cirrhosis should be treated with NA antiviral therapy that has a high genetic barrier to resistance[7] in order to improve the long-term response to antiviral therapy, to maintain an HBV DNA-negative status, and to prevent subsequent hepatitis activity. The early identification of HCC in patients with HBV-related cirrhosis remains difficult. Patients who receive antiviral therapy with NAs, especially those older than 60 years of age, should avoid smoking, control their blood sugar at a reasonable level, and undergo routine imaging examination of liver biochemistry and serum AFP evaluation. If space-occupying lesions are identified, the patient should undergo liver CT or MRI enhancement, or even liver DSA examination to identify HCC as promptly as possible, even if the AFP level is within the normal range.

ARTICLE HIGHLIGHTS

Research background

Antiviral therapy cannot completely block the progression of hepatitis B to hepatocellular carcinoma (HCC). Furthermore, there are few early predictors of HCC progression and early identification is difficult in patients with HBV-related cirrhosis who receive nucleos(t)ide analog (NA) therapy. The study is helpful to provide HCC prevention and control strategies by analyzing the risk factors of HCC progression and the diagnostic value of AFP for HCC in those people.

Research motivation

The study objective was to identify factors that affect the occurrence of HCC and how to identify early HCC in patients with hepatitis B virus (HBV)-related cirrhosis who receive NA therapy. The results can improve the understanding of the development of HCC in those patients so as to improve the early detection and prevention of HCC.

Research objectives

The study objectives were to clarify risk factors and the diagnostic value of alpha-fetoprotein (AFP) for HCC progression in patients with HBV-related cirrhosis treated with NAs and to provide new strategies for prevention and control of HCC in those

patients.

Research methods

Logistic regression analysis was used to analyze the risk factors of HCC progression. The diagnostic value of AFP for HCC was evaluated by receiver operating characteristic curve analysis.

Research results

The study showed that age ≥ 60 years, smoking history, family history of HCC, lamivudine resistance, HBV DNA negativity, fasting blood sugar ≥ 6.16 mmol/L were independent risk factors of HCC progression. Serum AFP had limited diagnostic value for HCC. The results provide a meaningful strategy for early prediction and identification for HCC in those patients.

Research conclusions

A retrospective cross-sectional study was conducted to analyze risk factors of HCC progression in HBV-related cirrhosis patients receiving NA therapy. Metabolic effects of fasting blood sugar levels on the progress of HCC were seen during the receipt of NA therapy. The diagnostic value of the serum AFP level was evaluated in those patients.

Research perspectives

The study results will change the strategies used to prevent HCC in patients with HBV-related cirrhosis an receive NA therapy.

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