

# Predicting the risk of hepatocellular carcinoma in chronic hepatitis B patients receiving antiviral therapy: Validating the CAMD and AASL scores in China

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## Abstract

**Background:** We aimed to validate the predictive value of the cirrhosis, age, male sex, and diabetes (CAMD) score and age, albumin, sex, and liver cirrhosis (AASL) score for chronic hepatitis B (CHB) patients, treated with nucleos(t)ide analogues (NUCs) in Northeast China.

**Methods:** From January 2009 to June 2020, 945 patients diagnosed with CHB who received NUC therapy at China-Japan Union Hospital of Jilin University were included. Comprehensive medical records were retrospectively analyzed, and the predictive values of the CAMD score and AASL score for hepatocellular carcinoma (HCC) were evaluated.

**Results:** A total of 58 patients (5.94%) were diagnosed with HCC. Multivariate analysis revealed that age [odds ratio (OR) = 1.041, 95% confidence interval (CI) 1.009–1.073,  $P < 0.011$ ] and cirrhosis (OR = 3.297, 95% CI 1.383–7.861,  $P < 0.007$ ) were independent predictors of HCC. Either the CAMD or AASL score was significantly higher in the HCC group compared to the non-HCC group. The area under the receiver operating characteristic (ROC) curve (AUC) of CAMD and AASL was 0.721 (95% CI 0.663–0.780) and 0.718 (95% CI 0.662–0.774), respectively. Risk stratification using either CAMD or AASL revealed significant differences in the one-, three-, and five-year cumulative incidence rates of HCC between the low-, intermediate-, and high-risk groups (all  $P < 0.001$ , log-rank test).

**Conclusions:** Both CAMD and AASL scores have predictive value for HCC risk of CHB patients in Northeast China. In future, the optimal monitoring frequency and methods should be personalized.

**Keywords:** Age, albumin, chronic hepatitis B, cirrhosis, diabetes score, hepatocellular carcinoma, sex

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## INTRODUCTION

Chronic hepatitis B (CHB) refers to liver injury resulting from chronic hepatitis B virus (HBV) infection for longer than 6 months, with histological examinations revealing different degrees of liver cell necrosis and inflammation.

There are approximately 20–30 million patients with CHB, accounting for 5%–6% of general population in China.<sup>[1]</sup> CHB is one of the most common causes of hepatocellular carcinoma (HCC). According to the latest

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global cancer burden data (Globocan 2020) released by the International Agency for Research on Cancer of the World Health Organization in December 2020,<sup>[2]</sup> the incidence of primary liver cancer ranks sixth in malignant tumors, and the mortality rate ranks third in China. The incidence of primary liver cancer ranks fifth in malignant tumors, and the mortality rate ranks second. In the past five years, the average annual incidence of primary liver cancer in the world is 995,000 cases, 732,000 cases in Asia, accounting for 73.6% of the world, and 423,000 cases in China, accounting for 42.5% of the world. The past two decades have seen a great improvement in the prognosis of CHB patients due to the wide use of anti-HBV medicine. The risk of HCC, however, has not been eliminated. Beyond viral suppression, it remains unclear how to lower the risk further. Therefore, HCC screening program, typically including ultrasonography and alpha-fetoprotein (AFP) test, is still recommended in CHB patients, regardless of whether they have received antiviral treatment.

So far, several HCC risk prediction models, such as the Chinese University of Hong Kong (CUHK) clinical scoring system,<sup>[3]</sup> guide with age, gender, HBV DNA, core promoter mutations and cirrhosis (GAG)-HCC risk score,<sup>[4]</sup> increased viral load and related liver disease/cancer-hepatitis B virus (REVEAL-HBV) nomogram risk assessment<sup>[5]</sup> and the age, diabetes, race, etiology of cirrhosis, sex, and severity (ADDRESS)-HCC risk model<sup>[6]</sup> have been validated in Asian CHB patients who have not been treated with nucleos(t)ide analogues (NUCs). However, in the current NUC era, the above models are unable to accurately predict the risk of HCC in patients receiving NUCs, resulting in an overestimation of the HCC onset rate.

Subsequently, THRI,<sup>[7]</sup> PAGE,<sup>[8]</sup> and m(PAGE-B)<sup>[9]</sup> scores were developed based on the NUCs antiviral cohort, but these were developed based on Caucasians. In 2018, scholars from Taiwan, China and Hong Kong, developed a CAMD scoring system based on age, male, diabetes, and cirrhosis to predict the risk of HCC in CHB patients; the two cohorts found that the CAMD index is easy to calculate and has good predictability.<sup>[10]</sup> In 2018, Korean scholars developed the AASL scoring system based on age, albumin, gender, and liver cirrhosis, which was then verified by scholars from many countries in Asia.<sup>[11]</sup> However, mainland China has not yet verified the CAMD score and AASL score. Therefore, the present study aimed to compare the CAMD scores with AASL scores for the prediction of HCC risk in CHB patients receiving antiviral therapy, with the goal of screening high-risk groups and improving the secondary prevention of HCC.

## METHODS

### Study subjects

CHB patients admitted to the China-Japan Union Hospital of Jilin University between 2009 and 2020 were retrospectively investigated. The inclusion criteria included: (a) patients  $\geq 18$  years of age diagnosed with CHB according to the “Guidelines for Prevention and Treatment of Chronic Hepatitis B (2010 Edition),”<sup>[12]</sup> “Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2015 Edition),”<sup>[13]</sup> and “Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2019 Edition)”<sup>[14]</sup>; (b) patients receiving lamivudine, adefovir, telbivudine, entecavir, or tenofovir disoproxil fumarate antiviral therapy for longer than 6 months, or patients receiving interferon antiviral therapy; and (c) patients with comprehensive clinical data that could be used to determine the Child-Pugh classification, CAMD score, and AASL score outcomes. The exclusion criteria were: (a) patients diagnosed with HCC before enrollment; (b) patients with hepatitis C, hepatitis D or human immunodeficiency virus infection, alcohol abuse, or a history of organ transplantation; (c) patients with acute liver failure, chronic renal failure, severe cardiac insufficiency, and the presence of other tumors or other major diseases; and (d) patients with incomplete clinical data. The research protocol complied with the ethics of the 1975 Declaration of Helsinki. Since this was a retrospective study, informed consent of the participants was waived.

### Diagnosis of cirrhosis and HCC

The diagnostic criteria for hepatitis B-related cirrhosis found in the Guidelines for Prevention and Treatment of Chronic Hepatitis B designated by the Chinese Medical Association of China<sup>[12-14]</sup> are (1) clear etiological evidence of HBV infection and (2) histological or clinical evidence of cirrhosis. The diagnostic criteria for HCC were based on “Primary Liver Cancer Diagnosis and Treatment Guidelines (2011 Edition)”<sup>[15]</sup> and “Primary Liver Cancer Diagnosis and Treatment Guidelines (2017 Edition)”<sup>[16]</sup> and positive results using ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) enhancement were required for imaging or pathological diagnosis.

### Clinical evaluation

The retrieved clinical data included the patients' gender, age, height, weight, and history of hypertension, diabetes, drinking, and smoking, as well as the time from symptom onset to diagnosis. The retrieved laboratory data included routine baseline blood tests [white blood cell (WBC) and platelet (PLT) counts], liver function tests [alanine aminotransferase (ALT), total bilirubin (TBIL), and

albumin (ALB)], renal function test [creatinine (CREA)], coagulation [prothrombin time (PT)], international normalized ratio (INR)], hepatitis B serological markers [surface antigen (HBsAg), e-antigen (HBeAg), and core antibody (HBcAb)], and HBV DNA quantification. The retrieved imaging data including results of abdominal color Doppler ultrasound, CT, MRI and FibroScan. Patients with cirrhosis were classified as either A, B, or C according to the Child-Pugh classification. Patients were divided into either low-risk, medium-risk, or high-risk groups according to the CAMD score or AASL score-based risk stratification.

### Follow-up

The initiation of antiviral treatment in our hospital was used as the starting point for retrospective observation, and patient data were collected through previous visits or telephone follow-ups until the end event (HCC diagnosis or death) or research end (the end date for this study was June 30, 2020). If a patient was lost to follow-up by phone during the study period, the last record prevailed.

### Statistical analysis

Count data was presented as the number of cases or percentage and measurement data was expressed as mean  $\pm$  standard deviation. The comparison of measurement data between two groups was performed using the t-test or nonparametric test, and the comparison of count data was performed using the  $\chi^2$  test or Fisher's exact test. SPSS 26.0 software and MedCalc v19.6.4 software were used for all statistical analyses according to

scientific treatment, and a  $P$  value  $< 0.05$  was considered statistically significant. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the accuracy of CAMD score and AASL score in predicting HCC. Cox regression analysis was used to assess the relevance of risk factors for HCC. The Kaplan–Meier method was used to calculate the cumulative incidence of HCC, and the log-rank test was used for comparison between groups.

## RESULTS

### Baseline characteristics

A total of 945 eligible CHB patients were enrolled, and baseline characteristics are described in Table 1. The average patient age was  $46.61 \pm 11.97$  years, with a male-to-female ratio of 2.6:1. Among them, 408 patients (43.17%) were HBeAg-positive, and 433 patients (45.82%) had cirrhosis. The median follow-up period was 51 months (interquartile range: 32–72 months). A total of 58 patients (5.94%) were diagnosed with HCC during the follow-up period, and 47 of these patients had cirrhosis. The remaining 887 cases did not develop HCC by the end of follow-up, loss of contact, or patient death. The average CAMD score was  $9.65 \pm 5.45$ , and the average AASL score was  $12.93 \pm 7.52$ . A total of 113 patients (11.96%) had received interferon therapy before receiving NUC antiviral drugs. The incidence of HCC in patients treated with entecavir and tenofovir disoproxil was compared, and the results revealed that there is no statistical difference in HCC incidence.

**Table 1: Baseline characteristics**

Variables	Overall (n=945)	Patients with HCC (n=58, 5.94%)	Patients without HCC (n=887, 94.06%)	P
Age, years	46.61 $\pm$ 11.97	52.36 $\pm$ 9.83	46.23 $\pm$ 12.01	0.000
Male gender (n, %)	685 (72.49)	46 (79.31)	639 (72.04)	0.230
Smoking (n, %)	334 (35.34)	24 (41.38)	310 (34.95)	0.321
Alcohol use (n, %)	352 (37.25)	27 (46.55)	325 (36.64)	0.130
Hypertension (n, %)	87 (9.21)	8 (13.79)	79 (8.91)	0.212
Diabetes mellitus (n, %)	122 (12.91)	9 (15.52)	113 (12.74)	0.541
Cirrhosis (n, %)	433 (45.82)	47 (81.03)	386 (43.52)	0.000
HBeAg positive (n, %)	408 (43.17)	20 (34.48)	388 (43.74)	0.168
HBVDNA, $\times 10^7$ IU	2.12 $\pm$ 7.46	1.50 $\pm$ 4.13	2.16 $\pm$ 7.62	0.212
Fatty liver (n, %)	140 (14.81)	1 (1.72)	139 (15.67)	0.004
Interferon (n, %)	113 (11.96)	2 (3.45)	111 (12.51)	0.039
ALT, IU/L	113.54 $\pm$ 247.34	58.37 $\pm$ 109.46	117.15 $\pm$ 253.36	0.001
Albumin, mg/dL	3.61 $\pm$ 0.68	3.53 $\pm$ 0.68	3.62 $\pm$ 0.68	0.244
Total bilirubin, mg/dl	42.15 $\pm$ 86.33	32.73 $\pm$ 36.32	42.77 $\pm$ 88.59	0.750
INR	1.32 $\pm$ 0.57	1.34 $\pm$ 0.29	1.32 $\pm$ 0.58	0.071
PT, s	14.27 $\pm$ 3.87	15.06 $\pm$ 3.75	14.21 $\pm$ 3.87	0.038
Creatinine, umol/L	74.47 $\pm$ 21.86	74.92 $\pm$ 16.28	74.35 $\pm$ 22.34	0.598
Platelet count, $10^9$ /L	121.68 $\pm$ 66.02	90.43 $\pm$ 45.08	123.72 $\pm$ 66.66	0.000
Zn, umol/L	13.58 $\pm$ 4.33	12.90 $\pm$ 4.56	13.62 $\pm$ 4.31	0.283
CAMD	9.65 $\pm$ 5.45	13.5 $\pm$ 3.85	9.40 $\pm$ 5.44	0.000
AASL	12.93 $\pm$ 7.52	18.40 $\pm$ 5.53	12.57 $\pm$ 7.49	0.000
Entecavir (n, %)	478 (50.58)	449 (50.62)	29 (50)	0.927
Tenofovir dipivoxil (n, %)	79 (8.36)	77 (8.68)	2 (3.45)	0.221

Values are expressed as (n, %) or mean $\pm$ standard deviation. HCC: hepatocellular carcinoma; ALT, alanine aminotransferase; INR, international normalized ratio; PT, prothrombin time.

**Table 2: Analysis of risk factors for HCC**

	Univariate			Multivariate		
	P	OR	95 CI	P	OR	95 CI
Age, years	0.000	1.059	1.035-1.084	0.011	1.041	1.009-1.073
Male gender	0.225	1.482	0.785-2.797	0.520	1.318	0.568-3.056
Alcohol use	0.046	1.694	1.009-2.843	0.198	1.575	0.789-3.145
Diabetes mellitus	0.467	1.302	0.639-2.651	0.734	1.148	0.519-2.539
INR	0.222	1.201	0.895-1.612	0.802	0.702	0.044-11.087
PT	0.016	1.064	1.012-1.120	0.477	1.091	0.859-1.385
Albumin	0.043	0.963	0.928-0.999	0.147	1.041	0.986-1.100
ALT	0.086	0.997	0.993-1.000	0.315	0.997	0.992-1.003
Cirrhosis	0.000	7.093	3.654-13.766	0.007	3.297	1.383-7.861
Interferon	0.042	0.298	0.093-0.958	0.058	0.142	0.019-1.066
Platelet count	0.000	0.988	0.983-0.994	0.286	0.996	0.990-1.003

HCC, hepatocellular carcinoma; OR, odds ratio; 95CI, 95% confidence interval; INR, international normalized ratio; PT, prothrombin time; ALT, alanine aminotransferase

### Analysis of risk factors for HCC

As shown in Table 2, univariate analysis revealed that age, drinking, PT, ALB, PLT, cirrhosis, and interferon treatment were significantly related to the occurrence of HCC (all  $P$  values  $< 0.05$ ). Further, multivariate analysis showed that age [odds ratio (OR) = 1.041, 95% confidence interval (CI) 1.009–1.073;  $P < 0.011$ ] and cirrhosis (OR = 3.297, 95% CI 1.383–7.861;  $P < 0.007$ ) were independent predictors of HCC.

### Cumulative incidence of hepatocellular carcinoma

Forty-eight (5.94%) of 945 patients were diagnosed with HCC during the follow-up period. The one-year cumulative incidence of HCC is 1.5%; the three-year cumulative annual incidence rate is 3.5%; and the five-year cumulative incidence rate is 6.3%. As the follow-up time increased, the cumulative incidence of HCC increased.

### Comparison of the incidence of HCC in patients with cirrhosis and different Child-Pugh classifications

Forty-seven (10.85%) of 433 patients with cirrhosis were diagnosed with HCC during the follow-up period. The one-year cumulative incidence of HCC in the noncirrhotic and cirrhotic groups were 0.2% and 3.1%, respectively; the three-year cumulative annual incidence rates were 0.9% and 6.7%, respectively; and the five-year cumulative incidence rates were 2% and 12.2%, respectively. As the follow-up time increased, the cumulative incidence of HCC in the cirrhosis group also increased; the log-rank test demonstrated a significant difference in the cumulative HCC incidence between these two groups ( $P < 0.001$ ).

The one-year cumulative incidence of HCC in Child-Pugh Class A, B, and C patients were 2.4%, 5.2%, and 3.0%, respectively; the three-year cumulative incidence rates were 4.9%, 7.7% and 7.5%, respectively, and the five-year cumulative incidence rates were 11.0%, 12.2% and 13.7%, respectively. No significant difference was revealed by the log-rank test [ $P = 0.550$ ; Figure 1].

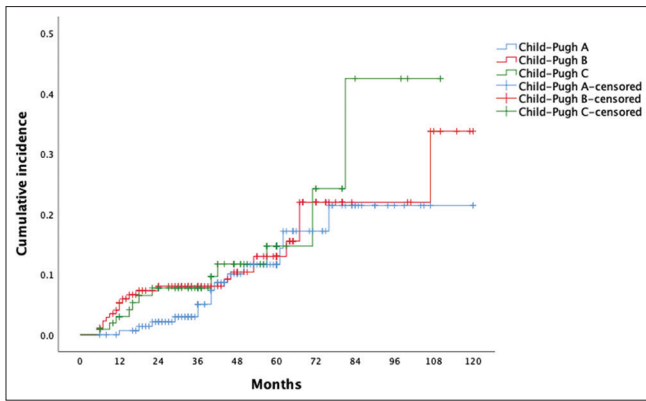
### Comparison of CAMD and AASL scores in predicting the risk of HCC in CHB patients

The CAMD and AASL scores of the HCC and non-HCC groups were analyzed. The results indicated that both the CAMD or AASL scores were significantly higher in the HCC group than in the non-HCC group [ $P < 0.05$ , Table 1]. The AUC of CAMD was 0.721 (95% CI 0.663–0.780,  $P < 0.001$ ) and the Youden index-based cutoff value was 10, with a sensitivity of 0.845 and a specificity of 0.529. The AUC of AASL was 0.718 (95% CI 0.662–0.774,  $P < 0.001$ ) and the Youden index-based cutoff value was 10, with a sensitivity of 0.879 and a specificity of 0.505. In addition, these two tools did not differ in their ability to predict HCC [ $P = 0.830$ , Figure 2].

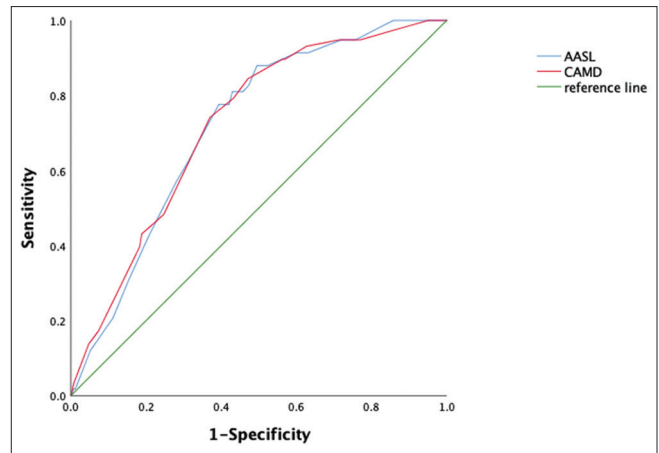
### Comparing the cumulative incidence of HCC across different risk strata in the CAMD model and AASL scoring systems

Risk stratification using the CAMD scores resulted in 336 low-risk cases (35.55%) with 5 HCC cases that occurred during the follow-up period, 364 medium-risk patients (38.52%) with 25 HCC cases that developed during the follow-up period, and 245 (25.93%) high-risk patients with 28 HCC cases that were diagnosed during the follow-up period. For low-, medium-, and high-risk strata, the one-year HCC incidence rates were 0.3%, 1.7%, and 3.0%, respectively; the three-year cumulative incidence rates were 0.6%, 4.0%, and 7.0%, respectively; and the five-year cumulative incidence rates were 1.0%, 7.6%, and 13.4%, respectively [Figure 3], the log-rank test showed a significant difference in the cumulative HCC incidence across these three CAMD risk strata ( $P < 0.001$ ).

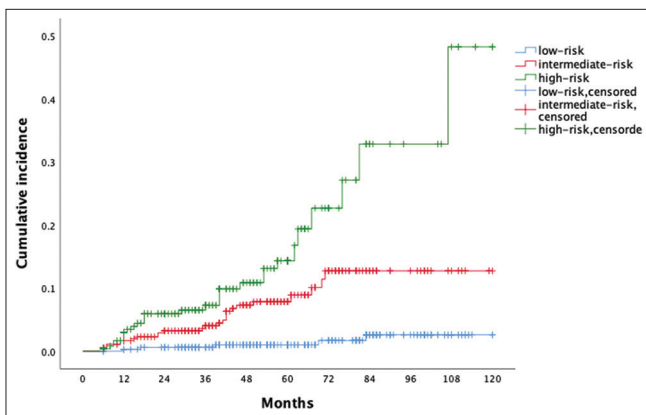
For HCC risk stratification according to AASL scores, there were 218 low-risk cases (23.07%) with three patients who were diagnosed with HCC during the follow-up period, 447 medium-risk cases (31.83%) with 22 patients who developed HCC during the follow-up period, and



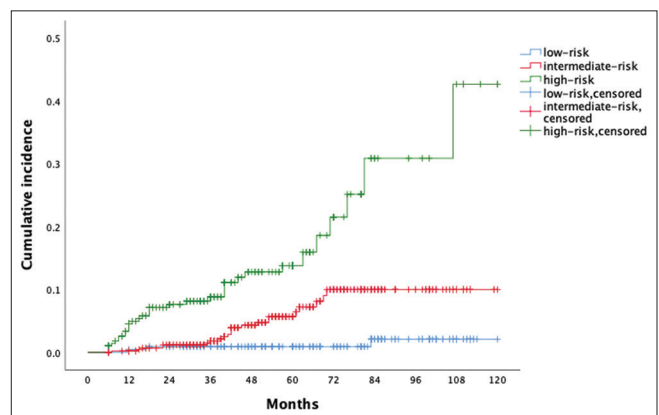
**Figure 1:** Comparison of cumulative incidence of hepatocellular carcinoma (HCC) in patients stratified by Child-Pugh score



**Figure 2:** CAMD and AASL scores for predictive values of hepatocellular carcinoma (HCC)



**Figure 3:** The cumulative incidence of hepatocellular carcinoma (HCC) stratified by CAMD scores



**Figure 4:** The cumulative incidence of hepatocellular carcinoma (HCC) stratified by AASL scores

280 high-risk cases (49.51%) with 33 patients who were diagnosed with HCC during the follow-up period. For low-, medium-, and high-risk strata, the one-year HCC incidence rates were 0.5%, 0.2%, and 4.4%, respectively; the three-year cumulative incidence rates were 0.9%, 1.8%, and 8.5%, respectively; and the five-year cumulative incidence rates were 0.9%, 5.5%, and 12.9%, respectively [Figure 4]; the log-rank test revealed a significant difference in the cumulative HCC incidence across these three AASL risk strata ( $P < 0.001$ ).

## DISCUSSION

In the past few decades, our research center has been mainly dedicated to the study of hepatitis B. Our main purpose is to find an HCC prediction model suitable for hepatitis B patients in Northeast China. In this study spanning more than 10 years, we found that CAMD and AASL scores were suitable for the CHB patients receiving NUCs antiviral therapy in Northeast China; AUC of the two scores is 0.721 and 0.718, which suggests higher sensitivity. This

finding can maximize the detection of high-risk groups, and regular follow-up is recommended to achieve earlier detection and earlier treatment of liver cancer.

Our study found that age and cirrhosis were the independent risk factors for HCC, but albumin was not, which is different from previous studies. It is well known that patients with cirrhosis develop hypoproteinemia due to poor albumin synthesis. Kim *et al.*<sup>[9]</sup> improved the PAGE model by adding albumin as a variable; they believed that albumin as a variable in AASL score was very important in predicting HCC. Yu *et al.*<sup>[11]</sup> research showed that the average albumin was 4 mg/dL, while in our study it was  $3.61 \pm 0.68$  mg/dL. The high proportion of cirrhosis in our study (45.82%) compared with 39.3% in Yu *et al.*'s study group may be responsible for this difference.

The results of a previous retrospective study involving 682 CHB patients treated with NUCs, and 430 CHB patients treated with interferon alone or in combination with NUCs showed that the cumulative incidence of HCC was

significantly lower in patients treated with interferon than in patients treated with NUCs (2.7% vs. 8%,  $P < 0.001$ ) during a median follow-up time of 5.41 years.<sup>[17]</sup> Consistent with this, our study shows that the incidence of HCC in patients receiving interferon therapy is lower than that of patients receiving oral antiviral drugs, indicating that interferon therapy can reduce the incidence of HCC.

China's 2019 Chronic Hepatitis B Prevention and Control Guidelines<sup>[14]</sup> recommend entecavir and tenofovir dipivoxil as first-line antiviral drugs, but there has been controversy regarding their ability to prevent HCC. Hu *et al.*<sup>[18]</sup> found that compared with entecavir, patients treated with tenofovir dipivoxil had a lower risk of HCC. In addition, a meta-analysis of 3698 CHB patients recently published by Zhang *et al.*<sup>[19]</sup> showed that the incidence of HCC in patients treated with tenofovir disoproxil was significantly lower compared to patients treated with entecavir (OR = 0.66, 95% CI 0.49–0.89,  $P = 0.008$ ). Another meta-analysis of 119,053 CHB patients revealed that the cumulative incidence of HCC in patients treated with entecavir or tenofovir dipivoxil was 3.44% (95% CI 3.08–3.80) and 3.39% (95% CI 2.94–3.83), respectively,<sup>[20]</sup> suggesting no difference ( $P = 0.87$ ). In a subgroup analysis using the same clinical cohort, there was still no significant difference in the incidence of HCC between these two groups [hazard ratio (HR) = 1.03, 95% CI 0.88–1.21,  $I^2 = 0\%$ ]. Similarly, Shin *et al.*<sup>[21]</sup> reported no difference between entecavir and tenofovir dipivoxil in reducing the risk of HCC occurrence and related death or liver transplantation ( $P > 0.05$ ), suggesting different antiviral drugs do not differ in their ability to prevent HCC. However, comparing the efficacy of different NUCs in the prevention of HCC still requires additional high-quality studies with longer follow-up periods.

In this study, 74.07% of patients were at low-medium risk in the CAMD score, and 50.49% of patients were at low-medium risk in the AASL score. A recent systematic review and meta-analysis showed that the sensitivity of ultrasound for HCC screening is poor. For HCC  $\leq 2$  cm, the sensitivity of ultrasound is lower than that of MRI (53% vs 82%).<sup>[22]</sup> Therefore, for high-risk patients, we must appropriately increase the frequency of MRI monitoring.

In summary, the current effective treatment option for viral hepatitis B is oral NUCs antiviral therapy, although it cannot provide complete cure. It is necessary to monitor HCC during oral antivirals. Based on our verification, we believe CAMD and AASL scores can be used in Northeast China, and perhaps in mainland China.

## CONCLUSION

In our study, we found age and cirrhosis as independent predictors of HCC. Furthermore, the incidence of HCC in patients treated with entecavir and tenofovir disoproxil was compared, and the results revealed that there is no statistical difference in HCC incidence. In addition, we found that classification of patients with cirrhosis, made no difference in the prevalence of HCC in Child-Pugh A, B, and C patients. We also found that both CAMD and AASL scores have predictive value for HCC risk of CHB patients in China.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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