

Validation of Hepatocellular Carcinoma Risk Prediction Models in Patients with Hepatitis B-Related Cirrhosis

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Purpose: Several risk models have been developed to predict the hepatocellular carcinoma (HCC) risk in patients with chronic hepatitis B (CHB); however, it remains unclear whether these models are useful for risk assessment in patients with hepatitis B virus (HBV)-related cirrhosis undergoing antiviral therapy.

Patients and Methods: A total of 252 treatment-naïve cirrhosis patients with no history of HCC who underwent treatment with nucleos(t)ide analogues between January 2010 and July 2014 were enrolled. Cox proportional hazards model was used to analyze the risk factors for HCC. “TimeROC” and “survival ROC” package, written for R, were used to compare the time-dependent area under the receiver operating characteristic (AUROC) curves for the predictability of the HCC risk scores.

Results: During the mean follow-up period of 56.96 months, 48 (19.0%) patients developed HCC. Cox multivariate stepwise regression analysis revealed that international normalized ratio (hazard ratio [HR] 2.771, 95% confidence interval [CI] 1.462–5.254; $P=0.002$), alpha-fetoprotein (HR 1.001, 95% CI 1.000–1.003; $P=0.035$), diabetes mellitus (HR 3.061, 95% CI 1.542–6.077; $P=0.001$), and alcohol intake (HR 2.250, 95% CI 1.042–4.856; $P=0.039$) were independent indicators of the HCC risk. AUROC at 3 (0.739) and 5 years (0.695) for the REAL-B score were consistently higher than those of the other risk models except RWS-HCC. The time-dependent AUROC value at 1 year for the REAL-B score was similar to those of the other risk models. According to REAL-B score stratification (0–3, low; 4–7, moderate; and 8–13, high), the HCC risk rates at 1, 3, and 5 years were 2.4%, 5.6%, and 9.0% in the intermediate-risk group, and 7.2%, 21.1%, and 26.3% in the high-risk group, respectively (all $P<0.001$ between each pair).

Conclusion: REAL-B score showed a persistently high prognostic capability in predicting the HCC risk in HBV-related cirrhosis patients undergoing antiviral therapy.

Keywords: HBV, antiviral therapy, liver cancer, risk prediction, cirrhosis

Introduction

Liver cancer is the fourth leading cause of cancer-related mortality and was the sixth most prevalent cancer in 2018 worldwide.^{1,2} Hepatocellular carcinoma (HCC) represents approximately 90% of all primary liver cancers and constitutes a major global health problem.³ Chronic hepatitis B (CHB) is the leading cause of HCC in China.^{4,5} The annual incidence of HCC is estimated to be 0.2% in chronic hepatitis B virus (HBV) inactive carriers, 0.6% in CHB patients without cirrhosis, and 3.7% in compensated cirrhotic patients with HBV infection.⁶ Universal HBV vaccination is the cornerstone of primary prevention of HBV-associated HCC.⁷ Recent advances in antiviral treatment have enabled the inhibition of viral replication^{8–10} and amelioration of necro-inflammation and resultant fibrosis,^{11,12} and significantly attenuated the development of HCC.^{13,14} Nevertheless, the risk of HCC development is reduced but not eliminated in CHB patients undergoing effective antiviral therapy, primarily owing to the complex mechanisms of hepatocarcinogenesis.^{15–17} Accordingly, HBV-related cirrhosis patients receiving maintenance antiviral treatment remain at high risk of HCC, and are recommended regular surveillance for early detection of HCC.^{3,18} Therefore, in patients with

HBV-related cirrhosis receiving nucleos(t)ide analogues (NAs), accurate stratification of the risk of hepatocarcinogenesis needs cautious surveillance. Given the strong association between HBV infection and HCC development, guidelines recommend surveillance for detection of HCC in the early stages to increase the curative opportunity and reduce the mortality.^{7,18}

Risk scores may help physicians improve the efficiency and implementation of HCC surveillance strategy. To date, several risk models have been constructed for the prediction of HCC development in HBV-related patients.^{19–28} However, few of them are widely used in clinical practice due to the differences in the selective population characteristics. Toronto hepatocellular carcinoma risk index (THRI) has been used to predict HCC in patients with cirrhosis of various categories.²⁹ Meanwhile, aMAP score has been reported to predict HCC development in patients with chronic hepatitis.³⁰ REACH-B²⁶ has been developed in only non-cirrhotic patients. GAG-HCC,²⁰ liver stiffness measurement (LSM)-HCC,²³ mREACH-B,²¹ CU-HCC score,²⁴ NGM-HCC,²⁷ PAGE-B,²² mPAGE-B,¹⁹ CAMD,²⁵ and AASL-HCC²⁸ were based on mixed patient populations with different cirrhosis proportions. Some determinants, including core promoter mutations (from GAG-HCC²⁰) and liver stiffness measurements (from LSM-HCC²³ and mREACH-B²¹) were not easy to acquire. A small number of studies have verified the prognostic value of the HCC prediction models.^{31–34} However, the usefulness of these models has not been fully verified in patients with HBV-related cirrhosis.

In this study, we aimed to examine the usefulness of the prediction scores for HCC development in HBV-related cirrhosis patients undergoing antiviral therapy.

Patients and Methods

Patients

This retrospective study enrolled 252 patients with HBV-associated cirrhosis, who were treated with NAs and admitted to Peking University First Hospital between January 2010 and July 2014. Liver cirrhosis was confirmed by liver biopsy, presence of esophageal or gastric varices on endoscopy, decompensated performance (ascites, variceal bleeding, or hepatic encephalopathy), or meeting at least two of the following four criteria: a. medical imaging findings of liver surface nodularity and echogenicity; b. platelets (PLT) $< 100 \times 10^9/L$ with no other cause; c. serum albumin (ALB) < 35.0 g/L or international normalized ratio (INR) > 1.3 ; d. LSM > 12.4 kPa (when alanine amino transferase [ALT] $< 5 \times$ upper limit of normal [ULN]). The inclusion criteria were as follows: (1) aged 18–75 years; (2) serologically positive for hepatitis B surface antigen (HBsAg) for at least 6 months with no antiviral treatment received before. The exclusion criteria were as follows: (1) other causes of chronic liver disease; (2) presence of HCC or other malignancies; (3) any other significant medical illness; (4) previous organ transplantation. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board of Peking University First Hospital, Beijing, China (approval no. 2020363). Written informed consent was obtained from the patients or their relatives to participate in the study, and data were analyzed anonymously.

Hepatocellular Carcinoma Surveillance and Diagnosis

Blood tests, including alpha-fetoprotein (AFP), and ultrasonography were performed every 6 months for HCC surveillance. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) were undertaken when the AFP level was abnormally elevated and/or ultrasonography detected a nodule suspected to be HCC. Liver biopsy was used to diagnose HCC without the typical imaging findings. The diagnosis of HCC was defined according to the American Association for the Study of Liver Diseases.³⁵

Selection and Scoring of HCC Prediction Models

LSM-HCC²³ and mREACH-B²¹ were excluded because of lack of transient elastography (TE). GAG-HCC²⁰ was not investigated owing to insufficient data regarding the basal core promoter mutation. REACH-B²⁶ was excluded because it was developed in only non-cirrhotic patients. We selected the HCC risk scores calculated based on the published formulae including THRI,²⁹ aMAP,³⁰ CU-HCC,²⁴ NGM-HCC,²⁷ PAGE-B,²² mPAGE-B,¹⁹ CAMD,²⁵ RWS-HCC,³⁶ REAL-B,³⁷ and AASL-HCC,²⁸ (Supplementary Table 1) at baseline and every year after NA therapy.

Data Collection

Demographic characteristics of all patients, including age, sex, family history of HCC, coexisting diabetes mellitus, and alcohol intake were recorded within 24 hours of admission. Laboratory test results, including ALB, total bilirubin (TBIL), ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ -glutamyl transpeptidase (GGT), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), PLT, INR, AFP, serum creatinine (Scr), hepatitis B e antigen (HBeAg), and HBV-DNA, were collected at baseline and every year until the last follow-up date.

Statistical Analysis

Statistical analysis was conducted by SPSS for Windows (version 22.0, IBM, Armonk, NY). Univariate analysis was performed to assess the significance of the characteristics. Multivariable Cox regression analysis was carried out to identify the prognostic predictors of HCC development, with calculation of the adjusted hazard ratio (HR) and 95% confidence interval (CI). Cumulative incidence rates of HCC were calculated using Kaplan–Meier analysis and compared using the Log rank test. The survival curves were generated using MedCalc software version 18.2. Two-tailed $P < 0.05$ was considered significant. Time-dependent receiver operating characteristic (ROC) curves were calculated to assess the discriminative abilities of these risk scores in predicting long-term HCC development. The analysis of the ROC curves and comparison of the area under the ROC curves (AUROCs) were performed using R software version 4.0.5, (<http://www.r-project.org>) with the “survival ROC” and the “time ROC” packages.

Results

Patient Characteristics

Between January 2010 and July 2014, a total of 528 patients with HBV-related cirrhosis who received antiviral therapy with NAs were eligible for our study. After applying the exclusion criteria, 252 patients were finally selected for the statistical analysis ([Supplementary Figure 1](#)). The baseline characteristics of the study population are summarized in [Table 1](#). The mean age was 52.13 ± 10.24 years, 195 (77.3%) patients were men, 89 (35.3%) patients were HBeAg-positive, and 108 (42.9%) patients received entecavir (ETV). During a mean follow-up of 56.96 months, 48 patients developed HCC. The 1-year, 3-year, and 5-year cumulative incidence rates of HCC were 4.8%, 13.0%, and 17.7%, respectively ([Figure 1](#)).

At the baseline, compared to patients who did not develop HCC, those with HCC were more likely to have a higher AFP, mPAGE-B, PAGE-B, and REAL-B score. Age, sex, body mass index (BMI), HBeAg status, baseline HBV-DNA, PLT, ALT, AST, ALB, TBIL, ALP, GGT, HDL, LDL, Scr, INR, AASL-H, aMAP, CU-HCC, CAMD, RWS-HCC, REAL-B, and THRI were similar in the two groups ([Table 1](#)).

Factors Affecting the Risk of HCC Development in Patients with NA Therapy

HCC occurred in 48 of the 252 patients during the treatment period. Variables for the Cox regression analysis were selected from the clinical and laboratory findings. The results showed that decompensation, INR, AFP, diabetes, and alcohol intake were associated with HCC ([Table 2](#)). Based on this, Cox multivariate stepwise regression analysis identified INR (HR 2.771, 95% CI 1.462–5.254; $P = 0.002$), AFP (HR 1.001, 95% CI 1.000–1.003; $P = 0.035$), diabetes (HR 3.061, 95% CI 1.542–6.077; $P = 0.001$), and alcohol intake (HR 2.250, 95% CI 1.042–4.856; $P = 0.039$) as the independent indicators of the risk of HCC development ([Table 2](#)). In our study, age, sex, ALT, PLT, ALB, TBIL, HBV-DNA, and positive HBeAg, which are common components of the risk models, were not identified as significant predictors of HCC development.

Predictive Performances of the Risk Models for HCC Development

Time-dependent AUROCs were calculated for comparing the accuracy of the predictive performances of the risk models for HCC development. [Table 3](#) shows the predictive performances of AASL-H, aMAP, CAMD, CU-HCC, mPAGE-B, PAGE-B, REAL-B, RWS-HCC, and THRI. The predictive performance of the REAL-B score was similar to RWS-HCC, and significantly better than that of the other models, including AASL-H, aMAP, CAMD, CU-HCC, mPAGE-B, PAGE-

Table 1 Baseline Characteristics of Patients with HBV-Related Cirrhosis

Parameters	Total (n=252)	Without HCC (n=204)	With HCC (n=48)	P-value
Age (year)	52.13±10.24	51.78±10.32	53.63±9.85	0.355
Male, n (%)	195 (77.3%)	161 (78.9%)	34 (70.8%)	0.228
Follow-up (month)	56.96±23.52	62.94±19.71	31.58±21.52	0.000*
BMI (kg/m ²)	24.2 (4.14)	24.27 (4.16)	24.19 (4.28)	0.569
HBV DNA (log ₁₀ IU/mL)	4.35 (2.85)	4.45 (2.88)	3.81 (2.68)	0.195
HBeAg(+), n (%)	89 (35.3%)	68 (33.3%)	21 (43.7%)	0.174
PLT, ×10 ⁹ /L	79 (62)	82 (67)	71 (41.5)	0.096
ALT, IU/L	36 (40.75)	36 (42.25)	34.5 (35.75)	0.801
AST, IU/L	45 (45.5)	45 (44.75)	44.5 (52)	0.944
Scr, μmol/L	78 (20)	78 (19.75)	79 (18.07)	0.889
TBIL, μmol/L	22 (23.63)	22.7 (25.08)	19.2 (17.33)	0.152
ALB, g/L	34.9 (11)	35.25 (11.53)	34.35 (10.1)	0.745
ALP, IU/L	90 (46)	88.5 (46.75)	95.5 (41.25)	0.871
GGT, IU/L	47 (57.75)	44.5 (58.5)	51 (57.25)	0.568
HDL, mmol/L	1.02 (0.53)	1.03 (0.55)	0.96 (0.46)	0.442
LDL, mmol/L	1.94 (1.09)	1.96 (1.06)	1.84 (1.1)	0.431
INR	1.19 (0.23)	1.18 (0.22)	1.26 (0.27)	0.259
AFP, ng/mL	4.97 (24.11)	4.31 (13.54)	21.86 (256.27)	<0.001*
Decompensation, n (%)	111 (44%)	85 (41.7%)	26 (54.1%)	0.117
VR at year 1, n (%)	187 (74.2%)	154 (75.7%)	33 (68.7%)	0.337
VB, n (%)	25 (9.9%)	17 (8.3%)	8 (16.6%)	0.082
ETV treatment, n (%)	108 (42.9%)	90 (44.1%)	18 (37.5%)	0.405
AASL-H	20 (4)	20 (5)	21 (3)	0.625
aMAP	63.74 (8)	63.16 (8.74)	64.78 (6.4)	0.205
CU-HCC	35 (20.5)	23.5 (20.5)	35 (20.75)	0.163
CAMD	16 (4)	16 (4)	16 (3)	0.266
mPAGE-B	14 (4)	14 (4)	15 (2)	0.009*
PAGE-B	18 (5)	18 (5)	19 (5)	0.041*
RWS-HCC	6 (2.5)	5.5 (2.5)	7 (1.87)	0.082
REAL-B	7 (2)	7 (2)	8 (2)	<0.001*
THRI	297 (69)	291.5 (69)	297 (77.25)	0.219

Note: *Statistically significant P values.

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine amino transferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BMI, body mass index; GGT, γ-glutamyl transpeptidase; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; HDL, High-density lipoprotein cholesterol; INR, international normalized ratio; LDL, Low-density lipoprotein cholesterol; PLT, blood platelet; Scr, serum creatinine; TBIL, total bilirubin; VB, virologic breakthrough; VR, virologic response.

B, and THRI at 3 and 5 years (Figure 2B and C). The AUROC value at 1 year for the REAL-B score was similar to that of the other risk models (Figure 2A).

The cumulative incidence rates of HCC based on the REAL-B score (Figure 3) were calculated using the Kaplan–Meier method. Patients were classified into three risk stratifications according to the REAL-B score using the cut-off values recommended by the original studies: low-risk group (score 0–3) vs intermediate-risk group (score 4–7) vs high-risk group (score 8–13). There were 13 (10.24%) and 35 (28%) patients in the intermediate-risk and high-risk groups, respectively. There were no patients in the low-risk group. High-risk group patients had a significantly higher probability of developing HCC ($P<0.001$). Using the REAL-B score, the HCC risk rates at 1, 3, and 5 years were 2.4%, 5.6%, and 9.0% in the intermediate-risk group, and 7.2%, 21.1%, and 26.3% in the high-risk group, respectively.

Changes in the Risk Models Over Time

The HCC risk models and components constituting each HCC prediction model were examined. The median changes in each HCC prediction score between the baseline and 1 year after NA administration are shown in Table 4. At 1 year after treatment,

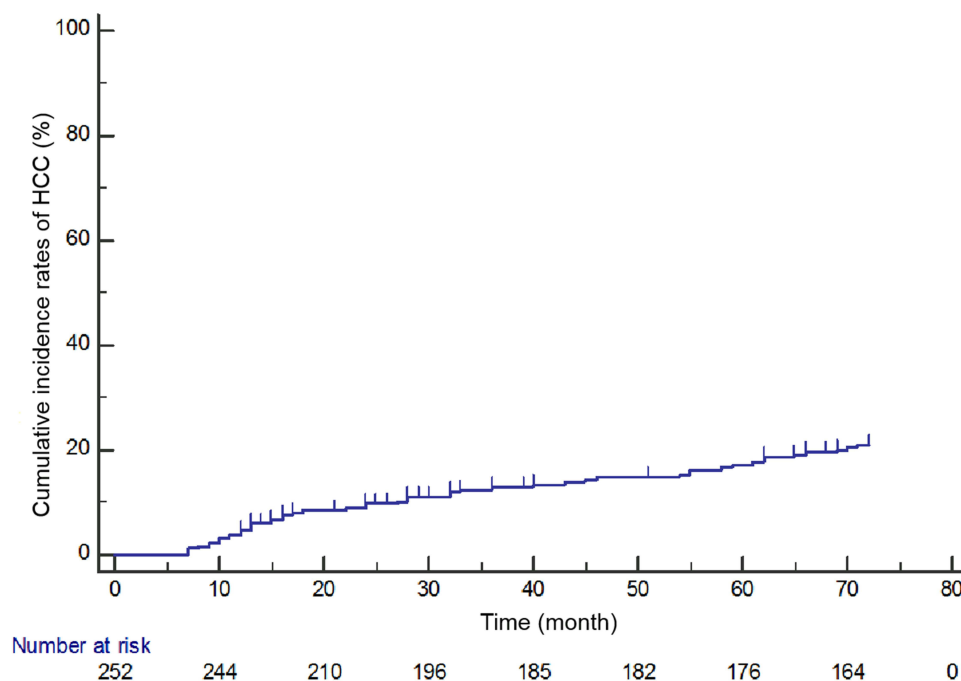


Figure 1 Cumulative incidence rates of hepatocellular carcinoma (Kaplan–Meier curve).

HBV DNA, ALT, AST, GGT, AFP, and ALB were ameliorated significantly ($P < 0.05$ for all). Nevertheless, the HCC risk scores, except for AASL-HCC and CU-HCC, did not change significantly at 1 year after NA treatment. In patients who developed HCC, all risk scores did not significantly alter at 1 year after NA treatment ($P > 0.05$ for all, [Table 5](#)).

Table 2 Univariate and Multivariate Analyses of Predictive Factors Associated with HCC

Parameters	Univariate Analysis	
	HR (95% CI)	P value
Age (year)	1.025 (0.996 1.054)	0.089
Male, <i>n</i> (%)	0.707 (0.380 1.318)	0.276
BMI (kg/m ²)	1.042 (0.958 1.134)	0.336
HBV DNA (log ₁₀ IU/mL)	0.864 (0.719 1.039)	0.120
HBeAg(+), <i>n</i> (%)	1.462 (0.827 2.587)	0.192
PLT, ×10 ⁹ /L	0.997 (0.991 1.003)	0.261
ALT, IU/L	0.998 (0.995 1.001)	0.241
AST, IU/L	0.999 (0.997 1.002)	0.697
Scr, μmol/L	0.998 (0.991 1.006)	0.624
TBIL, μmol/L	0.995 (0.984 1.006)	0.369
ALB, g/L	0.989 (0.951 1.029)	0.588
INR	2.063 (1.140 3.733)	0.017*
ALP, IU/L	1.000 (0.993 1.007)	0.962
GGT, IU/L	1.000 (0.997 1.004)	0.885
HDL, mmol/L	0.680 (0.334 1.384)	0.287
AFP, ng/mL	1.002 (1.001 1.003)	0.000*
ETV treatment, <i>n</i> (%)	0.799 (0.445 1.433)	0.451
Decompensation, <i>n</i> (%)	1.862 (1.054 3.291)	0.032*

(Continued)

Table 2 (Continued).

Parameters	Univariate Analysis	
	HR (95% CI)	P value
VB, n (%)	1.737 (0.813 3.713)	0.154
HBV-DNA positivity at year 1 of the treatment	1.463 (0.794 2.695)	0.222
Diabetes, n (%)	2.540 (1.358 4.217)	0.003*
Alcohol drinking, n (%)	1.883 (1.056 3.358)	0.032*
Multivariate analyses: Predictors of HCC		
INR	2.771 (1.462 5.254)	0.002*
AFP, ng/mL	1.001 (1.000 1.003)	0.035*
Diabetes, n (%)	3.061 (1.542 6.077)	0.001*
Alcohol drinking, n (%)	2.250 (1.042 4.856)	0.039*

Note: *Statistically significant P values.

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine amino transferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BMI, body mass index; GGT, γ -glutamyl transpeptidase; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; HDL, High-density lipoprotein cholesterol; INR, international normalized ratio; PLT, blood platelet; Scr, serum creatinine; TBIL, total bilirubin; VB, virologic breakthrough.

Table 3 Discrimination of the Prognostic Models

Parameters	1-Year tdROC (95% CI)	3-Year tdROC (95% CI)	5-Year tdROC (95% CI)
REAL-B	0.720 (0.523 0.917)	0.739 (0.628 0.851)	0.695 (0.597 0.792)
AaSl-hcc	0.674 (0.543 0.805)	0.568 (0.469 0.668)	0.524 (0.431 0.617)
aMAP	0.703 (0.527 0.879)	0.598 (0.487 0.709)	0.582 (0.483 0.681)
CAMD	0.644 (0.491 0.798)	0.647 (0.544 0.749)	0.582 (0.484 0.681)
CU-HCC	0.583 (0.421 0.744)	0.488 (0.376 0.599)	0.481 (0.384 0.579)
mPAGE-B	0.681 (0.515 0.847)	0.609 (0.500 0.717)	0.571 (0.474 0.667)
PAGE-B	0.660 (0.471 0.850)	0.599 (0.480 0.719)	0.564 (0.456 0.672)
RWS-HCC	0.670 (0.499 0.841)	0.679 (0.579 0.779)	0.667 (0.575 0.758)
THRI	0.664 (0.489 0.839)	0.581 (0.471 0.691)	0.574 (0.473 0.674)

Abbreviation: tdROC, time-dependent receiver operating characteristic.

For further analysis, we defined risk downgrade as the change from a high-risk group to a moderate-risk or low-risk group, and risk upgrade as the change from a moderate-risk group to a high-risk group at 1 year after NA treatment. The rate of HCC development was 16.7% in high-risk patients who experienced a downgrade to moderate risk (n=30), whereas it was 29.4% in moderate-risk patients who experienced an upgrade to the high-risk group (n=17).

Discussion

A previous study found that the overall HCC incidence per 100,000 kept increasing over three decades.³⁸ HCC surveillance is effective in prognostication and curative treatment of patients with cirrhosis. HCC screening is recommended in patients with an annual HCC risk threshold > 1.5%.^{35,39,40} Although the annual HCC risk in patients with baseline cirrhosis decreases after antiviral therapy, it remains above the cut-off value of 1.5%.⁴¹ While the utility of HCC risk prediction models in CHB has been reported, their utility in patients with cirrhosis during NA treatment has not been fully examined, as cirrhotic patients were usually excluded from previous studies. Therefore, we evaluated the known risk prediction models using data obtained during NA treatment and examined their utility.

In our study, ALT, ALB, TBIL, and viral factors (HBV-DNA and HBeAg) were not found to be predictors of HCC. We surmise that these factors may be greatly altered during NA treatment in most patients. INR and AFP were found to

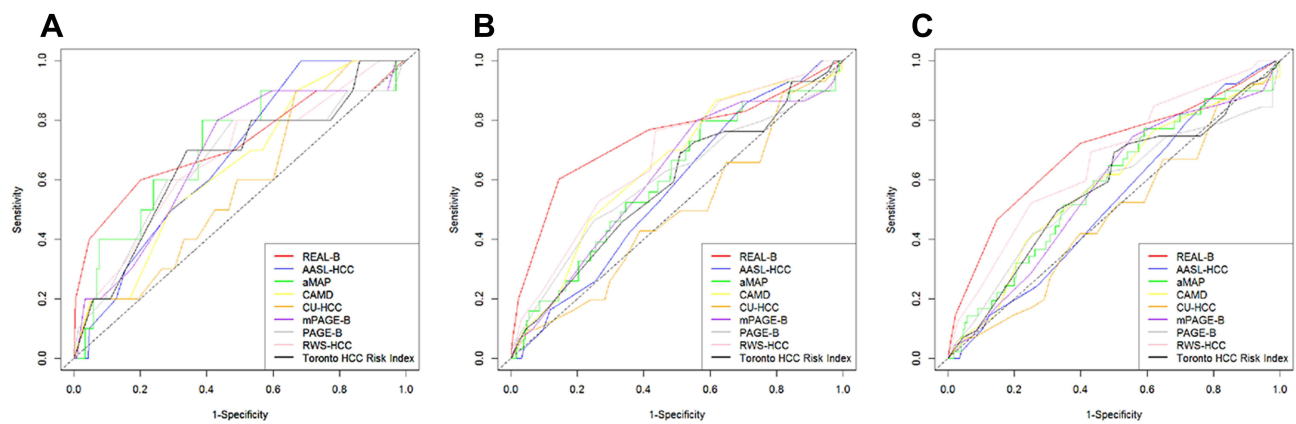


Figure 2 Time-dependent area under the receiver operating characteristic curves (AUROCs) for predicting hepatocellular carcinoma development; **(A)** time-dependent AUROCs for predicting hepatocellular carcinoma development at 1 year; **(B)** time-dependent AUROCs for predicting hepatocellular carcinoma development at 3 years; **(C)** time-dependent AUROCs for predicting hepatocellular carcinoma development at 5 years.

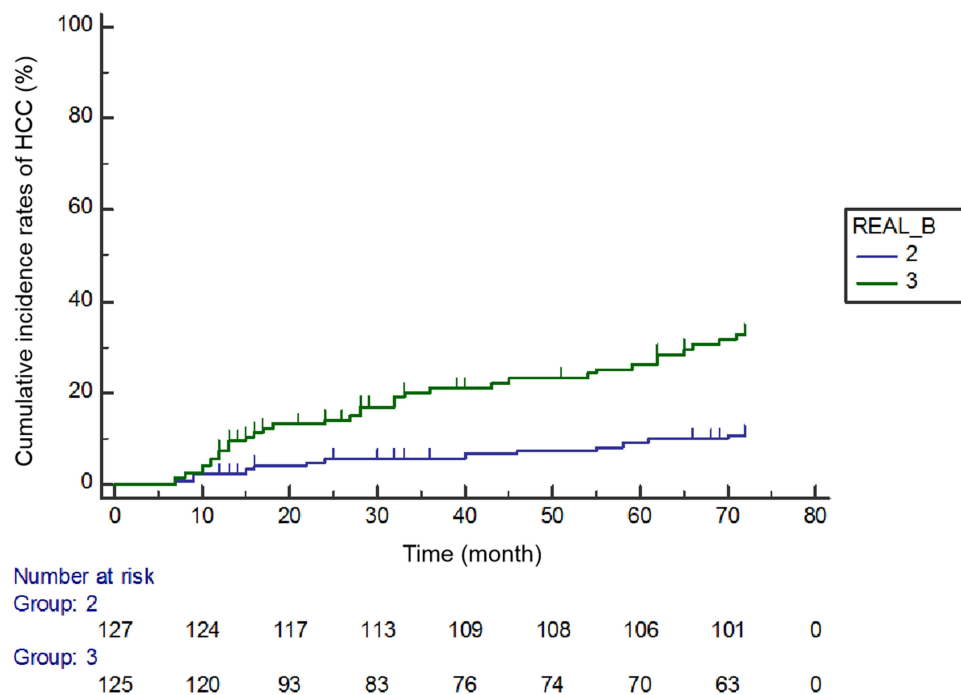


Figure 3 Cumulative incidence rates of hepatocellular carcinoma based on the REAL-B score.

be associated with HCC development in our study. This might be the reason why AFP, which is associated with necroinflammation and hepatocarcinogenesis, and INR, which is related to the severity of liver dysfunction, were found to be the leading factors associated with HCC. Furthermore, our results indicate that diabetes and alcohol intake may have a good predictive ability for HCC development in patients with cirrhosis, which was in line with the results of previous studies on CHB patients.⁴² Therefore, the importance of diabetes and alcohol intake cannot be overemphasized in the cirrhotic population.

Our second aim was to determine the risk score that could best identify CHB patients with high-risk of HCC. We focused on the risk models that used routine clinical data, and found that REAL-B score in patients with baseline cirrhosis could identify the high-risk patients, and was more effective than other models in predicting HCC development during antiviral therapy. REAL-B score is calculated using age, sex, baseline PLT, baseline AFP, alcohol use, cirrhosis status, and diabetes mellitus at baseline, and is effective for the stratification of HCC risk in patients receiving NA treatment. According to our

Table 4 Changes in Factors Constituting HCC Prediction Model

Parameters	Baseline (n=252)	1 year of NA Therapy (n=252)	P-value
PLT, $\times 10^9/L$	79 (62)	85.5 (64.25)	0.570
ALT, IU/L	36 (40.75)	26 (20.75)	<0.001*
AST, IU/L	45 (45.5)	35 (21.75)	<0.001*
Scr, $\mu\text{mol/L}$	78 (20)	82 (22)	0.003*
TBIL, $\mu\text{mol/L}$	22 (23.63)	19.6 (18.08)	0.178
ALB, g/L	34.9 (11)	38.5 (11.38)	<0.001*
ALP, IU/L	90 (46)	83.5 (55.75)	0.541
GGT, IU/L	47 (57.75)	33.5 (37.5)	<0.001*
HDL, mmol/L	1.02 (0.53)	1.01 (0.48)	0.946
LDL, mmol/L	1.94 (1.09)	2.01 (1.06)	0.422
INR	1.19 (0.23)	1.17 (0.24)	0.572
AFP, ng/mL	4.97 (24.13)	4.12 (7.11)	0.010*
HBV-DNA(\log_{10} IU/mL)	4.35 (2.85)	0 (2)	<0.001*
AASL-HCC	20 (4)	20 (4)	0.030*
aMAP	63.74 (8)	69.97 (7.43)	0.093
CU-HCC	35 (20.5)	20.5 (20)	0.010*
CAMD	16 (4)	16 (4)	1.000
mPAGE-B	14 (4)	14 (4)	0.062
PAGE-B	18 (5)	18 (6)	0.748
RWS-HCC	6 (2.5)	5.5 (2.5)	0.385
REAL-B	7 (2)	7 (2)	0.733
THRI	297 (69)	297 (69)	0.777

Note: *Statistically significant P values.

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine amino transferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BMI, body mass index; GGT, γ -glutamyl transpeptidase; HCC, hepatocellular carcinoma; HDL, High-density lipoprotein cholesterol; INR, international normalized ratio; LDL, Low-density lipoprotein cholesterol; NA, nucleos(t)ide analogs; PLT, blood platelet; Scr, serum creatinine; TBIL, total bilirubin.

Table 5 Changes in Prediction Model of HCC

Parameters	Baseline (n=48)	1 Year of NA Therapy (n=48)	P-value
AASL-HCC	21 (3)	21 (2.75)	0.573
aMAP	64.78 (6.4)	65.04 (5.61)	0.889
CU-HCC	35 (20.75)	29.25 (20)	0.766
CAMD	16 (3)	16 (3)	1.000
mPAGE-B	15 (2)	15 (3)	0.832
PAGE-B	19 (5)	19 (5)	0.691
RWS-HCC	7 (1.87)	6.25 (2.5)	0.181
REAL-B	8 (2)	8 (2)	0.561
THRI	297 (77.25)	297 (69)	0.787

Abbreviation: NA, nucleos(t)ide analogs.

results, none of the cirrhotic patients could be classified into the low-risk group. Therefore, all cirrhotic patients should be advised to undergo HCC surveillance for life. It should be noted that the validity of all risk scores for HCC prediction may decrease over time. Thus, reassessment of the HCC risk scores is required after 5 years of follow-up.

Previous studies have shown that a dynamic change is more important than unstable baseline viral load and/or biochemical parameters to predict HCC in the antiviral era. It was found that HBV DNA, ALT, AST, GGT, AFP, and ALB were significantly altered at 1 year after treatment, resulting in a decrease in AASL-HCC and CU-HCC, whereas the other scores did not change. In patients who developed HCC, none of the risk scores changed significantly at 1 year after NA treatment. Various variables that can be influenced by prolonged antiviral therapy include ALT, ALB, TBIL,

degree of fibrotic burden, and viral status. NA therapy effectively suppresses viral replication and reduces the risk of HCC. Nevertheless, high-risk patients still have a higher risk of HCC development despite a significant reduction in the risk score than low-risk patients who experience no changes in the risk score.⁴³

There are some limitations to our study. First, this was a single-center retrospective study. Second, many patients included in the study were initially treated with the low-genetic barrier NAs. Finally, cirrhosis was usually diagnosed based on clinical judgment using different criteria (liver biopsy, LSM, or videography). This bias cannot be eliminated.

Conclusions

The REAL-B score calculated using age, sex, alcohol use, cirrhosis status at baseline, presence of diabetes mellitus, baseline PLT, and baseline AFP demonstrated a high diagnostic accuracy for HCC development in patients with cirrhosis at all time points during NA treatment, indicating its potential usefulness for real-time monitoring of HCC development.

Abbreviations

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine amino transferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; AUROC, area under the receiver operating characteristic; BMI, body mass index; CHB, chronic hepatitis B; CI, confidence interval; CT, computed tomography; DNA, deoxyribonucleic acid; ETV, entecavir; GGT, γ -glutamyl transpeptidase; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDL, High-density lipoprotein cholesterol; HR, hazard ratio; INR, international normalized ratio; LDL, Low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; NA, Nucleos(t)ide analogs; PLT, blood platelet; Scr, serum creatinine; TBIL, total bilirubin; TE, transient elastography; ULN, upper limit of normal.

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Disclosure

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424. doi:10.3322/caac.21492
2. Villanueva A. Hepatocellular Carcinoma. *N Engl J Med*. 2019;380(15):1450–1462. doi:10.1056/NEJMra1713263
3. Galle PR, Forner A, Llovet JM, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019
4. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;63(1):261–283. doi:10.1002/hep.28156
5. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):661–662. doi:10.1002/hep.23190
6. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol*. 2008;48(2):335–352. doi:10.1016/j.jhep.2007.11.011
7. Lampertico P, Agarwal K, Berg T, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67(2):370–398. doi:10.1016/j.jhep.2017.03.021
8. Lai CL, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2006;354(10):1011–1020. doi:10.1056/NEJMoa051287
9. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2006;354(10):1001–1010. doi:10.1056/NEJMoa051285
10. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus Adefovir dipivoxil for chronic hepatitis B. *N Engl J Med*. 2008;359(23):2442–2455. doi:10.1056/NEJMoa0802878

11. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013;381(9865):468–475. doi:10.1016/S0140-6736(12)61425-1
12. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology*. 2010;52(3):886–893. doi:10.1002/hep.23785
13. Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology*. 2013;58(1):98–107. doi:10.1002/hep.26180
14. Sung JJ, Tsoi KK, Wong VW, Li KC, Chan HL. Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2008;28(9):1067–1077. doi:10.1111/j.1365-2036.2008.03816.x
15. Papatheodoridis GV, Chan HL, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. *J Hepatol*. 2015;62(4):956–967. doi:10.1016/j.jhep.2015.01.002
16. Yim HJ, Kim JH, Park JY, et al. Comparison of clinical practice guidelines for the management of chronic hepatitis B: when to start, when to change, and when to stop. *Clin Mol Hepatol*. 2020;26(4):411–429. doi:10.3350/cmh.2020.0049
17. Liu Y, Wang X, Yang Y. Hepatic Hippo signaling inhibits development of hepatocellular carcinoma. *Clin Mol Hepatol*. 2020;26(4):742–750. doi:10.3350/cmh.2020.0178
18. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology*. 2018;67(1):358–380. doi:10.1002/hep.29086
19. Kim JH, Kim YD, Lee M, et al. Modified PAGE-B score predicts the risk of hepatocellular carcinoma in Asians with chronic hepatitis B on antiviral therapy. *J Hepatol*. 2018;69(5):1066–1073. doi:10.1016/j.jhep.2018.07.018
20. Yuen MF, Tanaka Y, Fong DY, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol*. 2009;50(1):80–88. doi:10.1016/j.jhep.2008.07.023
21. Lee HW, Yoo EJ, Kim BK, et al. Prediction of development of liver-related events by transient elastography in hepatitis B patients with complete virological response on antiviral therapy. *Am J Gastroenterol*. 2014;109(8):1241–1249. doi:10.1038/ajg.2014.157
22. Papatheodoridis G, Dalekos G, Sypsa V, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. *J Hepatol*. 2016;64(4):800–806. doi:10.1016/j.jhep.2015.11.035
23. Wong GL, Chan HL, Wong CK, et al. Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. *J Hepatol*. 2014;60(2):339–345. doi:10.1016/j.jhep.2013.09.029
24. Wong VW, Chan SL, Mo F, et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. *J Clin Oncol*. 2010;28(10):1660–1665. doi:10.1200/JCO.2009.26.2675
25. Hsu YC, Yip TC, Ho HJ, et al. Development of a scoring system to predict hepatocellular carcinoma in Asians on antivirals for chronic hepatitis B. *J Hepatol*. 2018;69(2):278–285. doi:10.1016/j.jhep.2018.02.032
26. Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol*. 2011;12(6):568–574. doi:10.1016/S1470-2045(11)70077-8
27. Yang HI, Sherman M, Su J, et al. Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. *J Clin Oncol*. 2010;28(14):2437–2444. doi:10.1200/JCO.2009.27.4456
28. Yu JH, Suh YJ, Jin YJ, et al. Prediction model for hepatocellular carcinoma risk in treatment-naïve chronic hepatitis B patients receiving entecavir/tenofovir. *Eur J Gastroenterol Hepatol*. 2019;31(7):865–872. doi:10.1097/MEG.0000000000001357
29. Sharma SA, Kowgier M, Hansen BE, et al. Toronto HCC risk index: a validated scoring system to predict 10-year risk of HCC in patients with cirrhosis. *J Hepatol*. 2017;68:92–99.
30. Fan R, Papatheodoridis G, Sun J, et al. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. *J Hepatol*. 2020;73(6):1368–1378. doi:10.1016/j.jhep.2020.07.025
31. Kirino S, Tamaki N, Kaneko S, et al. Validation of hepatocellular carcinoma risk scores in Japanese chronic hepatitis B cohort receiving nucleot(s)ide analog. *J Gastroenterol Hepatol*. 2020;35(9):1595–1601. doi:10.1111/jgh.14990
32. Ji J, Park S, Son W, et al. External validation of CAGE-B and SAGE-B scores for Asian chronic hepatitis B patients with well-controlled viremia by antivirals. *J Viral Hepat*. 2021;28:951–958. doi:10.1111/jvh.13506
33. Güzelbulut F, Gökçen P, Can G, et al. Validation of the HCC-RESCUE score to predict hepatocellular carcinoma risk in Caucasian chronic hepatitis B patients under entecavir or tenofovir therapy. *J Viral Hepat*. 2021;28:826–836. doi:10.1111/jvh.13485
34. Wu S, Zeng N, Sun F, et al. Hepatocellular carcinoma prediction models in chronic hepatitis B: a systematic review of 14 models and external validation. *Clin Gastroenterol Hepatol*. 2021;19(12):2499–2513. doi:10.1016/j.cgh.2021.02.040
35. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020–1022. doi:10.1002/hep.24199
36. Poh Z, Shen L, Yang HI, et al. Real-world risk score for hepatocellular carcinoma (RWS-HCC): a clinically practical risk predictor for HCC in chronic hepatitis B. *Gut*. 2016;65(5):887–888. doi:10.1136/gutjnl-2015-310818
37. Yang HI, Yeh ML, Wong GL, et al. Real-world effectiveness from the Asia Pacific rim liver consortium for HBV risk score for the prediction of hepatocellular carcinoma in chronic hepatitis b patients treated with oral antiviral therapy. *J Infect Dis*. 2020;221(3):389–399. doi:10.1093/infdis/jiz477
38. Wang S, Sun H, Xie Z, et al. Improved survival of patients with hepatocellular carcinoma and disparities by age, race, and socioeconomic status by decade, 1983–2012. *Oncotarget*. 2016;7(37):59820–59833. doi:10.18632/oncotarget.10930
39. Goossens N, Singal AG, King LY, et al. Cost-effectiveness of risk score-stratified hepatocellular carcinoma screening in patients with cirrhosis. *Clin Transl Gastroenterol*. 2017;8(6):e101. doi:10.1038/ctg.2017.26
40. Sarasin FP, Giostra E, Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with Child-Pugh class A cirrhosis. *Am J Med*. 1996;101(4):422–434. doi:10.1016/S0002-9343(96)00197-0
41. Papatheodoridis GV, Idilman R, Dalekos GN, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. *Hepatology*. 2017;66(5):1444–1453. doi:10.1002/hep.29320
42. Cheuk-Fung Yip T, Wai-Sun Wong V, Lik-Yuen Chan H, et al. Effects of diabetes and glycemic control on risk of hepatocellular carcinoma after seroclearance of hepatitis B surface antigen. *Clin Gastroenterol Hepatol*. 2018;16(5):765–773.e762. doi:10.1016/j.cgh.2017.12.009
43. Chon HY, Lee JS, Lee HW, et al. Impact of antiviral therapy on risk prediction model for hepatocellular carcinoma development in patients with chronic hepatitis B. *Hepatol Res*. 2021;51(4):406–416. doi:10.1111/hepr.13600

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