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Original Article

Prediction model of hepatocellular carcinoma in patients with hepatitis B virus-related compensated cirrhosis receiving antiviral therapy

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Abstract: The feasibility and performance of predicting hepatocellular carcinoma (HCC) using a combined albumin-bilirubin (ALBI) and fibrosis-4 (FIB-4)-based model remain unclear in patients with compensated cirrhosis and chronic hepatitis B (CHB) receiving long-term nucleos(t)ide analog (NA) therapy. We enrolled 1158 NA-naïve patients with compensated cirrhosis and CHB treated with entecavir or tenofovir disoproxil fumarate. The patients' baseline characteristics, hepatic reserve, and fibrosis indices were analyzed. The combination of ALBI and FIB-4 was used to develop a prediction model of HCC. In this cohort, the cumulative incidence rates of HCC at 3, 5, and 10 years were 8.1%, 13.2%, and 24.1%, respectively. The combination of ALBI and FIB-4, Diabetes mellitus, and Alpha-fetoprotein (AFDA) were independent risk factors for HCC. The combined ALBI and FIB-4-based prediction model (i.e., AFDA) stratified the cumulative risk of HCC into three groups (with risk scores of 0, 1-3, 4-6) among all patients ($P < 0.001$). AFDA exhibited the highest area under the receiver operating characteristic (0.6812) for predicting HCC, which was higher than those of aMAP (0.6591), mPAGE-B (0.6465), CAMD (0.6379), and THRI (0.6356) and significantly higher than those of PAGE-B (0.6246), AASL-HCC (0.6242), and HCC-RESCUE (0.6242). Patients with a total score of 0 (n = 187, 16.1% of total patients) had the lowest cumulative HCC incidence of 3.4% at 5 years. The combined ALBI and FIB-4-based prediction model can stratify the risk of HCC in patients with compensated cirrhosis and CHB receiving NA therapy.

Keywords: Albumin-bilirubin (ALBI) grade, chronic hepatitis B, cirrhosis, FIB-4, hepatocellular carcinoma

Introduction

Nucleos(t)ide analogs (NAs) have been widely used to treat patients with cirrhosis and chronic hepatitis B (CHB). Although long-term NA therapy can lead to regression of hepatic fibrosis and cirrhosis through the suppression of hepatitis B virus (HBV) DNA replication and the amelioration of hepatic necroinflammation, liver disease may continue to progress, and liver-related complications, such as hepatocellular carcinoma (HCC), may occur [1-4]. Identification of the risk factors for HCC and development of an HCC prediction model in patients receiving long-term NA therapy have been critical research topics [5-7]. For patients with CHB receiving NA therapy, age, sex, diabetes mellitus (DM), alpha-fetoprotein (AFP), liver fibrosis, and hepatic dysfunction are critical risk factors for HCC [6, 8]. The albumin-bilirubin (ALBI) score was originally developed to objectively measure hepatic reserve and to predict survival in patients with HCC [9]. In one study, ALBI was determined to be one of the parameters in the aMAP score, which can stratify the 5-year risk of HCC, regardless of etiology or ethinicity [10]. The fibrosis-4 (FIB-4) index is a noninvasive fibrosis index widely used to assess

the severity of liver fibrosis and the risk of HCC in patients with CHB [11-14]. An FIB-4 cutoff of 1.70 or 1.29 indicates a higher risk of HCC in untreated patients with CHB [11, 13]. We previously demonstrated that FIB-4 at baseline or after 1 year of entecavir therapy and its on-treatment change during the first year could be used to stratify the 5-year risk of HCC in patients with CHB receiving entecavir therapy [13, 15]. However, whether simple and objective parameters representative of hepatic reserve, such as ALBI, or of liver fibrosis, such as FIB-4, can be combined to stratify the risk of HCC in patients with CHB receiving long-term NA therapy remains unclear. In the present study, we developed a risk prediction model by combining the hepatic reserve marker and liver fibrosis index and used this model to stratify the risk of HCC in patients with compensated cirrhosis and CHB receiving long-term NA therapy.

Material and methods

Study cohort

A total of 1560 NA-naïve patients with cirrhosis and CHB receiving entecavir or tenofovir disoproxil fumarate (TDF) monotherapy between 2008 and 2018 were retrospectively enrolled from three hospitals in Taiwan (China Medical University Hospital, Taichung [n = 346]; Chia-Yi Christian Hospital, Chia-Yi [n = 268]; and Kaohsiung Chang Gung Memorial Hospital, Kaohsiung [n = 946]). Patients were included in this study if they had received entecavir or TDF monotherapy for at least 12 months prior to study enrolment and if they had been diagnosed with liver cirrhosis defined as either METAVIR stage 4 according to liver histology or abdominal ultrasonography that was suggestive of cirrhosis, with typical clinical signs of gastroesophageal varices, splenomegaly, ascites, or thrombocytopenia [16]. We excluded patients with HCC at baseline; within 1 year of NA therapy; and patients coinfected with human immunodeficiency virus, hepatitis C virus, hepatitis D virus, or other forms of liver disease (including autoimmune hepatitis and alcoholic liver disease) prior to study enrolment. We further excluded patients with decompensated liver cirrhosis (including ascites, encephalopathy, jaundice, and variceal bleeding) (n = 241) and patients with prior NA treatment (n = 207). Finally, a total of 1158 patients with compensated cirrhosis were included for further analysis (Figure S1).

Clinical and laboratory parameters

Baseline clinical characteristics and laboratory data were collected, including age, sex, hepatitis B e antigen, diagnosis of DM, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, international normalized ratio, platelet count, AFP, and HBV DNA. The baseline time point was defined as the time before patients initiated NA therapy, usually within one month.

The ALBI score and FIB-4 were calculated using the following formula: ALBI score = [$\log_{10}$ bilirubin (μmol/L) × 0.66] + [albumin (g/L) × -0.085], where the ALBI grades comprise grade 1 (ALBI score ≤ -2.60), 2 (-2.60 < ALBI score ≤ -1.39), and 3 (ALBI score > -1.39) [9]. FIB-4 = [age (years) × AST (U/L)]/[platelet count (10^9/L) × √ALT (U/L)] [11].

We defined DM as HbA1c ≥ 6.5%, fasting blood glucose ≥ 126 mg/dL, or 2-h plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test or based on medical records of antidiabetic medications [17]. HCC was diagnosed based on a typical dynamic computed tomography or magnetic resonance imaging study or pathological diagnosis [18, 19]. Abdominal ultrasonography and serum AFP measurement were performed every 3 months for HCC surveillance.

To assess the performance of our HCC prediction model, we chose seven extant prediction models of HCC for comparison, namely aMAP [10], mPAGE-B [20], CAMD [21], THRI [22], PAGE-B [23], AASL-HCC [24], and HCC-RESCUE [25], because the essential components of these models are all derived from baseline characteristics and blood test parameters.

Ethics

This study was conducted in accordance with the 1975 Declaration of Helsinki and was approved by the Research Ethics Committee of China Medical University Hospital (CMUH104-REC1-070), Taichung, Taiwan, and each study site. Written informed consent were obtained from all patients prior to enrollment.

Statistical analysis

Categorical variables were analyzed using the chi-square test. Continuous variables were analyzed using the Mann-Whitney U test and are expressed as median ± interquartile range. Cox regression analyses were applied to identify the predictors of HCC risk by calculating hazard ratios (HRs). The parameters with a P value of less than 0.2 in the univariate Cox regression analysis were included in multivariate Cox regression analyses. The performance of each predictor was evaluated using receiver operating characteristic (ROC) curves. The optimal cutoff values of predictors (ALBI score and FIB-4) were estimated according to ROC curves and the Youden index. We used Kaplan-Meier analysis to compare the cumulative HCC incidence among three groups of patients exhibiting distinct combinations of ALBI and FIB-4. The β coefficients of predictors were estimated using the multivariate Cox regression model and were converted into integer risk scores to develop the prediction model. For calibration, we used the Hosmer-Lemeshow test as a goodness-of-fit test for the risk prediction models. A P value of less than 0.05 indicated an unsatisfactory fit. A higher P value for a risk prediction model indicated a more satisfactory fit. For internal validation of the model through multivariate Cox regression analysis, we used the bootstrap method to estimate the β coefficient and P value, which were derived from developed empirical bootstrap distribution models employing the resampling technique. The bootstrap method relies on random sampling with replacement and 1000 replications to evaluate and validate the parameters of interest in the original sample. Finally, the area under the receiver operating characteristic (AUROC) of our prediction model was compared with those of other prediction models individually through the DeLong test. Statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA) and Stata version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX, USA). A P value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The median age of the study group was 55 ± 16 years, 72.2% (n = 836) were men, and 19.8% (n = 229) had DM. During the median follow-up of 4.6 years, 161 (13.9%) patients developed HCC. The cumulative incidence rates of HCC at 3, 5, and 10 years were 8.1%, 13.2% and 24.1%, respectively. Age, DM, albumin, AST, total bilirubin, platelet count, creatinine, AFP, ALBI score and grade, and FIB-4 were significantly different between the subgroups with and without HCC (**Table 1**). Patients with HCC had significantly higher FIB-4 values and ALBI scores than those without HCC.

Baseline factors associated with HCC occurrence

Age, DM, albumin, platelet count, AFP, ALBI score, and FIB-4 were significantly associated with HCC occurrence, as determined by univariate Cox regression analysis (**Table 2**). Because age, AST, ALT, platelet count, albumin, and total bilirubin are the components of FIB-4 and ALBI, we did not include them in the multivariate analysis to avoid confounding. These associated factors are indicated in gray in **Table 2**. In the multivariate Cox regression analysis, DM, AFP, ALBI score, and FIB-4 were independent predictors of HCC occurrence, with respective P values of 0.018, 0.003, 0.009, and 0.001, as determined using the bootstrap method (**Table 2**). The AUROC was used to evaluate the performance of AFP, FIB-4, and ALBI in predicting HCC occurrence. The optimal cutoff values of AFP (5.28 ng/mL), ALBI score (-2.66), and FIB-4 (2.54) were determined according to the Youden index.

Cumulative incidence of HCC stratified by the combination of FIB-4 and ALBI

In the multivariate Cox regression analysis, both the ALBI score (cutoff value: -2.66) and the FIB-4 value (cutoff value: 2.54) were independent factors for predicting HCC risk in patients with cirrhosis (**Table 2**). We combined the status of ALBI and FIB-4 as one risk factor to stratify the risk of HCC. In the multivariate Cox analysis (**Table 3**), DM (HR: 1.462, 95% confidence interval [CI]: 1.030-2.074, P = 0.034), AFP (HR: 1.926, 95% CI: 1.313-2.825, P = 0.001), and the combined ALBI and FIB-4 (high [n = 340]: ALBI > -2.66/FIB-4 > 2.54 [HR: 2.862, 95% CI: 1.833-4.469, P < 0.001]; intermediate [n = 411]: ALBI ≤ -2.66/FIB-4 > 2.54 or ALBI > -2.66/FIB-4 ≤ 2.54 [HR: 1.927, 95% CI: 1.218-3.049, P = 0.005]; and low [n = 407]: ALBI ≤

Table 1. Baseline characteristics of treatment-naïve patients with compensated cirrhosis with or without HCC

Variables Median ± IQR or n (%)	Total n = 1158	HCC occurrence		P value
		Yes (n = 161)	No (n = 997)	
Age (year)	55 ± 16	60 ± 14	55 ± 17	< 0.001
Sex (male)	836 (72.2)	124 (77.0)	712 (71.4)	0.141
HBeAg (positive)	253 (21.8)	39 (24.2)	214 (21.5)	0.436
Diabetes mellitus (yes)	229 (19.8)	43 (26.7)	186 (18.7)	0.017
Albumin, g/dL	4.2 ± 0.6	4.1 ± 0.7	4.2 ± 0.6	< 0.001
AST, U/L	48 ± 40	52 ± 43	47 ± 39	0.001
ALT, U/L	54 ± 53	59 ± 47	53 ± 56	0.171
Total bilirubin, mg/dL	0.9 ± 0.5	1.0 ± 0.6	0.9 ± 0.6	0.041
INR	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.1	0.097
Platelet, × 10^3/μL	139 ± 73	126 ± 71	142 ± 71	< 0.001
AFP, ng/mL	6.3 ± 8.9	8.1 ± 12.7	6.1 ± 8.1	< 0.001
HBV DNA, log IU/mL	5.3 ± 1.9	5.3 ± 2.0	5.3 ± 2.0	0.226
ALBI score	-2.76 ± 0.57	-2.60 ± 0.56	-2.77 ± 0.57	< 0.001
ALBI grade				0.001
Grade 1 (≤ -2.60)	746 (64.4)	83 (51.6)	663 (66.5)	
Grade 2 (> -2.60 to ≤ -1.39)	396 (34.2)	74 (46.0)	322 (32.3)	
Grade 3 (> -1.39)	16 (1.38)	4 (2.48)	12 (1.20)	
FIB-4	2.69 ± 2.78	3.57 ± 3.54	2.54 ± 2.59	< 0.001

AFP, alpha-fetoprotein; ALBI score, albumin-bilirubin score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; FIB-4, fibrosis index based on four factors; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; IQR, interquartile range; IU, international unit.

-2.66/FIB-4 ≤ 2.54 [HR: 1 as reference]) were independent risk factors. Using the bootstrap method, all three parameters were validated as independent risk factors (**Table 3**). The combination of ALBI and FIB-4 was used to stratify the risk of HCC, with significant differences between groups as indicated by Kaplan-Meier analysis (log rank P < 0.0001; group 1 vs. group 2, group 1 vs. group 3, and group 2 vs. group 3, with P = 0.002, P < 0.001, and P = 0.003, respectively, **Figure 1A**). The 3-year risk of HCC for groups 1, 2, and 3 stratified by the combination of ALBI and FIB-4 was 3.7%, 8.1%, and 13.4%, respectively, and the 5-year cumulative incidence rates were 5.9%, 13.1%, and 21.7%, respectively.

Risk score for predicting HCC

We developed a risk model to predict HCC occurrence based on the *β* coefficient of each of the following three predictors: the combination of ALBI and FIB-4, DM, and AFP (AFDA). The total risk score ranged from 0 to 6 (**Table 4**). We categorized patient groups into low-risk, medium-risk, and high-risk groups according to a total risk score of 0, 1-3, and 4-6, respectively. Patients with a total risk score of 0 had the lowest risk of HCC, with 2-year, 3-year, and 5-year cumulative incidence rates of HCC calculated as 1.1%, 2.6%, and 3.4%, respectively (Table S1). We assessed the cumulative HCC incidence through Kaplan-Meier analysis according to the risk groups. HCC incidence was significantly different among the groups (score 0 vs. score 1-3, score 0 vs. score 4-6, and score 1-3 vs. score 4-6, with P = 0.015, P < 0.001, and P < 0.001, respectively, **Figure 1B**). Detailed information on the 2-, 3-, 5-, and 10-year cumulative incidence rates of HCC according to the risk scores and groups are provided in Table S1 and Figure S2. We used the Hosmer-Lemeshow test to examine the calibration of the model, with the logistic regression results indicating a satisfactory model fit (P > 0.05) (Figure S3B).

Performance of the AFDA model and other models for predicting HCC occurrence

The AFDA model exhibited numerically higher performance for predicting HCC occurrence

Table 2. Univariate and multivariate Cox regression analyses of risk factors for HCC in patients with compensated cirrhosis and CHB

Risk factors	Univariate		Multivariate*		Bootstrap method	
	HR (95% CI)	P value	HR (95% CI)	P value	β (95% CI)	P value
Age (year)	1.032 (1.108-1.045)	< 0.001				
Sex, male *vs.* female	1.260 (0.872-1.819)	0.218				
HBeAg, positive *vs.* negative	1.122 (0.783-1.610)	0.530				
Diabetes mellitus, yes *vs.* no	1.547 (1.091-2.194)	0.014	1.469 (1.035-2.085)	0.031	0.385 (0.035-0.715)	0.018
Albumin, g/dL	0.580 (0.429-0.784)	< 0.001				
AST, U/L	1.000 (0.998-1.001)	0.705				
ALT, U/L	0.999 (0.998-1.001)	0.347				
Total bilirubin, mg/dL	1.012 (0.912-1.122)	0.828				
INR	1.191 (0.608-2.334)	0.611				
Platelet, × 10^3/μL	0.995 (0.992-0.998)	0.002				
AFP, ng/mL	1.001 (1.000-1.001)	< 0.001				
AFP ≤ 5.28 (n = 466)	1		1			
AFP > 5.28 (n = 692)	2.315 (1.592-3.367)	< 0.001	1.904 (1.298-2.794)	0.001	0.644 (0.266-1.086)	0.003
HBV DNA, log IU/mL	1.035 (0.928-1.155)	0.535				
ALBI score	1.781 (1.304-2.432)	< 0.001				
ALBI ≤ -2.66 (n = 681)	1		1			
ALBI > -2.66 (n = 477)	2.038 (1.489-2.791)	< 0.001	1.575 (1.132-2.191)	0.007	0.454 (0.121-0.832)	0.009
FIB-4	1.060 (1.033-1.087)	< 0.001				
FIB-4 ≤ 2.54 (n = 544)	1		1			
FIB-4 > 2.54 (n = 614)	2.300 (1.630-3.246)	< 0.001	1.746 (1.212-2.515)	0.003	0.558 (0.195-0.951)	0.001

*The gray color indicates confounding risk factors in the analysis model, which were not included in the multivariate analysis. AFP, alpha-fetoprotein; ALBI score, albumin-bilirubin score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; FIB-4, fibrosis index based on four factors; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalized ratio; IU, international unit.

(C-statistic AUROC = 0.6828, Figure S3A) than the aMAP (C-statistic AUROC = 0.6591), modified PAGE-B (C-statistic AUROC = 0.6465), CAMD (C-statistic AUROC = 0.6379), and THRI (C-statistic AUROC = 0.6356) models, as determined using the DeLong test (**Tables 5**, S2). Compared with PAGE-B (C-statistic AUROC = 0.6246), AASL-HCC (C-statistic AUROC = 0.6242), and HCC-RESCUE (C-statistic AUROC = 0.6242), the AFDA model exhibited significantly higher performance for predicting HCC occurrence (Table S2).

We further investigated the incidence of HCC in the low-risk group, as defined using each of the HCC risk models. The cumulative incidence rates of HCC at 2 to 5 years of antiviral therapy in the low-risk groups, as calculated using each prediction model, are listed in Table S3. In the AFDA model, the lowest cumulative incidence rates of HCC at 2 to 5 years were 1.1%, 2.6%, 3.4%, and 3.4%, respectively, in patients with a total score of 0 (n = 187, 16.1% of total patients). In the present cirrhotic cohort, no patient fulfilled low-risk criteria according to CAMD (< 8 points) and AASL-HCC (≤ 5 points, Table S3). The three models with the lowest predicted risks of HCC at 5 years of antiviral therapy were AFDA (3.4%), HCC-RESCUE (4.8%), and aMAP (6.4%) in 16.1%, 2.5%, and 10.2% of the present cohort, respectively.

Discussion

In this study, we developed the simple and objective HCC risk model of AFDA, which incorporated the combination of ALBI and FIB-4, DM, and AFP. This model is feasible and easy to use, because the required information is baseline laboratory data and DM history. AFDA was used to stratify HCC risk among patients with compensated cirrhosis and CHB receiving long-term NA therapy. Patients who had ALBI ≤ -2.66/FIB-4 ≤ 2.54, no DM, and AFP ≤ 5.28 ng/mL had the lowest risk of HCC; the 5-year cumulative incidence was 3.4%. Compared with the low-risk group of AFDA (score = 0), the risk of HCC was 2.8-fold and 5.9-fold higher in

Table 3. Univariate and multivariate Cox regression analyses of risk factors for HCC in patients with compensated cirrhosis and CHB (combined ALBI and FIB-4 model)

Risk factors	Univariate		Multivariate*		Bootstrap method	
	HR (95% CI)	P value	HR (95% CI)	P value	β (95% CI)	P value
Age (year)	1.032 (1.108-1.045)	< 0.001				
Sex, male *vs.* female	1.260 (0.872-1.819)	0.218				
HBeAg, positive *vs.* negative	1.122 (0.783-1.610)	0.530				
Diabetes mellitus, yes *vs.* no	1.547 (1.091-2.194)	0.014	1.462 (1.030-2.074)	0.034	0.380 (0.018-0.717)	0.034
Albumin, g/dL	0.580 (0.429-0.784)	< 0.001				
AST, U/L	1.000 (0.998-1.001)	0.705				
ALT, U/L	0.999 (0.998-1.001)	0.347				
Total bilirubin, mg/dL	1.012 (0.912-1.122)	0.828				
INR	1.191 (0.608-2.334)	0.611				
Platelet, × 10^3/μL	0.995 (0.992-0.998)	0.002				
AFP, ng/mL	1.001 (1.000-1.001)	< 0.001				
AFP ≤ 5.28 (n = 466)	1		1			
AFP > 5.28 (n = 692)	2.315 (1.592-3.367)	< 0.001	1.926 (1.313-2.825)	0.001	0.655 (0.274-1.069)	0.002
HBV DNA, log IU/mL	1.035 (0.928-1.155)	0.535				
Combination of ALBI and FIB-4						
ALBI ≤ -2.66 and FIB4 ≤ 2.54 (n = 407)	1		1			
ALBI > -2.66 and FIB4 ≤ 2.54 or ALBI ≤ -2.66 and FIB4 > 2.54 (n = 411)	2.048 (1.295-3.237)	0.002	1.927 (1.218-3.049)	0.005	0.656 (0.192-1.219)	0.006
ALBI > -2.66 and FIB4 > 2.54 (n = 340)	3.416 (2.203-5.297)	< 0.001	2.862 (1.833-4.469)	< 0.001	1.051 (0.619-1.601)	0.001

*The gray color indicates confounding risk factors in the analysis model, which were not included in the multivariate analysis. AFP, alpha-fetoprotein; ALBI score, albumin-bilirubin score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; FIB-4, fibrosis index based on four factors; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalized ratio; IU, international unit.

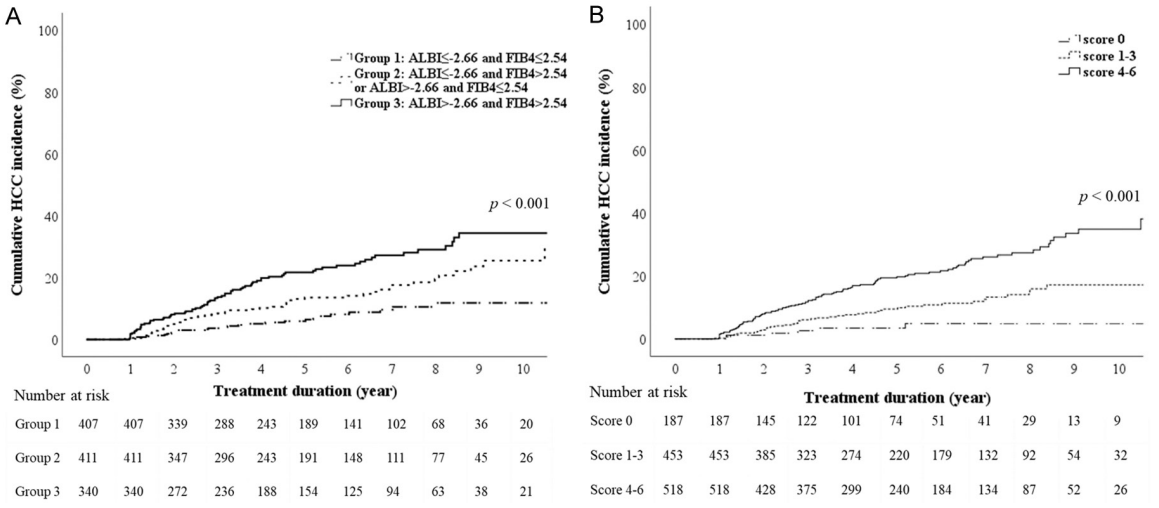

Figure 1. A. Cumulative HCC incidence stratified by the combination of ALBI and FIB-4. B. Cumulative HCC incidence stratified by risk score. ALBI, albumin-bilirubin; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma.

the medium-risk group (score 1-3) and high-risk group (score 4-6) of AFDA, respectively.

Patients with cirrhosis and CHB exhibit a high risk of HCC despite NA therapy. This may be attributed to genetic alterations accumulating over the course of CHB as a result of repeated necroinflammation and hepatocyte regeneration, which may cause irreversible progression in the multistep process of hepatocarcinogenesis [26]. However, the risk of HCC is not homogeneous among patients with cirrhosis. Studies have revealed factors such as age, race, sex, comorbidity, cirrhosis etiology, and liver dys-

Table 4. The risk score model (AFDA) for predicting HCC

Risk factor		Adjusted HR (95% CI)	Parameter (β coefficient)	P value	Risk score
Combination of ALBI and FIB-4	ALBI ≤ -2.66, FIB4 ≤ 2.54	1			0
	ALBI > -2.66, FIB4 ≤ 2.54 ALBI ≤ -2.66, FIB4 > 2.54	1.927 (1.218-3.049)	0.656	0.005	2
	ALBI > -2.66, FIB4 > 2.54	2.862 (1.833-4.469)	1.051	< 0.001	3
Diabetes mellitus	no	1			0
	yes	1.462 (1.030-2.074)	0.380	0.034	1
AFP	≤ 5.28	1			0
	> 5.28	1.926 (1.313-2.825)	0.655	0.001	2

AFP, alpha-fetoprotein; ALBI score, albumin-bilirubin score; CI, confidence interval; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; HR, hazard ratio.

function severity as crucial factors determining the individual risk of HCC in patients with cirrhosis [22, 27]. For patients with CHB receiving antiviral therapy, some models for HCC risk prediction have been proposed [8, 10, 20, 21, 23-25, 28, 29]. Notably, none of these models have been developed specifically for patients with HBV-related cirrhosis. We compared the predictive performance of the AFDA model with that of seven extant risk models of HCC, including one derived from patients with cirrhosis of varying etiologies [22], because all of their components consist of baseline characteristics or laboratory data (**Table 5**). We demonstrated that the AFDA model had the highest AUROC (0.6812), which was higher than those of aMAP, mPAGE-B, CAMD, and THRI and significantly higher than those of PAGE-B, AASL-HCC, and HCC-RESCUE. We further stratified patients into three groups according to risk scores of 0, 1-3, and 4-6, revealing distinct risks of HCC over a follow-up period of up to 10 years (**Figure 1B**). The present study verified the heterogeneous risk of HCC among patients with HBV-related cirrhosis receiving NA therapy and demonstrated the potential utility of the AFDA model in further stratifying HCC risk among patients with cirrhosis. Compared with the other risk models, the AFDA model identified the highest proportion of patients (16.1%) who exhibited the lowest 5-year cumulative incidence of HCC (3.4%) (Table S3). Whether the low-risk group, who had a calculated annual incidence rate of HCC of less than 1.5%, could be spared from future HCC surveillance requires further study [18, 19]. Notably, the high-risk group exhibited a 10-year cumulative HCC incidence of 34.8%; thus, the implementation of different surveillance strategies for HCC may be warranted for this group. Because studies have demonstrated the superior performance of an abbreviated or noncontrast magnetic resonance imaging protocol for HCC detection compared with ultrasound in patients with cirrhosis, this surveillance strategy can be applied to the high-risk group identified in the present study as ideal candidates in the future [30, 31].

Multiple studies have demonstrated that the ALBI score can predict HCC risk in patients with chronic viral hepatitis [32-34]. Fujita et al. reported that the ALBI score can be used to predict the risk of HCC-free survival not only in patients with HBV but also in those with HCV infection [33, 34]. The serum albumin level was an independent predictor of HCC occurrence in the mPAGE-B and AASL-HCC risk models, and the ALBI score is one of the predictors in the aMAP risk model [10, 19, 23]. Consistent with these findings, we determined that the risk of HCC was 1.6-fold higher in patients with an ALBI score of > -2.66 than in those with an ALBI score of ≤ -2.66. This result indicates that the ALBI score, which is representative of hepatic functional reserve, can been utilized as a valid variable in HCC prediction models. Another critical question is whether a marker of the severity of liver fibrosis can serve as a predictor of HCC in patients with compensated cirrhosis and CHB receiving long-term NA therapy. Several available noninvasive methods and modalities accurately reflect the severity of liver fibrosis [35]. The most commonly used method is the FIB-4 index, which incorporates age, AST, ALT, and platelet count [36-38]. In the published prediction models for patients with treated CHB, the proportions of liver cirrhosis varied from 19.1% to 46.9% [6]. The proposed liver fibrosis-related component variables of these models include platelet count, cirrhosis,

Table 5. C-statistic and time-dependent AUROCs for predicting HCC risk using different risk scores

Risk scores	AFDA	aMAP	mPAGE-B	CAMD	THRI	PAGE-B	AASL-HCC	HCC-RESCUE
	AUROC (95% CI)	AUROC (95% CI)	AUROC (95% CI)	AUROC (95% CI)	AUROC (95% CI)	AUROC (95% CI)	AUROC (95% CI)	AUROC (95% CI)
3 years	0.6681 (0.6138-0.7224)	0.6705 (0.6143-0.7266)	0.6745 (0.6179-0.7312)	0.6581 (0.5974-0.7189)	0.6504 (0.5910-0.7099)	0.6316 (0.5696-0.6935)	0.6513 (0.5908-0.7119)	0.6389 (0.5775-0.7003)
5 years	0.6812 (0.6349-0.7275)	0.6659 (0.6159-0.7158)	0.6578 (0.6075-0.7080)	0.6496 (0.5969-0.7023)	0.6478 (0.5963-0.6993)	0.6304 (0.5773-0.6835)	0.6434 (0.5912-0.6955)	0.6342 (0.5821-0.6864)
C-statistic	0.6828 (0.6419-0.7248)	0.6591 (0.6142-0.7040)	0.6465 (0.6018-0.6913)	0.6379 (0.5917-0.6841)	0.6356 (0.5894-0.6819)	0.6246 (0.5773-0.6719)	0.6242 (0.5780-0.6705)	0.6242 (0.5776-0.6708)

AUROC, area under the receiver operating characteristic; CI, confidence interval; HCC, hepatocellular carcinoma.

and liver stiffness measurement (LSM) [8, 10, 20, 21, 23-25, 28, 29, 39]. Because cirrhosis is often diagnosed according to suggestive ultrasonographic findings and compatible clinical features without pathological verification, patients with early cirrhosis might be underdiagnosed in clinical settings, leading to the overestimation of the HCC risk associated with cirrhosis. Although LSM can be used to accurately measure the severity of liver fibrosis [35], modalities such as FibroScan and Acoustic Radiation Force Impulse are not widely available because of their cost. A risk model of HCC that incorporates a noninvasive fibrosis index such as FIB-4 is desirable considering its simplicity, reproducibility, and availability in routine clinical practice. Herein, we demonstrated that in addition to the ALBI score, FIB-4 is an independent predictor of HCC occurrence. Furthermore, we demonstrated that FIB-4 and the ALBI score can act in a complementary manner as a combined variable in a prediction model for stratifying the risk of HCC in patients with cirrhosis and CHB receiving long-term NA therapy.

Although having long been regarded as a diagnostic marker of HCC, AFP also has been identified as an independent predictor of HCC in patients with CHB receiving long-term NA therapy and has therefore been incorporated into the risk model of HCC [8, 28]. In the present study, we verified this previous finding and demonstrated that AFP can serve as independent predictor of HCC and a valid component in a HCC risk model.

The present study has several clinical implications. First, it is a cohort study of numerous patients with HBV-related cirrhosis receiving long-term first-line therapy with entecavir or TDF, which provides a valuable opportunity for delineating the cumulative incidence of HCC during long-term NA treatment in patients with cirrhosis. Second, AFDA is the first HCC-risk-prediction model that was developed and validated in a homogeneous population of patients with HBV-related cirrhosis receiving long-term NA therapy. The AFDA model is a simple, reproducible, and inexpensive risk score model; it exhibited the highest predictive performance for HCC occurrence compared with seven extant risk models of HCC, and the AFDA model was used to stratify the risk of HCC in patients with HBV-related cirrhosis during long-term NA therapy. Although long-term NA therapy and surveillance for HCC is the current standard of care for patients with HBV-related cirrhosis, further stratification of HCC risk among these patients will facilitate patient counselling, implementation of individualized surveillance strategies, and future design of chemoprevention trials for HCC. Nonetheless, this study has several limitations. First, most of our patients were diagnosed with cirrhosis according to clinical criteria, including abdominal ultrasonographic findings suggestive of cirrhosis and clinical evidence of portal hypertension (splenomegaly, esophageal or gastric varices, and thrombocytopenia), instead of liver biopsy. Patients with early cirrhosis might have been under-diagnosed and were therefore excluded from this study, and the risk of HCC associated with cirrhosis might have been overestimated. Second, the present model was developed using a cohort of Asian patients who acquired HBV genotype B or C infection during the neonatal period. Although internal validation was performed using the bootstrap method in this study, further external validation in patients of different ethnicities or HBV genotypes is required to verify its predictive performance. Third, despite exhibiting the highest predictive performance for HCC among patients with cirrhosis, the AUROC of AFDA was suboptimal. Future efforts could be directed toward elucidating the multistep process of hepatocarcinogenesis to explore potential predictive biomarkers of HCC to facilitate its early prediction and diagnosis.

In conclusion, the AFDA model can be used noninvasively and conveniently to assess and stratify the risk of HCC in compensated cirrhotic patients with CHB receiving long-term NA therapy. Risk stratification of these patients may assist in the individualization of HCC surveillance programs in the era of antiviral therapy.

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Disclosure of conflict of interest

Cheng-Yuan Peng has served as an advisory committee member for AbbVie, Bristol-Myers Squibb, Gilead, and Roche.

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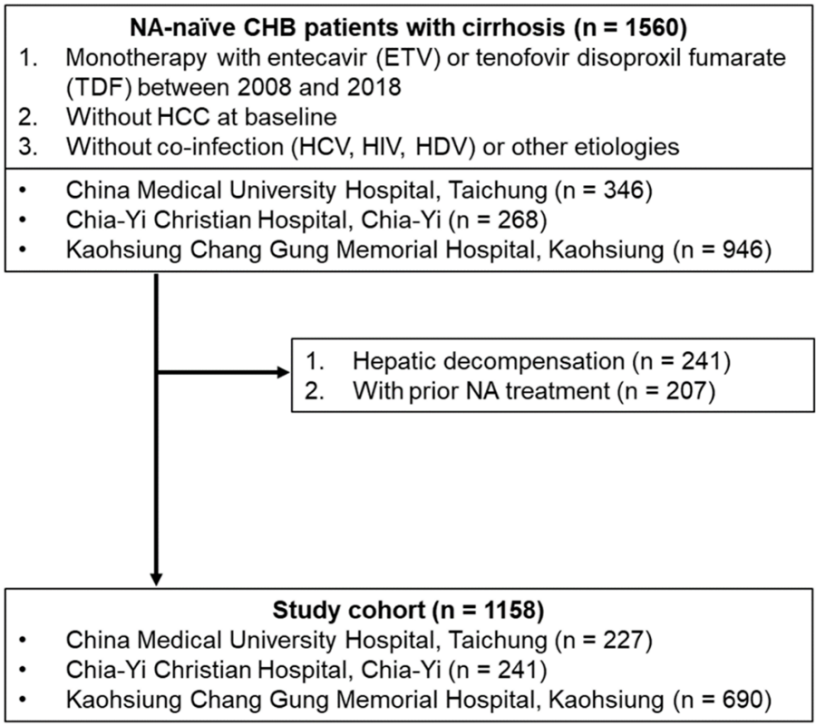
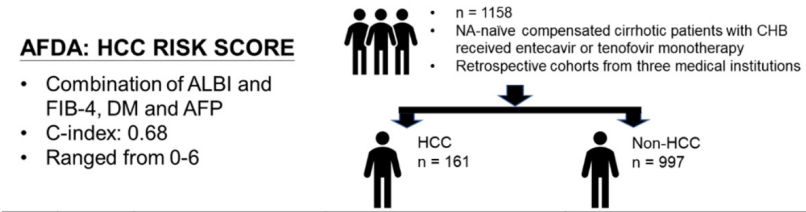


Figure S1. Study flow chart of the cohort. CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; NA, nucleos(t)ide analog.

Table S1. Total risk score of the AFDA model and the predicted 2-, 3-, 5-, and 10-year risks of HCC (n = 1158)

Risk score	Year 2	Year 3	Year 5	Year 10
Total risk score				
0 (n = 187)	1.1%	2.6%	3.4%	4.9%
1 (n = 27)	0%	4.3%	10%	10%
2 (n = 293)	1.8%	3.9%	6.5%	14.4%
3 (n = 133)	5.7%	11.4%	16.3%	24.9%
4 (n = 203)	6.3%	8.0%	12.4%	31.7%
5 (n = 259)	9.7%	14.6%	23.9%	36.7 %
6 (n = 56)	5.6%	11.8%	23.2%	36.9 %
Risk model				
3 groups				
0 (n = 187)	1.1%	2.6%	3.4%	4.9%
1-3 (n = 453)	2.9%	6.1%	9.5%	17.1%
4-6 (n = 518)	7.9%	11.7%	19.4%	34.8%

HCC, hepatocellular carcinoma.



AFDA score	Score	Risk group	Accounting for (%)	5yr HCC incidence
	0	Low-risk group	187/1158 = 16 %	3.4 %
	1-3	Medium-risk group	453/1158 = 39 %	9.5 %
	4-6	High-risk group	518/1158 = 45 %	19.4 %

Figure S2. Graphical abstract of this study. AFP, alpha-fetoprotein; ALBI score, albumin-bilirubin score; CHB, chronic hepatitis B; DM, diabetes mellitus; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogue.

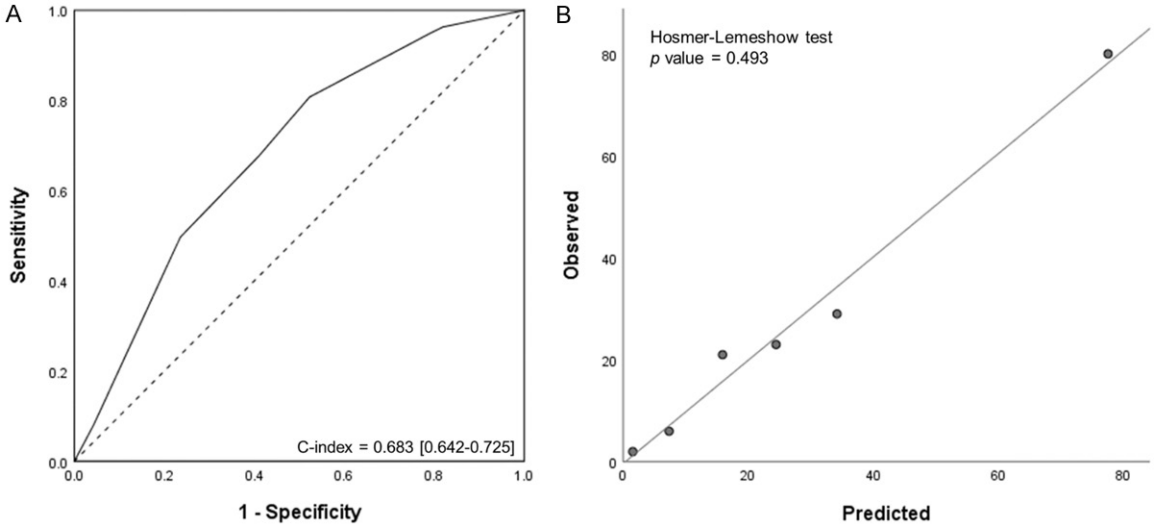


Figure S3. Discrimination assessed using the receiver operating characteristic curve (A) and calibration plot (B).

Table S2. Comparison of different prediction models of HCC according to the AUROC in patients with CHB

Risk scores	AUROC (95% CI)	Pair-wise comparison of AUROC (P value)							
	C-statistic								
		AFDA	aMAP	mPAGE-B	CAMD	THRI	PAGE-B	AASL-HCC	HCC-RESCUE
AFDA	0.6828 (0.6419-0.7248)								
aMAP	0.6591 (0.6142-0.7040)	0.2708							
mPAGE-B	0.6465 (0.6018-0.6913)	0.0930	0.1735						
CAMD	0.6379 (0.5917-0.6841)	0.0866	0.2716	0.5743					
THRI	0.6356 (0.5894-0.6819)	0.0592	0.0507	0.4994	0.9140				
PAGE-B	0.6246 (0.5773-0.6719)	0.0223*	0.0085*	0.1807	0.5478	0.3798			
AASL-HCC	0.6242 (0.5780-0.6705)	0.0250*	0.0244*	0.0546	0.2720	0.5397	0.9852		
HCC-RESCUE	0.6242 (0.5776-0.6708)	0.0374*	0.0422*	0.1639	0.2178	0.5204	0.9840	0.9982	
	3 years								
		AFDA	aMAP	mPAGE-B	CAMD	THRI	PAGE-B	AASL-HCC	HCC-RESCUE
AFDA	0.6681 (0.6138-0.7224)								
aMAP	0.6705 (0.6143-0.7266)	0.9364							
mPAGE-B	0.6745 (0.6179-0.7312)	0.8307	0.7303						
CAMD	0.6581 (0.5974-0.7189)	0.7803	0.6198	0.4143					
THRI	0.6504 (0.5910-0.7099)	0.6147	0.1933	0.2537	0.7815				
PAGE-B	0.6316 (0.5696-0.6935)	0.3065	0.0209*	0.0460*	0.3511				
AASL-HCC	0.6513 (0.5908-0.7119)	0.6384	0.3107	0.1057	0.6933	0.9689	0.4262		
HCC-RESCUE	0.6389 (0.5775-0.7003)	0.4449	0.1422	0.0794	0.1685	0.6170	0.7663	0.3886	
	5 years								
		AFDA	aMAP	mPAGE-B	CAMD	THRI	PAGE-B	AASL-HCC	HCC-RESCUE
AFDA	0.6812 (0.6349-0.7275)								
aMAP	0.6659 (0.6159-0.7158)	0.5277							
mPAGE-B	0.6578 (0.6075-0.7080)	0.3441	0.4286						
CAMD	0.6496 (0.5969-0.7023)	0.2927	0.4653	0.6442					
THRI	0.6478 (0.5963-0.6993)	0.2441	0.1816	0.5845	0.9400				
PAGE-B	0.6304 (0.5773-0.6835)	0.0795	0.0123*	0.6442	0.4568	0.2200			
AASL-HCC	0.6434 (0.5912-0.6955)	0.1992	0.1965	0.2536	0.6595	0.8346	0.5642		
HCC-RESCUE	0.6342 (0.5821-0.6864)	0.1349	0.1023	0.1831	0.1956	0.4964	0.8633	0.4638	

AUROC, area under the receiver operating characteristic; CHB, chronic hepatitis B; CI, confidence interval; HCC, hepatocellular carcinoma. *$P < 0.05$.

Table S3. Cumulative incidence of HCC at 2 to 5 years of antiviral therapy in low-risk patients with CHB according to different prediction models

Low-risk Group (percentage, case number of eligible patients)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)
AFDA (score = 0)[1] (16.1%, n = 187 of 1158)	1.1	2.6	3.4	3.4
aMAP (score < 50) (10.2%, n = 118 of 1158)	1.9	1.9	3.3	6.4
mPAGE-B (score ≤ 8) (8.6%, n = 100 of 1158)	1.2	2.6	7.0	8.8
CAMD (score < 8) (0%, n = 0 of 1158)	NA	NA	NA	NA
THRI (score < 120) (1.7%, n = 20 of 1158)	0	0	0	7.1
PAGE-B (score ≤ 9) (6.5%, n = 75 of 1158)	4.3	4.3	6.5	9.4
AASL-HCC (score ≤ 5) (0%, n = 0 of 1158)	NA	NA	NA	NA
HCC-RESCUE (score ≤ 64) (2.5%, n = 29 of 1158)	0	0	0	4.8

[1]The low-risk group of the AFDA model with score = 0. CHB, chronic hepatitis B; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; NA, not available.