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Prediction models for development of hepatocellular carcinoma in chronic hepatitis B patients

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Abstract

Chronic hepatitis B (CHB)-related hepatocellular carcinoma (HCC) is a major health problem in Asian-Pacific regions. Antiviral therapy reduces, but does not completely prevent, HCC development. Thus, there is a need for accurate risk prediction to assist prognostication and decisions on the need for antiviral therapy and HCC surveillance. A few risk scores have been developed to predict the occurrence of HCC in CHB patients. Initially, the scores were derived from untreated CHB patients. With the development and extensive clinical application of nucleos(t)ide analog(s) (NA), the number of risk scores based on treated CHB patients has increased gradually. The components included in risk scores may be categorized into host factors and hepatitis B virus factors. Hepatitis activities, hepatitis B virus factors, and even liver fibrosis or cirrhosis are relatively controlled by antiviral therapy. Therefore, variables that are more dynamic during antiviral therapy have since been included in risk scores. However, host factors are more difficult to modify. Most existing scores derived from Asian populations have been confirmed to be accurate in predicting HCC development in CHB patients from Asia, while these scores have not offered excellent predictability in Caucasian patients. These findings support that more relevant variables should be considered to provide individualized predictions that are easily applied to CHB patients of different ethnicities. CHB patients should receive different intensities of HCC surveillance according to their risk category.

Key Words: Antiviral agents; Hepatitis B virus; Hepatocellular carcinoma; Liver cirrhosis; Risk factors; Proportional hazards models

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Core Tip: Risk scores are useful in estimating hepatocellular carcinoma (HCC) risk in chronic hepatitis B (CHB) patients. While antiviral therapy does not eliminate the risk of hepatitis B virus (HBV)-related HCC, it modifies the natural disease course to reduce the HCC risk. CU-HCC (Chinese University-HCC), GAG-HCC (guide with age, gender, HBV DNA, core promoter mutations and cirrhosis), and REACH-B (risk estimation for HCC in CHB) scores derived from Asian CHB patients were also accurate in treated patients. The PAGE-B (platelet, age, and gender-hepatitis B) score has persistently high predictability for treated Caucasian and Asian patients with different HCC risk profiles.

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INTRODUCTION

Hepatocellular carcinoma (HCC) was the sixth most common cancer and the fourth leading cause of cancer-related deaths worldwide in 2018[1]. Chronic hepatitis B virus (HBV) infection is a major cause of HCC[2]. It is well known that HBV-related carcinogenesis is considered a multifactorial and multistep process. HBV DNA integration into the host genome can potentially disrupt host-gene function or alter host-gene regulation[3,4]. HBV X protein may regulate cell apoptosis, DNA damage repair, and epigenetic changes[5,6]. This direct HBV oncogenic activity is further enhanced by chronic active inflammation, triggering a complex cascade of oxidative stress, hypoxia, necrosis, regeneration, angiogenesis, and cellular senescence[7,8]. The incidence of HCC is variable during different stages of chronic hepatitis B (CHB). Natural history studies in untreated patients have reported that the 5-year HCC cumulative incidences were 0.1%-1% in inactive carriers, 1%-3% in CHB without cirrhosis, and 10%-17% in compensated cirrhosis[9].

HBV vaccinations at birth have become the primary preventative intervention for HBV infection[10] and further decrease the HCC incidence[11]. Long-term antiviral therapy may suppress HBV replication and reduce the risk of HBV-related HCC[12]. However, antiviral therapy fails to completely eliminate the risk of HCC[13]. The 5-year cumulative incidence of HCC under long-term entecavir or tenofovir treatment was 0.5%-6.9% in patients without cirrhosis, 4.5%-21.6% in patients with compensated cirrhosis, and 36.3%-46.5% in patients with decompensated cirrhosis[14]. Therefore, a surveillance strategy is needed to detect HCC earlier in the disease course. Thus, the factors that previously identified patients as being at risk for HCC need to be refined.

Previous studies have identified patient and viral factors for HCC in patients with chronic HBV infection, including older age, male sex, cirrhosis, diabetes, family history of HCC, alcoholic drinking, elevated serum alanine aminotransferase (ALT), increased bilirubin, elevated α -fetoprotein (AFP), low platelet count, low albumin, and increased international normalized ratios at baseline, hepatitis B surface antigen (HBsAg) levels, positive hepatitis B e antigen (HBeAg), high HBV DNA, genotype C virus, and HBV mutations[7,15-20]. Recently, risk scores for HCC have been proposed by different researchers for CHB based on these risk factors. Therefore, we will describe the presently used prediction models that have been developed in CHB patients.

HCC PREDICTION SCORES IN UNTREATED PATIENTS

In 2009, the GAG-HCC (guide with age, gender, HBV DNA, core promoter mutations and cirrhosis) score was derived from a cohort from Hong Kong, which included 15.1% of patients with cirrhosis. Age, sex, HBV DNA, core mutations, and cirrhosis were identified as independent risk factors for the development of HCC[21]. This score achieved an area under the receiver operating characteristic curve (AUROC) of 0.88 and 0.89 for 5- and 10-year HCC prediction, respectively, when the cutoff was optimized to 101. Patients with a GAG-HCC score ≥ 101 were considered to have an

increased HCC risk. Since core promoter mutations cannot be easily tested in routine clinical practice, this variable was removed. Then, the optimal cutoff of the HCC score for the prediction of 5- and 10-year development of HCC was changed to 100 and 82 points, respectively. The score was not externally validated and was validated by the statistical method of leave-one-out cross-validation (LOOCV). The AUROCs for predicting HCC at 5 and 10 years were 0.87 and 0.88, respectively. The negative predictive value (NPV) at a cutoff of 82 points to exclude HCC in 10 years was 98.8%.

The CU-HCC (Chinese University-HCC) score was developed from a prospective study among HBV carriers from the Chinese University of Hong Kong[16]. Age, hypoalbuminemia, bilirubin, HBV DNA, and cirrhosis were used to construct a prediction score ranging from 0 to 44.5. It was validated in an independent cohort of 424 Chinese CHB patients in Hong Kong. Although all patients were untreated at baseline, 15.1% and 25.0% of patients from the training and validation cohorts, respectively, received antiviral therapy during the long-term follow-up. Using a cutoff point of 5, the sensitivity to detect HCC was 88.6%, and the NPV was 97.8%. The cutoff values (5 and 20) discriminated HCC risk into three groups: Low- (< 5), intermediate- (5-19), and high- (≥ 20) risk groups. At a cutoff of 5 points, the AUROCs for predicting HCC at 5 years and 10 years in the validation cohort were 0.76 and 0.78, respectively. The sensitivity was 78.3% and 81.0%, and the NPV was 98.3% and 97.3% at 5 years and 10 years, respectively, in the validation cohort. The 5/10-year HCC-free survival rates were 98.3%/97.1%, 90.5%/71.0%, and 78.9%/67.7% in the low-, medium-, and high-risk groups, respectively.

The REACH-B (risk estimation for HCC in CHB) score was developed from a cohort of 3584 community patients without cirrhosis in Taiwan and validated in 1505 hospital patients from Hong Kong and Korea[22]. Sex, age, serum ALT, HBeAg status, and serum HBV DNA level were used to construct a 17-point risk score. Instead of discriminating different risk categories, the lowest to highest HCC risk for patients ranged from 0.0%-23.6%, 0.0%-47.4%, and 0.0%-81.6% at 3, 5, and 10 years, respectively. The AUROCs for predicting HCC at 3, 5, and 10 years in the validation cohort were 0.811, 0.796 and 0.769, respectively, and 0.902, 0.783, and 0.806, respectively, after exclusion of cirrhosis patients in the validation cohort. The REACH-B score was derived in a community-based cohort and was useful for patients who did not meet the current treatment recommendations.

Chen *et al*[23] further developed a model for predicting long-term HCC risk in CHB patients from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer in HBV cohort. A total of 3340 participants were randomly allocated into derivation and validation sets at a ratio of 2:1. Older age, male sex, and increasing levels of ALT, HBsAg, HBeAg, genotype C, and HBV DNA were included in the risk score, which ranged from 0-19[24]. It was also called REACH-B II model. The risk scores categorized patients into low, medium, and high HCC risk groups in the validation set (risk score < 9 for low-, 9-12 for medium-, and ≥ 13 for high-risk groups). The HCC risk ranged from 0.01%-36.19%, 0.03%-79.72%, and 0.07%-98.16% at 5, 10, and 15 years, respectively. The AUROCs for predicting 5-year, 10-year, and 15-year HCC risk in the derivation set were 0.89, 0.85, and 0.86 and were 0.84, 0.86, and 0.87 for 5-, 10-, and 15-year HCC risk, respectively, in the validation set. The study suggested that quantitative serum HBsAg levels in patients with low HBV DNA levels (< 10⁶ copies/mL) and HBV genotype C in participants with high HBV DNA levels were associated with the development of HCC. These results implied that different risk factors are involved in the natural history of HBV infection.

Although GAG-HCC, CU-HCC, and REACH-B scores were derived in cohorts of untreated CHB patients, their predictability was subsequently confirmed in patients treated with entecavir[25]. However, the discriminatory performance of all these scores has been limited in Caucasians so far. In a large, multicenter, retrospective cohort of Caucasian CHB patients with entecavir and tenofovir, the C-indexes of these scores for the prediction of HCC (GAG-HCC: 0.76; CU-HCC: 0.62; REACH-B: 0.61) were not excellent in all patients nor in noncirrhotic (GAG-HCC: 0.76; CU-HCC: 0.60; REACH-B: 0.64) or cirrhotic patients (GAG-HCC: 0.62; CU-HCC: 0.64; REACH-B: 0.61)[26]. In another ethnically diverse cohort (Caucasian, Asian and other), the discriminatory performances of CU-HCC, GAG-HCC, and REACH-B scores were 0.70, 0.57, and 0.55, respectively, at baseline. Performance was further reduced in Caucasians with C-statistics (0.63, 0.61, and 0.52, respectively). After 1 year of treatment, predictive performances were comparable to those at baseline[27].

Many prediction models include cirrhosis as a major component. However, routine clinical imaging may not be accurate enough to diagnose cirrhosis. Therefore, the introduction of a test to assess the degree of liver fibrosis may further refine the prediction of HCC risk. Transient elastography is one of the most widely validated

noninvasive tools to detect early liver cirrhosis in CHB patients[28].

The LSM-HCC (liver stiffness measurement-HCC) score was derived using a prospective cohort of 1035 CHB patients and validated in 520 patients from Hong Kong in 2014[29]. The score refined the CU-HCC score by substituting clinical liver cirrhosis with LSM using transient elastography. LSM, age, serum albumin, and HBV DNA constituted a 30-point risk score. The AUROC of the LSM-HCC score was 0.83 at 3 years and 0.83 at 5 years in the training cohort. By applying 11 as the cutoff value, patients were divided into low- and high-risk categories. The AUROCs of the LSM-HCC score were higher than those of the CU-HCC (0.89 *vs* 0.81 at 3 years; 0.83 *vs* 0.79 at 5 years); however, the difference in the AUROC was not statistically significant. The sensitivity to identify patients at risk for HCC was 100%, and the NPV was 100% at 3 years and 92.3% and 99.7% at 5 years in the validation cohort. The corresponding CU-HCC scores were 75% and 99.3% at 3 years and 69.2% and 98.6% using 5 as the cutoff point.

In 2016, a 'real-world score' for HCC was developed and validated to predict the risk of HCC development in a real-world setting in patients with CHB in Singapore[30]. Age, sex, cirrhosis, and AFP were generated using the 8-point score model. A cutoff point of ≥ 4.5 predicted a significant risk of developing HCC over the next 10 years with an AUROC of 0.915. The sensitivity was 88.1%, and the NPV was 98.8%. The score was further externally validated from the REACH-B, GAG-HCC, and CU-HCC cohorts with AUROCs of 0.767, 0.830, and 0.902, respectively.

The D²AS model was developed from 971 CHB patients with HBV DNA > 2000 IU/mL and normal or mildly elevated ALT levels (< 80 U/L) in South Korea in 2017. The score was validated from an independent cohort of 507 patients[31]. These patients did not receive antiviral therapy due to normal or mildly elevated ALT levels. Patients with cirrhosis were excluded. Age, HBV DNA, and sex were used to construct the D²AS model with a 4-point risk scale. The time-dependent AUROCs of the D²AS score were 0.895 and 0.884 in the derivation cohort at 3 and 5 years, respectively. The AUROCs were 0.889 and 0.876 in the validation cohort. The D²AS model showed significantly higher AUROCs than REACH-B (0.942 *vs* 0.869 at 2 years, 0.880 *vs* 0.750 at 4 years, and 0.876 *vs* 0.773 at 5 years). The patients were stratified into four subgroups: Very low- (< 1), low- (1.0-1.9), intermediate- (2.0-2.4), and high-risk (≥ 2.5). Therefore, patients (ALT < 80 U/L) with a D²AS score ≥ 2.5 may require antiviral therapy to reduce HCC risk.

HBeAg seroclearance (ESC) has traditionally been viewed as an important outcome of immune clearance and a treatment endpoint for HBeAg-positive patients[32]. However, a significant proportion of patients who undergo ESC may develop HCC. Therefore, it is meaningful to predict HCC development to evaluate the dynamic changes in patients and HBV parameters after ESC. The HCC-ESC score was derived from a cohort of 723 CHB patients who underwent ESC in Hong Kong[33]. Age at ESC, male sex, cirrhosis, hypoalbuminemia, HBV DNA, and ALT composed the HCC-ESC score. The AUROCs to predict HCC at 5, 10, and 20 years after ESC were 0.95, 0.91, and 0.92, respectively, with optimal cutoffs of 129, 121, and 114 derived by maximizing the Youden index. The sensitivities were 98.5%, 87.2%, and 90.7%, and the NPVs were 99.97%, 99.4%, and 99.1% at 5, 10, and 20 years after ESC, respectively. In the authors' cohort, 296 (40.9%) patients remained treatment naïve during the entire follow-up period. The HCC-ESC score was assessed by LOOCV and has not been externally validated.

In 2019, age, sex, HBeAg, and HBV DNA were used to generate a 12-point risk score 'AGED' based on a community-based prospective cohort without cirrhosis from Qidong, China[34]. The AUCs were 0.76, 0.76, 0.79, and 0.80 at 5, 10, 15, and 20 years, respectively. The AUCs at 5 and 10 years were 0.73 and 0.74, respectively, in the validation data set. Compared to the REACH-B score, ALT was not included in the AGED score. Notably, in multivariate analysis, compared to an HBV DNA level of 10^6 copies/mL, an HBV DNA level of 10^4 - 10^6 had a high regression coefficient and was assigned one more point in the risk score, which was consistent with the REACH-B score[22]. In addition, age between 50 and 60 years was also assigned one more point than age > 60 years.

The characteristics and performance of HCC risk scores for untreated patients are described in Table 1.

HCC PREDICTION SCORES IN TREATED PATIENTS AT BASELINE

A proportion of patients with CHB received antiviral therapy during the study

Table 1 Risk scores for prediction of hepatocellular carcinoma in untreated chronic hepatitis B patients

Ref.	Risk score	Patients in derivation, <i>n</i>	Country or area	Age (yr)	HBeAg-positive, <i>n</i> (%)	Cirrhosis in Derivation, <i>n</i> (%)	Follow-up (yr), median	Antiviral therapy during follow-up, <i>n</i> (%)	Variables of the risk score	AUROC for 5 yr	Cut-off
Yuen <i>et al</i> [21]	GAG-HCC	820	Hong Kong	40.6 (13.5-83.2)	356 (43.4)	124 (15.1)	6.6	0	Age, sex, HBV DNA, cirrhosis, Core promoter mutation	0.88	101
Wong <i>et al</i> [16]	CU-HCC	1005	Hong Kong	48 ± 7	-	383 (38.1)	9.9	152 (15.1)	Age, albumin, bilirubin, cirrhosis, HBV DNA	0.76	Low-risk < 5; Intermediate risk 5-19; High risk ≥ 19
Yang <i>et al</i> [22]	REACH-B	3584	Taiwan	45.7 ± 9.8	545 (15.2)	0	12.0	0	Age, sex, ALT, HBeAg, HBV DNA	0.796	-
Lee <i>et al</i> [24]	REACH-B II	2227	Taiwan	30-65	-	0	-	0	Sex, age, ALT, family history of HCC, HBeAg, HBV DNA, HBsAg, genotype	0.89	-
Wong <i>et al</i> [29]	LSM-HCC	1035	Hong Kong	46 ± 12	256 (24.7)	331 (32.0)	5.8	390 (37.8)	Age, albumin, HBV DNA, LSM	0.83	11
Poh <i>et al</i> [30]	RWS-HCC	538	Singapore	56.4 ± 12.1	167 (31.0)	80 (14.9)	4.9	-	Sex, age, cirrhosis, AFP	0.915 ¹	4.5
Sinn <i>et al</i> [31]	D ² AS risk score	971	South Korea	42.6 ± 10.6	547 (56.3)	0	4.5	0	HBV DNA, sex, age	0.884	Very low < 1; Low-risk 1.0-1.9; Intermediate risk 2.0-2.4; High risk ≥ 2.5
Fung <i>et al</i> [33]	HCC-ESC	723	Hong Kong	32 (18-83)	723 (100)	-	18.3	427 (59.1)	Age, sex, cirrhosis, HBV DNA, ALT, albumin	0.95	129
Fan <i>et al</i> [34]	AGED	628	Chinamainland	-	193 (30.7)	0	21.0	-	Age, sex, HBeAg, HBV DNA	0.76	Low-risk 0-4; Intermediate risk 5-9; High risk 10-12

¹Ten-year hepatocellular carcinoma prediction. HBeAg: Hepatitis B e antigen; AUROC: Area under the receiver operating characteristic curve; GAG-HCC: Guide with age, gender, hepatitis B virus DNA, core promoter mutations and cirrhosis; CU-HCC: Chinese University-hepatocellular carcinoma; REACH-B: Risk estimation for hepatocellular carcinoma in chronic hepatitis B; LSM: Liver stiffness measurement; RWS: Real-world score; ESC: Hepatitis B e antigen seroclearance; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HBsAg: Hepatitis B surface antigen.

period[21,29]. Antiviral therapy reduces HBV DNA and results in regression of liver fibrosis and may even reverse cirrhosis. It may be unsuitable for CHB patients on antiviral therapy because serum HBV DNA is usually undetectable during long-term antiviral therapy. Considering that the risk of HCC can be substantially modified by antiviral therapy, models designed for treatment-naïve patients may not adequately predict its risk in patients undergoing NAs.

In 2014, a modified REACH-B (mREACH-B) score was developed from a small prospective cohort of 192 patients who achieved complete virological response (HBV DNA < 20 IU/mL) in South Korea[35]. Sex, age, ALT, HBeAg status, and liver stiffness

instead of HBV DNA level were incorporated into the REACH-B scoring model. The AUROC was 0.805-0.814, compared with that of REACH-B (0.629) for the 3-year prediction of HCC. The risk score was not invalidated owing to its small sample size. However, the mREACH-B score was validated in another study by the authors, including 1308 patients[36]. The AUROCs of the mREACH-B score were 0.828 and 0.806 at 3 and 5 years for HCC development, respectively. The AUROCs were 0.813 and 0.795 for HCC development at 3 and 5 years, respectively, in patients treated with antiviral therapy (848/1308), which indicated better performance. At the same time, the performances of other HCC prediction models (GAG-HCC, CU-HCC, REACH-B, and LSM-HCC scores) were evaluated. The AUROCs of mREACH-B for HCC risk were significantly higher (0.828/0.806) than those of GAG-HCC (0.751/0.757), CU-HCC (0.698/0.700), REACH-B (0.717/0.699), and LSM-HCC (0.777/0.759) scores at 3/5 years. It should be noted that the mREACH-B score was derived from CHB patients with HBV DNA < 20 IU/mL. However, GAG-HCC, CU-HCC, REACH-B, and LSM-HCC scores were established mainly from patients without antiviral therapy. Therefore, the performances of the mREACH-B score were comparable to those of the abovementioned prediction models when only the untreated patients were analyzed.

Nearly all HCC risk scores were developed in Asian populations. Consequently, these risk scores may not be suitable for Caucasian patients with CHB. The first HCC risk score in Caucasian patients was produced in 2016[37]. The PAGE-B (platelet, age, and gender-hepatitis B) model was developed from a multicenter study with 1325 patients and validated with 490 patients. These CHB patients received entecavir/tenofovir treatment for at least one year. It was the first risk score developed for patients treated with first-line NAs, entecavir (ETV) and tenofovir. The PAGE-B score was developed based on age, sex, and platelet count. The C-index of the model was 0.82. When cirrhosis was added into the risk score, the discrimination was not substantially improved (C-index = 0.84). The score ranged from 0 to 25. In the validation dataset, the C-index of the PAGE-B risk score was 0.82. Using a cutoff point of 10, the PAGE-B score was associated with a 100% sensitivity and 100% NPV within the first 5 years for predicting HCC in both the derivation and validation cohorts. The PAGE-B score shows good predictive performance in assessing the likelihood of developing HCC. PAGE-B is also the only risk score that has been validated in both Western and Eastern populations so far[38-42].

HCC-RESCUE stands for HCC-Risk Estimating Score in CHB patients Under Entecavir. The risk score model was developed based on a cohort of 990 and was validated in a cohort of 1071 treatment-naïve patients with CHB treated with entecavir[43]. Since most patients (933/1071) in the testing cohort achieved complete virological response (HBV DNA < 69 IU/mL), HBV DNA was not identified as a risk factor in multivariable analysis. HCC-RESCUE comprised age, sex, and liver cirrhosis, with scores ranging from 18-113 points. The AUROCs for predicting HCC development at 3 and 5 years were 0.788 and 0.817 in the testing cohort and 0.810 and 0.809, respectively, in the validation cohort. Using 65 and 85 points as cutoff values, risk groups were categorized into the low-risk group, ≤ 64 points; intermediate-risk group, 65-84 points; and high-risk group, ≥ 85 points. A significant difference in HCC development in each risk group was observed (low-risk group, 2.1%; intermediate-risk group, 9.3%; high-risk group, 41.2%, $P < 0.001$) in the validation cohort.

In 2018, the CAMD (cirrhosis, age, male sex, and diabetes mellitus) score was constructed based on a nationwide cohort of 23851 adult CHB patients on entecavir or tenofovir treatment from Taiwan and validated in a cohort including 19321 Hong Kong patients[44]. The score ranged from 0 to 19 points. In the development cohort, the C-indices were 0.83, 0.82, and 0.82 at 1, 2, and 3 years for HCC occurrence, respectively. The C-indices were 0.74, 0.75, and 0.75, respectively, in the validation cohort. The C-indices were 0.76 and 0.76 at 4 and 5 years, respectively, when the CAMD score was extrapolated beyond 3 years. The C-indices of the CAMD and PAGE-B scores were comparable at 3 (0.74 *vs* 0.73) and 5 years (0.75 *vs* 0.74) in Hong Kong patients who had baseline platelet data ($P > 0.05$). Cutoff points of 8 and 13 points were set to stratify patients into low- (< 8), intermediate- (8-13), and high-risk (> 13) subgroups. In the validation cohort, the 3-year cumulative incidences of HCC were 0.72%, 3.35%, and 9.17% in the low-, intermediate-, and high-risk subgroups, respectively. The prognostic performance of the CAMD score was externally validated in an independent cohort of patients with CHB who were treated with entecavir or tenofovir from South Korea. The predictive performance of the CAMD score was significantly superior to that of the PAGE-B score (0.790 *vs* 0.760, $P = 0.030$)[45].

A modified PAGE-B score (mPAGE-B) was developed in 2001 CHB patients with entecavir/tenofovir therapy and validated in 1000 patients from South Korea[46]. The mPAGE-B score was constructed using PAGE-B parameters (age, sex, and platelet

count) and albumin, ranging from 0 to 21 points. The AUROC of mPAGE-B was 0.82 at 5 years in the derivation set. Cutoff values (9 and 12) discriminated HCC risk into three groups: Low- (score ≤ 8), intermediate- (score 9-12), and high- (score ≥ 13) risk groups. The cutoff value of 13 maximized both the sensitivity and specificity of the mPAGE-B risk score (sensitivity 72.4%, specificity 71.7%, PPV 14.4%, and NPV 97.5%) at 5 years in the derivation set. The AUROC of mPAGE-B was 0.82 at 5 years in the validation set. The AUROC indicated significantly higher predictive performance (0.82) of the mPAGE-B scores for HCC development at 5 years in the validation set than that of the PAGE-B (0.72), CU-HCC (0.70), GAG-HCC (0.71), and REACH-B (0.61) models. In addition, the authors found that HCC risk was significantly decreased after 4 years of therapy in the total study population or in each risk group stratified by mPAGE-B score compared to the risk beyond the first 4 years of antiviral treatment. The AUROC (95%CI) of the mPAGE-B score for the prediction of HCC at 5 years was 0.80 (0.79-0.81), and the discriminatory ability for low-risk patients was excellent in a large cohort from Hong Kong[40].

In 2019, the AASL (age, albumin, sex, liver cirrhosis)-HCC model was constructed from a cohort of 944 patients and validated from a cohort of 298 treatment-naïve CHB patients initially administered entecavir or tenofovir. AASL-HCC scores ranged from 0 to 29. The C-statistics were not significantly different between the derivation and validation datasets (0.814 *vs* 0.850 within 3 years and 0.802 *vs* 0.805 within 5 years, respectively). The AASL-HCC score showed higher accuracy for predicting HCC development at 10 years (AUROC: 0.814) than CU-HCC (0.758), GAG-HCC (0.810), REACH-B (0.640), or PAGE-B (0.719). Using scores of 6 and 20 as cutoff values, patients in the derivation dataset were stratified into three groups: Low- (score: ≤ 5), intermediate- (score: 6-19), and high-risk groups (score: ≥ 20). The 5-year cumulative HCC incidence rates of these three risk groups were comparable in the derivation and validation datasets (0 *vs* 0 in the low-risk group, 3.7% *vs* 7.4% in the intermediate-risk group, and 17.6% *vs* 30.9% in the high-risk group)[47]. Since Child-Pugh Class B or C cirrhotic patients were included in the development of the model, the AASL-HCC model might better reflect the real clinical scenario. The AASL score was externally validated in an independent, large-scale cohort. The AUCs of the AASL score were the highest for 3- and 5-year HCC predictions (0.818 and 0.816, respectively) compared to the RESCUE-B score (0.815 and 0.814, respectively, $P > 0.05$), mPAGE-B score (0.781 and 0.786, respectively, $P < 0.05$) and PAGE-B score (0.780 and 0.769, respectively, $P < 0.05$)[38].

In 2019, a two-step algorithm combining the LSM-HCC score and ELF (enhanced liver fibrosis) score was derived to predict HCC risk in CHB patients with antiviral treatment[48]. ELF is another noninvasive assessment for liver fibrosis based on an algorithm composed of serum hyaluronic acid, procollagen type III N-terminal peptide, and tissue inhibitor of metalloproteinases 1[49]. The improved LSM-HCC score of the majority of patients resulted in a significant change in the distribution of risk categories from the baseline data after antiviral treatment. The ELF score could stratify the risk categories for CHB patients with intermediate risk by the LSM-HCC score at baseline. A combined LSM-HCC and ELF score had a higher sensitivity (86.7%) and NPV (95.3%) than each score alone.

The REAL-B score (Real-world Effectiveness from the Asia Pacific Rim Liver Consortium for HBV) was developed to predict HCC risk in a large cohort of CHB-treated Asian Americans and Asians residing in Asia[50]. There were 5365 patients in the derivation group and 2683 in the validation group. Male sex, age, alcohol use, diabetes, baseline cirrhosis, platelet count, and AFP were used to construct a 13-point risk score. The AUROCs for the prediction of HCC at 3, 5, and 10 years in the derivation cohort were 0.81, 0.80, and 0.80, respectively. The AUROCs were 0.83, 0.81, and 0.81 for the prediction of HCC risk at 3, 5, and 10 years, respectively, in the validation cohort. The patients were stratified into low- (0-3 points), intermediate- (4-7 points), and high-risk (8-13 points) groups. The REAL-B score performed significantly better at 3/5/10 years (0.83/0.81/0.81) than the PAGE-B (0.74/0.73/0.74), REACH-B (0.66/0.66/0.64), GAG-HCC (0.78/0.77/0.76), CU-HCC (0.77/0.77/0.74), and mPAGE-B (0.77/0.76/0.77) scores in the validation cohort.

The CAMPAS score was derived from a cohort of 1511 Korean CHB patients who achieved virological response (HBV-DNA < 2000 IU/mL) by NAs and was externally validated among an independent cohort of 252 CHB patients. Cirrhosis, age, male sex, platelet count, albumin, and liver stiffness were used to construct the CAMPAS model, ranging from 0 to 284 points[51]. The overall C-index was 0.874. By applying two cutoff points (75 and 161), the patients were stratified into the low- (score ≤ 75), intermediate- (score 75-161), and high-risk groups (score > 161). By using 75 as the cutoff value, a sensitivity of 97.2% and NPV of 99.4% for predicting HCC at 7 years

were determined in the development group. The AUROC was 0.884 for the prediction of HCC development at 7 years. The C-index was 0.847 in the external validation cohort. The overall C-index of the CAMPAS model was significantly higher than those of REACH-B (0.660) and mREACH-B (0.745) in the external validation cohort. However, it was not significantly higher than those of PAGE-B (0.766) and mPAGE-B (0.798).

The characteristics and performance of HCC risk scores for patients treated with NAs at baseline are described in Table 2.

HCC PREDICTION SCORES IN TREATED PATIENTS DURING NAS TREATMENT

Most HCC prediction models are composed of baseline characteristics. As the duration of treatment increases, the risk of HCC may change. Long-term ETV therapy achieves hepatic histological improvements and regression of fibrosis and cirrhosis[52]. The HCC risk decreases after 5 years of entecavir or tenofovir therapy in Caucasian CHB patients, particularly in those with compensated cirrhosis, older age (especially ≥ 50 years), lower platelet counts, and liver stiffness ≥ 12 kPa at year 5[53]. Therefore, new prediction models are emerging based on dynamic changes in host or viral factors combined with baseline characteristics.

The APA-B score is the first risk score to predict HCC development during NA therapy in Asian CHB patients, which involved 883 patients in the development group and 442 in the validation group[54]. They were NA-naïve CHB patients with entecavir monotherapy for > 12 mo. Age, platelet count, and AFP level at 12 mo of treatment were used to generate APA-B scores, with the total risk scores ranging from 0 to 15. The C-statistic of the model was 0.85. Applying 6 and 10 as the cutoff risk scores, patients were categorized into low- (0-5), medium- (6-9), and high- (10-15) risk groups. The AUROCs for predicting the 3- and 5-year HCC risks in the development group were 0.842 and 0.827, respectively. The AUROC of APA-B showed significantly better performance than CU-HCC (0.760), REACH-B (0.620), REACH-B II (0.638), and PAGE-B (0.696) at 5 years in the development group. In the validation group, the AUROCs were 0.892 and 0.862 at 3 and 5 years, respectively. The C-statistic was 0.87 for the validation group. The on-treatment prediction model exhibited a significantly higher predictive value than the baseline model (0.863 *vs* 0.807). By using ≥ 6 as the cutoff value, a sensitivity of 90.3% and NPV of 99.1% for predicting HCC within the initial 5 years of ETV therapy were obtained in the validation group. In a cohort of 1397 NA-naïve CHB patients with ETV monotherapy ≥ 12 mo from Taiwan, the APA-B score had a statistically higher C-index than the PAGE-B score to predict HCC within (0.82 *vs* 0.71, $P < 0.001$) and beyond (0.77 *vs* 0.64, $P = 0.003$) year 5[55].

As mentioned above, only 169 (23%) patients underwent antiviral therapy at the time of ESC, and the majority of patients achieved spontaneous ESC[33]. The HCC-ESC score may be more suitable for patients without antiviral treatment. In 2020, a new risk prediction model for HCC development after ESC in CHB patients with antiviral therapy was established[56]. The HCC-ESC_{AVT} (antiviral therapy) model was derived from a cohort of 769 and validated from a cohort of 1061 patients with CHB who experienced ESC during entecavir or tenofovir treatment. The fibrosis-4 (FIB-4) index is also a frequently applied noninvasive method for predicting liver fibrosis in chronic viral hepatitis[57]. Male sex, cirrhosis, and FIB-4 were used to compose the HCC-ESC_{AVT} model. The AUCs for predicting HCC development at 3, 5, and 10 years after ESC were 0.791, 0.771, and 0.790 in the training cohort, respectively. The AUCs were statistically higher than those of the GAG-HCC model (0.642, 0.650, and 0.645 at 3, 5, and 10 years, respectively) and similar to those of the CU-HCC, PAGE-B, and mPAGE-B models. The cumulative risk for HCC development was categorized into low- (0-1), intermediate- (2-4), and high-risk (5) groups. When the patients were stratified into two groups (low *vs* intermediate + high-risk group), the sensitivities were 90.9%, 85.7%, and 88.1%, and the NPVs were 99.3%, 98.4%, and 98.4% for predicting HCC risk at 3, 5, and 10 years, respectively, in the training cohort. The AUCs were 0.802, 0.774, and 0.776 at 3, 5, and 10 years in the validation cohort, respectively.

Although the PAGE-B score was claimed to not usually be affected by antiviral therapy[37], some parameters, such as LSM, would have changed with the extension of treatment time. Therefore, two new HCC risk scores were generated based on the ongoing PAGE-B cohort, in which 1427 patients had completed > 5 years of follow-up under therapy without developing HCC within the first 5 years. The cirrhosis and age (CAGE-B) score was based on age at year 5 and baseline cirrhosis in relation to LSM at

Table 2 Risk scores for prediction of hepatocellular carcinoma in treated chronic hepatitis B patients at baseline

Ref.	Risk score	Patients in derivation, n	Country or area	Age (yr)	HBeAg-positive, n (%)	Cirrhosis in derivation, n (%)	Follow-up (yr), median	Variables of the risk score	AUROC for 5-yr	Cut-off
Lee <i>et al</i> [35]	mREACH-B	192	South Korea	49 (42-56)	100 (52.1)	90 (46.9)	3.6	Age, sex, ALT, HBeAg, LSM	0.805 ¹	-
Papatheodoridis <i>et al</i> [37]	PAGE-B	1325	Europe	52 ± 21	210 (15.8)	269 (20.3)	4.2	Age, sex, platelets	0.82	Low-risk ≤ 9; Intermediate risk 10-17; High risk ≥ 18
Sohn <i>et al</i> [43]	HCC-RESCUE	990	South Korea	47.4 ± 10.5	556 (56.2)	389 (39.3)	2.1	Age, sex, cirrhosis	0.768	Low-risk ≤ 64; Intermediate risk 65-84; High risk ≥ 85
Hsu <i>et al</i> [44]	CAMD	23851	South Korea	47.5 (37.8-56.5)	-	6308 (26.4)	2.2	Age, sex, diabetes, cirrhosis	0.82 ¹	Low-risk < 8; Intermediate risk 9-13; High risk > 13
Kim <i>et al</i> [46]	mPAGE-B	2001	South Korea	50 (42-57)	678 (33.9)	383 (19.1)	4.1	Age, sex, platelets, albumin	0.82	Low-risk ≤ 8; Intermediate risk 9-12; High risk ≥ 13
Yu <i>et al</i> [47]	AASL	944	South Korea	50 (41-57)	528 (55.9)	371 (39.3)	4.1	Age, sex, albumin, cirrhosis	0.802	Low-risk ≤ 5; Intermediate risk 6-19; High risk ≥ 20
Liang <i>et al</i> [48]	LSM-HCC and ELF	453	Hong Kong	51.7 ± 10.3	155 (36.1)	-	4.7	Age, albumin, HBV DNA, LSM, ELF	-	LSM-HCC 20 or ELF 9.8
Yang <i>et al</i> [50]	REAL-B	5365	United States and Asia-Pacific area	48.4 ± 12.7	1886 (37.4)	1085 (20.2)	-	Age, sex, alcohol, diabetes, cirrhosis, platelet, AFP	0.80	Low-risk 0-3; Intermediate risk 4-7; High risk 8-13
Lee <i>et al</i> [51]	CAMPAS	1511	South Korea	49.7 (42.1-56.2)	795 (52.6)	602 (39.8)	-	Age, sex, cirrhosis, platelet, albumin, LSM	0.884 ²	Low-risk ≤ 75; Intermediate risk 75-161; High risk > 161

¹Three-year hepatocellular carcinoma prediction.²7-yr hepatocellular carcinoma prediction. HBeAg: Hepatitis B e antigen; AUROC: Area under the receiver operating characteristic curve; mREACH-B: Modified Risk estimation for hepatocellular carcinoma in chronic hepatitis B; PAGE-B: Platelet, age, and gender-hepatitis B; mPAGE-B: Modified platelet, age, and gender-hepatitis B; CAMD: Cirrhosis, age, male sex, and diabetes mellitus; AASL: Age, albumin, sex, liver cirrhosis; LSM: Liver stiffness measurement; REAL-B: Real-world Effectiveness from the Asia Pacific Rim Liver Consortium for hepatitis B virus; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; ELF: Enhanced liver fibrosis; AFP: α-fetoprotein.

year 5[58]. The C-index of the model was 0.814. After internal validation using bootstrapping, the C-index was 0.806, and the calibration slope was 0.962. The score ranged from 0 to 16. The patients were stratified into low- (0-5), medium- (6-10), and high- (11-16) risk groups according to cutoffs of 6 and 10 points. The stiffness and age (SAGE-B) score was further simplified, in which only age and LSM at year 5, regardless of cirrhosis baseline status, were retained in the final model. The score ranged from 0 to 15. The C-index of the model was 0.809. The C-index was 0.805 in the internal validation using bootstrapping. The patients were categorized into low- (0-5), medium- (6-10), and high-risk (11-15) groups using two cutoff values (6 and 10). HCC only developed in patients with intermediate or high scores in both models. For both scores, 6 points was the highest cutoff associated with a 100% sensitivity and 100% NPV. CAGE-B and SAGE-B scores partly evaluated the risk of HCC following reversal of cirrhosis in patients who commence antiviral therapy with initial cirrhosis. They should be further validated in another independent cohort.

Table 3 Risk scores for prediction of hepatocellular carcinoma in treated chronic hepatitis B patients during treatment

Ref.	Score	Patients in derivation, n	Country or area	Age (yr)	HBeAg-positive, n (%)	Cirrhosis in derivation, n (%)	Follow-up (yr), median	Variables of the risk score	AUROC for 5 yr	Cut-off
Chen <i>et al</i> [54]	APA-B	883	Taiwan	50 ± 17	311 (35.2)	317 (35.9)	4.1	Age, platelets, AFP at 12 mo	0.827	Low-risk 0-5; Intermediate risk 6-9; High risk 10-15
Lim <i>et al</i> [56]	HCC-ESC _{AVT}	769	South Korea	47.0 (37.0-55.0)	0	319 (41.5)	-	Sex, age, cirrhosis, ALT, AST, platelet	0.771	Low-risk 0-1; Intermediate risk 2-4; High risk 5
Papatheodoridis <i>et al</i> [58]	CAGE-B	1427	Europe	52.1 ± 13.1	261 (18.4)	370 (25.9)	8.4	Age, LSM at year 5, baseline cirrhosis	0.814	Low-risk 0-5; Intermediate risk 6-10; High risk 11-16
Papatheodoridis <i>et al</i> [58]	SAGE-B	1427	Europe	52.1 ± 13.1	261 (18.4)	370 (25.9)	8.4	Age, LSM at year 5	0.809	Low-risk 0-5; Intermediate risk 6-10; High risk 11-16

HBeAg: Hepatitis B e antigen; AUROC: Area under the receiver operating characteristic curve; HCC: Hepatocellular carcinoma; ESC: Hepatitis B e antigen seroclearance; AVT: Antiviral therapy; CAGE-B: Cirrhosis and age; SAGE-B: Stiffness and age; AFP: α -Fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LSM: Liver stiffness measurement.

The characteristics and performance of HCC risk scores for treated patients during NAs treatment are described in Table 3.

CONCLUSION

A number of HCC risk scores have been developed for the prediction of HCC risk in CHB patients. All these risk scores use clinical variables and appear readily generalizable to most CHB patients. Inclusion of dynamic changes in variables, especially the results of noninvasive tests of fibrosis, could further improve the accuracy of predicting HCC in CHB patients after antiviral treatment. The direct comparison of the predictability of different risk scores is not reliable due to different races, ages, and proportions of liver cirrhosis, courses of disease, and HBV DNA levels in the development cohorts. Although different HCC risk scores present variable performance in different populations, they all display high NPVs for excluding HCC development in CHB patients. Patients at high risk of HCC should undergo increased HCC surveillance. Patients in the low-risk profile need HCC minimal surveillance due to their negligible HCC risk. Different levels of intensities of HCC surveillance should be offered according to the risk category of patients. The intensity of HCC surveillance needs to be assessed. To date, PAGE-B demonstrates good predictability for HCC development in treated Asian and Caucasian CHB patients. Most HCC prediction models from Asia have not been confirmed in Caucasian CHB patients. Further studies are needed to directly validate and compare the HCC risk scores in independent patient cohorts of different races.

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