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Review Article

Hepatocellular Carcinoma Risk Scores from Modeling to Real Clinical Practice in Areas Highly Endemic for Hepatitis B Infection

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Abstract

Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers and represents a global health challenge. Liver cancer ranks third in cancer-related mortality with 830,000 deaths and sixth in incidence with 906,000 new cases annually worldwide. HCC most commonly occurs in patients with underlying liver disease, especially chronic hepatitis B virus (HBV) infection in highly endemic areas. Predicting HCC risk based on scoring models for patients with chronic liver disease is a simple, effective strategy for identifying and stratifying patients to improve the early diagnosis rate and prognosis of HCC. We examined 23 HCC risk scores published worldwide in CHB patients with (n=10) or without (n=13) antiviral treatment. We also described the characteristics of the risk score's predictive performance and application status. In the future, higher predictive accuracy could be achieved by combining novel technologies and machine learning algorithms to develop and update HCC risk score models and integrated early warning and diagnosis systems for HCC in hospitals and communities.

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Keywords: Hepatocellular carcinoma; Chronic hepatitis B; HCC risk score; HCC screening.

Abbreviations: AI, artificial intelligence; ALT, serum alanine aminotransferase; AUROC, area under the receiver operating characteristic curve; AVT, antiviral treatment; CHB, chronic hepatitis B; C index, concordance index; CI, confidence interval; ESC, seroclearance; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; LSM, liver stiffness measurement; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RR, relative risk; WHO, World Health Organization.

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Introduction

According to the most recent global cancer statistics from the World Health Organization (WHO), primary liver cancer was the sixth most common cancer worldwide and the third leading cause of cancer death in 2020, accounting for approximately 906,000 new cases and 830,000 deaths.[1] Primary liver cancer includes hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and other rare types. HCC accounts for 75–85% of all primary liver cancers. Globally, the major causes of HCC have changed in recent years,[2] and the distribution of major risk factors for HCC varies by region.[3] Elimination of viral hepatitis remains the most important strategy for primary prevention of liver cancer worldwide, as hepatitis B virus (HBV) and hepatitis C virus (HCV) infection account for 56% and 20% of liver cancer deaths, respectively.[4] In most areas with a high incidence of HCC, such as China, South Korea, and sub-Saharan Africa, chronic HBV infection remains the leading cause of liver cancer.[3] Owing to the lack of simple and effective detection strategies and tools, fewer than 5% of chronic hepatitis patients worldwide are aware of their hepatitis status.[5] The WHO has proposed a goal of reducing the incidence of HBV infection by 90% and mortality by 65% by 2030 compared with 2015 baseline data.[6] Ninety percent of chronic viral hepatitis patients should be diagnosed, and 80% of patients should receive timely treatment.[7] Of particular importance is how to effectively identify and prevent high-risk factors for HCC and how to identify and implement standardized surveillance and treatment for high-risk liver cancer populations.

HCC surveillance is considered to help improve early diagnosis rates and prolong overall survival in at-risk populations, including patients with chronic hepatitis B (CHB).[8–11] Guidelines from various hepatology societies recommend upper abdominal ultrasonography every 6 months with or without serologic markers, mainly α-fetoprotein (AFP), for HCC screening.[12–14] However, patient compliance with conventional screening still needs to be improved,[15] and it remains questionable whether this single screening model can satisfy all HCC risk populations. An HCC risk prediction model could serve as a personal guide for disease management, as it could divide the population into different risk groups according to the characteristics of the disease.

Cost effectiveness studies indicate that surveillance strategies are required for patients with CHB when the annual incidence of HCC exceeds 0.2%.[10] HCC risk prediction models can be used as an objective method for risk quantification. According to Voulgaris *et al*.,[16] the main clinical benefit of a risk score is to accurately distinguish whether or not HCC surveillance is needed in patients with chronic liver disease. In low-risk populations, unnecessary anxiety and potential harm from screening could be avoided and limited medical resources could be used wisely. On the other hand, the HCC risk score may serve as a predictive guide for high-risk patients who should receive interventions that can effectively reduce such risk. HCC risk scores are considered a foundation for proper medical practice because they can guide individualized HCC screening and are cost effective.[16,17] This review explains HCC risk factors and the construction and application of HCC risk scores.

HCC risk factors

Etiologies

HBV: HBV infection is one of the main risk factors for HCC. According to estimates from the WHO, 296 million people, or 3.8% of the world's population, have chronic HBV infection.[18] HBV is a DNA virus that integrates into the host genome, leading to the activation of oncogenes through insertional mutagenesis.[19] HBV causes an immune response in the human body that leads to liver cell damage and inflammatory necrosis. Persistent and recurrent inflammatory necrosis leads to cirrhosis and even HCC.[20] According to a meta-analysis, patients with HBV infection are 15 to 20 times more likely to develop HCC than those without HBV infection.[21] Numerous factors have been found to increase HCC risk in HBV carriers, including demographics, viral parameters, liver cirrhosis, and environmental or lifestyle factors.

Among viral parameters, long duration of HBV infection, persistent hepatitis B e antigen (HBeAg) positivity, high HBV DNA and hepatitis B surface antigen (HBsAg) levels, HBV genotype C, and coinfection with HCV and hepatitis D virus may predict a higher risk of HCC. The incidence of HCC in 30–65-year-old men who were $HBsAg^-$ and $HBeAg^-$, $HBsAg^+$ and $HBeAg^-$, and $HBsAg^+$ and $HBeAg^+$ were 39.1, 324.3, and 1,169.4/100,000 person-years, respectively, suggesting that HBeAg positivity is associated with increased HCC risk.[22] A large cohort study showed that HCC risk was increased in a dose-dependent manner compared with undetectable HBV DNA [(<5.15E+01 IU/mL), 5.15E+01–1.72E+03 IU/mL, 1.72E+03–1.72E+04 IU/mL, 1.72E+04–1.72E+05 IU/mL, and ≥1.72E+05 IU/mL, hazard ratio (HR) 1.4, 4.5, 11.3, and 17.7, $p<0.001$)].[23] The 20-year cumulative incidence of HCC increased with increasing quantification of HBsAg (qHBsAg) levels, and the risk of HCC was significantly increased in partial patients with qHBsAg>1,000 IU/mL (HR=13.7 [95% confidence interval (CI): 4.8–39.3]).[24] Genotype C is prevalent in patients with CHB in East and Southeast Asia and is associated with an increased risk of developing HCC of other genotypes, which may be associated with delayed HBeAg seroconversion, a longer HBV replication cycle, and a higher HBV DNA burden in those patients.[23,25] A meta-analysis found that patients with HBV and HCV coinfection had a higher risk of HCC than patients with infected with only HBV or HCV, or not infected with HBV or HCV [odds ratio (OR)=51.1 (95% CI: 33.7–77.6) vs. OR=27.6 (95% CI: 19.8–38.4) vs. OR=23.4 (95% CI: (17.2–31.7) vs. 1.0].[26] A 20-year follow-up study in Taiwan reported that HBV vaccine reduced the risk of HCC [OR=0.31 (95% CI: 0.24–0.41)] in populations that received more than three doses and were seropositive for hepatitis B immunoglobulin.[27]

Cirrhosis is present in nearly 90% of HCC patients.[28] The annual incidence of HCC in patients with HBV-associated cirrhosis is 3–6%,[29–31] but it is only 0.5% to 1.0% in HBV patients without cirrhosis.[32] A 15-year follow-up study in South Korea[33] confirmed that the risk of HCC was 18.2 times higher in patients with HBV-associated cirrhosis than in patients without cirrhosis [HR=18.2 (95% CI: 17.8–23.4)]. Liver stiffness values at baseline were found to be predictive of the development of HCC in CHB patients, and the cumulative incidence rate of HCC increased in association with a high liver stiffness measurement (LSM) ($p<0.001$).[34]

Antiviral therapy suppresses HBV replication to improve liver inflammation and reduce the progression of cirrhosis and the occurrence of HCC, but cannot eliminate the risk of HCC. Regardless of the type of oral agent administered, antiviral therapy reduces the risk of HCC in CHB patients compared with untreated controls (6.4% vs. 2.8%, $p=0.003$).[35] Entecavir[36] [HR=0.03 (95% CI: 0.009–0.013)], lamivudine[37] [HR=0.49 (95% CI: 0.25–0.99)], and interferon[33] [HR=0.31 (95% CI: 0.18–0.63)] have been shown to reduce HCC risk to varying degrees.

HCV

Chronic HCV infection is the most common cause of HCC in North America, Europe, and Japan. Because HCV is an RNA virus, it is not integrated into the host genome. The occurrence of HCV-related HCC is most commonly observed in patients with cirrhosis or chronic liver injury with bridging fibrosis.[38] A meta-analysis of case-control studies found that the risk of HCC was 17-fold higher in HCV antibody (Ab)-positive than in HCV Ab-negative patients.[39] Even in HCV patients who achieve sustained virologic response (SVR) after direct-acting antiviral treatment, there is a persistent risk of developing HCC of >2% per year).[40,41]

Host factors

Demographic factors such as male sex and an age of more than 40 years, a family history of first-degree relatives with HCC, and an unhealthy lifestyle including consumption of foods containing aflatoxin B1,[42] excessive alcohol consumption,[43,44] smoking,[45] and obesity[46] are associated with an increased risk of HCC. Patients with concomitant diabetes mellitus relative risk (RR) [RR=1.93 (95% CI: 1.35–2.76)47] and metabolic syndrome [RR: 1.81 (95% CI: 1.37–2.41)[48] have an increased risk of HCC, and the prevalence is increasing, especially in developed countries. In conclusion, these adverse factors further increase the risk of HCC based on the initial chronic liver disease.

Host genetics

Carcinogenesis of HCC is a multifactorial and complex process that includes genetic factors. Meta-analyses have shown that tumor necrosis factor variants are associated with significantly higher HCC risk.[49,50] Another meta-analysis of case-control studies examined the effects of polymorphisms in genes encoding glutathione S-transferase on HCC risk. Two genetic variants, *GSTT1* null [OR: 1.19 (95% CI: 0.99–1.44)] and *GSTM1* null [OR: 1.16 (95% CI: 0.89–1.53)], were associated with increased risk of HCC.[51]

HCC risk scores

Given the causal relationship between chronic HBV infection and progression to HCC, several international studies have developed and validated risk scores to accurately predict

progression to HCC in CHB patients and guide individualized surveillance. Most of the current HCC risk scores were developed based on conventional regression models. The variables commonly used to generate HCC risk scores consist of host factors including sex, age, family history, and comorbidities; virological indicators including HBeAg, HBV DNA, and HBsAg; parameters reflecting the severity of liver disease including platelets, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), albumin, bilirubin, LSM, cirrhosis and AFP; and other variables associated with the occurrence of HCC including HBV genotype, pretreatment core promoter mutations, HBV pre-S mutants, N-glycan biosignature, gamma-glutamyl transferase isoenzyme II, etc.[52]

Clinical assessment indicators of the HCC risk score include negative predictive value (NPV), positive predictive value (PPV), the area under the receiver operating characteristic curve (AUROC), and Harrell's C (concordance) index. These indicators can be used to evaluate the predictive efficiency and discriminatory accuracy of the risk scores. Because the predictive power of all HCC risk scores may decrease over time,[16] we record the first 5 years of the predictive performance of each risk score. In this review, we tracked 23 HCC risk scores. These risk scores are grouped according to whether or not the patient population received antiviral treatment (AVT). The risk scores reviewed here were published in academic journals indexed in PubMed, with the last update on January 18, 2023.

HCC risk scores in untreated patients with hepatitis B

The HCC risk score was based on a CHB population without antiviral therapy and including mainly Asian individuals. The risk scores, listed in alphabetical order, were APRI/FIB4,[53] AGED,[54] D2AS,[55] NGM-HCC,[56] REACH -B,[57] and REACH -B II.[58] We also found some risk scores based on partially treated CHB patients whenever they are in the initial or follow-up phase. Those risk score prediction models are CU-HCC,[59] GAG-HCC,[60] HCC-ESC[61] LS Model,[62] LSM-HCC,[63] LSPS,[64] and RWS-HCC.[65] The characteristics of the 13 scores are summarized in Table 1 and the specific parameters of each HCC risk score are shown in Table 2. The untreated risk scores were mainly generated by research institutions in Asia. With the exception of the community-based cohorts REVEAL-HBV and Qidong Hepatitis B (commonly known as QBC), all others are hospital-based cohorts. The predictive power of these scores is quite good in the derivation cohort. The AUROCs for predictability at 5 years ranged from 0.73 to 0.95, but the calibration power and an external validation study were not available for each risk score.

The NGM-HCC, REACH-B, and REACH-B II scores were constructed from the same REVEAL-HBV cohort.[56–58] The AUROCs for the three NGM-HCC subscores were all greater than 0.8 for predicting the 5-year HCC risk.[56] The HCC-ESC was developed in 723 HBeAg-positive patients with HBeAg seroclearance (ESC). Older age at ESC, male sex, higher HBV DNA, cirrhosis, hypoalbuminemia, and persistent abnormal ALT were predictive factors for the occurrence of HCC. The authors also reported the HBsAg seroclearance rate after HBeAg seroclearance (ESC) in this cohort. The first two parameters were the same as HCC-ESC, lower HBV DNA levels, and absence of AVT were significant predictors of HBsAg seroclearance.[61] Two noninvasive tests, APRI and FIB-4 were combined to differentiate HCC risk for chronic HBV-infected patients with low-level viremia, defined as HBV DNA of <2,000 IU/mL). The AUROC value for the APRI/FIB-4 score reached 0.78 (95% CI: 0.75–0.81).[55] The D^2AS score (age, sex, HBV DNA) was constructed in CHB patients with elevated HBV DNA levels (>2.000 IU/mL) with normal or slightly elevated ALT levels (<80 U/L). This score is a four point risk scale, with 0% and 17.8% corresponding to the 5-year HCC risk in very low-risk and high-risk groups, respectively, and the AUROC reached 0.88 in both the derivation and validation cohorts.[55] The RWS-HCC risk score was developed in a real-world CHB cohort for 10-year HCC prediction [AUROC: 0.915 (95% CI: 0.880–0.949)]. This score was further validated in the REACH-B [AUROC: 0.767 (95% CI: 0.725–0.810)], GAG-HCC [AUROC: 0.830 (95% CI:0.747–0.913)], and CU-HCC [AUROC: 0.902 (95% CI: 0.856–0.948)] cohorts.[65]

Comments for clinical application in untreated risk scores

The transferability and generalizability of the HCC prediction score based on cohorts of subjects not receiving AVT remains to be confirmed. First, the widespread application of untreated prediction models is hampered by the current international academic framework advocating AVT strategies for viral hepatitis. Although the untreated risk score had reasonably good predictive power at the time it was derived, patients classified as being at risk for HCC would not be consistently untreated. Therefore, it is reasonable to question the predictive power of scores developed from untreated cohorts that include parameters of viral activity (qHBsAg, HBeAg, HBV DNA, etc.) and degree of cirrhosis, which may change after antiviral therapy.[66,67] Therefore, it is rare to compare the predictive efficacy of risk scores in untreated CHB patients. We found one comparative study including CU-HCC [AUROC: 0.737 [95% CI: 0.677–0.797]), LSM-HCC [AUROC: 0.709 (95% CI: 0.638–0.780)], and REACH-B [AUROC: 0.681 (95% CI: 0.596–0.766)] scores in 922 untreated Korean patients.[68] The predictive performance of these risk scores is similar in the context of this study.

Considering that a discrimination efficiency (AUROC/C-index) of less than 0.7 would be considered an unsatisfactory prediction model,[17] the risk score developed from untreated cohorts performed satisfactorily in the original queues. However, when extended to other scenarios, the prediction efficiency may decrease. When the REACH-B score was applied to the cohort of treated populations, the discrimination score for predicting HCC risk was only 0.61 [AUROC: 0.61 (95% CI: 0.54–0.68)].[69] In the external validation study for the four scores CU-HCC, GAG-HCC, REACH-B, and LSM-HCC, it was confirmed that the predictive efficiency was lower in the treated populations than in the original untreated scenario.[70] Interestingly, CU-HCC [AUROC: 0.74 (95% CI: 0.68–0.81)] and GAG-HCC [AUROC: 0.80 (95% CI: 0.75–0.86)] were significantly more accurate than REACH-B [AUROC: 0.57 (95% CI: 0.47–0.68)] in a Korean treated cohort.[71] Similar results were reported by Abu-Amara *et al*.[72] It might contribute that parameters of cirrhosis and liver dysfunction were included in the GAG-HCC and CU-HCC score but not in the REACH-B score. In addition, the REVEAL-HBV cohort, which is the derived cohort of the REACH-B score, is composed of populations from communities where patients may have an earlier stage of natural history and a milder disease state. In addition, patients with liver cirrhosis were excluded from the REVEAL-HBV cohort. The lower effectiveness of external validation in the hospital population can be explained by differences in baseline components. On the other hand, it is helpful to show that viral replication is the natural driver of CHB disease progression, as a large proportion of the parameters representing viral activity in untreated scores can be determined in this way.[73,74] Individual recommendations can also

Table 1. HCC risk scores in untreated patients with CHB

Risk score/ Country/Region/Year	Setting	Patients, *n*	Follow-up duration/HCC occurred, *n* (%)	Characteristics of patients			Predictability at 5 years				Independent Validation
				Cirrhosis,%	HBeAg (+), %	Antiviral/exposure, %	AUROC	NPV/ pts, %	PPV/ pts, %	Calibration	
NGM-HCC/Taiwan, China/2010	Community-based	Derivation, 2,435	–	–	15.0	0	–	–/–	–/–	–	Yes/ Yes/No
		Validation, 1,218	–	–	16.3	0	0.848, 0.882, 0.883	–/–	–/–	Yes	
REACH-B/Taiwan, China/Hong Kong, China/Korea/2011	Community-based	Derivation, 3,584	12.0 (11.5–12.4) years*/131 (3.7)	0	15.2	0	–	–/–	–/–	Yes	Yes
	Hospital-based	Validation, 1,505	7.0 (5.0–10.3) years*/111 (7.4)	18.4	38.9	0	0·796	99.2/–	21.0/–		
REACH-B II/ Taiwan, China/2013	Community-based	Derivation, 2,227	39,016 person-years/164 (306.3/100,000 person-years)	14.7	15.1	0	0.89	–/–	–/–	–	Yes
		Validation, 1,113				0	0.84	–/–	–/–		
AGED/China/2018	Community-based	Derivation, 628	21 years*/110 (–)	0	30.7	–	0.76	–/32.2	–/9.5	–	No
	–	Validation, 1,663	10 years*/87 (–)	–	–	–	0.73	–/54.0	–/5.5		
GAG-HCC/Hong Kong, China/2009	Hospital-based	Derivation, 820	76.8±36.2 months#/40 (4.9)	15.1	43.4	10.7	0.88	98.3/–	14.0/–	–	Yes
CU-HCC/Hong Kong, China/2010	Hospital-based	Derivation, 1,005	10 years*/105 (10.4)	38.1		15.1	–	97.8/54.3	29.0/17.6	–	Yes
	Hospital-based	Validation, 424	10 years*/45 (10.6)	16.3		25.0	0.76	98.3/70.0	27.0/14.2		
LSM-HCC/Hong Kong, China/2014	Hospital-based	Derivation, 1,035	69±9 months#/38 (3.7)	32.0	25.0	38.0	0.83	99.4/68.0	8.8/32.0	–	Yes
		Validation, 520	69 months*/17 (3.4)	31.0	25.0	32.0	0.83	99.7/70.0	7.6/30.0		
HCC-ESC/Hong Kong, China/2018	Hospital-based	Derivation, 723	18.3 (2.8–32.9) years*/44 (–)	–	100.0	32.0	0.95	100.0/–	3.2/–	–	No
LS Model/ Korea/2013	Hospital-based	Derivation, 1,110	30.7 months*/56 (–)	16.3	36.0	37.8	0.806[a]	–/–	–/–	Yes	No
LSPS/Korea/2015	Hospital-based	Derivation, 227	61.7 (49.0–74.5) months*/18 (7.9)	–	–	78.0	0.834	97.5/75.0	36.0/11.0	–	Yes
APRI/FIB4/ Korea/2017	Hospital-based	Derivation, 1,006	5.1 (0.1–9.6)*/36 (3.6)	13.8	0	0	0.78[$]	99.3/55.4	11.2/19.5	–	Yes
D^2AS risk score/ Korea/2017	Hospital-based	Derivation, 971	4.5 (1.0–8.7)*/26 (2.7)	0	56.3	0	0.884[$]	99.4/65.0	22.0/14.0	Yes	No
	Hospital-based	Validation, 507	–	0	41.6	0	0.876	99.6/60.0	14.0/18.0	Yes	
RWS-HCC/ Singapore/2016	Hospital-based	Derivation, 538	58.9 months*/42 (7.8)	14.9	31.0	16.7	0.915[b]	98.8/77.3	–/22.7	–	Yes
		Validation, 3,353	–	–	–	–	0.767, 0.830, 0.902	97.0/–, 97.9/–, 93.0/–	–/–		

AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CHB, chronic hepatitis B; HBV, hepatitis B virus; LS, liver stiffness; NPV, negative predictive value; PLT, platelets; PPV, positive predictive value; pts, percentages. [a]For 3-year prediction; [b]For 10-year prediction; *Median duration of follow-up; #Mean duration of follow-up; [$]Time-dependent AUROC.

Table 2. Parameters of HCC risk scores in untreated patients with CHB

Risk score	Demographics			Viral activity				Hepatic inflammation		Hepatic dysfunction		Cirrhosis			Neoplastic	Other
	Age	Sex	Other	qHBsAg	HBeAg	HBV DNA	Other	ALT	AST	ALB	Bilirubin	Cirrhosis diagnosis	LSM	PLT	AFP	
Parameters of HCC risk scores in untreated patients with hepatitis B																
REACH-B	•	•			•	•		•								
REACH-B II	•	•	Family history (HCC)	•	•	•	HBV genotype	•								
NGM1-HCC	•	•	Family history (HCC)		•			•								Alcohol consumption
NGM2-HCC	•	•	Family history (HCC)		•	•		•								Alcohol consumption
NGM3-HCC	•	•	Family history (HCC)		•	•	HBV genotype	•								Alcohol consumption
AGED	•	•			•	•										
GAG-HCC	•	•				•	±core promoter mutations					•				
CU-HCC	•					•				•	•	•				
LSM-HCC	•					•				•			•			
HCC-ESC	•	•				•		•		•						
LS Model	•					•							•			
LSPS													•	•		Spleen diameter
APRI/FIB4	•							•	•					•		
D2AS	•	•				•										
RWS-HCC	•	•										•			•	
Parameters of HCC risk scores in treated patients with hepatitis B																
mREACH-B	•	•			•			•					•			
PAGE-B	•	•												•		
mPAGE-B	•	•								•				•		
HCC-RESCUE	•	•										•				
AASL	•	•								•		•				
CAMPAS	•	•								•		•	•	•		
APA-B	•													•	•	
CAMD	•	•	DM									•				
REAL-B	•	•	DM									•		•	•	Alcohol consumption
aMAP	•	•								•	•			•		

AFP, α-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; DM, diabetes mellitus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; PLT, platelets.

be made for high-risk populations as to whether they should receive AVT in the future.

HCC risk scores in treated patients with hepatitis B

HCC risk score models based on patients receiving antiviral therapy include mREACH-B,[75] PAGE-B,[76] mPAGE-B,[69] HCC-RESCUE,[77] AASL-HCC,[78] CAMPAS,[79] APA-B,[80] CAMD,[81] REAL-B[82] and aMAP risk score.[83] The characteristics of these 10 scores are summarized in Table 3. Most scores were developed using hospital-based cohorts, with the exception of the CAMD score, which was developed using a population-based cohort from a national health database. In addition to age, all scores included parameters reflecting liver dysfunction and cirrhosis. Because virologic indicators can change after treatment,[8–10] these parameters (ie, qHBsAg, HBeAg, and HBV DNA) were not included in the treated risk scores, with the exception of the mREACH-B score. The discriminatory power of the treated scores at 5 years ranged from 0.75 to 0.90 (AUROC or C-index). As with the untreated scores, calibration performance and external validation studies were not available for all risk scores.

The mREACH-B score replaced the original HBV DNA parameters in the REACH-B score with LSM values, and its predicted efficacy in the population receiving ETV AVT increased from 0.699 to 0.732.[75] The PAGE-B score was developed from nine European cohorts. The 5-year HCC risk was 0.0% in the low-risk group (≤9), the NPV reached 100%, and the discrimination was 0.82.[76] A multicenter retrospective study in South Korea assigned 3,001 treated CHB patients to the external validation cohort of the PAGE-B model, and a modified PAGE-B (mPAGE-B) prediction model was developed based on four variables, age, sex, platelet count, and albumin level. In the validation cohort, mPAGE-B had the highest 5-year HCC prediction efficiency [AUROC: 0.82 (95% CI: 0.76–0.88)], compared with the PAGE-B, CU-HCC, GAG-HCC, and REACH-B scores (Table 4).[69] The discrimination data of the queue-verified risk scores of mPAGE-B, AASL-HCC, APA-B, CAMD, REAL-B, and aMAP risk score are shown in Table 4. Most of the treated scores were constructed from Asian cohorts, with the exception of PAGE-B, REAL-B, and the aMAP risk score. REAL-B score was constructed based on data from centers in the USA and the Asia-Pacific region, with an ethnic composition that was primarily Chinese (82%).[82] The aMAP risk score was constructed based on 11 global prospective observational cohorts and randomized controlled trials of 17,374 patients with pan-etiologic chronic liver disease.[83] The 11 cohorts, including seven with chronic hepatitis B, were included in the review. The discrimination (C-index) of this model was 0.82–0.87, and the cutoff value of 50 corresponded to an NPV of 99.3–100% for discriminating patients without HCC risk. To our knowledge, aMAP is the first score constructed in the Asian CHB cohort and has been externally validated using data from Caucasian and Melanoderma populations. The aMAP score performed well in the UK realistic world cohort [C-index: 0.81 (95% CI: 0.79–0.82)],[84] the UK cohort of HCV-related cirrhosis and SVR patients [C-index: 0.77 (95% CI: 0.73–0.81)],[85] the Japanese HCV SVR cohort (AUROC: 0.757)[86] and the Egyptian HCV-related cirrhosis cohort (C-index: 0.713)[87] to predict 3- or 5-year HCC incidence.

Comparison of the performance of the treated score (aMAP, mREACH-B, PAGE-B, mPAGE-B), the partially treated score (CU-HCC, LSM-HCC), and the untreated score (REACH-B) was described in the original report of the aMAP risk score.[83] In both the Asian and Caucasian CHB cohorts, the aMAP score provided the highest discrimination among the scores and subgroups (Table 4). Compared with the PAGE-B score, the aMAP score had better performance in predicting HCC in the European PAGE-B cohort (C-index: 0.82 vs. 0.76) and the cirrhosis subgroup (C-index: 0.71 vs. 0.66). Other comparative data are more commonly found at PAGE-B, mPAGE-B, and CAMD scores. For example, a Hong Kong territory-wide database analysis showed that mPAGE-B was slightly more accurate than PAGE-B, with a 5-year AUROC of 0.80 (95% CI: 0.79–0.81) vs. 0.77 (95% CI: 0.76–0.78).[88] A Korean multicenter cohort study by Kim *et al*.[89] showed that the AUROC was higher with CAMD (0.79, 95% CI: 0.77–0.81) than with PAGE -B [0.76 (95% CI: 0.74–0.78)] and mPAGE-B [0.77 (95% CI: 0.75–0.79)]. Compared with the untreated risk scores, the treated risk scores had better transferability. Jung *et al*.[70] found that mREACH-B [AUROC: 0.80 (95% CI: 0.76–0.84)] had the highest predictive performance for 5-year prediction in a Korean cohort of treated CHB patients, outperforming LSM-HCC [AUROC: 0.75 (95% CI: 0.71–0.80)], GAG-HCC [AUROC: 0.75 (95% CI: 0.69–0.80)], CU-HCC [AUROC: 0.69 (95% CI: 0.63–0.75)], and REACH-B [AUROC: 0.66 (95% CI: 0.60–0.72)]. The trend is similar to that in the aMAP study.

Comments for clinical application in treated risk scores

When applying these scores in clinical practice, it should be noted that the inclusion criteria in the original study were different for each score. All subjects in the cohort received AVT, whereas the mREACH-B and CAMPAS score cohorts included patients who received AVT until a virologic response was achieved. The timing of AVT was not the same in all cohorts. Treatment-naïve patients participated in the derivation studies for AASL and APA-B, whereas other studies included treatment-experienced patients (e.g., PAGE-B, mPAGE-B, CAMD, REAL-B, and aMAP). All risk scores were derived from patients receiving continuous AVT. The predictive efficacy of risk scores for patients receiving intermittent treatment has not been clarified.

Novel risk prediction score based on artificial intelligence (AI)

In addition to traditional HCC risk scores, novel technologies such as liquid biopsy, metabolomics, and microbiota have shown increasing potential for health status classification prediction of disease progression, and high predictive accuracy for early cancer detection, including HCC. However, difficulties can arise in analyzing multidimensional data using conventional statistical modeling. Under these circumstances, algorithmic approaches offer a promising alternative for dealing with the dimensionality of the data. A prediction of liver cancer using AI-driven model for network-hepatitis B (PLAN-B) model was developed based on the gradient boosting machine algorithm. The PLAN-B HCC risk score was generated in 6,501 CHB patients treated with ETV or tenofovir dipivoxil (referred to as TDF herein) and underwent independent external validation in South Korea and Western countries.[90] The PLAN-B model contains 10 parameters, cirrhosis, age, platelet count, ETV or TDF antiviral agent used, sex, serum ALT levels, baseline serum HBV DNA levels, serum albumin and bilirubin levels, and HBeAg status. The PLAN-B model achieved high predictive accuracy in South Korea (C-index: 0.79) and in multicenter external cohorts in Western countries (C-index: 0.81), which is superior to conventional prediction models such as PAGE-B, mPAGE-B, REACH-B, and CU-HCC. However, although the machine learning algorithm pursues high accuracy, the methods are not simple, opaque, or even interpretable, which limits their

Table 3. HCC risk scores in treated patients with CHB

Risk score/ Country/Region/Year	Setting	Patients, *n*	Follow-up duration/HCC occurred, *n*(%)	Characteristics of patients			Predictability at 5-years					Independent Validation
				Cirrhosis, %	HBeAg (+), %	AVT	AUROC	C-index	NPV/ pts,%	PPV/ pts, %	Calibration	
mREACH-B/ Korea/2014	Hospital-based	Derivation, 192	43.0 (25.1–49.2) months*/15 (7.8)	46.9	52.1	ETV	0.805[a]	–	–/–	–/–	–	Yes
PAGE-B/ Europe/2016	Hospital-based	Derivation, 1,325	50 (31–62) months*/51 (3.8)	20.0	16.0	ETV/ TDF	–	0.82	100.0/24.7	17.0/28.1	Yes	Yes
	Hospital-based	Validation, 490	50 (31–62) months*/34 (6.9)	48.0	18.0		–	0.82	100.0/11.4	16.0/40.7	Yes	
mPAGE-B/ Korea/2018	Hospital-based	Derivation, 2,001	49 (33–68) months*/132 (6.6)	19.1	33.9	ETV/ TDF	0.82	–	99.3/22.4	14.4/31.0	Yes	Yes
		Validation, 1,000	49 (33–68) months*/72 (7.2)	20.1	34.5		0.82	–	98.1/23.5	18.0/29.3	Yes	
HCC-RESCUE/ Korea/2017	Hospital-based	Derivation, 990	2.1 (1.3–4.2) years*/58 (5.9)	39.0	56.0	ETV	0.768	–	99.5/–	37.0/–	–	No
		Validation, 1,071	3.5 (2.4–4.9) years*/85 (6.3)	35.0	61.0		0.809	–	98.0/–	41.0/–	–	
AASL-HCC/ Korea/2019	Hospital-based	Derivation, 944	48.6 (29–69.7) months*/56 (5.9)	39.3	55.9	ETV/ TDF	–	0.802	100.0/24.7	18.0/24.9	Yes	No
	Hospital-based	Validation, 298	41.4 (25.7–62.8) months*/24 (8.8)	38.9	65.4		0.814[b]	0.805	100.0/26.5	31.0/31.2	–	
CAMPAS/ Korea/2019/	Hospital-based	Derivation, 1,511	7 years after viral remission/143 (9.5)	39.8	52.6	NUCs	–	0.874[c]	99.4/33.4	33.5/17.9	Yes	No
	Hospital-based	Validation, 252	–	–	–	–	–	0.847	–	–	Yes	
APA-B/Taiwan/ China/2017	Hospital-based	Derivation, 883	49.1 (12–130.6) months*/105 (7.9)	35.9	35.2	ETV	0.827	0.85	98.1/73.0	–/7.0	Yes	No
		Validation, 442		37.1	37.1		0.862	0.87	99.1/73.5	–/8.0	Yes	
CAMD/Taiwan/ Hong Kong/ China/2018	Population-based	Derivation, 23,581	25.8 (12.7–35.7) months*/596 (2.50)	26.5	–	ETV/ TDF	–	0.82[a]	99.7/35.9	11.0/21.2	Yes	Yes
		Validation, 19,321	33.3 (13.4–36.0) months*/383 (1.98)	7.1	–		–	0.76	99.1/42.3	14.0/7.1	Yes	
REAL-B/USA./ Asia-Pacific/2020	Hospital-based	Derivation, 5,365	29,571.84 person-years/378 (7.0)	20.2	37.4	NUCs	0.80	–	–/–	–/–	Yes	No
		Validation, 2,683	14,945.27 person-years/202 (7.5)	22.1	37.9	NUCs	0.81	–	–/35.2	–/11.0	Yes	
aMAP/ Worldwide/2020	Hospital-based	Derivation, 3,688	42.7 (35.5–55.4) months*/95 (2.6)	19.3	39.5[a]	ETV/ TDF	0.81	0.82	99.5/58.9	13.3/8.8	Yes	Yes
	Hospital-Based[&]	Validation, 13,686	33.6 (27.6–40.1) – 105.4 (100.8–108.4) months*/536 (3.9)	11.4–10.0	18.0–72.0[$]	ETV/ TDF/ ADV/ TAF	–	0.82–0.87	99.3–100.0/39.4	6.6–15.7/20.4	Yes	

ADV, adefovir dipivoxil; AVT, antiviral treatment; CHB, chronic hepatitis B; ETV, entecavir; NUCs, nucleoside analogues; TAF, tenofovir alafenamide; TDF, tenofovir dipivoxil. [a]For 3-year prediction; [b]For 10-year prediction; [c]For 7-year prediction; *Median duration of follow-up; [&]For nine validation cohorts; [$]For 6 CHB validation cohorts.

Table 4. Comparison of predictability of HCC risk scores in different cohorts

Risk scores	Validation cohorts						
	REACH-B, Asian	**mREACH-B, Asian**	**GAG-HCC, Asian**	**CU-HCC, Asian**	**LSM-HCC, Asian**	**PAGE-B, Europe**	**mPAGE-B, Asian**
	0.796 (0.775–0.816)	**0.805 (0.678–0.925)**	**0.88 (0.82–0.93)**	**0.76 (0.66–0.86)**	**0.83 (0.71–0.94)**	**0.82**	**0.82 (0.76–0.88)**
mPAGE-B/Asian/0.82 (0.76–0.88)	•		•	•		•	
	0.61 (0.54–0.68)		0.71 (0.65–0.79)	0.70 (0.63–0.78)		0.72 (0.65–0.78)	
AASL-HCC/Asian/0.805 (0.671–0.939)	•		•	•		•	
	0.640 (0.561–0.719)		0.810 (0.764–0.856)	0.758 (0.705–0.811)		0.719 (0.656–0.782)	
APA-B/Asian/0.827 (0.771–0.883)	•			•		•	
	0.620 (0.535–0.705)			0.760 (0.698–0.821)		0.696 (0.620–0.773)	
CAMD/Asian/0.75 (0.73–0.77)						•	
						0.74 (0.72–0.76)	
REAL-B/USA. & Asia-pacific/0.81 (0.77–0.85)						•	
						0.73 (0.69–0.78)	
aMAP/Worldwide/0.82 (0.77–0.86)	•	•		•	•	•	•
	0.64 (0.59–0.70)	0.78 (0.73–0.83)		0.73 (0.66–0.79)	0.77 (0.72–0.82)	0.79 (0.75–0.84)	0.80 (0.76–0.85)

The display above showcases the characteristic curve or concordance index.

wide clinical application. In addition, model selection often results in overfitting.[17]

Caveats and status quo of clinical application of HCC risk scores

In addition to high model discrimination and calibration, handy model parameters, and a simple calculation process are also crucial for the clinical application of the risk score. For example, it is technically and economically challenging to determine HBV genotype and core promoter mutations in the REACH-B II, NGM-HCC, and GAG-HCC score, respectively, which may hinder widespread application in hospitals and communities.

The basic purpose of the HCC prediction score is to cost-effectively identify patients who do or do not require HCC monitoring. An HCC prediction score with an NPV of ≥99% for 5 years (or ≥98% for 10 years) could be considered an acceptable screening tool in clinical practice. Otherwise, the risk score is not considered meaningful enough to safely exclude low-risk patients from HCC surveillance.[16] Five of thirteen untreated scores[53,55,57,61,63] and five of ten treated[76,78,79,81,83] met the standard in both the derivation and validation cohorts in their original study (Tables 1 and 3). Although NPV was not reported in all original studies, some independent studies reported NPV predictability. Two independent studies from CU-HCC had an NPV of >99% for 5-year prediction.[66,72] The PAGE-B score has a good predictive effect for discriminating low-risk populations (NPV>99%), not only in the original study but also in independent studies of Caucasian, mixed,[91,92] and Asian populations.[71,89,93] Two Asian studies reported an NPV of 99.3–100% for the mPAGE-B score.[89,93] In studies with available data, the proportion in the low-risk group ranged from 32.2–77.3% in untreated cohorts, which was higher than in treated cohorts (11.4–73.5%). That may be due to the more advanced disease status of patients receiving AVT.

The PPVs of the risk scores provide clues for stratifying patients in need of HCC surveillance, and the proportion of patients classified in the high-risk group is equally important. The PPVs and proportion of the high-risk group reported in the original study for untreated risk scores ranged from 3.2–36% and 5.5–32%, respectively. For treated risk scores, the PPVs ranged from 6.6% to 33.5% and the proportion of the high-risk group ranged from 7.0% to 40.7%. The key to establishing an HCC risk score lies in its clinical application to provide guidelines for monitoring patients at risk. The aMAP score, developed by the author team,[83] is currently being actively used in clinical practice. In addition to predicting HCC risk in patients with chronic liver disease [C-index: 0.81 (95% CI: 0.79–0.82)],[84] it can also be used as an effective tool to predict late recurrence of HCC after radiofrequency ablation [C-index: 0.79 (95% CI: 0.74–0.84)].[94] The aMAP score was also shown to be an independent risk factor for rehospitalization [OR=1.112 (95% CI: 1.021–1.211)], HCC recurrence [HR=2.277 (95% CI: 1.014–5.114)], and mortality [HR: 1.366 (95% CI: 1.041–1.794)] in patients with HBV-associated acute-on-chronic liver failure.[95] Of note, although the aMAP score was based on the design of tertiary hospitals in different countries, it also proved to be applicable for 3,629 patients with chronic liver disease from a primary hospital in China with 52.6% low-risk patients).[96] The aMAP score has shown good transferability and generalizability in subsequent studies and different settings. However, like other risk scores, the aMAP score has weaknesses. First, the constructed scores did not capture dynamic changes, particularly in patients who achieved SVR after AVT, which may be more important than baseline data. Second, all risk scores were derived for treated cohorts of patients who received continuous AVT. The predictive efficacy of a risk score for patients receiving intermittent treatment has not been clarified. Third, the PPV value of the aMAP score was not optimal at a cutoff value of 60. The combination of other variables, such as liver stiffness and circulating cell-free DNA signatures, may be used to improve the predictive efficacy in the high-risk group.

Conclusions

Before extensive clinical application, the applicable population for each score should be determined to ensure predictive efficiency. Because of the different details in the derivation cohorts for each risk score, it is critical to match the "right" score and the "right" target population. To truly and accurately predict HCC risk, the dynamic changes in parameters and treatment interruption should be accounted for in future HCC risk scores.

The ability of conventional prognostic models to accurately identify high-risk HCC populations needs to be improved. Published HCC risk scores can be combined with novel indicators and technologies such as cell-free DNA signatures gene traits, metabolomics, and AI, and investigators need to explore whether they can further improve the accuracy of predictive models in high-risk populations. These novel indicators and technologies have mostly been studied in retrospective analyses and case-control studies. Large prospective multicenter studies with higher levels of evidence are urgently needed. In addition, it should be comprehensively demonstrated and validated whether predictive models using novel technologies are suitable for large-scale application and whether the cost-benefit ratio is correct.

The transformation of risk scores into applications may occur on a larger scale through real-life channels such as the use of cell phones or Internet platforms. Risk scores posted on Internet platforms can help physicians and patients make an initial understanding and assessment of a disease easily and effectively.[97,98] Only by promoting HCC risk prediction models in medical institutions at all levels and through other convenient channels will it be possible to broadly distinguish HCC risk in patients with chronic liver disease, identify low-risk patients who do not require frequent HCC surveillance, and provide timely and rational follow-up for high-risk HCC populations, thereby providing a theoretical basis for transforming risk prediction into HCC screening decisions. For developing countries with large populations and a high incidence of HBV infection, it is important to develop a predictive scoring model that can be readily applied in primary hospitals and communities to predict HCC risk and enable hierarchical management. To facilitate implementation and guide patient management in clinical practice, the risk score can also be incorporated into the liver function test panel and the electronic hospital system.

HCC screening and surveillance is a public health program at the national level. Implementation at all levels should create a hospital-community integrated HCC screening model. Based on HCC risk scores, high-risk populations can be accurately identified and enrolled in a lifelong surveillance program. Effective stratified management can provide the basis for improving early diagnosis and treatment rates of HCC patients and subsequently reducing HCC-related mortality.

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Conflict of interest

JLH has been an executive associate editor of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Data analysis and interpretation, manuscript writing (XH), critical revision and technical support (RF, HMZ), study design, critical revision and technical support (JLH).

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