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REVIEW

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Clinical utility of hepatocellular carcinoma risk scores in chronic hepatitis B

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Abstract

Background: Several risk scores have been recently developed to predict hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients. We systematically assessed the performance of the available HCC risk scores.

Methods: Literature search was performed to identify all published studies reporting development or external validation of HCC risk scores in CHB patients.

Results: Until March 2019, 12 scores were developed in untreated Asian and 7 scores in treated Asian (n = 6) or Caucasian (n = 1) patients. All scores provided significant predictions for HCC development in the derivation and validation cohorts of their original studies (c-statistic: 0.76-0.95) and usually classified patients into low, medium and high HCC risk groups. Eleven independent studies and three studies developing their own scores have validated externally some scores in Asian (GAG-HCC:5, CU-HCC:6, REACH-B:6, REACH-Bm:4, LSM-HCC:3, PAGE-B:5) or Caucasian/mixed origin patients (GAG-HCC:4, CU-HCC:4, REACH-B:4, PAGE-B:2). All scores offered acceptable predictability in almost all independent Asian cohorts (c-statistic: 0.70-0.86), but only PAGE-B and recently modified PAGE-B (mPAGE-B) offered good predictability in all independent Caucasian and/or Asian cohorts. Negative predictive values for 5-year HCC prediction were ≤99% (95%-99%) in most independent cohorts assessing Asian risk scores and 99%-100% in all independent cohorts (Caucasian/mixed origin:2; Asian:3) assessing PAGE-B and/or recently mPAGE-B.

Conclusions: Direct comparison of the newest HCC risk scores in independent patient cohorts of different origin remains intriguing, although statistical associations may not be directly transferable to clinical practice. PAGE-B and recently mPAGE-B score seem to offer persistently high predictability for Caucasian and/or Asian treated patients with low HCC risk who require no surveillance.

KEYWORDS

hepatitis B, hepatocellular carcinoma, prediction, risk score

Abbreviations: AASL, age, albumin, gender and cirrhosis; aFP, alfa-foetoprotein; AGED, age, gender, HBeAg status and HBV DNA; APA-B, age, platelets and aFP; APRI, AST to platelet ratio; AUROC, area under the receiver-operating characteristic curve; CAMD, cirrhosis, age, gender and diabetes; CHB, chronic hepatitis B; CU-HCC, Chinese University-HCC; D^2AS, HBV DNA, age and sex; ETV, entecavir; FIB-4, fibrosis-4; GAG-HCC, Guide with age, gender, HBV DNA, core promoter mutations, and cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCC-ESC, HCC after HBeAg seroconversion; HCC-RESCUE, HCC-Risk Estimating Score in CHB patients under entecavir; LSM, liver stiffness measurement(s); LSPS, LSM-spleen diameter to platelet ratio score; mPAGE-B, modified PAGE-B; NA, nucleos(t)ide analogue; NPV, negative predictive value; PAGE-B, platelets, age and gender; REACH-B, risk estimation for HCC in CHB; REACH-Bm, modified REACH-B; RWS-HCC, HCC risk based on real-world data; TDF, tenofovir disoproxil fumarate; THRI, Toronto HCC risk index.

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1 | INTRODUCTION

Chronic infection with hepatitis B virus (HBV) is the most common cause of hepatocellular carcinoma (HCC) globally.[1] The annual incidence of HCC is estimated to be 0.2% in all chronic HBV carriers older than 40 years and 3%-8% in patients with HBV cirrhosis.[2] Universal HBV vaccination at birth is the cornerstone of primary prevention of HBV-related HCC and is expected to yield dramatic decrease in the HCC incidence among the current children and adolescents in the future.[3,4] However, the existing chronic HBV cases remain at risk for HCC which is increasing as they are becoming older.[3,4] As secondary prevention, effective antiviral therapy, usually with a nucleos(t)ide analogue (NA), reduces but does not eliminate the HCC risk in patients with chronic hepatitis B (CHB),[5] which remains the key factor adversely affecting the overall good long-term survival of CHB patients.[6] Development of HCC in chronic HBV patients has been associated with multiple risk factors, only some of which can be modified by either therapy or behavioural changes (Table S1).[2,7]

Given the strong association between chronic HBV infection and HCC development, all guidelines recommend surveillance for HCC in various chronic HBV patient subgroups based on both their presumed HCC risk and cost-effectiveness analyses for HCC screening in each specific setting.[2-4,8] Nevertheless, accurate identification of patients in need of cautious surveillance entails concealed difficulties, since cost-effectiveness and clinical risk are not always in concordance.

Recently, several groups have tried to develop and validate risk scores for accurate prediction of HCC development in CHB patients to guide personalized surveillance.[9-15] In particular, based on univariable and then multivariable analyses, independent HCC risk factors and their corresponding weights are initially identified in a cohort of CHB patients (training or derivation cohort). These factors are used to construct a risk score, the accuracy of which is frequently validated in an independent cohort of patients (validation cohort). Based on these scores, CHB patients are usually classified in subgroups of low, intermediate and high HCC risk.

However, given the heterogeneity of CHB patients and the current availability of numerous HCC risk scores, it is often difficult for clinicians to decide whether these scores can be safely applied in their clinical practice and which score may be optimal for their specific patient subgroups. A few years ago, some reviews have tried to critically approach the use of HCC risk scores,[9-15] but newer scores and several independent validation studies have been published since then. The aim of this review was to assess the predictability and accuracy of all published HCC risk scores to date and to provide guidance on their clinical utility in different CHB settings.

Key points

- Hepatocellular carcinoma (HCC) represents the main complication of both untreated and treated chronic hepatitis B patients.
- Over the last years, several risk scores have been developed for prediction of HCC in chronic hepatitis B patients.
- HCC risk scores developed originally in Asian cohorts have been reported to have variable predictive performance in several independent studies of Caucasian/mixed origin or even Asian patients.
- PAGE-B, the only HCC risk score developed in a Caucasian cohort, and recently mPAGE-B, a score developed in an Asian cohort, have been found to offer good predictability in all independent studies of Caucasian/mixed origin or Asian patients having 99%-100% negative predictive value for 5-year HCC prediction.

2 | SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified through systematic searches of PubMed from 2000 until March 2019 using the terms 'hepatitis B' and 'carcinoma' and 'score'. In addition, a manual search of all relevant review articles and of the retrieved original studies was performed. All studies published in English as full papers were included, if they fulfilled the following criteria: (a) they included untreated or treated adult patients with CHB, with or without cirrhosis (compensated or decompensated) and (b) they reported the development and/or validation of ≥1 HCC risk score. Studies reporting only predictors of HCC in CHB patients without development of a specific score as well as studies including exclusively patients with HBV cirrhosis were not included. Moreover, studies including patients with HBV and hepatitis D or C and/or human immunodeficiency virus co-infections were excluded. The diagram of study selection is depicted in Figure S1.

Literature search was performed by two independent reviewers (TV and MP), who determined which studies could be potentially included. Two lists of selected papers were compared for concordance and discrepancies, were discussed, and, if necessary, arbitrated by a third reviewer (GP). Each study in the list of selected papers was evaluated by two independent reviewers (TV and MP) to determine whether it fulfilled all the inclusion criteria. The same two independent reviewers (TV and MP) extracted data from the selected papers using a predefined form. Two data summary tables were compared for concordance. The studies are presented in relation to the clinical settings in which the HCC risk scores were developed and/or validated. In studies providing cut-off(s) of their scores to define their patient subgroups in relation to their HCC risk, the cut-off of the low-risk group was used to define negative predictive value (NPV), sensitivity and specificity and the cut-off of high-risk group was used to report positive predictive value (PPV).

3 | DEVELOPMENT OF RISK SCORES FOR HCC PREDICTION IN UNTREATED PATIENTS

In total, 12 studies with 12 different HCC risk scores in untreated CHB patients, all from East Asia, were identified (Tables 1and

S2).[9-12,16-23] First, GAG-HCC score (Guide with Age, Gender, HBV DNA, core mutations and cirrhosis score) developed in a cohort from Hong-Kong achieving an area under the receiver-operating characteristic curve (AUROC) of 0.88/0.89 for 5-/10-year HCC prediction.[9] Since core promoter mutations cannot be easily detected, the score without this variable was examined and found to maintain accuracy. Patients with GAG-HCC score <101 were considered to be of low HCC risk, but intermediate and high-risk groups were not clearly defined. For the cut-off of 101, GAG-HCC score had NPV of 98%/99% for 5-/10-year HCC prediction. The CU-HCC (Chinese University-HCC) score was developed and validated also in Hong-Kong.[10] Hypoalbuminaemia, cirrhosis, HBV DNA, age and bilirubin were used to construct a prediction score ranging from 0 to 44.5. Cut-off values of 5 and 20 distinguished low- (<5), intermediate- (5-19.5) and high- (≥20) risk groups. In 2011, Asian investigators developed the REACH-B (risk estimation for HCC in CHB) score.[11] Data from Taiwanese patients from the REVEAL-HBV study were used to develop a 17-point score including sex, age, ALT, HBeAg and HBV DNA, which was validated in hospital patients from Hong-Kong and South Korea. The original cohort did not include patients with cirrhosis and the score did not offer similar predictability in the cirrhotics of the validation cohort. Subsequently, the REACH-B score was revised with addition of quantitative HBsAg and HBV genotype and removal of HBV DNA.[12] REACH-B II score had better AUROCs for HCC prediction, but no REACH-B score provided clear cut-off to classify patients according to HCC risk and most importantly to identify patients requiring no HCC surveillance.

A group from South Korea developed a predictive HCC risk score based on liver stiffness measurements (LSM),[16] which has been independently associated with HCC risk,[24] together with age and male gender. The CU-HCC score was also refined by replacing ultrasonography with LSM for diagnosis of cirrhosis.[17] The LSM-HCC score was based on LSM, age, albumin and HBV DNA and ranged from 0 to 30. Using the cut-off value of 11, the score offered high NPV (99.4%-100%) for 5-year HCC development. More recently, LSM-spleen diameter to platelet ratio score (LSPS), which has been shown to be useful in the prediction of high-risk oesophageal varices and hepatic decompensation,[25,26] was evaluated in a small study of 227 untreated CHB patients.[18]

In 2016, a group from Singapore developed a HCC risk score based on real-world data (RWS-HCC) including gender, age, cirrhosis and alfa-foetoprotein (aFP) and offered AUROC of 0.915 for 10-year HCC prediction with 98.8% NPV for the cut-off of 4.5. Upon validation in 3353 patients from the REACH-B, GAG-HCC and CU-HCC cohorts, AUROCs of RWS-HCC risk score were 0.767, 0.830 and 0.902 and NPV were 97.0%, 97.9% and 93.0%, respectively.[19]

Some groups have developed scores to assess the HCC risk in patients with low HBV DNA and/or low ALT. The 4-point scale D^2AS score including age, gender and HBV DNA levels aimed to predict HCC in patients with HBV DNA >2000 IU/mL and ALT <80 IU/mL.[20] Moreover, a combination of AST to platelet ratio (APRI) score and Fibrosis-4 (FIB-4) score was suggested as an accurate predictor of HCC risk in chronic HBV patients with low viraemia (HBV DNA <2000 IU/mL).[21] However, it is currently unclear whether substantial HCC risk exists for patients with low HBV viraemia without progression to CHB and whether HCC scores are useful in such patients.

In 2018, a group from Hong-Kong developed a score to predict HCC in treated or untreated patients who achieved HBeAg seroconversion.[22] The HCC-ESC score including age, gender, cirrhosis, hypoalbuminemia, HBV DNA and ALT elevations or flares. Finally, a new 12-point HCC risk score including age, gender, HBeAg status and HBV DNA levels (AGED) was developed and validated by a group from China.[23]

4 | DEVELOPMENT OF RISK SCORES FOR HCC PREDICTION IN TREATED PATIENTS

Since the HCC risk is not eliminated in treated CHB patients and HCC may develop even after several years of effective NA therapy,[27] HCC risk scores in this setting are also needed and are more clinically relevant, as diagnosed CHB patients are usually on treatment over the last two decades. Seven scores have been developed aiming to accurately predict the HCC risk in CHB patients treated with NA.[13,28-33] All but one such score were developed in treated CHB patients from East Asia as well (Tables 2and S2).

In 2014, the predictability of a modified REACH-B score (REACH-Bm) was evaluated in a small cohort of 192 patients with virological remission under entecavir (ETV).[30] Compared to REACH-B, REACH-Bm, which included the REACH-B variables except for HBV DNA that was replaced by LSM, performed better for 3-year prediction of HCC.[30]

The first and only so far study in Caucasian patients treated with ETV or tenofovir disoproxil fumarate (TDF) produced the PAGE-B score which was based on age, gender and platelets.[13] The addition of cirrhosis did not substantially improve the predictability. Both in derivation and validation cohort, no low-risk patient developed HCC (NPV: 100%).

In 2017, a South Korean group published the HCC-RESCUE (HCC-Risk Estimating Score in CHB patients Under Entecavir) score based on age, gender and cirrhosis.[31] The same year, a group from Taiwan developed the APA-B score including age, platelets and aFP levels (scale: 0-15).[33] Compared to previous scores, higher AUROCs for 5-year HCC prediction were reported both in derivation and validation cohort. Using the cut-off of 6, NPV for 5-year HCC development was 98.1% and 99.1% in derivation and validation cohort. A score free of laboratory tests (CAMD: cirrhosis, age, gender, diabetes) was developed from a large cohort of Taiwanese patients treated with ETV or TDF and validated in another large cohort of patients from Hong-Kong.[28] Since follow-up did not exceed 36 months, risk prediction was extrapolated through mathematical models to 5 years. Low-risk patients had annual HCC incidence <0.3%.

In 2018, a modified PAGE-B score (mPAGE-B), which was based on PAGE-B parameters (age, gender and platelets) plus albumin levels, was suggested to offer optimized HCC prediction in a cohort

TABLE 1 Risk scores for prediction of hepatocellular carcinoma (HCC) in untreated chronic hepatitis B patients

Risk score, country/area; 1st author, year	Cohort	Patients, n (cirrhosis)	HCC, n (5-year cumulative rate)	Risk score parameters	Predictability at 5 years								
								Low-risk group			High-risk group		
					AUROC	Sensitivity	Specificity	Cut-off	Pts %	NPV	Cut-off	Pts %	PPV
GAG-HCC, Hong-Kong; Yuen, 2009[9]	Derivation	820 (15%)	40 (4.4%)	Sex, age, HBV DNA, cirrhosis	0.88	84%	79%	101	–	98%	101	–	14%
	Validation	0	–	±Core promoter mutations	–	–	–	–	–	–	–	–	–
CU-HCC, Hong-Kong; Wong, 2010[10]	Derivation	1055 (38%)	105 (NA)	Age, albumin, bilirubin, HBV DNA, cirrhosis	–	89%	71%	5	54%	98%	19	18%	29%
	Validation	428 (16%)	45 (NA)		0.76	78%	73%		70%	98%		15%	27%
REACH-B, Taiwan/Hong-Kong/S. Korea Yang, 2011[11]	Derivation	3584 (0%)	131 (NA)	Sex, Age, ALT, HBeAg, HBV DNA	0.80	–	–	9	–	99.2%	15	–	21%
	Validation	1505 (18%)	111 (NA)		0.78	–	–	–	–	–	–	–	–
REVEAL risk model (REACH-B II), Taiwan; Lee, 2013[12]	Derivation	2227 (0%)	164	Sex, age, ALT, family history of HCC, HBeAg, HBV DNA, HBsAg, genotype	0.89	–	–	–	–	–	–	–	–
	Validation	1113 (0%)	164		0.84	–	–	–	–	–	–	–	–
LS Model, S Korea; Kim, 2013[16]	Derivation	1250 (16%)	56 (NA)	Age, sex, liver stiffness, HBV DNA	0.80 (for 3-year HCC prediction)								
	Validation	0			–								
LSM-HCC, Hong-Kong; Wong, 2014[17]	Derivation	1035 (32%)	38 (3.3%)	Age, albumin, HBV DNA, liver stiffness	0.83	88%	–	11	68%	99.4%	11	32%	8.8%
	Validation	520 (31%)	17 (2.9%)		0.83	100%	–		70%	99.7%		30%	7.6%
LSPS, S Korea; Shin, 2015[18]	Derivation	227 (50%)	18 (7.9%)	Liver stiffness, spleen diameter, platelet count	0.83	–	–	1.1	75%	97.5%	2.6	11%	36%
	Validation	0			–	–	–	–	–	–	–	–	–
RWS-HCC, Singapore; Poh, 2016[19]	Derivation	583 (13.7%)	42 (NA)	Sex, age, cirrhosis, aFP	0.92[a]	88%[a]	83%[a]	4.5	–	98.9%[a]		–	–
	Validation	3353[a] (NA)	538 (NA)		0.77/0.83/0.90[a]				–	97%/97%/93%[a]		–	–
D^2AS risk score, S Korea; Sinn, 2017[20]	Derivation	971 (0%)	26 (3.2%)	HBV DNA, sex, age	0.89	–	–	2.0	65%	99.4%	2.5	14%	22%
	Validation	507 (0%)	15 (3.0%)		0.88	–	–		60%	99.6%		18%	14%
	(HBV DNA > 2000 & ALT < 80 IU/L)												

(Continues)

TABLE 1 (Continued)

Risk score, country/area; 1st author, year	Cohort	Patients, n (cirrhosis)	HCC, n (5-year cumulative rate)	Risk score parameters	Predictability at 5 years								
					AUROC	Sensitivity	Specificity	Low-risk group			High-risk group		
								Cut-off	Pts %	NPV	Cut-off	Pts %	PPV
APRI/FIB4, S Korea; Paik, 2018[21]	Derivation	1006 (14%)	36 (NA)	AST, platelets, age, ALT	0.78	87%	57%	APRI < 0.5 or FIB-4 < 1.45	55%	99.3%	APRI ≥ 0.5 and FIB-4 ≥ 1.45	19%	11%
	Validation	0			–	–	–		–	–		–	–
	(HBV DNA < 2000 IU/mL)												
HCC-ESC, Hong-Kong; Fung, 2018[22]	Derivation	723 (NA)	44 (2.2%)	Age, sex, cirrhosis, HBV DNA, ALT, albumin	0.95	99%	87%	129	–	100%	129	–	13%
	Validation	0			–	–	–	–	–	–	–	–	–
AGED, China; Fan, 2019[23]	Derivation	628 (0%)	NA	Age, Sex, HBeAg, HBV DNA	0.76	–	–	5	32%	–	10	10%	–
	Validation	1663 (0%)	87 (NA)		0.73	–	–		54%	–		5%	–

Note: Low-risk groups include patients with score below the reported cut-off; high-risk groups include patients with score above or equal to the reported cut-off; Sensitivities and specificities have been based on the low-cut-off values.

Abbreviations: AUROC, area under the receiver-operating characteristics curve; NPV, negative predictive value; PPV, positive predictive value.

[a]Three validation cohorts and 10-year HCC prediction.

of patients from South Korea treated with ETV or TDF.[29] Lately, another group from South Korea proposed and validated the AASL score based on age, albumin, gender and cirrhosis.[32]

5 | INDEPENDENT VALIDATION OF HCC RISK SCORES IN ASIAN PATIENTS

First, the predictability of five HCC risk scores developed for untreated Asian patients was evaluated in six independent studies including not only untreated but NA-treated Asian patients as well (Table S3).[34-39] Since NA therapy usually modifies several parameters often included in the HCC risk scores developed in untreated patients, such as HBV DNA levels and perhaps HBeAg status and HBsAg levels, LSM and even cirrhosis status,[3,4,8] the applicability of these scores in treated CHB patients warranted attention.

First, in ETV-treated patients from Hong-Kong,[34] CU-HCC, GAG-HCC and REACH-B score offered acceptable AUROCs for 5-year HCC prediction when estimated at baseline which improved when estimated at 2 years of therapy (0.80, 0.76 and 0.71 vs 0.85, 0.86 and 0.79, respectively). NPV was 99.6%, 98.2% and 99.5% for CU-HCC, GAG-HCC and REACH-B score at baseline and 99.6%, 99.4% and 100% for the same scores at year-2, respectively. Patients with low score both at baseline and year-2 had lower HCC risk compared to those with intermediate/high score at any time point. Maintained on-therapy virological remission was an independent predictor of lower HCC risk.

The predictability of CU-HCC, GAG-HCC, REACH-B, LSM-HCC and REACH-Bm risk scores was assessed in untreated or treated patients from South Korea. REACH-Bm score offered higher AUROCs for 3-/5-year HCC prediction, compared to LSM-HCC, GAG-HCC, REACH-B and CU-HCC scores (all $P < .05$), but the superiority of the predictive performance of REACH-Bm was observed only in treated but not in untreated patients. NPV for 5-year HCC prediction ranged from 95.2% to 97.1% for all scores.[35]

In a small study from Japan including 225 treated patients, CU-HCC and GAG-HCC scores determined at baseline or year-2 offered acceptable predictability for HCC.[36] Patients reclassified from intermediate/high risk at baseline to low risk at year-2 by either score had lower HCC probability ($P \leq .004$).

In a study from South Korea, REACH-Bm, PABE-B and LSM-HCC score performed similarly in predicting HCC development, but PPV and NPV were not provided.[37]

Another group from South Korea[38] the 3-/5-year HCC predictability was good for GAG-HCC and PAGE-B, moderate for CU-HCC and poor for REACH-B. The predictability of PAGE-B slightly improved when the score was assessed at year-1. PAGE-B offered the highest NPV for its low-risk group (99.6%).

Again from South Korea, the dynamic performance of CU-HCC, REACH-B, LSM-HCC and REACH-Bm was assessed in a cohort of treated and untreated patients.[39] All scores determined either at baseline or 14 months later, but not their changes, had acceptable HCC predictability. For 5-year HCC prediction in treated/untreated

TABLE 2 Risk scores for prediction of hepatocellular carcinoma (HCC) in treated chronic hepatitis B patients

Risk score, country/area; 1st author, year	Cohort	Patients, n (cirrhosis)	Type of therapy	HCC, n (5-year cumulative rate)	Risk score parameters	Predictability at 5 years								
									Low-risk group			High-risk group		
						AUROC	Sensitivity	Specificity	Cut-off	Pts	NPV	Cut-off	Pts	PPV
REACH-Bm, S Korea; Lee, 2014[30]	Derivation	192 (46.9%)	ETV	15 (NA)	Sex, age, ALT, HBeAg, liver stiffness	0.81 (for 3-year HCC prediction)	–	–	–	–	–	–	–	–
	Validation	0												
PAGE-B, Europe; Papatheodoridis, 2016[13]	Derivation	1325 (20%)	ETV or TDF	51 (5.7%)	Age, sex, platelets	0.82	100%	41%	10	25%	100%	18	28%	17%
	Validation	490 (48%)		34 (8.4%)		0.82	100%	20%	10	11%	100%	18	41%	16%
HCC-RESCUE, S Korea; Sohn, 2017[31]	Derivation	990 (39%)	ETV	58 (11.2%)	Age, sex, cirrhosis	0.77	–	–	65	–	99.5%	85	–	37%
	Validation	1071 (35%)		85 (8.9%)		0.81	–	–	65	–	98%	85	–	41%
APA-B, Taiwan; Chen, 2017[33]	Derivation	883 (36%)	ETV	70 (10.3%)	Age, platelets, alpha-fetoprotein	0.83	78%	80%	6	76%	98.1%	10	7%	46%
	Validation	442 (36%)		35 (9.2%)		0.86	90%	79%		74%	99.1%		8%	45%
CAMD, Taiwan/ Hong- Kong; Hsu, 2018[28]	Derivation	23 851 (27%)	ETV or TDF	596 (3.6%)[a]	Age, sex, diabetes, cirrhosis	0.82[a]	–	–	8	32%	99.7%	14	23%	11%
	Validation	19 321 (7%)		383 (2.7%)[a]		0.76	–	–	8	40.5%	99.1%	14	5.8%	14%
mPAGE-B, S Korea; Kim, 2018[29]	Derivation	2001 (19%)	ETV or TDF	132 (6.6%)	Age, sex, platelets, albumin	0.82	–	–	9	22%	99.3%	13	31%	18%
	Validation	1000 (20%)		72 (7.2%)		0.82	–	–	9	23%	98.1%	13	29%	18%
AASL, S Korea; Yu, 2019[32]	Derivation	944 (39%)	ETV or TDF	56 (6.5%)	Age, albumin, sex, cirrhosis	0.80	–	–	6	24%	100%	20	25%	18%
	Validation	298 (39%)		24 (11.6%)		0.81	–	–	6	27%	100%	20	31%	31%

Note: Low-risk groups include patients with score below the reported cut-off; high-risk groups include patients with score above or equal to the reported cut-off; Sensitivities and specificities have been based on the low-cut-off values.

Abbreviations: AUROC, area under the receiver-operating characteristics curve; NPV, negative predictive value; PPV, positive predictive value.

[a]At 3 years of follow-up.

patients, AUROCs were good for REACH-Bm and then CU-HCC, moderate for LSM-HCC and poor for REACH-B, while NPVs were suboptimal (93.6%-94.6%) for REACH-B and varied for CU-HCC, REACH-Bm and LSM-HCC (97.7%-100%).

Some of the available HCC risk scores were also externally validated in cohorts of three Asian studies which originally aimed to develop their own scores (Table S3).[28,29,33] In the APA-B score study, AUROCs for 2-/5-year HCC prediction were worst for other scores from previous Taiwanese cohorts (REACH-B, REACH-B II) (0.64-0.69), intermediate but acceptable for PAGE-B (0.79/0.70) and numerically highest for CU-HCC (0.81/0.76).[33] In the large validation cohort included in the CAMD score study, the 3-/5-year HCC predictability of PAGE-B was similar to that of CAMD score.[28] Finally, in the validation cohort of mPAGE-B study, the researchers also assessed the predictability of PAGE-B, CU-HCC, GAG-HCC and REACH-B as well as of the Toronto HCC risk index (THRI) score,[40] which was originally introduced to predict HCC development in patients with cirrhosis regardless of aetiology. AUROCs for 5-year HCC prediction were numerically similar for PAGE-B, THRI, CU-HCC and GAG-HCC and lower for REACH-B. Apparently, mPAGE-B performed better than all other risk scores ($P < .01$).[29] Unfortunately, details on the predictive performances of the scores including NPVs were not provided in any of the latter three studies.

The predictability of PAGE-B and mPAGE-B was also confirmed in two recent Korean studies which were not included in our review, as they were published after March 2019.[41,42] First, in a cohort of 1330 treated patients, similar performances among mPAGE-B, PAGE-B and GAG-HCC (AUROCs: 0.74-0.77) were reported, which were better than the performances offered by CU-HCC or REACH-B (AUROCs: 0.62-0.69). In that study, NPVs for 5-year HCC prediction were 100% for both PAGE-B and mPAGE-B and suboptimal for the other three scores (95.8%-98.5%).[41] Second, in a cohort of 3277 patients treated with ETV/TDF, CAMD, PAGE-B and mPAGE-B were found to have similar AUROCs (0.76-0.79) for 5-year HCC prediction offering NPV of 98.7%, 99.0% and 99.3%, respectively.[42]

6 | INDEPENDENT VALIDATION OF HCC RISK SCORES IN CAUCASIAN/MIXED PATIENTS

The performance of the first three HCC risk scores developed in Asian cohorts has been evaluated in five cohorts of Caucasian or mixed origin patients (Table S3),[43-47] while the performance of PAGE-B score has been evaluated in two such cohorts.[46,47] First, in a multicentre European cohort of Caucasians treated with ETV or TDF, CU-HCC, GAG-HCC and REACH-B score offered poor to modest predictability for 5-year HCC development,[43] while NPV was 98% for all three scores (unpublished data).

In another multicentre European cohort of ethnically diverse patients treated with ETV,[44] AUROCs for 4-year HCC prediction by GAG-HCC, CU-HCC and REACH-B scores at baseline were acceptable in all patients but suboptimal in Caucasians. AUROCs for HCC prediction in Caucasians improved only numerically when the scores were estimated at year-1 (0.77, 0.71 and 0.65). The decline in HCC scores from baseline to year-1 was comparable in patients who developed HCC and those who did not.

The predictability of GAG-HCC, CU-HCC and REACH-B score was also assessed in a North American cohort of treated and untreated CHB patients of mixed ethnicities.[45] HCC incidence did not differ between low- and intermediate-risk patients by any score. Independently of treatment, all three scores could accurately identify patients at low-risk. Low-risk group by REACH-B, CU-HCC and CAG-HCC score included 14%, 67% and 78% of patients, respectively. AUROCs for HCC prediction were not significantly different between Asian and non-Asian patients.

In a study from Netherlands, the predictive performances of PAGE-B, REACH-B, GAG-HCC and CU-HCC were evaluated in patients of various ethnicities (Caucasians: 47%, Asians: 31%, Africans: 19%).[46] Among non-invasive scores, PAGE-B offered the best predictive performance with excellent AUROC of 0.91, whereas GAG-HCC score with the diagnosis of cirrhosis based on Ishak's stage offered similarly high AUROC. REACH-B and CU-HCC score had good but lower predictive performances. The severity of liver fibrosis assessed by either liver biopsy (Ishak's stage) or a non-invasive marker (FIB-4, log APRI) also offered good HCC predictability. The addition of cirrhosis by Ishak's stage to PAGE-B improved only modestly the performance of PAGE-B score (AUROC: 0.92). Importantly, no low-risk patient according to baseline PAGE-B score (<10) developed HCC.

Lastly, PAGE-B score has also been validated in prospectively monitored CHB patients of the Spanish national registry treated with ETV or TDF.[47] PAGE-B score had moderate predictability, but it again offered 100% NPV in the low-risk group.

7 | CLINICAL UTILITY OF HCC RISK SCORES

The assessment of the predictive performance of each HCC risk score has been mainly based on AUROC values for HCC development over a 5- to 10-year period. However, it should be kept in mind that AUROC values may not be so helpful for the clinical utility of risk scores, since the main clinical benefit from the HCC risk scores is the accurate identification of CHB patients who require, or not, to be under HCC surveillance. Thus, the most important characteristic of each score should be its NPV, which is of course associated but is not identical with its AUROC value.

Unfortunately, the existing HCC risk scores do not cover all chronic HBV patients. First, no score has been developed or at least evaluated in some ethnicities/races, such as African CHB patients who may develop HCC at an earlier age,[2] and therefore the predictability of all HCC risk scores in such settings remains unknown. Second, there are reasonable limitations in the use of

HCC risk scores in patients who do not fulfil the current treatment indications and remain untreated, such as patients with HBeAg-positive or HBeAg-negative chronic HBV infection (immunotolerant or inactive carriers), who can progress to CHB having fluctuating disease activity and may need frequent reassessments of the HCC risk scores. However, the predictability of HCC risk scores for untreated patients (Table 1) has been evaluated only for the assessment of these scores at the onset of follow-up without any information for potential changes of their predictive performance with reassessment of the scores upon changes of HBV activity. The predictability of some scores has been shown to improve with reassessment after 1-2 years of antiviral therapy,[34,36] but such a setting does not represent patients who remain untreated. Moreover, HCC risk scores for untreated patients have been developed and validated only in Asian cohorts, as there have been no cohorts of Caucasian CHB patients who fulfilled treatment indications but remained untreated over the last two decades. In any case, HCC risk scores for untreated patients who fulfil treatment indications are not clinically relevant today, as such diagnosed CHB patients should and usually start treatment.

According to all scientific guidelines, patients with HBV-related cirrhosis should remain under surveillance for HCC due to their high risk.[3,4,8] The clinical utility of the existing HCC risk scores in patients with cirrhosis is currently doubtful, as cirrhotic patients were excluded from many studies (Tables 1 and 2) and there has been no study focusing on this subgroup. In addition, the proportions and actual numbers of cirrhotic patients who could be classified into low-risk groups were so small that do not allow any safe conclusion in this setting. As we have previously shown, the annual HCC risk is decreasing after 5 years of therapy in patients with baseline cirrhosis but it remains far above the 0.2% cut-off (1.6%) that justifies HCC surveillance.[27] Therefore, we think that all patients with cirrhosis should be currently advised to remain under HCC surveillance for life.

Whether reassessment of the HCC risk scores during therapy could improve the predictive performance of all scores is unclear. It is reasonable to speculate that the predictability of scores usually developed for untreated patients which include variables that obviously change with therapy (eg ALT, HBV DNA, HBeAg status, LSM, etc) may improve after reassessment on therapy, as it has already been suggested by some independent studies.[34,36] On the other hand, scores with parameters which are not usually affected by therapy (eg age, gender, platelets range, etc) are not expected to show improved predictability upon on-therapy reassessment. It is of interest that the HCC risk scores developed in treated patients are quite homogenous, as six of seven such scores include age, gender and one parameter of liver disease severity (platelets, cirrhosis and LSM) only or usually combined with one additional parameter (Table 2). It should be noted, however, that all HCC risk scores have been developed and validated for HCC prediction within a certain period, usually 5-10 years, while their validity of HCC prediction may decrease over time as the patients remaining at risk were decreasing in all studies. Thus, reassessment not only of the HCC risk scores but also of their predictability in the original and independent cohorts are required after the first 5 years of follow-up. According to our unpublished data, new HCC risk scores will be required for HCC prediction beyond year 5 of antiviral therapy.

7.1 | Comparing the predictive performances of HCC risk scores

Comparisons of the predictive performances in the same patient populations of independent studies have been reported for only a few scores, mainly GAG-HCC, CU-HCC, REACH-B and PAGE-B score (Tables 2 and S3). Similar variability in the AUROCs for 5-year HCC prediction has been reported for GAG-HCC (0.70-0.91) in nine,[29,33-36,38,43-45] CU-HCC (0.70-0.84) in ten[29,33-36,38,39,43-45] and PAGE-B score (0.70-0.91) in seven independent studies including Caucasian and/or Asian patients,[28,29,33,37,38,46,47] while greater variability for REACH-B score (0.57-0.81) has been observed in ten studies.[29,33-36,38,39,43-45] In four of the above studies with Asian patients, REACH-Bm score was also assessed showing similarly variable AUROCs (0.64-0.81),[33,35,37,39] whereas the AUROCs for LSM-HCC were inferior than some of the above scores in three of the latter studies.[35,37,39] Moreover, PAGE-B and mPAGE-B scores were also found to have good predictability in two recent Asian studies.[41,42]

7.2 | Selection of non-cirrhotic patients with low risk for HCC and no need for HCC surveillance

Although there are variable recommendations for HCC surveillance in CHB patients without cirrhosis, a surveillance programme is generally considered to be cost-effective and thus recommended if the annual HCC incidence of a specific subgroup is ≥0.2%.[2] Therefore, a risk score with NPV of ≤99% for 5-year (or ≤98% for 10-year) HCC prediction cannot be considered to be an acceptable screening tool in clinical practice.

Negative predictive values have been provided in some but not all original studies which developed HCC risk scores[9,10,13,17-21,28,29,31-33] as well as in eight of the independent studies which assessed the predictability of several HCC risk scores[34-36,38,39,43-45] (Tables 1, 2 and S3) (Figure 1).

Most of the developed HCC risk scores in their original and/or subsequent independent studies do not seem to offer NPV high enough to safely exclude non-cirrhotic patients from HCC surveillance. In particular, NPV ≤99% (95%-99%) for 5-year HCC prediction has been reported in the original Asian study as well as in all seven independent studies with Asian and/or Caucasian patients assessing GAG-HCC score.[9,34-36,38,43-45] The NPV of CU-HCC score was also ≤99% (95%-99%) for 5-year HCC prediction in the original Asian study and in five of eight independent studies,[10,35,36,38,43,44] variable in one (98.6%-99.2%)[39] and >99% in two independent studies,[34,45] although the NPV for 10-year HCC prediction was ≤98% in one of the latter two studies.[34] NPV was not provided in the original studies

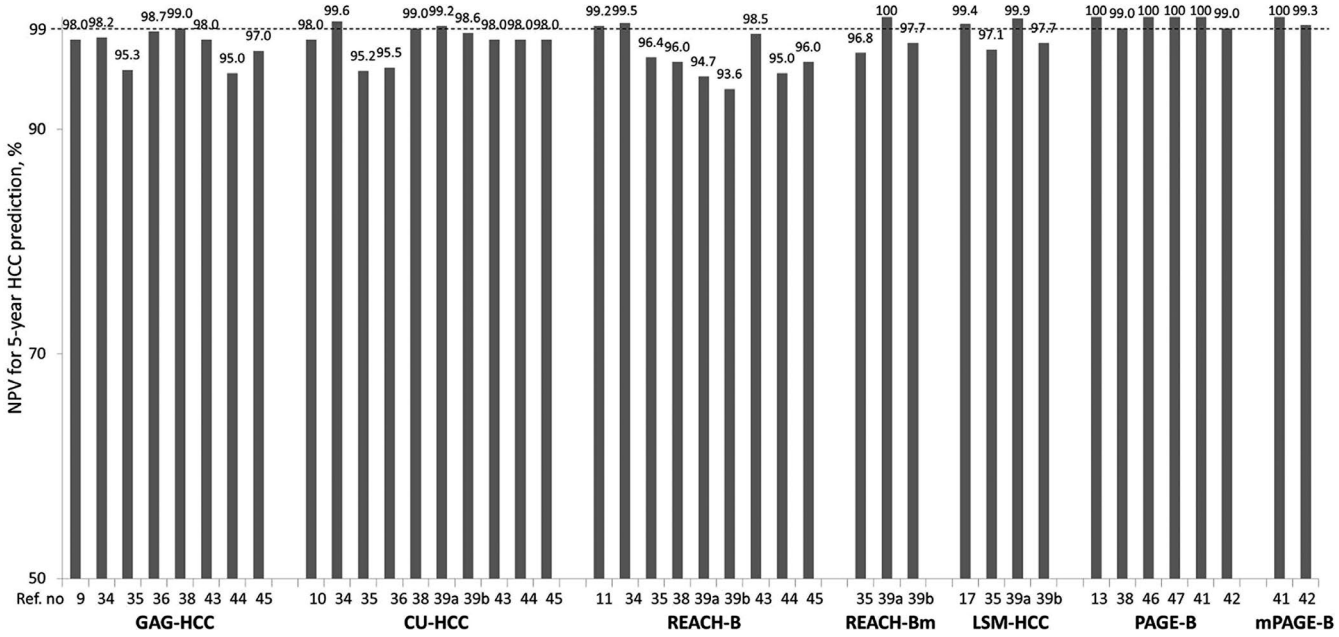

FIGURE 1 Negative predictive values (NPV) of the low-risk cut-off for 5-year prediction of hepatocellular carcinoma (HCC) in chronic hepatitis B patients. Only risk scores with at least two studies reporting such data have been included (References [Ref.]: Yuen 2009,[9] Wong 2010,[10] Yang 2011,[11] Wong 2014,[17] Papatheodoridis 2016,[13] Wong 2013,[34] Jung 2015,[35] Tawada 2016,[36] Kim 2017,[38] Jeon 2018[39] [treated[39a], untreated: [39b]], Papatheodoridis 2015,[43] Arends 2015,[44] Abu-Amara 2016,[45] Brouwer 2017,[46] Riveiro-Barciela 2017,[47] Lee 2019,[41] Kim 2019[42]]

of REACH-B II[12] and REACH-Bm,[30] while it was <99% (95%-98.5%) for REACH-B in five of the six independent studies[35,38,43-45] (and for REACH-Bm in one study[35]), >99% in the original[11] and one independent study[34] and variable in one independent study (for REACH-Bm too).[39] Of the remaining scores, NPV by the original and five independent studies were available for PAGE-B, which offered 100% NPV in the original and two independent studies with Caucasian or mixed origin patients[13,46,47] as well as in one recent study with Asian patients[41] and 99% NPV in another two studies with Asian patients.[38,42] NPV for LSM-HCC was also reported to be 99.4% in its original study,[17] but 97% in an independent study in Asian patients.[35] Recently, NPVs of 99.3%-100% were reported for mPAGE-B in two Asian studies.[41,42] Of the risk scores assessed only in their original cohorts, NPV was >99% in six[20,28,29,31-33] and ≤99% (96%-99%) in three of these Asian studies.[18,19,21]

Another important parameter of the clinical utility of the HCC risk scores is the proportion of patients who are classified in the low HCC risk group and therefore do not require HCC surveillance. In the five studies using risk scores which offered NPV >99% for 5-year HCC prediction and provided such data,[13,17,20,28,29] the proportions of patients classified in the low HCC risk groups ranged widely from 11% to 70% being higher in the derivation and validation cohorts of untreated Asian patients (60%-70%, Table 1) and lower in the cohorts of treated Asian or Caucasian patients (11%-32%, Table 2). Such a difference seems to mainly reflect the different characteristics between the two settings, as treated CHB patients are usually older and have more frequently advanced liver disease and cirrhosis.

7.3 | Selection of patients with high risk for HCC and potential need for intensified HCC surveillance

Hepatocellular carcinoma risk scores could further be of considerable value for the identification of patients with high HCC risk who would benefit from stricter HCC surveillance. Currently, HCC surveillance is based on abdominal ultrasonography every 6 months, as this is a cheap screening tool with acceptable performance, but its diagnostic accuracy is far from excellent, particularly for early HCC.[2] On the other hand, computed tomography or magnetic resonance imaging offer higher sensitivity and specificity in detecting HCC, but with several limitations for general use in HCC surveillance.[2] Thus, it remains under investigation whether there is a specific annual HCC risk cut-off justifying intensified HCC surveillance and which type of intensified surveillance (test, interval) might be optimal.[2]

Despite the uncertainties in the need and especially the cost-effectiveness of specific HCC surveillance, the HCC risk scores can offer clinically useful information by identifying subgroups of CHB patients with annual HCC risk exceeding 3%-5%. In this context, the cumulative HCC incidence and the PPV in the high-risk group are also important. In nine studies providing such data,[11,13,18,20,28,29,31-33] the mean yearly HCC incidence in the high-risk patients ranged from 2.3% to 9.2% (Tables 1 and 2). Unfortunately, such data cannot be easily compared among different studies, but only in the same patient population. In an Asian cohort of treated CHB patients, GAG-HCC risk score offered numerically higher PPV at 5 years (22%) than CU-HCC, REACH-B, LSM-HCC and REACH-Bm (16%, 12%, 14% and 20%, respectively).[35]

In another Asian cohort, PPV at 5 years in the high-risk group was 20% for GAG-HCC and only 8% for CU-HCC score.[36] According to unpublished data from the PAGE-B cohort, PPV for 5-year HCC prediction were 17% for PAGE-B score, 10% for both GAG-HCC and CU-HCC and 7% for REACH-B score in Caucasian treated CHB patients classified in the high HCC risk subgroup by each score.

The proportions of patients who are classified in the high-risk group and could be candidates for specific surveillance are also important. Such proportions ranged from 10% to 31% in seven studies which reported these data (Tables 1 and 2).[10,13,18,20,23,28,29] Based again on unpublished data from the PAGE-B cohort, 30% of Caucasian CHB patients by GAG-HCC and CU-HCC and 28% of the same patients by REACH-B and PAGE-B were classified into the high-risk group.

7.4 | Clinical applicability of HCC risk scores

In addition to the predictive performance, the components of each score and its formulas are crucial factors for the clinical utility of any risk score. Thus, an ideal HCC risk score should be simple, cheap and easy to calculate including commonly available objective parameters. Consequently, HCC risk scores including parameters amenable to subjectivity (eg cirrhosis in GAG-HCC, CU-HCC, RWS-HCC, HCC-Rescue, CAMD, ESC-HCC), special virological markers (eg mutations of HBV genome in the original GAG-HCC, HBV genotype and HBsAg levels in the REACH-B II) and/or complicated formulas (eg LS-Model, D^2AS) will probably have restricted applicability in clinical practice. Similarly, HCC risk scores with parameters of high cost, potential variability and/or limited availability, such as serum HBV DNA levels and LSM, may also restrain their clinical usefulness. Thus, HCC risk scores based on simple routinely available epidemiological and laboratory parameters appear to serve their cause better and have the potential to achieve the greatest clinical applicability.

In clinical practice, it might have been useful to know whether the predictive performances of HCC risk scores differ in different patient settings (eg with or without cirrhosis, treatment with ETV or TDF), but such conclusions cannot be drawn by the available data. Moreover, it will be of interest to determine whether the predictability of the scores will change with re-assessment of the scores during therapy.

8 | CONCLUSIONS

To date, a number of studies have developed various HCC risk scores for the prediction of HCC risk in untreated and treated CHB patients. The applicability and predictability of HCC risk scores for untreated patients have several limitations mainly due to the fluctuating course of untreated chronic HBV infection and the uncertainty of the benefit of frequent score reassessments, while the utility of these scores in untreated patients with HBV activity and indications for treatment is not clinically relevant. On the other hand, the clinical utility of the scores in treated CHB patients is of great clinical relevance due to the high HCC risk in patients who fulfil the current treatment indications and the relative homogeneity of this setting.[3,4] There has been no study to externally validate all proposed HCC risk scores in the same cohort of Asian, Caucasian or mixed patient populations. Therefore, direct comparisons of the predictability of scores are unsafe. Whenever the performances of HCC risk scores are compared, it should be kept in mind that the most useful characteristic of HCC risk scores is the NPV of their low cut-off. Using this cut-off, clinicians may be able to identify patients for whom HCC surveillance is not needed due to negligible or ideally null HCC risk. The first three scores (GAG-HCC, CU-HCC, REACH-B) developed in untreated Asian CHB patients have shown variable predictive performances in Asian cohorts of treated CHB patients and poor to moderate predictive performances in treated Caucasian or mixed population. Except for REACH-Bm and LSM-HCC, the more recent HCC risk scores developed in treated Asian CHB patients (CAMD, APA-B and AASL) have not undergone extensive external validation and therefore safe deductions cannot be made. PAGE-B score has been externally validated in independent cohorts of Caucasian, mixed ethnicity or Asian patients usually offering at least good predictability and high NPV in the low-risk group. Thus, according to both HBV and HCC European guidelines, PAGE-B is the only score that offers good predictability for HCC development in treated Caucasian CHB patients.[2,4] In the same direction, mPAGE-B seems to offer good predictability and high NPV in independent Asian cohorts so far. Based on the existing data, PAGE-B and mPAGE-B seem to represent simple scores that could be used in clinical practice to identity non-cirrhotic Caucasian or Asian CHB patients treated with oral antivirals who do and do not require HCC surveillance, while all cirrhotic patients should be under HCC surveillance. Direct comparisons of the newest HCC risk scores in independent patient cohorts of different origin would be of interest, as they appear to offer promising results.

CONFLICT OF INTEREST

Thodoris Voulgaris: none; Margarita Papatheodoridi: none; Pietro Lampertico: speaking bureau/advisor for Abbvie, Eiger, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck/Merck Sharp & Dohme, MYR Pharma, Roche; George Papatheodoridis: advisor/lecturer for Abbvie, Bristol-Myers Squibb, Dicerna, Gilead, GlaxoSmithKline, Ipsen, Janssen, Merck Sharp & Dohme, Roche, Spring Bank; research grants Abbvie, Bristol- Myers Squibb, Gilead.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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