Predictive performance of newer Asian hepatocellular carcinoma risk scores in treated Caucasians with chronic hepatitis B

Authors

George V. Papatheodoridis, George N. Dalekos, Ramazan Idilman, Vana Sypsa, Florian Van Boemmel, Maria Buti, Jose Luis Calleja, John Goulis, Spilios Manolakopoulos, Alessandro Loglio, Margarita Papatheodoridi, Nikolaos Gatselis, Rhea Veelken, Marta Lopez-Gomez, Bettina E. Hansen, Savvoula Savvidou, Anastasia Kourikou, John Vlachogiannakos, Kostas Galanis, Cihan Yurdaydin, Rafael Esteban, Harry L.A. Janssen, Thomas Berg, Pietro Lampertico

Correspondence

gepapath@med.uoa.gr (G.V. Papatheodoridis).

Graphical abstract

HCC risk score	Low/High-risk group cut-off	AUROC, c-statistic (95% CI)	Sensitivity, %	NPV, %
At baseline		5-year HCC prediction		
PAGE-B	10/18	0.80 (0.76, 0.83)	99.3%	99.8%
HCC-Rescue	65/85	0.81 (0.78, 0.84)	97.2%	99.5%
CAMD	8/14	0.79 (0.74, 0.83)	100%	100%
mPAGE-B	9/13	0.82 (0.78, 0.85)	97.8%	99.3%
AASL	6/20	0.81 (0.77, 0.84)	99.3%	99.7%
At baseline		10-year HCC prediction		
PAGE-B	10/18	0.78 (0.75, 0.81)	99.3%	99.8%
HCC-Rescue	65/85	0.81 (0.79, 0.84)	97.2%	99.5%
CAMD	8/14	0.80 (0.76, 0.83)	100%	100%
mPAGE-B	9/13	0.81 (0.78, 0.84)	97.8%	99.3%
AASL	6/20	0.80 (0.77, 0.83)	99.3%	99.7%

Highlights

- In treated Caucasian patients with chronic hepatitis B, newer Asian hepatocellular carcinoma risk scores offer good 5- and 10-year predictability, similar to that of PAGE-B.
- PAGE-B and mPAGE-B scores are simpler in clinical practice, as they do not require an accurate diagnosis of cirrhosis.
- The addition of albumin in mPAGE-B does not seem to offer an advantage in patients with well-compensated liver disease.

Lay summary

Several risk scores for prediction of hepatocellular carcinoma (HCC) were recently developed in cohorts of treated Asian patients with chronic hepatitis B (CHB). In Caucasian patients with CHB treated with oral antivirals, newer Asian HCC risk scores offer good 5- and 10-year HCC predictability, similar to that of PAGE-B. For clinical practice, PAGE-B and mPAGE-B scores are simpler, as they do not require an accurate diagnosis of cirrhosis.

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Research article

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Predictive performance of newer Asian hepatocellular carcinoma risk scores in treated Caucasians with chronic hepatitis B

George V. Papatheodoridis,[1,*] George N. Dalekos,[2] Ramazan Idilman,[3] Vana Sypsa,[4] Florian Van Boemmel,[5] Maria Buti,[6] Jose Luis Calleja,[7] John Goulis,[8] Spilios Manolakopoulos,[1,9] Alessandro Loglio,[10] Margarita Papatheodoridi,[1] Nikolaos Gatselis,[2] Rhea Veelken,[5] Marta Lopez-Gomez,[7] Bettina E. Hansen,[11,12] Savvoula Savvidou,[8] Anastasia Kourikou,[9] John Vlachogiannakos,[1] Kostas Galanis,[2] Cihan Yurdaydin,[13] Rafael Esteban,[6] Harry L.A. Janssen,[12] Thomas Berg,[5] Pietro Lampertico[10,14]

[1]Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens "Laiko", Athens, Greece; [2]Department of Medicine and Research Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Larissa, Greece; [3]Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkey; [4]Department of Hygiene, Epidemiology & Medical Statistics, Medical School of National and Kapodistrian University of Athens, Athens, Greece; [5]Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany; [6]Hospital General Universitario Vall Hebron and Ciberehd, Barcelona, Spain; [7]Hospital U Puerta de Hierro, IDIPHIM CIBERehd, Madrid, Spain; [8]4th Department of Internal Medicine, ristotle University of Thessaloniki Medical School, Thessaloniki, Greece; [9]2nd Department of Internal Medicine, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens "Hippokratio", Athens, Greece; [10]Division of Gastroenterology and Hepatology, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [11]Department of Gastroenterology & Hepatology, Erasmus MC University Medical Center, Rotterdam, Netherlands; [12]Liver Clinic, Toronto Western & General Hospital, University Health Network, Toronto, ON, Canada; [13]Department of Gastroenterology & Hepatology, Koc University Medical School, Istanbul, Turkey; [14]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

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Background & Aims: Recently, several risk scores for prediction of hepatocellular carcinoma (HCC) were developed in cohorts of treated Asian patients with chronic hepatitis B (CHB), but they have not been assessed in non-Asian patients. We evaluated the predictability and comparative utility of our PAGE-B and recent Asian HCC risk scores in nucleos(t)ide analogue (NA)-treated adult Caucasian patients with CHB, with or without well-documented compensated cirrhosis but not previous diagnosis of HCC.

Methods: We included 1,951 patients treated with entecavir/tenofovir and followed up for a median of 7.6 years. The c-statistic was used to estimate the predictability of PAGE-B, HCC-Rescue, CAMD, mPAGE-B, and AASL score for HCC development within 5 or 10 years. The low- and high-risk group cut-offs were used for estimation of negative (NPV) and positive predictive values (PPV), respectively.

Results: HCC developed in 103/1,951 (5.3%) patients during the first 5 years and in another 39/1,428 (2.7%) patients between years 5 and 10. The 3-, 5-, and 10-year cumulative HCC rates were 3.3%, 5.9%, and 9.6%, respectively. All scores offered good 5- and 10-year HCC prediction (c-statistic: 0.78–0.82). NPVs were always >99% (99.3–100%), whereas PPV ranged between 13% and 24%.

Conclusions: In NA-treated Caucasian patients with CHB including compensated cirrhosis, HCC risk scores developed in NA-treated Asian patients offer good 5- and 10-year HCC predictability, similar to that of PAGE-B. PAGE-B and mPAGE-B scores are simpler in clinical practice, as they do not require an accurate diagnosis of cirrhosis, but the addition of albumin in mPAGE-B score does not seem to offer an advantage in patients with well compensated liver disease.

Lay summary: Several risk scores for prediction of hepatocellular carcinoma (HCC) were recently developed in cohorts of treated Asian patients with chronic hepatitis B (CHB). In Caucasian patients with CHB treated with oral antivirals, newer Asian HCC risk scores offer good 5- and 10-year HCC predictability, similar to that of PAGE-B. For clinical practice, PAGE-B and mPAGE-B scores are simpler, as they do not require an accurate diagnosis of cirrhosis.

Keywords: Cirrhosis; Entecavir; Tenofovir; Prediction.
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* Corresponding author. Address: Department of Gastroenterology, School of Medicine, National and Kapodistrian University of Athens, Laiko General Hospital of Athens, 17 Agiou Thoma Street, 11527 Athens, Greece. Tel: +30-2132061115, Fax: +30-2107462601.
E-mail address: gepapath@med.uoa.gr (G.V. Papatheodoridis).

Introduction

The risk of hepatocellular cancer (HCC) is decreased in effectively treated compared with untreated patients with chronic hepatitis B (CHB), but HCC remains the only factor that affects liver-related mortality and the main challenge in the management of CHB.[1–6] Given the difficulties for identification of patients with CHB

requiring cautious HCC surveillance, the accurate HCC risk prediction particularly in patients treated with a nucleos(t)ide analogue (NA) remains of great importance.[7] Therefore, several groups have focused on the development of scores for the optimisation of HCC prediction in NA-treated patients.[7–9]

The initial HCC risk scores published between 2009 and 2011 such as GAG-HCC, CU-HCC, and REACH-B were developed and validated in cohorts of untreated Asian patients with CHB,[10–12] but their predictability was found to vary widely in independent untreated or NA-treated Asian cohorts and to be poor to moderate in NA-treated Caucasian cohorts.[7,13,14] In 2016, we developed the PAGE-B (including Platelets, Age, GEnder) score, which offered accurate prediction for HCC development within the first 5 years of entecavir (ETV) or tenofovir disoproxil fumarate (TDF) treatment in Caucasian patients with CHB,[8] whereas, recently, we also developed CAGE-B (Cirrhosis and Age) and SAGE-B (Stiffness and Age) scores for HCC prediction after the first 5 years of therapy in the same setting.[15] PAGE-B score has now been found to offer accurate HCC prediction in several independent NA-treated Caucasian and Asian cohorts[7] and has been included in the recent European guidelines for the management of both HBV and HCC.[1,16] Over the last 3 years, several new HCC risk scores such as HCC-Rescue (HCC-Risk Estimating Score in CHB patients Under Entecavir; including age, gender, cirrhosis), CAMD (including Cirrhosis, Age, Male gender, Diabetes), mPAGE-B (modified PAGE-B; including Platelets, Age, GEnder, albumin), and AASL (including Age, Albumin, Sex, Liver cirrhosis) were developed in cohorts of NA-treated Asian patients with CHB mainly based on parameters similar to those of PAGE-B score, usually including age, gender, and a marker of liver disease severity,[7,17–20] but their predictive performance has not been evaluated in Caucasians.

This study aimed to assess the predictability and comparative utility of the recent Asian HCC risk scores (HCC-Rescue, CAMD, mPAGE-B, and AASL) in the Caucasian NA-treated patients of the PAGE-B cohort.

Patients and methods

This study included all 1,951 patients currently followed up at the liver clinics of the 10 centres participating in the PAGE-B ongoing cohort. All patients were Caucasian adults with CHB, with or without compensated cirrhosis, who had received ≥12 months of ETV and/or TDF therapy started until December 2012. No patient had HCC diagnosed before the onset of ETV/TDF, decompensated cirrhosis, or history of liver transplantation or coinfection(s) with hepatitis D, hepatitis C, or HIV. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All patients consented for the anonymous use of their data.

All patients were treated with ETV or TDF and followed up at each participating centre according to international and/or national clinical practice guidelines. ETV and TDF were given orally at a dose of 0.5 and 300 mg once daily, respectively, except for patients with estimated creatinine clearance of <50 ml/min in whom appropriate dosage adjustments were made according to each summary product characteristics. The PAGE-B cohort study was approved by each hospital ethics committee, and patients consented for anonymous use of their data, according to the local requirements. Clinical examination and routine laboratory tests were performed at least every 6 months, whereas serum HBV DNA levels were determined every 6–12 months. Ultrasonography, with or without alpha-foetoprotein measurements, was performed at least every 6 or 12 months in patients with and without cirrhosis, respectively.

Entry into this study (baseline) was defined as the onset of ETV/TDF. Follow-up was considered as the time interval between the study entry and the last available clinical information (end of follow-up). Analysis time was the time interval between study entry and HCC diagnosis or end of follow-up in the absence of HCC development. The follow-up time for 5- or 10-year HCC prediction was censored at 5 or 10 years, respectively.

The diagnosis of CHB was based on HBsAg seropositivity for ≥6 months, serum HBV DNA >2,000 IU/ml, and elevated alanine aminotransferase (ALT) levels. ALT levels were considered to be elevated if they exceeded the traditional cut-off for the upper limit of normal (ULN) of 40 IU/L.[1] The severity of liver disease before therapy was classified into CHB only (without cirrhosis) according to findings from liver biopsies and CHB with compensated cirrhosis according to histological, ultrasonographic, and/or endoscopic findings. Patients without ultrasonographic or endoscopic findings of cirrhosis and without liver biopsy before ETV/TDF onset were considered to have an unclassified status of cirrhosis. Virological remission was considered to be present in case of HBV DNA <80 IU/ml that was maintained throughout ETV/TDF treatment. HCC was diagnosed by standard histological and/or compatible radiological findings.[21]

Based on our patients' data at ETV/TDF onset, we determined PAGE-B,[8] HCC-Rescue,[17] CAMD,[18] mPAGE-B,[19] and AASL score[20] (Table S1). In addition, Year 5 data from patients who were followed up for >5 years without HCC development within the first 5 years of therapy were used for the calculation of PAGE-B, HCC-Rescue, and CAMD as well as our 2 new Year 5 scores CAGE-B and SAGE-B[15] (Table S1); mPAGE-B and AASL were not determined at Year 5 because of lack of Year 5 data for albumin in our database. All HCC risk scores were calculated according to their published formulas, and patients were classified into low-, intermediate-, and high-risk groups based on the original cut-offs of each score.[8,15,17–20]

Statistical analysis

Continuous variables were summarised using mean values ±SD or median values (IQR). Categorical variables were summarised as frequencies and percentages. HCC incidence rates were obtained using information on the number of new HCC diagnoses and the person-time at risk. Univariable and multivariable Cox proportional hazards models were used to identify prognostic factors of the HCC risk. Hazard ratios (HRs) and their 95% CIs along with corresponding p values are presented.

The accuracy of HCC risk scores for 5- and 10-year prediction of HCC in our patient population was evaluated by the Harrell c-index, which is a generalisation of the area under the receiver operating characteristic (AUROC) curve. The diagnostic accuracy of each risk score was considered to be excellent, good, modest, and poor in case of a c-statistic of ≥0.85, 0.75–0.84, 0.65–0.74, and <0.65, respectively. The low-risk group cut-off of each score

was used for the estimation of sensitivity, specificity, and negative predictive value (NPV) and the high-risk group cut-off for the estimation of positive predictive value (PPV).

Results

HCC incidence and predictors

The main characteristics of the 1,951 patients at ETV/TDF onset are shown in Table 1. The median patients' follow-up was 7.6 years. HCC developed in 103 (5.3%) patients during the first 5 years and in another 39 (2.0%) patients from Year 6 to 10. The latter 39 (2.7%) HCCs developed in 1,428 patients followed up for >5 years without HCC development in the first 5 years of therapy. The 3-, 5-, and 10-year cumulative HCC rates were 3.3%, 5.9%, and 9.6%, respectively.

In univariable Cox regression analyses, older age, male gender, HBeAg negativity, normal ALT, lower platelets, undetectable HBV DNA, no history of prior interferon-alpha therapy, and presence of cirrhosis were found to be associated with increased 5- and 10-year incidence of HCC (Table 2). In multivariable Cox regression analyses models including all the above parameters, the 5-year incidence of HCC was independently associated with older age (adjusted HR per year: 1.06, 95% CI 1.03–1.08; p <0.001), male gender (adjusted HR: 2.91, 95% CI: 1.54–5.50; p = 0.001), lower platelets (adjusted HR per 10^4 platelets/mm^3: 0.91, 95% CI: 0.87–0.95; p <0.001), and presence of baseline cirrhosis (adjusted HR: 2.67, 95% CI: 1.66–4.29; p <0.001). Similarly, the 10-year incidence of HCC was independently associated with older age (adjusted HR per year: 1.06, 95% CI: 1.04–1.08; p <0.001), male gender (adjusted HR: 2.39, 95% CI: 1.44–3.95; p = 0.001), lower platelets (adjusted HR per 10^4 platelets/mm^3: 0.93, 95% CI: 0.89–0.96; p <0.001), presence of baseline cirrhosis (adjusted HR: 2.89, 95% CI: 1.94–4.33; p <0.001), and no history of prior interferon-alpha therapy (adjusted HR: 1.73, 95% CI: 1.05–2.88; p = 0.033). Finally, 6- to 10-year HCC development was independently associated with older age at Year 5 (adjusted HR per year: 1.06, 95% CI: 1.02–1.11; p = 0.003) and presence of baseline cirrhosis (adjusted HR: 2.91, 95% CI: 1.08–7.87; p = 0.034) and had a trend for independent associations with lower platelets at Year 5 (adjusted HR per 10^3/mm^3: 0.99, 95% CI: 0.98–1.00; p = 0.075) and presence of liver stiffness ≥12 kPa at Year 5 (adjusted HR: 2.34, 95% CI: 0.92–5.93; p = 0.074).

Table 1. Main characteristics of 1,951 Caucasian patients with CHB at the onset of ETV or TDF treatment.

Characteristic	
Age, years	53 ± 14
Male gender, n (%)	1,379 (71)
BMI (in 1,632 patients), kg/m^2	26.1 ± 4.7
Obesity (BMI ≥30 kg/m^2), n/N (%)	212/1,632 (13)
Alcohol use, n/N (%)	
None/mild	1,010/1,257 (80)
Moderate	157/1,257 (13)
Abuse (past or present)	90/1,257 (7)
Diabetes mellitus, n/N (%)	118/1,286 (9)
Family history of HCC, n/N (%)	60/1,247 (5)
HBeAg-positive patients, n/N (%)	348/1,943 (18)
HBeAg-negative patients, n/N (%)	1,595/1,943 (82)
Patients with normal ALT, n/N (%)	892/1,844 (48)
ALT in cases with abnormal ALT, IU/L	84 (96)
Platelets, × 10^3/mm^3	191 ± 66
Patients with HBV DNA <80 IU/ml, n/N (%)	503/1,821 (28)
HBV DNA in cases with HBV DNA ≥80 IU/ml, log$_{10}$ IU/ml	5.6 ± 1.9
(Pegylated-)interferon-alpha in the past, n (%)	446 (23)
Other NAs before ETV/TDF, n (%)	820 (42)
Disease severity, n (%)	
CHB without cirrhosis	1,379 (71)
Compensated cirrhosis	526 (27)
Unclassified	46 (2)
Initial antiviral therapy, n (%)	
ETV monotherapy	756 (39)
ETV and TDF (or adefovir)*	45 (3)
TDF monotherapy	824 (42)
TDF and lamivudine (or telbivudine)†	326 (17)
Final antiviral therapy, n (%)	
ETV	772 (39.6)
TDF	1,163 (59.6)
ETV and TDF	16 (0.8)
Follow-up, years	7.6 (4.5)

Quantitative variables: mean ± SD or median (IQR) values.
ALT, alanine aminotransferase; CHB, chronic hepatitis B; ETV, entecavir; HCC, hepatocellular carcinoma; NAs, nucleos(t)ide analogues; TDF, tenofovir disoproxil fumarate.
* ETV and adefovir in 14 patients.
† TDF and telbivudine in 7 patients.

HCC prediction by risk scores

All scores offered similarly good 5-year HCC prediction (c-statistic: 0.75–0.84), as c-statistic (95% CI) was 0.80 (0.76–0.83) for PAGE-B, 0.81 (0.78–0.84) for HCC-Rescue, 0.79 (0.74–0.83) for CAMD, 0.82 (0.78–0.85) for mPAGE-B, and 0.81 (0.77–0.84) for AASL. Likewise, all scores offered similarly good 10-year HCC prediction (c-statistic: 0.75–0.84), as c-statistic was 0.78 (0.75–0.81) for PAGE-B, 0.81 (0.79–0.84) for HCC-Rescue, 0.80 (0.76–0.83) for CAMD, 0.81 (0.78–0.84) for mPAGE-B, and 0.80 (0.77–0.83) for AASL. The 5- and 10-year predictability of all scores remained very similar in the subgroup of patients without cirrhosis at baseline (c-statistics: 0.78–0.83). When only patients who were alive under follow-up and HCC-free at 5 years of ETV/TDF therapy were analysed, prediction of HCC during years 6–10 was good for HCC-Rescue (c-statistic [95% CI]: 0.82 [0.75–0.88]), CAMD (0.83, [0.78–0.87]), CAGE-B (0.83 [0.76–0.89]), and SAGE-B (0.81 [0.74–0.87]), whereas the c-statistic was moderate, just <0.75, for PAGE-B (0.74 [0.66–0.82]) (Table 3). The predictability of all scores did not substantially change when only patients without cirrhosis as baseline were included in the analyses (Table 3).

The proportion of patients classified into low-risk groups at baseline were 21% for PAGE-B, 42% for HCC-Rescue, 30% for CAMD, 24% for mPAGE-B, and 22% for AASL. Sensitivity and NPV for 5-year HCC prediction were 100% for PAGE-B, CAMD, and AASL; 97% and 99.6% for HCC-Rescue; and 98% and 99.5% for mPAGE-B, respectively, whereas specificity ranged from 23% to 45%. The proportion of patients classified into high-risk groups at baseline were 31% for PAGE-B, 24% for HCC-Rescue, 24% for CAMD, 36% for mPAGE-B, and 19% for AASL, whereas PPV for 5-year HCC development ranged from 13% to 18% (Table 3).

For 10-year HCC prediction, sensitivity and NPV were similarly high ranging from 97% to 100% and 99.3% to 100%, respectively, whereas specificity ranged from 23% to 46% and PPV from 16% to 24% (Table 3).

Based on the data at 5 years of ETV/TDF therapy, the proportion of patients classified into low-risk groups were 19% for PAGE-B, 36% for HCC-Rescue, 21% for CAMD, 35% for CAGE-B, and 37% for SAGE-B. For 6- to 10-year HCC prediction, sensitivity ranged from 97% to 100% and specificity from 20% to 37%, whereas NPV was >99% for all scores (99.6–100%). The

Table 2. Univariable and multivariable Cox regression analyses for associations of baseline variables with development of HCC within 5 or 10 years of ETV and/or TDF treatment in 1,951 Caucasian patients with CHB, with or without compensated cirrhosis.

	5-year HCC prediction				10-year HCC prediction			
	Univariable		Multivariable		Univariable		Multivariable	
Characteristic at ETV/TDF onset	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (per year)	1.07 (1.05–1.09)	<0.001	1.06 (1.03–1.08)	<0.001	1.07 (1.06–1.09)	<0.001	1.06 (1.04–1.08)	<0.001
Gender (male *vs.* female)	3.58 (1.92–6.69)	<0.001	2.91 (1.54–5.50)	0.001	2.93 (1.79–4.81)	<0.001	2.39 (1.44–3.95)	0.001
BMI* (per kg/m^2)	1.02.(0.99–1.05)	0.253			1.02 (1.00–1.04)	0.091	1.00 (0.95–1.06)	0.992
Alcohol use (≤mild *vs.* ≥mod.)	0.69 (0.32–1.51)	0.355			0.83 (0.46–1.53)	0.556		
Diabetes (no *vs.* yes)	0.61 (0.30–1.23)	0.166			0.57 (0.33–1.01)	0.053	1.00 (0.55–1.84)	0.991
Family HCC history (no *vs.* yes)	1.59 (0.39–6.52)	0.516			0.94 (0.38–2.31)	0.892		
HBeAg positive (yes *vs.* no)	0.44 (0.22–0.86)	0.017	0.61 (0.28–1.33)	0.210	0.47 (0.26–0.83)	0.009	0.75 (0.40–1.40)	0.366
Normal ALT (yes *vs.* no)	1.56 (1.05–2.32)	0.027	1.09 (0.66–1.79)	0.741	1.69 (1.20–2.37)	0.003	0.93 (0.60–1.44)	0.738
Platelets (per 10^4/mm^3)	0.87 (0.84–0.90)	<0.001	0.91 (0.87–0.95)	<0.001	0.88 (0.86–0.91)	<0.001	0.93 (0.89–0.96)	<0.001
HBV DNA <80 IU/ml (yes *vs.* no)	1.73 (1.15–2.62)	0.009	1.00 (0.66–1.67)	0.983	2.31 (1.64–3.25)	<0.001	1.43 (0.93–2.20)	0.105
(Peg-)IFNα in past (yes *vs.* no)	0.51 (0.29–0.89)	0.018	0.64 (0.35–1.17)	0.145	0.47 (0.29–7.62)	0.002	0.58 (0.35–0.95)	0.033
NA in the past (yes *vs.* no)	1.05 (0.71–1.55)	0.812			1.40 (1.00–1.94)	0.048	1.22 (0.88–1.72)	0.205
Cirrhosis (yes *vs.* no)	6.23 (4.08–9.49)	<0.001	2.67 (1.66–4.29)	<0.001	6.13 (4.29–8.78)	<0.001	2.89 (1.94–4.33)	<0.001
NA therapy (ETV *vs.* TDF)	1.17 (0.78–1.77)	0.454			1.20 (0.85–1.70)	0.304		

CHB, chronic hepatitis B; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; mod., moderate; NA, nucleos(t)ide analogue; (Peg-)IFNα, (pegylated) interferon-alpha; TDF, tenofovir disoproxil fumarate.
* BMI was available in 1,632 patients.

Table 3. Predictive performance of HCC risk scores for HCC development during 5 or 10 or 6–10 years of ETV or TDF in Caucasian patients with CHB.

HCC risk score	Low*/high†-risk group cut-off	Patients in low/high-risk group	AUROC, c-statistic (95% CI), all patients	AUROC, c-statistic (95% CI), patients without cirrhosis	Sensit.‡	Specif.‡	NPV‡	PPV§
At baseline				**5-year HCC prediction**				
PAGE-B	10*/18†	21%/31%	0.80 (0.76–0.83)	0.81 (0.74–0.87)	99.3%	23.0%	99.8%	16.3%
HCC-Rescue	65*/85†	42%/24%	0.81 (0.78–0.84)	0.78 (0.76–0.85)	97.2%	46.1%	99.5%	20.8%
CAMD	8*/14†	30%/24%	0.79 (0.74–0.83)	0.79 (0.73-0.85)	100%	33.0%	100%	21.4%
mPAGE-B	9*/13†	24%/36%	0.82 (0.78–0.85)	0.83 (0.78–0.88)	97.8%	25.4%	99.3%	17.9%
AASL	6*/20†	22%/19%	0.81 (0.77-0.84)	0.80 (0.75-0.85)	99.3%	23.5%	99.7%	24.3%
At baseline				**10-year HCC prediction**				
PAGE-B	10*/18†	21%/31%	0.78 (0.75–0.81)	0.79 (0.73–0.85)	99.3%	23.0%	99.8%	16.3%
HCC-Rescue	65*/85†	42%/24%	0.81 (0.79–0.84)	0.81 (0.76–0.86)	97.2%	46.1%	99.5%	20.8%
CAMD	8*/14†	30%/24%	0.80 (0.76–0.83)	0.80 (0.75–0.85)	100%	33.0%	100%	21.4%
mPAGE-B	9*/13†	24%/36%	0.81 (0.78-0.84)	0.82 (0.77–0.88)	97.8%	25.4%	99.3%	17.9%
AASL	6*/20†	22%/19%	0.80 (0.77-0.83)	0.80 (0.75–0.85)	99.3%	23.5%	99.7%	24.3%
At Year 5				**6- to 10-year HCC prediction**				
PAGE-B	10*/18†	19%/31%	0.74 (0.66-0.82)	0.74 (0.57–0.90)	97.3%	19.9%	99.6%	6.2%
HCC-Rescue	65*/85†	36%/32%	0.82 (0.75–0.88)	0.82 (0.68-0.97)	97.4%	37.2%	99.8%	7.7%
CAMD	8*/14†	21%/25%	0.83 (0.78-0.87)	0.86 (0.80-0.91)	100%	21.9%	100%	10.2%
CAGE-B	6*/11†	35%/16%	0.83 (0.76–0.89)	0.79 (0.65–0.92)	97.2%	35.4%	99.8%	12.6%
SAGE-B	6*/11†	37%/6%	0.81 (0.74–0.87)	0.78 (0.65-0.91)	97.2%	38.3%	99.8%	15.8%

AUROC, area under the receiving characteristic curve; CHB, chronic hepatitis B; ETV, entecavir; HCC, hepatocellular carcinoma; NPV, negative predictive value; PPV, positive predictive value; Sensit., sensitivity; Specif., specificity; TDF, tenofovir disoproxil fumarate
* Cut-off value of the corresponding score for low-risk groups.
† Cut-off value of the corresponding score for high-risk groups. 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.
‡ The low-risk group cut-off of each score was used for estimation of Sensit., Specif., and NPV.
§ The high-risk group cut-off of each score was used for estimation of PPV.

proportion of patients classified into high-risk groups were 31% for PAGE-B, 32% for HCC-Rescue, 25% for CAMD, 16% for CAGE-B, and 6% for SAGE-B, whereas PPV ranged from 6% to 16% (Table 3).

Discussion

Because HCC currently represents the main cause of liver-related morbidity and mortality in diagnosed and treated patients with CHB,[1,2,4] its accurate prediction remains of great clinical relevance.[7,22] Over the last few years, at least 7 risk scores have been developed for HCC prediction in patients with CHB receiving long-term NA therapy,[7,22] while we also developed 2 scores for prediction of HCC after Year 5 of therapy.[15] All but our scores (PAGE-B, CAGE-B, and SAGE-B) have been developed and validated in cohorts of patients with CHB from East Asia, particularly from South Korea, Taiwan, and Hong Kong, but have not been assessed in non-Asian patients with CHB.[7,22] According to the findings of this study, our PAGE-B score and 4 of the risk scores developed in NA-treated Asian patients, HCC-Rescue, CAMD, mPAGE-B, and AASL, can offer similarly good 5- and 10-year HCC prediction in treated Caucasian patients with CHB, with or without compensated cirrhosis. Previous reports from our group

and others suggested poor to modest predictability from older Asian HCC risk scores such as GAG-HCC, CU-HCC, and REACH-B,[7,13,14] which were developed in Asian cohorts of untreated patients and often included several variables expressing the activity of liver disease such as ALT and HBV DNA but were usually normalised by NA therapy.[7] However, the 4 Asian HCC risk scores developed in NA-treated patients with CHB that were assessed in the current study included variables similar to those of PAGE-B score (age, gender, and platelets).[8] In particular, age and gender were included in all 4 Asian scores,[17–20] cirrhosis was included in 3 (HCC-Rescue, CAMD, and AASL),[17,18,20] platelets were included in 1 score (mPAGE-B),[19] albumin levels were included in 2 (mPAGE-B and AASL),[19,20] and diabetes was included in another score (CAMD).[18]

In addition to the similar HCC predictability expressed by the c-statistics of AUROC curves (0.78–0.82), all 5 risk scores offered excellent NPV of >99% (99.3–100%) for excluding HCC development during the next 5 or even 10 years. This is probably the most clinically relevant characteristic of such scores, as it reassures that low-risk patients can safely remain without HCC surveillance having no or acceptably low risk of HCC (<0.2% annually).[16] The proportions of patients who were classified into the low-risk group by each score varied from approximately 20% to 40%, but such a proportion depends strongly on the patients' characteristics.

Besides the predictive performance of each score, its components and formulas are important factors for its clinical utility. An ideal HCC risk score should be simple, cheap, and easy to calculate including commonly available objective parameters. Thus, HCC risk scores, such as HCC-Rescue, CAMD, and AASL, that require the diagnosis of cirrhosis,[17,18,20] may not be as accurate in routine clinical practice as in cohorts of patients who are closely followed up at expert tertiary liver centres and have an accurate assessment of liver histological lesions. In that respect, PAGE-B and mPAGE-B scores seem to be simpler and more reliable for daily clinical practice, as they do not require an accurate diagnosis of cirrhosis, which could be occasionally misleading. The addition of albumin levels in 2 risk scores (mPAGE-B and AASL)[19,20] was not found to offer an advantage in our patients with CHB and with well-compensated liver disease, but it seems reasonable to speculate that it might offer additional benefit if cases with advanced liver disease such as decompensated cirrhosis are also included.

Another limitation of HCC risk scores including cirrhosis is that patients with confirmed HBV cirrhosis should anyway remain under surveillance for HCC according to all scientific guidelines.[1,2,16,23] In any case, patients with CHB and cirrhosis are almost exclusively classified into high or at least moderate HCC risk by any score.[7] Thus, the numbers of patients with CHB and cirrhosis who were classified into low-risk groups by any score were so small in all relevant studies that safe conclusions cannot be drawn for this setting and such patients cannot be considered as potential cases who might not require HCC surveillance.[7] However, it was reassuring that the predictive performance of all scores did not substantially change in our cohort of well-characterised patients without cirrhosis (Table 3).

Whether reassessment of HCC risk scores during treatment can improve their predictive performance is unclarified. According to our findings, the 10-year HCC predictability of 3 scores assessed at baseline (PAGE-B, HCC-Rescue, and CAMD) was similar to the 6- to 10-year HCC predictability of the same scores assessed at Year 5 (wide overlap of 95% CI of c-statistics), and most importantly their NPVs were always excellent (99.5–100%). In particular, for our PAGE-B score, which was originally developed for 5-year HCC prediction,[8] its predictability based on Year 5 data seemed numerically lower for 6- to 10-year HCC prediction (c-statistic: 0.74) compared with the 5- or even 10-year prediction of the score assessed at baseline (c-statistic: 0.78–0.80), but the sensitivity and NPV were always excellent. In any case, we also developed CAGE-B, which has the limitation of requiring the diagnosis of baseline cirrhosis, and the simpler SAGE-B score for more accurate 5- to 10-year HCC prediction in our patients (c-statistic: 0.81–0.83).[15]

Based on the above discussion, reassessment of the current HCC risk scores does not seem to offer a clear benefit for HCC predictability up to 10 years of therapy. An improvement in HCC predictability by score reassessment was initially suggested for a few risk scores originally developed in untreated patients and including variables that are modified by therapy (*e.g.* ALT, HBV DNA, and HBeAg status).[24,25] However, improvement of HCC predictability with on-therapy reassessment does not seem to be achieved for scores with parameters that are not usually affected by therapy (*e.g.* age, gender, and platelets). In particular, for patients with CHB and baseline cirrhosis, even if their annual HCC risk is decreasing after 5 years of therapy, it remains far above the cut-off that justifies maintenance of HCC surveillance for life.[26]

The subgroup of our patients who were classified into high HCC risk ranged from 19% to 36% at baseline and from 6% to 32% at Year 5 depending on the score. Given that the annual probability of HCC in such patients was rather high (2.6–3.6% for the first 5 years and 1.2–3.2% for years 5–10), stricter HCC surveillance may be considered in this setting. However, it is yet not clear whether patients with CHB and high HCC risk would benefit from more frequent (*e.g.* every 3–4 months) assessments with abdominal ultrasonography or from surveillance-based methods with higher sensitivity and specificity in detecting HCC such as computed tomography or magnetic resonance imaging.[16]

Our study has some limitations. First, our cohort may favour the predictive performance of PAGE-B, CAGE-B, and SAGE-B, as it is the cohort used for the development of these scores. It should be noted, however, that, although there is substantial overlap, the cohort of this study is not identical with the previous cohorts used for the development of our HCC risk scores, as patients from 1 new centre (Leipzig) have now been added and, more importantly, patients from all centres have now longer follow-up (median follow-up: 7.6 years for the current cohort and 3.7 years for the cohort used for the development of PAGE-B) with many of them having developed new HCCs (patients with HCC: 142 in the current cohort and 85 in the original PAGE-B cohort). Unfortunately, no other similar cohort of Caucasian patients with CHB is available to us for independent assessment of the predictive performance of these HCC risk scores. However, the predictability of our PAGE-B score has been comparatively assessed in several original cohorts used for the development of Asian risk scores.[18,19] Another limitation is that all our findings refer only to Caucasian patients with CHB treated with ETV/TDF, as patients of other origin or patients with chronic HBV but without the current treatment indications such as cases with HBeAg-positive or HBeAg-negative chronic HBV infection were not included in our cohort. Finally, we could not evaluate the potential changes of the 6- to 10-year HCC predictability of mPAGE-B and AASL assessed at Year 5, because Year 5 data for albumin were not available in our database.

In conclusion, in treated Caucasian patients with CHB, with or without compensated cirrhosis, HCC risk scores recently developed in treated Asian patients offer good 5- and 10-year HCC predictability, similar to that of PAGE-B score, whereas all scores offer excellent NPV for the exclusion of HCC development in their low-risk groups. Given that the inclusion of baseline cirrhosis represents a limitation for the accurate and wide applicability of an HCC risk score in routine clinical practice, PAGE-B and mPAGE-B scores are simpler because they do not require the diagnosis of cirrhosis. The addition of serum albumin in mPAGE-B score does not seem to offer an advantage for HCC predictability in treated patients with CHB and well-compensated liver disease.

Abbreviations

ALT, alanine aminotransferase; AUROC, area under receiver operating characteristic; CHB, chronic hepatitis B; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; NA, nucleos(t)ide analogue; NPV, negative predictive value; PPV, positive predictive value; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

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Conflicts of interest

GVP has served as advisor/lecturer for Abbvie, Dicerna, Gilead, GlaxoSmithKline, Ipsen, Janssen, Merck Sharp & Dohme, Roche, and Spring Bank and has received research grants from Abbvie and Gilead. GND has served as advisor/lecturer for Abbvie, Bayer, Bristol-Myers Squibb, Gilead, Janssen, Novartis, and Roche and has received grant support from Bristol-Myers Squibb, Gilead, and Roche. VS has served as advisor/lecturer for Abbvie, Gilead, and Janssen and has received research grants from Abbvie and Gilead. FVB has served as advisor/lecturer for Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme, Novartis, and Roche; has received research grants from Bristol-Myers Squibb, Gilead, Janssen, Roche, and Siemens; and has served as consultant for Abbvie, Gilead, and Roche. MB has served as advisor/lecturer for Abbvie, Arbutus, Bristol-Myers Squibb, Gilead, Glaxo Smith-Kleine, Merck, Roche, and Spring Bank. JLC has served as advisor/lecturer for Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck. JG has served as advisor/lecturer for Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, and Roche and has received a research grant from Bristol-Myers Squibb. SM has served as advisor/lecturer for Abbvie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, and Roche and has received grants from Bristol-Myers Squibb and Gilead. AL has served as lecturer for Gilead and MYR Pharmaceuticals.

JV has served as advisor/lecturer for Abbvie, Bristol-Myers Squibb, Gilead, Merck Sharp & Dohme, Novartis, and Roche. CY has served as speaker's bureau and/or advisor for AbbVie, Bristol-Myers Squibb, Gilead, Merck, and Roche and has received a research grant from Bristol-Myers Squibb. RE has served as advisor/lecturer for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, and Novartis. HLAJ has served as consultant for and has received grants from AbbVie, Arbutus, Bristol Myers Squibb, Enyo, Gilead Sciences, Janssen, Medimmune, Merck, Roche, Vir Biotechnology Inc., and Viroclinics. TB has served as advisor/consultant/lecturer for Abbvie, Alexion, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme/Merck, Novartis, Roche, and Vertex and has received research support from Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme/Merck, Novartis, and Roche. PL has served as speaker's bureau/advisor for Abbvie, Eiger, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck/ Merck Sharp & Dohme, MYR Pharma, and Roche. RI, MP, NG, RV, ML-G, BEH, SS, AK, and KG have nothing to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conception of the study: GVP, MB, PL. Design of the study: GVP, GND, MB, JG, SM, BEH, CY, HLAJ, PL. Data collection: RI, FVB, MB, JLC, SM, AL, MP, NG, RV, ML-G, BEH, SS, AK, IV, KG. Assembly of data: GVP. Analysis of data: GVP. Statistical analysis of data: VS. Interpretation of data: GVP, GND, RI, VS, FVB, MB, JLC, JG, SM, AL, MP, NG, RV, ML-G, BEH, SS, AK, IV, KG, CY, RE, HLAJ, TB, PL. Drafting of the manuscript: GVP, PL. Revision of the manuscript: GND, RI, VS, FVB, MB, JLC, JG, AL, MP, NG, ML-G, BEH, SS, AK, IV, KG, CY, RE, HLAJ, TB. Approval of the final version of the manuscript: GVP, GND, RI, VS, FVB, MB, JLC, JG, SM, AL, MP, NG, RV, ML-G, BEH, SS, AK, IV, KG, CY, RE, HLAJ, TB, PL

Data availability

The data that support the findings of this study are available on request from the corresponding author (GP).

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2021.100290.

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Author names in bold designate shared co-first authorship

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