THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis

OPEN ACCESS

Research Article
Viral hepatitis

aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis

Rong Fan[1,†], George Papatheodoridis[2,†], Jian Sun[1,†], Hamish Innes[3], Hidenori Toyoda[4], Qing Xie[5], Shuyuan Mo[6], Vana Sypsa[7], Indra Neil Guha[8], Takashi Kumada[9], Junqi Niu[10], George Dalekos[11], Satoshi Yasuda[4], Eleanor Barnes[12], Jianqi Lian[13], Vithika Suri[6], Ramazan Idilman[14], Stephen T. Barclay[15], Xiaoguang Dou[16], Thomas Berg[17], Peter C. Hayes[18], John F. Flaherty[6], Yuanping Zhou[1], Zhengang Zhang[19], Maria Buti[20], Sharon J. Hutchinson[3], Yabing Guo[1], Jose Luis Calleja[21], Lanjia Lin[6], Longfeng Zhao[22], Yongpeng Chen[1], Harry L.A. Janssen[23], Chaonan Zhu[24], Lei Shi[24], Xiaoping Tang[25], Anuj Gaggar[6], Lai Wei[26], Jidong Jia[27], William L. Irving[8], Philip J. Johnson[28,*], Pietro Lampertico[29,30,*], Jinlin Hou[1,*]

[1]State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China; [2]Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece; [3]Glasgow Caledonian University, School of Health and Life Sciences, Glasgow, UK; [4]Department of Gastroenterology and Hepatology, Ogaki Municipal Hospital, Ogaki, Japan; [5]Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [6]Gilead Sciences, Foster City, CA, USA; [7]Department of Hygiene, Epidemiology & Medical Statistics, Medical School of National and Kapodistrian University of Athens, Athens, Greece; [8]NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK; [9]Department of Nursing, Gifu Kyoritsu University, Ogaki, Japan; [10]Department of Hepatology, First Hospital, Jilin University, Changchun, China; [11]Department of Internal Medicine, Thessalia University Medical School, Larissa, Greece; [12]Peter Medawar Building for Pathogen Research, Nuffield Department of Medicine and the Oxford NIHR Biomedical Research Centre, Oxford University, Oxford, UK; [13]Centers of Infectious Diseases, Tangdu Hospital, the Fourth Military Medical University, Xi'an, China; [14]Department of Gastroenterology, University of Ankara Medical School, Ankara, Turkey; [15]Glasgow Royal Infirmary, Glasgow, UK; [16]Department of Infectious Diseases, Shengjing Hospital of China Medical University, Shenyang, China; [17]Division of Hepatology, Clinic and Polyclinic for Gastroenterology, Hepatology Infectious Disease and Pneumology, University Clinic Leipzig, Leipzig, Germany; [18]Royal Infirmary of Edinburgh, Edinburgh, UK; [19]Department of Gastroenterology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [20]Hospital General Universitario Valle Hebron and Ciberehd, Barcelona, Spain; [21]Hospital U Puerta de Hierro, IDIPHIM CIBERehd, Madrid, Spain; [22]Department of Infectious Diseases, First Hospital of Shanxi Medical University, Taiyuan, China; [23]Liver Clinic, Toronto Western & General Hospital, University Health Network, Toronto, ON, Canada; [24]Big Data Research and Biostatistics Center, Hangzhou YITU Healthcare Technology Co. Ltd., Hangzhou, China; [25]Guangzhou Eighth People's Hospital, Guangzhou, China; [26]Peking University Hepatology Institute, Peking University People's Hospital, Beijing, China; [27]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China; [28]Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK; [29]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico - Division of Gastroenterology and Hepatology - CRC 'A.M. and A. Migliavacca' Center for Liver Disease, Milan, Italy; [30]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Background & Aims: Hepatocellular carcinoma (HCC) is the leading cause of death in patients with chronic hepatitis. In this international collaboration, we sought to develop a global universal HCC risk score to predict the HCC development for patients with chronic hepatitis.

Methods: A total of 17,374 patients, comprising 10,578 treated Asian patients with chronic hepatitis B (CHB), 2,510 treated Caucasian patients with CHB, 3,566 treated patients with hepatitis C virus (including 2,489 patients with cirrhosis achieving a sustained virological response) and 720 patients with non-viral hepatitis (NVH) from 11 international prospective observational cohorts or randomised controlled trials, were divided into a training cohort (3,688 Asian patients with CHB) and 9 validation cohorts with different aetiologies and ethnicities (n = 13,686).

Results: We developed an HCC risk score, called the aMAP score (ranging from 0 to 100), that involves only age, male, albumin–bilirubin and platelets. This metric performed excellently in assessing HCC risk not only in patients with hepatitis of different aetiologies, but also in those with different ethnicities (C-index: 0.82–0.87). Cut-off values of 50 and 60 were best for discriminating HCC risk. The 3- or 5-year cumulative incidences of HCC were 0–0.8%, 1.5–4.8%, and 8.1–19.9% in the low- (n = 7,413,

43.6%), medium- (n = 6,529, 38.4%), and high-risk (n = 3,044, 17.9%) groups, respectively. The cut-off value of 50 was associated with a sensitivity of 85.7–100% and a negative predictive value of 99.3–100%. The cut-off value of 60 resulted in a specificity of 56.6–95.8% and a positive predictive value of 6.6–15.7%.

Conclusions: This objective, simple, reliable risk score based on 5 common parameters accurately predicted HCC development, regardless of aetiology and ethnicity, which could help to establish a risk score-guided HCC surveillance strategy worldwide.

Lay summary: In this international collaboration, we developed and externally validated a simple, objective and accurate prognostic tool (called the aMAP score), that involves only age, male, albumin–bilirubin and platelets. The aMAP score (ranged from 0 to 100) satisfactorily predicted the risk of hepatocellular carcinoma (HCC) development among over 17,000 patients with viral and non-viral hepatitis from 11 global prospective studies. Our findings show that the aMAP score had excellent discrimination and calibration in assessing the 5-year HCC risk among all the cohorts irrespective of aetiology and ethnicity.

Introduction

With the vision of 'ending viral hepatitis', the World Health Organization (WHO) set the ambitious goal of reducing hepatitis-related mortality by 65% by the year 2030.[1] In the era of the widespread application of antiviral treatment, hepatocellular carcinoma (HCC) is the leading cause of death in patients with chronic viral hepatitis and the fourth most frequent cause of cancer-related death globally.[2] Therefore, the key to achieving the ambitious global goal proposed by the WHO is to reduce the mortality of viral hepatitis-associated HCC.

The success of treatment for HCC largely depends on the stage at which it is diagnosed. Patients with HCC diagnosed at an early stage have 5-year survival rates of 70–75%,[3,4] whereas the average survival time of patients with advanced HCC is less than 1 year.[5] An effective and successful HCC surveillance programme could offer early diagnosis and improve prognosis. The key is an easy and accurate tool to identify patients with different HCC risks and then individualise HCC surveillance.

HBV and HCV infections are the leading causes of HCC development. Over the past few decades, several HCC risk scores have been developed and validated to stratify the risk of HCC development.[6–13] However, most of these risk scores assign heavy weighting to viral factors and perform only satisfactorily among populations with specific aetiologies (HBV or HCV) and ethnicities (Asian or Caucasian), thus limiting their widespread promotion and application worldwide in the current era of sustained viral suppression or clearance by using antiviral treatment.

In this international, multi-aetiological, multi-ethnic, prospective chronic hepatitis cohort study, we aimed to develop and validate a novel, accurate, globally applicable risk score for predicting HCC development.

Patients and methods

This study was based on 11 prospective observational cohorts or randomised controlled trials (RCTs) involving patients with chronic HBV (CHB; n = 7), chronic HCV (n = 3) and non-viral hepatitis (NVH; n = 1).

CHB patients

Search-B cohort: a prospective multicentre observational cohort in China

In this cohort study (NCT02167503), adult patients with CHB were recruited from May 2014 to January 2018 from 15 centres in 8 provinces in China. All the patients enrolled in this cohort received antiviral treatment at the discretion of their physicians (71.3% treated with either entecavir or tenofovir) and underwent follow-up for up to 5 years. The data included in the analysis were as of July 2019.

REALM trial: a global randomized controlled trial (RCT)

In this trial (NCT00388674), adult patients with CHB enrolled from 299 centres in 24 countries were screened and recruited from December 2006 to July 2008. All eligible patients were randomly assigned (1:1) to receive either entecavir or an investigator-selected non-entecavir HBV nucleos(t)ide analogue and followed for up to 10 years.[14] The analysis included the data from patients treated with entecavir from 50 centres in 16 provinces in China.

European PAGE-B cohort

This cohort study included adult patients with CHB followed in 10 European centres who had started treatment with either entecavir or tenofovir between January 2004 and December 2012 and had completed at least 12 months of therapy, as previously described.[15] The data included in the analysis were as of May 2019.

Four global Gilead CHB RCTs

Adult patients with CHB from the 4 global RCTs sponsored by Gilead Pharmacy (NCT00117676, NCT00116805, NCT01940341 and NCT01940471) were recruited from May 2005 to June 2006 (the first 2 trials) and from September 2013 to October 2014 (the last 2 trials). The patients in the first 2 trials were randomised to receive either double-blind tenofovir or adefovir for 1 year before starting tenofovir open-label treatment for up to 9 years. The patients in the last 2 trials were randomised to receive either double-blind tenofovir or tenofovir alafenamide (TAF) for up to 3 years before starting TAF open-label treatment until year 8.[16,17] The analysis was performed based on the anonymised data including Asian and Caucasian patients who met the anonymisation criteria to protect patient privacy.

In the above 7 CHB cohorts/trials, patients with decompensated cirrhosis, HCC, liver transplantation, or co-infection(s) with hepatitis D, HCV or HIV were excluded. The laboratory results collected at enrolment were used for the analysis.

Patients with HCV

Japanese HCV cohort

Adult patients with HCV were enrolled from 1 centre in Japan between 1998 and 2016. Adult patients who received either interferon (IFN) or direct-acting antiviral agent (DAA) treatment were enrolled in the analysis. The laboratory results collected after the completion of antiviral treatment were used for the analysis.

UK HCV sustained virological response cirrhotic cohort

This cohort was assembled by combining patients with HCV, a sustained virological response (SVR) and cirrhosis (88.5% Caucasians) from 2 UK studies: (i) a previously described cohort of patients with HCV cirrhosis from Scotland, achieving an SVR

Table 1. Clinical characteristics of patients in the training cohort and 9 validation cohorts.

	Search-B training cohort	Asian CHB validation cohort			Caucasian CHB validation cohort		HCV infection cohort			Japanese NVH cohort
		Search-B validation cohort	REALM cohort	Gilead Asian CHB cohort	European PAGE-B cohort	Gilead Caucasian CHB cohort	Japanese HCV cohort	UK SVR cirrhotic cohort	Gilead SVR cirrhotic cohort	
Total No. of patients	3,688	2,847	2,548	1,495	1,938	572	1,077	1,230	1,259	720
Male, n (%)	2,977 (80.7)	2,071 (72.7)	2,061 (80.9)	977 (65.4)	1,369 (70.6)	443 (77.4)	532 (49.4)	900 (73.2)	866 (68.8)	337 (46.8)
Age, years										
Median	38	44	36	40	54	38	62	52	60	65
IQR	32, 46	37, 53	29, 43	32, 48	44, 63	28, 48	55, 70	46, 59	56, 63	57, 72
Cirrhosis, n (%)	710 (19.3)	565 (19.8)	307 (12.0)	167/1,466 (11.4)	518/1,892 (27.4)	98/558 (17.6)	195 (18.1)	1,230 (100)	1,259 (100)	189 (26.3)
Platelet, ×10³/mm³										
Median	186	162	170	191	187	201	180	136	137	216
IQR	144, 225	116, 203	127, 211	157, 228	153, 226	171, 239	140, 226	93, 185	94, 188	154, 267
Total No. with data	3670	2791	2469	1493	1865	571	1077	1230	1259	720
ALT, IU/L										
Median	29	26	75	84	43	103	n.a.	74	23	n.a.
IQR	20, 43	18, 38	42, 139	56, 135	24, 88	69, 169	n.a.	48, 120	17, 31	n.a.
Total No. with data	3670	2794	2547	1495	1830	572	n.a.	1230	1259	n.a.
Albumin, g/L										
Median	45	46	47	43	44	43	n.a.	39	44	n.a.
IQR	43, 47	43, 48	44, 49	41, 45	40, 46	40, 45	n.a.	35, 42	41, 46	n.a.
Total No. with data	3670	2793	2547	1495	1797	572	n.a.	1230	1259	n.a.
Total bilirubin, μmol/L										
Median	12.2	14.9	14.2	10.3	12.0	10.3	n.a.	13.0	10.3	n.a.
IQR	9.2, 16.6	11.3, 20.6	10.6, 19.5	8.6, 15.4	8.6, 17.1	6.8, 13.7	n.a.	9.0, 19.0	6.8, 17.1	n.a.
Total No. with data	3671	2790	2546	1495	1821	572	n.a.	1230	1259	n.a.
ALBI score										
Median	−3.1	−3.1	−3.2	−3.0	−3.0	−3.0	−3.0	−2.6	−3.1	−3.0
IQR	−3.3, −2.9	−3.3, −2.9	−3.4, −3.0	−3.2, −2.8	−3.3, −2.7	−3.2, −2.8	−3.2, −2.8	−2.9, −2.2	−3.3, −2.8	−3.2, −2.7
Total No. with data	3669	2789	2546	1495	1763	572	1077	1230	1259	720
LSM, kPa										
Median	7.2	7.2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	14.1	n.a.
IQR	5.5, 11.1	5.2, 12.0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	9.4, 21.3	n.a.
Total No. with data	3598	2451	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1063	n.a.
Follow-up, months										
Median	42.7	50.7	105.4	55.3	91.2	63.4	67.1	38.9	33.6	60.0
IQR	35.5, 54.4	42.5, 55.0	100.8, 108.4	44.1, 60.8	61.0, 115.0	55.5, 94.2	19.6, 126.7	25.0, 51.1	27.6, 40.1	51.2, 61.5
HCC cases during follow-up, n	95	54	67	27	139	8	94	57	71	19

For the characteristics of HBV-related parameters in the CHB cohorts, please see Table S1.

ALBI, albumin-bilirubin; ALT, alanine aminotransferase; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; LSM, Liver stiffness measurement; n.a., not applicable or not available; NVH, non-viral hepatitis; SVR, sustained virologic response.

between 1997 and 2016[18]; and (ii) English participants of the STOP-HCV cirrhosis study who had achieved an SVR. The STOP-HCV cirrhosis study comprised patients with HCV cirrhosis recruited from 31 liver clinics in the UK between January 2015 and July 2016. In both UK cohorts, the laboratory tests conducted <1 year before treatment initiation were used for the analysis. Follow-up time was commenced at the date of achieving an SVR.

Gilead HCV SVR cirrhotic cohort
This cohort enrolled patients with cirrhosis (93.7% Caucasians) with or without decompensated liver disease who achieved an SVR after receiving a sofosbuvir-based regimen without IFN while participating in a Gilead-sponsored HCV study or commercially at selected sites (NCT02292706). The laboratory results collected at enrolment (*i.e.* after completing antiviral treatment) were used for the analysis.

Patients with NVH
The origin of the cohort of patients with NVH was the same as that of the Japanese HCV cohort. Most of these cases were attributable to non-alcoholic fatty liver disease (NAFLD); excessive alcohol was considered an additional risk factor in 11% of cases.

Cirrhosis and HCC assessment
The diagnoses of cirrhosis and HCC were based on standard histological and/or compatible radiological findings. Patients underwent evaluation at least every 6 months. For detailed information, please see the supplementary material.

Albumin–bilirubin score calculation
The albumin–bilirubin (ALBI) score, a simple index reflecting the underlying liver function, was calculated for each patient by the following formula based on the albumin and bilirubin levels:

$$\text{ALBI score} = (\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085),$$

where bilirubin is in μmol/L and albumin in g/L.[19]

Statistical analysis
Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 20.0, Chicago, IL, USA) and R (Version 3.5.1). Patients in each cohort who had a follow-up time of less than 6 months or had been found to have HCC within 6 months were excluded from the analysis. Data were expressed as counts and percentages for categorical variables and as the median and interquartile range (IQR) for continuous variables. The cumulative probabilities of HCC occurrence at year 5 were estimated by the Kaplan–Meier (K–M) method and compared using the log-rank test.

Univariable and multivariable Cox proportional hazards regression models were used to estimate the effects of various variables on the hazard of HCC occurrence and to develop the HCC prediction model. The patients from the centre with the largest sample size (Nanfang Hospital, Guangzhou, China) in the Search-B CHB cohort were used as the training cohort to derive a score for predicting HCC within 5 years. The patients from the other centres of the Search-B cohort and from the other HBV, HCV and NVH cohorts/trials were used for the external validation of the scoring system. The time-dependent receiver operating characteristic (ROC) curve was used to evaluate the prediction accuracy of the model. The performance of model discrimination was assessed using Harrell's C-index. Z-score tests were used to compare Harrell's C-index in different models. A calibration plot was used to graphically assess the agreement between the probability of remaining HCC free as predicted by the model and the observed probability. X-tile plots were used to generate 2 optimal cut-off values with the highest χ^2 value to separate patients into low-, medium- and high-risk groups.[20] The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were also estimated for the 2 optimal cut-offs of the risk model. For more information regarding the development of the HCC risk score, please see the supplementary material.

This study was approved by the Ethics Committee of Nanfang Hospital, and was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of good clinical practice. All patients provided written informed consent to have their data used (anonymously) for research purposes.

Results
In this study, a total of 17,374 patients, comprising 10,578 Asian patients with CHB, 2,510 Caucasian patients with CHB, 3,566 patients with HCV and 720 patients with NVH, were included in the analysis. Patients were grouped into 1 training cohort as well as 3 Asian CHB, 2 Caucasian CHB, 3 HCV infection and 1 NVH validation cohorts. Table 1 and Table S1 show the clinical and laboratory data of each cohort. Other than the 2 HCV SVR cirrhotic cohorts, the percentages of patients with cirrhosis in the other cohorts ranged from 11.4% to 27.4%.

Table 2. Cox regression analysis in the training cohort.

	Univariable analysis			Multivariable analysis			
	Hazard ratio	95% CI	*p* value	Coefficient	Hazard ratio	95% CI	*p* value
Cirrhosis (Yes *vs.* No)	6.826	4.492, 10.375	<0.0001				
HBV DNA, per $\log_{10}$ IU/mL	0.917	0.812, 1.036	0.168				
HBeAg (positive *vs.* negative)	0.382	0.226, 0.645	<0.001				
HBsAg, per $\log_{10}$ IU/mL	0.771	0.635, 0.936	0.009				
ALT, per IU/L	0.998	0.992, 1.003	0.353				
LSM, per kPa	1.057	1.045, 1.068	<0.0001				
Risk model parameters							
Age, per year	1.083	1.064, 1.103	<0.0001	0.060	1.062	1.041, 1.084	<0.0001
Sex (male *vs.* female)	2.513	1.222, 5.168	0.013	0.894	2.446	1.185, 5.046	0.016
ALBI score	4.456	3.229, 6.149	<0.0001	0.484	1.623	1.056, 2.493	0.028
Platelet, per 10^3/mm^3	0.983	0.980, 0.987	<0.0001	−0.012	0.988	0.985, 0.992	<0.0001

ALBI, albumin-bilirubin; ALT, alanine aminotransferase; LSM, liver stiffness measurement.

Predictors of HCC

In the training cohort, 95 patients developed HCC during a median follow-up time of 42.7 (IQR: 35.5, 54.4) months. The cumulative 1-, 3- and 5-year incidences of HCC were 0.4%, 1.8% and 3.7%, respectively (Figure S1A). In the univariable Cox regression analysis, age, sex, cirrhosis, HBeAg status, levels of quantitative HBsAg, liver stiffness measurement (LSM), ALBI and platelets were associated with HCC occurrence within year 5 (Table 2). Patients with ALBI < −3 had significantly lower risk of HCC compared with those with ALBI ≥ −3 (5-year cumulative incidences of HCC: 2.0% vs. 6.5%, p <0.0001) (Figure S2).

Derivation of the HCC risk score

Considering that the cirrhosis diagnosis in clinical practice is relatively subjective, and the LSM level is not easily accessible in most primary care settings, we confined our risk score to the following non-viral variables: age, sex, ALBI and platelets. ALBI and platelets are variables that reflect the underlying liver function and fibrosis stage, respectively.

A risk score, known as the age–male–ALBI–platelets (aMAP) score, was devised using the above 4 variables weighted by their regression coefficients in the multivariable Cox model (Table 2), and then the score range was standardised to 1–100:

$$
\begin{aligned}
\text{aMAP risk score} = (\{&0.06 \times \text{age} + 0.89 \times \text{sex (Male: 1, Female: 0)} \\
&+ 0.48 \times [(\log_{10} \text{bilirubin} \times 0.66) \\
&+ (\text{albumin} \times -0.085)] - 0.01 \\
&\times \text{platelets}\} + 7.4) / 14.77 \times 100,
\end{aligned}
$$

where age is in year, bilirubin in μmol/l, albumin in g/l and platelets in $10^3/\text{mm}^3$. The 5-year baseline survival function of the aMAP Risk Score was:

$$S_0(t) = \exp(-H_0(t)) = 0.984.$$

The C-index of the aMAP score was 0.82 (95% CI: 0.77–0.86). The C-index did not improve substantially when cirrhosis (0.82, 95% CI: 0.78–0.87) or the LSM value (0.82, 95% CI: 0.78–0.87) was included in the model. The C-index was 0.80 (95% CI: 0.74–0.87) and 0.84 (95% CI: 0.77–0.90) among patients with or without achieving a negative HBV DNA status, respectively, and 0.74 (95% CI: 0.67–0.81) and 0.75 (95% CI: 0.67–0.84) in patients with and without cirrhosis, respectively (Table 3). The time-dependent ROC curves of aMAP score for predicting 1-, 2-, 3-, 4- and 5-year HCC showed that the prediction model had good prediction accuracy during each period of follow-up (Figure S3).

HCC risk stratification based on the aMAP score

The X-tile plots were used to generate 2 optimal cut-off values (50 and 60) to separate the training cohort into low-, medium- and high-risk groups (Figure S4). Figure S5 also showed that the HCC risk increased significantly when the aMAP score was either 50 or 60. Of the 3,662 patients with evaluable aMAP risk scores, 2,158 (58.9%), 1,181 (32.3%) and 323 (8.8%) were assigned to the low-, medium- and high-risk groups, respectively. The 5-year cumulative incidences of HCC were 0.8% (95% CI: 0.3–1.3%), 4.2% [95% CI: 2.6–5.7%; hazard ratio (HR) = 5.1 (95% CI: 3.3–8.0)] and 19.9% [95% CI: 12.8–26.5%; HR = 27.1 (95% CI: 12.5–58.8)] in the low-, medium- and high-risk groups, respectively (p <0.0001)

Table 3. C-index (95% CI) values of aMAP score for hepatocellular carcinoma development among patients in each cohort and its subgroups.

	Search-B training cohort	Search-B validation cohort	REALM cohort	Gilead Asian CHB cohort	European PAGE-B cohort	Gilead Caucasian CHB cohort	Japanese HCV cohort	UK SVR cirrhotic cohort	Gilead SVR cirrhotic cohort	Japanese NVH cohort
Overall	0.82 (0.77, 0.86)	0.84 (0.79, 0.89)	0.87 (0.82, 0.91)	0.83 (0.74, 0.92)	0.82 (0.78, 0.86)	0.87 (0.78, 0.97)	0.85 (0.79, 0.91)	—	—	0.85 (0.79, 0.90)
Cirrhosis	0.74 (0.67, 0.81)	0.75 (0.68, 0.82)	0.64 (0.54, 0.74)	0.83 (0.66, 1.00)	0.71 (0.65, 0.77)	0.61 (0.29, 0.94)	0.74 (0.64, 0.85)	0.77 (0.71, 0.83)	0.68 (0.61, 0.74)	0.61 (0.49, 0.73)
Non-cirrhosis	0.75 (0.67, 0.84)	0.77 (0.66, 0.89)	0.89 (0.82, 0.95)	0.82 (0.71, 0.93)	0.83 (0.77, 0.90)	0.96 (0.93, 0.99)	0.82 (0.73, 0.91)	—	—	0.84 (0.71, 0.98)
Negative HBV DNA	0.80 (0.74, 0.87)	0.81 (0.71, 0.90)			0.80 (0.73, 0.87)					
Positive HBV DNA	0.84 (0.77, 0.90)	0.88 (0.84, 0.91)			0.81 (0.75, 0.87)					

CHB, chronic hepatitis B; NVH, non-viral hepatitis; SVR, sustained virologic response.
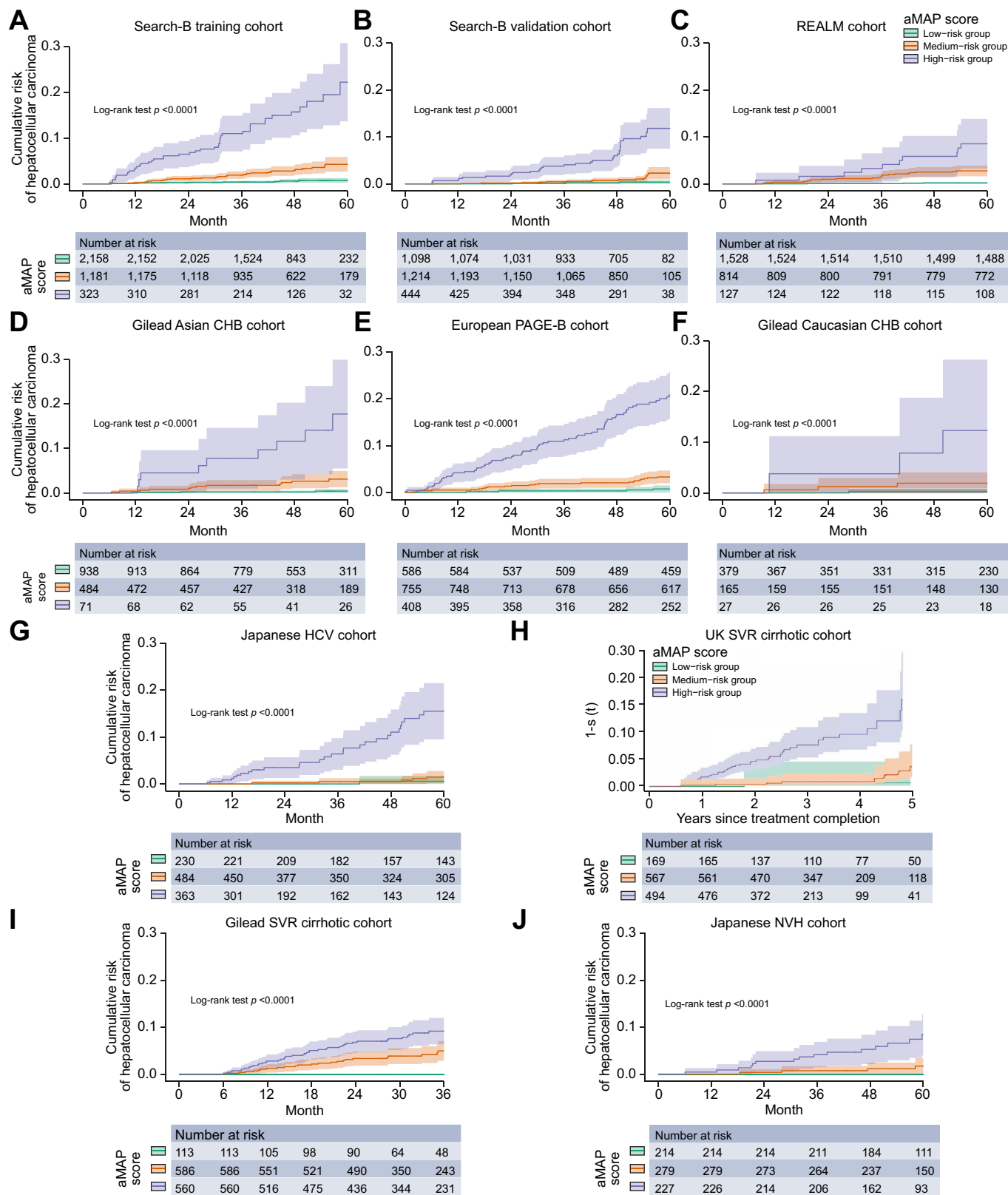
Fig. 1. Cumulative risk of HCC according to the aMAP scores in each cohort. (A) Search-B training cohort, (B) Search-B validation cohort, (C) REALM cohort, (D) Gilead Asian chronic hepatitis B virus (CHB) cohort, (E) European PAGE-B cohort, (F) Gilead Caucasian CHB cohort, (G) Japanese HCV cohort, (H) UK sustained virological response (SVR) cirrhotic cohort, (I) Gilead SVR cirrhotic cohort and (J) non-viral hepatitis (NVH) cohort.

(Figure 1A). The cut-off value of 50 was associated with a sensitivity of 86.5% and an NPV of 99.5%. The cut-off value of 60 resulted in a specificity of 92.2% and a PPV of 13.3% (Table 4). The calibration plot for the 5-year probability of remaining free of HCC performed well in the training cohort (Figure 2A).

External validation of the aMAP risk score in the CHB, HCV and NVH validation cohorts

The 3- or 5-year HCC incidences in the 9 validation cohorts ranged from 1.3% to 7.0% (Figure S1B–J).

In the 3 Asian and 2 Caucasian CHB validation cohorts, the aMAP score performed well in predicting HCC development, with C-index values ranging from 0.82 to 0.87. Similarly, the C-index values were 0.85 (95% CI: 0.79–0.91) and 0.85 (95% CI: 0.79–0.90) in the Japanese HCV and NVH validation cohorts, respectively. Within the subgroup of patients with cirrhosis, the C-index values for predicting HCC ranged from 0.61 to 0.83 (Table 3).

Among the 13,324 patients with evaluable aMAP scores in the validation cohorts, 5,255 (39.4%), 5,348 (40.1%) and 2,721 (20.4%) of the overall validation population were assigned to the low-, medium- and high-risk groups, respectively. The K–M curves also showed equally good discrimination among the 3 risk groups in the validation cohorts. The 3- or 5-year cumulative incidences of HCC were 0–0.8%, 1.5–4.8% and 8.1–17.8% in the low-, medium- and high-risk groups, respectively (all p <0.0001) (Figure 1B–J). In the 9 validation cohorts, the cut-off value of 50 was associated with a sensitivity of 85.7–100% and an NPV of 99.3–100%. The cut-off value of 60 resulted in a specificity of 56.6–95.8% and a PPV of 6.6–15.7% (Table 4). The calibration plots of the model in the validation cohorts are depicted in Figure 2B–J.

Comparison of the predictive performance of the aMAP score and other existing HBV-related HCC risk scores

The 6 existing HBV-related HCC risk scores [Risk Estimation for HCC in Chronic Hepatitis B (REACH-B), Chinese University HCC (CU-HCC), Liver Stiffness Measurement HCC (LSM-HCC), modified REACH-B (mREACH-B), PAGE-B and modified PAGE-B (mPAGE-B) scores] were each calculated on the basis of the clinical and laboratory parameters collected (Table S2).

In the training cohort, the C-index of the aMAP score was significantly higher than those of the other HCC risk scores [p <0.0001 (vs. REACH-B), p <0.0001 (vs. CU-HCC); p = 0.016 (vs. LSM-HCC); p = 0.027 (vs. mREACH-B); p = 0.041 (vs. PAGE-B); and p = 0.049 (vs. mPAGE-B)] (Table 5). The time-dependent AUC curve analyses showed that the aMAP score obtained the highest AUCs in dynamic trends among all risk scores within 5 years (Figure S6). Compared with the mPAGE-B score, which had the second highest C-index value, the aMAP score could identify a significantly higher percentage of patients with a low HCC risk (58.9% vs. 53.3%, p <0.001) (Figure S7). Moreover, compared with the other 6 existing risk scores, the aMAP score also showed significantly, or a trend towards, better performance for predicting HCC in the both Asian and Caucasian HBV validation cohorts and their subgroups (Table 5 and Table S3).

Discussion

In this study, we developed and externally validated a simple, objective and accurate prognostic tool (called the aMAP score) comprising routinely available laboratory parameters (albumin, bilirubin and platelets) plus age and sex that could satisfactorily predict the risk of HCC development among over 17,000 patients with viral hepatitis and NVH from 11 global prospective studies. Our findings showed that the aMAP score had excellent discrimination and calibration in assessing the 5-year HCC risk among all the cohorts irrespective of aetiology and ethnicity. To our knowledge, this is the first study to assess the performance of an HCC risk score among patients with differing aetiologies and ethnicities as well as the first-ever data on a HCC risk score from mainland China.

Table 4. Accuracy for prediction of hepatocellular carcinoma development in the training and validation cohorts using the aMAP score cut-off values of 50 and 60.

aMAP score	Cut-off value: 50		Cut-off value: 60		Cut-off value: 50		Cut-off value: 60		Cut-off value: 50		Cut-off value: 60	
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
	Search-B training cohort				**Search-B validation cohort**				**REALM cohort**			
Sensitivity, %	86.5	79.4, 93.6	48.3	37.9, 58.7	92.5	85.3, 99.6	64.2	51.2, 77.1	91.4	82.2, 100	28.6	13.6, 43.5
Specificity, %	60.4	58.8, 61.9	92.2	91.3, 93.1	42.4	40.6, 44.2	85.3	84.0, 86.6	63.8	61.9, 65.7	95.3	94.5, 96.2
PPV, %	5.1	4.0, 6.2	13.3	9.6, 17.0	3.0	2.1, 3.8	7.7	5.2, 10.1	3.4	2.2, 4.6	7.9	3.2, 12.6
NPV, %	99.5	99.1, 99.8	98.6	98.2, 99.0	99.7	99.3, 100	99.2	98.9, 99.6	99.8	99.6, 100	99.0	98.6, 99.4
	Gilead Asian CHB cohort				**European PAGE-B cohort**				**Gilead Caucasian CHB cohort**			
Sensitivity, %	87.5	74.3, 100	37.5	18.1, 56.9	95.5	91.1, 99.8	72.7	63.4, 82.0	85.7	59.8, 100	42.9	6.2, 79.5
Specificity, %	63.6	61.2, 66.1	95.8	94.8, 96.8	35.0	32.7, 37.3	79.3	77.3, 81.2	67.0	63.1, 70.9	95.7	94.1, 97.4
PPV, %	3.8	2.2, 5.4	12.7	4.9, 20.4	7.2	5.7, 8.7	15.7	12.2, 19.2	3.1	0.7, 5.6	11.1	0, 23.0
NPV, %	99.7	99.3, 100	98.9	98.4, 99.5	99.3	98.7, 100	98.2	97.5, 98.9	99.7	99.2, 100	99.3	98.5, 100
	Japanese HCV cohort				**UK SVR cirrhotic cohort**				**Gilead SVR cirrhotic cohort**			
Sensitivity, %	97.1	91.4, 100	82.4	69.5, 95.2	98.2	89.4, 99.9	78.9	65.8, 88.2	100	94.4, 100	64.6	52.5, 75.1
Specificity, %	22.0	19.4, 24.5	67.9	65.0, 70.7	14.3	12.4, 16.5	61.7	58.9, 64.5	9.5	7.9, 11.3	56.6	53.8, 59.4
PPV, %	3.9	2.6, 5.2	7.7	5.0, 10.5	5.3	4.0, 6.8	9.1	6.8, 12.1	5.7	4.5, 7.2	7.5	5.6, 10.0
NPV, %	99.6	98.7, 100	99.2	98.5, 99.8	99.4	96.2, 100	98.4	97.1, 99.1	100	96.7, 100	96.7	95.1, 97.8
	Japanese NVH cohort											
Sensitivity, %	100	100, 100	78.9	60.6, 97.3								
Specificity, %	30.5	27.1, 33.9	69.8	66.4, 73.2								
PPV, %	3.8	2.1, 5.4	6.6	3.4, 9.8								
NPV, %	100	100, 100	99.2	98.4, 100								

CHB, chronic hepatitis B; NPV, Negative predictive value; NVH, non-viral hepatitis; PPV, positive predictive value; SVR, sustained virologic response.
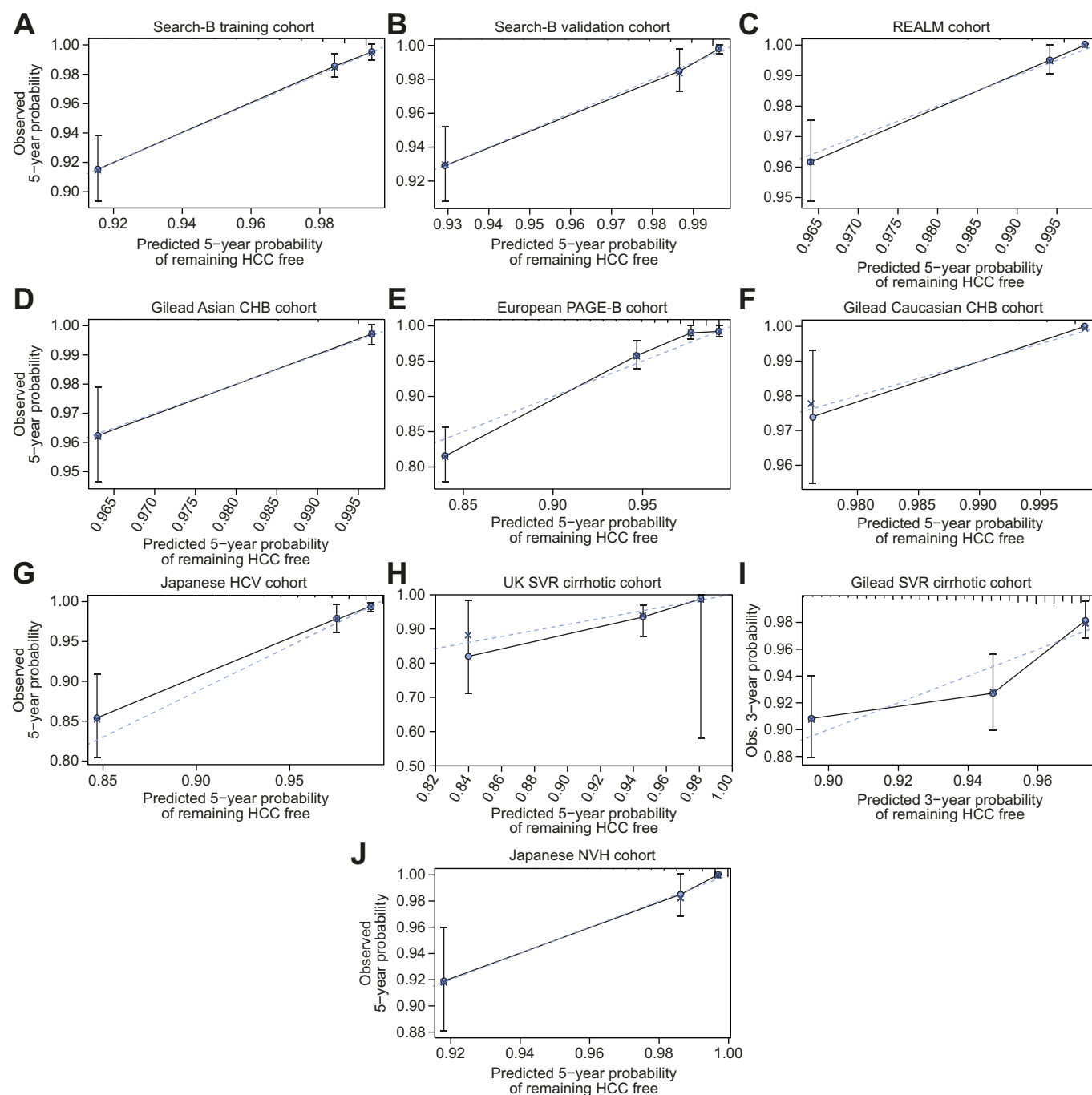
Fig. 2. Calibration curves of the aMAP score to predict HCC in each cohort. (A) Search-B training cohort, (B) Search-B validation cohort, (C) REALM cohort, (D) Gilead Asian chronic hepatitis B virus (CHB) cohort, (E) European PAGE-B cohort, (F) Gilead Caucasian CHB cohort, (G) Japanese HCV cohort, (H) UK sustained virological response (SVR) cirrhotic cohort, (I) Gilead SVR cirrhotic cohort and (J) non-viral hepatitis (NVH) cohort. The graphs represent the relationship between observed (vertical blue bar indicate the 95% CI of estimated value) and predicted 5-year probability of remaining HCC free. The dashed blue lines indicated the ideal calibration.

In recent decades, the healthcare costs of chronic disease have increased yearly. Promoting early screening and developing individualised HCC surveillance strategies remain the most cost-effective measures for reducing HCC-related mortality. A previous study showed that annual or semi-annual surveillance is considered cost-effective when the annual incidence of HCC exceeds 1–2%.[21,22] By using the aMAP score, we identified a group of low-risk patients (aMAP score <50) who accounted for ~45% of the overall population with an HCC probability of <0.2% per year, meaning that approximately half of patients with chronic hepatitis could undergo less intensive HCC surveillance. By contrast, patients who are classified in the high-risk group

Table 5. Comparison of performance of the aMAP score with other existing risk scores for hepatocellular carcinoma development in the chronic hepatitis B cohorts.

	aMAP	REACH-B	CU-HCC	LSM-HCC	mREACH-B	PAGE-B	mPAGE-B
Search-B training cohort	0.82 (0.77, 0.86)	0.64 (0.59, 0.70)	0.73 (0.66, 0.79)	0.77 (0.72, 0.82)	0.78 (0.73, 0.83)	0.79 (0.75, 0.84)	0.80 (0.76, 0.85)
Search-B validation cohort	0.84 (0.79, 0.89)	0.68 (0.62, 0.74)	0.79 (0.73, 0.85)	0.78 (0.71, 0.85)	0.79 (0.73, 0.85)	0.80 (0.74, 0.85)	0.82 (0.77, 0.87)
REALM cohort	0.87 (0.82, 0.91)	0.74 (0.65, 0.83)	0.76 (0.65, 0.86)	/	/	0.77 (0.70, 0.84)	0.84 (0.80, 0.88)
Gilead Asian CHB cohort	0.83 (0.74, 0.92)	0.77 (0.69, 0.86)	0.68 (0.56, 0.80)	/	/	0.79 (0.70, 0.89)	0.82 (0.74, 0.90)
European PAGE-B cohort	0.82 (0.78, 0.86)	/	/	/	/	0.76 (0.72, 0.80)	/
Gilead Caucasian CHB cohort	0.87 (0.78, 0.97)	0.72 (0.55, 0.89)	0.85 (0.78, 0.92)	/	/	0.87 (0.78, 0.96)	0.83 (0.67, 0.98)

Note: 1. The LSM values were not collected in the REALM cohort and the two Gilead CHB cohorts, so LSM-HCC and mREACH-B scores were not calculated for the patients in these cohorts. 2. All the hepatocellular carcinoma risk scores were not calculated in the European PAGE-B cohort, except for aMAP and PAGE-B scores.
CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; LSM, Liver stiffness measurement.

(aMAP score >60) should undergo intensive surveillance to detect early HCC. We believe that a surveillance strategy based on the aMAP risk score could direct limited resources to the right population, thereby significantly reducing the healthcare burden in each country.

Cirrhosis and LSM values are well-known risk factors for HCC, as confirmed in our study. However, the diagnosis of cirrhosis in clinical practice is subject to substantial inter- and intra-observer variations, especially for cirrhosis at an early stage, and the LSM value is not easily accessible in most primary care settings. According to our results, the addition of the cirrhosis or LSM value did not substantially improve the predictive power of the aMAP score. Furthermore, some variables, such as viral status and alanine aminotransferase levels, can change dramatically with the initiation or withdrawal of treatment. Therefore, although the cirrhosis, LSM values and virus-related variables were related to future HCC development, our study suggests that the aMAP score, which includes only objective clinical and laboratory parameters that are not usually affected by antiviral treatment, is more suitable for patients in the antiviral treatment era when the impact of aetiological factors is diminishing. Indeed, the aMAP score demonstrated significantly better and more stable predictive performance for HCC development compard with the other HBV-related HCC risk prediction models not only in the CHB training cohort, but also in each of the CHB independent validation cohorts, irrespective of ethnicity. The aMAP score also identified significantly more patients at low HCC risk, suggesting that more patients should be exempted from intensive HCC surveillance. Given that the aMAP score performed well irrespective of HBV DNA status, it could be applied at different stages of treatment. More importantly, this viral factor-free score also showed an excellent performance in predicting HCC risk in patients with either HCV or NVH. The different characteristics, treatment strategies and recruitment periods of each independent cohort further strengthen the reliability of our score. All the above evidence supports the finding that the aMAP score is a reliable tool that can accurately stratify HCC risk caused by HBV, HCV or NAFLD, which are the leading risk factors for HCC worldwide.

The aMAP score involves just 2 laboratory parameters, the ALBI score and platelets. The ALBI score was originally developed to predict prognosis in patients with HCC in an international setting.[19] It is a simple, evidence-based and objective index and can reflect the underlying liver function of patients at all disease stages. A growing body of studies has demonstrated that ALBI grade is also predictive of survival in patients with advanced liver disease without HCC.[23,24] In the current study, we demonstrated that ALBI score was associated with HCC development and included it in the aMAP risk score. Platelets are a well-known parameter associated with the fibrosis stage. These observations suggest that the aMAP score is an objective index reflecting both liver function and fibrosis stage. Furthermore, the components of the model imply that liver function is worthy of investigation as another, perhaps major, determinant of HCC risk. However, the total bilirubin level could be influenced by certain diseases, such as haemolysis and inherited enzyme defects. Therefore, it is recommended that the aMAP score is not suitable for predicting HCC risk among patients with non-liver diseases that could significantly affect the bilirubin level.

Despite the significant findings in this report, our study also has a few limitations. First, the patients were recruited from tertiary hospitals and were especially likely to have active

disease before treatment. It is likely that more patients would belong to the low-risk category in a primary care setting, which would further increase the NPV of the score. Second, similar to existing HCC risk scores, the PPV value of the aMAP score at a cut-off value of 60 was not optimal. We plan to combine other variables (such as LSM, circulating cell-free DNA signatures, proteins or metabolites) with the aMAP score to further improve the PPV among patients in the high-risk group. Third, the discriminatory ability of the aMAP score was suboptimal in the case of patients with cirrhosis, a situation common to existing HCC risk scores. One of the possible reasons is that the cirrhosis diagnosis might be inaccurate, especially in routine clinical practice. Fourth, most patients in this study were Asians and Caucasians with viral hepatitis. Therefore, the performance of the aMAP score in patients of other ethnicities (e.g. African) and other aetiologies (e.g. NAFLD, primary biliary cirrhosis, etc.) requires further investigation. Fifth, the laboratory data were collected at different time points across different cohorts, which might weaken the reliability of the study results. Finally, the formula for the aMAP score is relatively complex. However, the parameters included in the score are very common, and a mobile app or web-based calculator could calculate the score easily and rapidly in the current high-tech era. In the future, we could also merge the aMAP score into liver function test panels or hospital electronic systems to facilitate its implementation and guide patient management in clinical practice.

In conclusion, the aMAP score is the first risk score to facilitate accurate, reliable and simple-to-use prediction of the risk of HCC development irrespective of aetiology and ethnicity. It is entirely objective, being based on 5 routine clinical and laboratory parameters without the inclusion of viral factors. Thus, this score will be a useful tool for realising individualised HCC surveillance to improve early HCC detection and reduce mortality, ultimately helping to achieve the ambitious goals of the WHO to reduce hepatitis-related mortality by 65% by 2030.

Abbreviations

ALBI, albumin–bilirubin; aMAP, age, male, albumin-bilirubin and platelets; CHB, chronic hepatitis B virus; CU-HCC, Chinese University HCC; DAA, direct-acting antiviral agent; HCC, hepatocellular carcinoma; HR, hazard ratio; IFN, interferon; K–M, Kaplan–Meier; LSM, liver stiffness measurement; NAFLD, non-alcoholic fatty liver disease; NPV, negative predictive value, NVH, non-viral hepatitis; (m)PAGE-B, modified PAGE-B; RCT, randomised controlled trial; (m)REACH-B, (modified) Risk Estimation for HCC in Chronic Hepatitis B; ROC, receiver operating characteristic; PPV, positive predictive value, SVR, sustained virological response; TAF, tenofovir alafenamide; WHO, World Health Organization.

Conflicts of interest

GP 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. VS has served as an advisor or lecturer for Abbvie and Gilead, and has received research grants from Abbvie and Gilead. GD has served as an advisor/lecturer for Genkyotex, Ipsen, Pfizer and Novartis, and has received research grants from Abbvie and Gilead. 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. MB has served as an advisor/lecturer for Abbvie, Dicerna, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Roche and Spring Bank, and has received research grants from Abbvie and Gilead. JLC has served as a consultant and/or speaker for Abbvie, Gilead, Ipsen, and Merck Sharp & Dohme. HLAJ has served as a consultant for Arbutus, Arena, Enyo, Gilead Sciences, GlaxoSmithKline, Janssen, Medimmune, Merck, Roche, Vir Biotechnology Inc., and Viroclinics, and has received grants from AbbVie, Arbutus, Bristol Myers Squibb, Gilead Sciences, Janssen, Medimmune, Merck and Roche. PH has spoken to, or been on, advisory boards for AbbVie, BMS, Eisai Ltd, Falk, Ferring, Gilead, Gore, Janssen, Lundbeck, MSD, Norgine, Novartis, ONO Pharmaceuticals, Pfizer and Roche. WLI has received speaker and consultancy fees from Roche, Janssen Cilag, Gilead Sciences and Novartis, educational grants from Boehringer Ingelheim, Merck Sharp & Dohme, and Gilead Sciences, and research grant support from GlaxoSmithKline, Pfizer, Gilead Sciences, Janssen Cilag, Abbvie and Bristol-Myers Squibb. PL has served as advisor for Abbvie, Eiger, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck/Merck Sharp & Dohme, MYR Pharma and Roche. JH has received consulting fee from AbbVie, Arbutus, Bristol Myers Squibb, Gilead Sciences, Johnson &Johnson, and Roche and received grants from Bristol Myers Squibb and Johnson & Johnson. SM, VS, JFF, LL and AG are employees of, and own stock in, Gilead Sciences. CZ and LS are employees of Hangzhou YITU Healthcare Technology Co. Ltd. The other authors declare no conflicts of interest that pertain to this work.

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

Authors' contributions

Concept and design: JH and RF. Data collection: RF, JS, QX, JN, JL, XD, YZ, ZZ, YG, LZ, YC, XT, LW, JJ, HT, TK, SY, GP, GD, RI, TB, MB, JLC, HLAJ, PL, HI, ING, EB, STB, PCH, SJH and WLI. Data analysis: RF, VS, HI, SM, VS, JFF, LL and AG. Drafting of the manuscript: RF and JH. Statistical support: RF, CZ and LS. Critical revision of the manuscript: GP, JS, GD, RI, TB, MB, JLC, HLAJ, PL, HI, ING, EB, STB, PCH, SJH and WLI. Supervision: JH, PL and PJJ.

Acknowledgements

The authors thank the study investigators, coordinators, nurses, patients and their families for their contributions. The STOP-HCV cirrhosis cohort was funded by a grant from the Medical Research Council, UK (MR/K01532X/1 – STOP-HCV Consortium). EB was funded by the Medical Research Council UK and the Oxford NIHR Biomedical Research Centre, and is an NIHR Senior Investigator. The views expressed in this article are those of the author and not necessarily those of the NHS, the NIHR, or the Department of Health. REALM cohort data was obtained through

the Bristol-Myers Squibb (BMS) and Duke Clinical Research Institute's Supporting Open Access for Research (SOAR) data sharing program, which allows access to de-identified patient results from BMS sponsored trials that have been completed for at least 2 years.

Data availability statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.07.025.

References

Author names in bold designate shared co-first authorship

[1] WHO. Global Health Sector Strategy on Viral Hepatitis 2016-2021. Geneva: WHO; 2016.

[2] WHO. Cancer. Geneva: WHO; 2018.

[3] Llovet JM, Bruix J. Early diagnosis and treatment of hepatocellular carcinoma. Baillieres Best Pract Res Clin Gastroenterol 2000;14:991–1008.

[4] Ioannou GN, Perkins JD, Carithers Jr RL. Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. Gastroenterology 2008;134:1342–1351.

[5] Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019;380:1450–1462.

[6] Yang H-I, Yuen M-F, Chan HL-Y, Han K-H, Chen P-J, Kim D-Y, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 2011;12:568–574.

[7] **Wong VW**, **Chan SL**, Mo F, Chan TC, Loong HH, Wong GL, et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. J Clin Oncol 2010;28:1660–1665.

[8] Wong GL-H, Chan HL-Y, Wong CK-Y, Leung C, Chan CY, Ho PP-L, et al. Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. J Hepatol 2014;60:339–345.

[9] Papatheodoridis G, Dalekos G, Sypsa V, Yurdaydin C, Buti M, Goulis J, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64:800–806.

[10] Ioannou GN, Green PK, Beste LA, Mun EJ, Kerr KF, Berry K. Development of models estimating the risk of hepatocellular carcinoma after antiviral treatment for hepatitis C. J Hepatol 2018;69:1088–1098.

[11] Harris PS, Hansen RM, Gray ME, Massoud OI, McGuire BM, Shoreibah MG. Hepatocellular carcinoma surveillance: an evidence-based approach. World J Gastroenterol 2019;25:1550–1559.

[12] Ioannou GN, Green P, Kerr KF, Berry K. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. J Hepatol 2019;71:523–533.

[13] Sharma SA, Kowgier M, Hansen BE, Brouwer WP, Maan R, Wong D, et al. Toronto HCC risk index: a validated scoring system to predict 10-year risk of HCC in patients with cirrhosis. J Hepatol 2018;68:92–99.

[14] Hou JL, Zhao W, Lee C, Hann HW, Peng CY, Tanwandee T, et al. Outcomes of long-term treatment of chronic HBV infection with entecavir or other agents from a randomized trial in 24 countries. Clin Gastroenterol Hepatol 2020;18:457–467.

[15] Papatheodoridis GV, Dalekos GN, Yurdaydin C, Buti M, Goulis J, Arends P, et al. Incidence and predictors of hepatocellular carcinoma in Caucasian chronic hepatitis B patients receiving entecavir or tenofovir. J Hepatol 2015;62:363–370.

[16] Marcellin P, Wong DK, Sievert W, Buggisch P, Petersen J, Flisiak R, et al. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. Liver Int 2019;39:1868–1875.

[17] Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, et al. 96weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 2018;68:672–681.

[18] Innes H, Barclay ST, Hayes PC, Fraser A, Dillon JF, Stanley A, et al. The risk of hepatocellular carcinoma in cirrhotic patients with hepatitis C and sustained viral response: role of the treatment regimen. J Hepatol 2018;68:646–654.

[19] Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. J Clin Oncol 2015;33:550–558.

[20] Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res 2004;10:7252–7259.

[21] Nouso K, Tanaka H, Uematsu S, Shiraga K, Okamoto R, Onishi H, et al. Cost-effectiveness of the surveillance program of hepatocellular carcinoma depends on the medical circumstances. J Gastroenterol Hepatol 2008;23:437–444.

[22] Andersson KL, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2008;6:1418–1424.

[23] Hiraoka A, Kumada T, Michitaka K, Toyoda H, Tada T, Ueki H, et al. Usefulness of albumin-bilirubin grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2016;31:1031–1036.

[24] **Pinato DJ**, **Sharma R**, Allara E, Yen C, Arizumi T, Kubota K, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol 2016;66:338.