**Title**

aMAP risk score predicts hepatocellular carcinoma development in chronic hepatitis patients: an international cohort collaboration

**Running Title**

aMAP hepatocellular carcinoma risk score

**Authors**

Rong Fan1#, MD; George Papatheodoridis2#, MD; Jian Sun1#, MD; Hamish Innes3, PhD; Hidenori Toyoda4, MD; Qing Xie5, MD; Shuyuan Mo6, PhD; Vana Sypsa7, PhD; Indra Neil Guha8, PhD; Takashi Kumada9, MD; Junqi Niu10, MD; George Dalekos11, MD; Satoshi Yasuda4, MD; Eleanor Barnes12, PhD; Jianqi Lian13, MD; Vithika Suri6, MS; Ramazan Idilman14, MD; Stephen T Barclay15, MD; Xiaoguang Dou16, MD; Thomas Berg17, MD; Peter C Hayes18, PhD; John F. Flaherty6, PharmD; Yuanping Zhou1, MD; Zhengang Zhang19, MD; Maria Buti20, MD; Sharon J Hutchinson3, PhD, Yabing Guo1, MD; Jose Luis Calleja21, MD; Lanjia Lin6, PhD; Longfeng Zhao22, MD; Yongpeng Chen1, MD; Harry LA Janssen23, MD; Chaonan Zhu24, MD; Lei Shi24, MD;Xiaoping Tang25, MD; Anuj Gaggar6, MD; Lai Wei26, MD; Jidong Jia27, MD; William L Irving8, FRCPath; Philip J. Johnson28\*, MD; Pietro Lampertico29,30\*, MD; Jinlin Hou1\*, MD.

# RF, GP and JS contributed equally to this work.

**Affiliations**

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, United Kingdom;

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, United Kingdom;

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, United Kingdom;

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, United Kingdom;

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, Germany;

18 Royal Infirmary of Edinburgh, Edinburgh, United Kingdom;

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, United Kingdom;

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

**Corresponding authors**

**Jinlin Hou**

Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, 510515, China

Tel: +86 20 61641941

Fax: +86 20 62786530

Email: jlhousmu@163.com

**Pietro Lampertico**

CRC “AM e A Migliavacca” Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milano, Italy

Tel.: +39 0255035432

Fax: +39 0250320410

Email: pietro.lampertico@unimi.it

**Philip J. Johnson**

Department of Molecular and Clinical Cancer Medicine, University of Liverpool

2nd floor Sherrington Building, Ashton Street, Liverpool L69 3GE, United Kingdom

Tel: +44 121 414 3801

Fax: +44 121 414 4486

Email: Philip.Johnson@liverpool.ac.uk

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Vana Sypsa has served as advisor or lecturer for Abbvie, Gilead and has received research grants from Abbvie and Gilead.

George Dalekos has served as Advisor/Lecturer for Genkyotex, Ipsen, Pfizer, Novartis and has received research grants from Abbvie and Gilead.

Thomas Berg has served as advisor/consultant/lecturer for Abbvie, Alexion, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme/Merck, Novartis, Roche, Vertex and has received research support from Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme/Merck, Novartis and Roche.

Maria Buti has served as advisor/lecturer for Abbvie, Dicerna, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Roche, Spring Bank and has received research grants from Abbvie and Gilead.

Jose Luis Calleja has served as consultant and/or Speaker for Abbvie, Gilead, Ipsen, Merck Sharp & Dohme.

Harry LA Janssen has served as consultant for Arbutus, Arena, Enyo, Gilead Sciences, GlaxoSmithKline, Janssen, Medimmune, Merck, Roche, Vir Biotechnology Inc., Viroclinics and has received grants from: AbbVie, Arbutus, Bristol Myers Squibb, Gilead Sciences, Janssen, Medimmune, Merck, Roche.

Peter Hayes has spoken or been on advisory boards for AbbVie, BMS, Eisai Ltd, Falk, Ferring, Gilead, Gore, Janssen, Lundbeck, MSD, Norgine, Novartis, ONO Pharmaceuticals, Pfizer and Roche.

William L Irving has received speaker and consultancy fees from Roche, Janssen Cilag, Gilead Sciences and Novartis, educational grants from Boehringer Ingelheim, Merck Sharp and Dohme and Gilead Sciences, and research grant support from GlaxoSmithKline, Pfizer, Gilead Sciences, Janssen Cilag, Abbvie and Bristol-Myers Squibb.

Pietro Lampertico has served as advisor for Abbvie, Eiger, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck/ Merck Sharp & Dohme, MYR Pharma, Roche.

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Shuyuan Mo, Vithika Suri, John F. Flaherty, Lanjia Lin and Anuj Gaggar are employees of and own stock in Gilead Sciences.

Chaonan Zhu and Lei Shi are employees of Hangzhou YITU Healthcare Technology Co., Ltd.

The other authors declare no conflicts of interest that pertain to this work.

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**Author’s Contribution**

Concept and design: Jinlin Hou, Rong Fan

Data collection: Rong Fan, Jian Sun, Qing Xie, Junqi Niu, Jianqi Lian, Xiaoguang Dou, Yuanping Zhou, Zhengang Zhang, Yabin Guo, Longfeng Zhao, Yongpeng Chen, Xiaoping Tang, Lai Wei, Jidong Jia, Hidenori Toyoda, Takashi Kumada, Satoshi Yasuda, George Papatheodoridis, George Dalekos, Ramazan Idilman, Thomas Berg, Maria Buti, Jose Luis Calleja, Harry LA Janssen, Pietro Lampertico, Hamish Innes, Indra Neil Guha, Eleanor Barnes, Stephen T Barclay, Peter C Hayes, Sharon J Hutchinson, William L Irving.

Data analysis: Rong Fan, Vana Sypsa, Hamish Innes, Shuyuan Mo, Vithika Suri, John F. Flaherty, Lanjia Lin, Anuj Gaggar.

Drafting of the manuscript: Rong Fan, Jinlin Hou.

Statistical support: Chaonan Zhu, Lei Shi.

Critical revision of the manuscript: George Papatheodoridis, Jian Sun, George Dalekos, Ramazan Idilman, Thomas Berg, Maria Buti, Jose Luis Calleja, Harry LA Janssen, Pietro Lampertico, Hamish Innes, Indra Neil Guha, Eleanor Barnes, Stephen T Barclay, Peter C Hayes, Sharon J Hutchinson, William L Irving.

Supervision: Jinlin Hou, Pietro Lampertico, Philip J. Johnson.

**Abstract**

**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 chronic hepatitis patients.

**Methods**

A total of 17,374 patients, comprising 10,578 treated Asian chronic hepatitis B (CHB) patients, 2510 treated Caucasian CHB patients, 3566 treated hepatitis C virus (HCV)-infected patients (including 2489 patients with cirrhosis achieving a sustained virologic response) and 720 non-viral hepatitis (NVH) patients from 11 international prospective observational cohorts or randomized controlled trials, were divided into a training cohort (3688 Asian CHB patients) 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=7413, 43.6%), medium- (N=6529, 38.4%), and high-risk (N =3044, 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 five common parameters accurately predicts HCC development, regardless of aetiology and ethnicity, which may 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) could satisfactorily predict the risk of HCC development among over 17 thousand 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](#_ENREF_1)]. In the era of 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](#_ENREF_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. HCC patients diagnosed at an early stage have 5-year survival rates of 70 - 75% [[3](#_ENREF_3), [4](#_ENREF_4)], whereas the average survival time of patients with advanced HCC is less than 1 year [[5](#_ENREF_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 individualize HCC surveillance.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the leading causes of HCC development. Over the past few decades, a number of HCC risk scores have been developed and validated to stratify the risk of HCC development [[6-13](#_ENREF_6)]. 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 randomized controlled trials involving patients with chronic hepatitis B (CHB; N =7), chronic HCV infection (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 CHB patients 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 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 CHB patients 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 entecavir or an investigator-selected non-entecavir HBV nucleos(t)ide analogue and followed for up to 10 years [[14](#_ENREF_14)]. The analysis included the data from entecavir-treated patients from 50 centres in 16 provinces in China.

***European PAGE-B cohort***

This cohort study included adult CHB patients followed in 10 European centres who had started entecavir or tenofovir between January 2004 and December 2012 and had completed at least 12 months of therapy, as has been previously described [[15](#_ENREF_15)]. The data included in the analysis were as of May 2019.

***Four global Gilead CHB RCTs***

Adult CHB patients from the 4 global RCTs sponsored by Gilead Pharmacy (NCT00117676, NCT00116805, NCT01940341, NCT01940471) were recruited from May 2005 to June 2006 (the first two trials) and from September 2013 to October 2014 (the last two trials). The patients in the first two trials were randomized to receive double-blind tenofovir or adefovir for 1 year before starting tenofovir open-label treatment for up to 9 years. The patients in the last two trials were randomized to receive double-blind tenofovir or tenofovir alafenamide (TAF) for up to 3 years before starting TAF open-label treatment until year 8 [[16](#_ENREF_16), [17](#_ENREF_17)]. The analysis was performed based on the anonymized data including Asian and Caucasian patients who met the anonymization criteria to protect patient privacy.

In the above seven CHB cohorts/trials, patients with decompensated cirrhosis, HCC; liver transplantation; or coinfection(s) with hepatitis D, hepatitis C or human immunodeficiency virus were excluded. The laboratory results collected at enrolment were used for the analysis.

**HCV-infected patients**

***Japanese HCV cohort***

HCV-infected adult patients were enrolled from one centre in Japan between 1998 and 2016. Adult patients who received 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.

***United Kingdom (UK) HCV sustained virologic response (SVR) cirrhotic cohort***

This cohort was assembled by combining HCV SVR cirrhotic patients (88.5% Caucasians) from two UK studies: 1) A previously described cohort of HCV cirrhotic patients from Scotland, achieving an SVR between 1997 and 2016 [[18](#_ENREF_18)], and 2) English participants of the STOP-HCV cirrhosis study who have achieved an SVR. The STOP-HCV cirrhosis study comprises 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 prior to 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 cirrhotic participants (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 (that is after completing antiviral treatment) were used for the analysis.

**NVH patients**

The origin of the cohort was the same as that of the Japanese HCV cohort. The great majority 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 diagnosis 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 (ALBI) score calculation**

The 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: ALBI score = (log10 bilirubin × 0.66) + (albumin × -0.085), where bilirubin is in μmol/L and albumin in g/L [[19](#_ENREF_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 diagnosed with 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 Search-B cohort, the other HBV, HCV and NVH cohorts/trials were used for the external validation of the scoring system. 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 model. 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 two optimal cut-off values with the highest χ2 value to separate patients into low-, medium-, and high-risk groups [[20](#_ENREF_20)]. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also estimated for the two optimal cut-offs of the risk model. For more information regarding the development of the HCC risk score, please see the supplementary material.

The study 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 CHB patients, 2510 Caucasian CHB patients, 3566 HCV-infected patients, and 720 NVH patients, 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 Supplementary Table 1 shows the clinical and laboratory data of each cohort. Other than the two HCV SVR cirrhotic cohorts, the percentages of cirrhotic patients in the other cohorts ranged from 11.4% to 27.4%.

**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 (Supplementary Figure 1A). 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 than those with ALBI ≥ -3 (5-year cumulative incidences of HCC: 2.0% vs. 6.5%, p <0.0001) (Supplementary Figure 2).

**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 standardized to 1-100:

aMAP Risk Score = ((0.06 × age + 0.89 × sex (Male: 1, Female: 0) + 0.48 × ((log10 bilirubin × 0.66) + (albumin × -0.085)) -0.01 × platelets) +7.4) /14.77 × 100, where age is in year, bilirubin in μmol/L, albumin in g/L and platelets in 103/mm3. The 5-year baseline survival function of aMAP Risk Score .

The c-index of the aMAP score was 0.82 (95% Confidence Interval [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 (Supplementary Figure 3).

**HCC risk stratification based on the aMAP score**

The X-tile plots were used to generate two optimal cut-off values (50 and 60) to separate the training cohort into low-, medium- and high-risk groups (Supplementary Figure 4). Supplementary Figure 5 also showed that the HCC risk increased significantly when the aMAP score were 50 and 60. Of the 3662 patients with evaluable aMAP risk scores, 2158 (58.9%), 1181 (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%; 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) (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 was 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% (Supplementary Figure 1B-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 cirrhotic patients, 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, 5255 (39.4%), 5348 (40.1%) and 2721 (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 three 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 six existing HBV-related HCC risk scores, including the REACH-B, CU-HCC, LSM-HCC, mREACH-B, PAGE-B, and mPAGE-B scores, were each calculated on the basis of the clinical and laboratory parameters collected (Supplementary Table 2). In the training cohort, the c-index of 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]; P =0.049 [vs. mPAGE-B]) (Table 5). The time-dependent AUC curve analyses showed that aMAP score obtained the highest AUCs in dynamic trends among all risk scores within 5 years (Supplementary Figure 6). Compared to mPAGE-B score which had the second highest c-index value, the aMAP score could identify significantly higher percentage of low HCC risk patients (58.9% vs. 53.3%, P <0.001) (Supplementary Figure 7). Moreover, compared to the other six 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 Supplementary Table 3).

**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 thousand 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. To our knowledge, this study is the first to assess the performance of an HCC risk score among patients with differing aetiologies and ethnicities as well as the first-ever data on an HCC risk score from mainland China.

In recent decades, the health care costs of chronic disease have increased yearly. Promoting early screening and developing individualized 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](#_ENREF_21), [22](#_ENREF_22)]. By using the aMAP score, we identified a group of low-risk patients (aMAP score <50) who accounted for approximately 45% of the overall population with an HCC probability of less than 0.2% per year, meaning that approximately half of patients with chronic hepatitis could undergo less intensive HCC surveillance. In contrast, patients who are classified in the high-risk group (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-observer 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 does 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 the 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, would be more suitable for patients in the antiviral treatment era when the impact of etiologic factors is diminishing. Indeed, the aMAP score demonstrated significantly better and more stable predictive performance for HCC development than 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 could also identify significantly more patients at low HCC risk, suggesting that more patients could be exempted from intensive HCC surveillance. Since 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 HCV-infected patients and in patients with 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 two 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](#_ENREF_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 had demonstrated that ALBI grade is also predictive of survival in patients with advanced liver disease without HCC [[23](#_ENREF_23), [24](#_ENREF_24)]. In the current study, we demonstrated that ALBI score was associated with HCC development and included it in the aMAP risk score. Platelets is 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 model’s components imply that liver function is worthy of investigation as another, perhaps major, determinant of HCC risk. However, it should be mentioned that the total bilirubin level could be influenced by certain diseases, such as hemolysis and inherited enzyme defects. Therefore, it is recommended that the aMAP score is not suitable for predicting HCC risk amongst patients who suffer from 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 liver stiffness measurements, 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 cirrhotic patients, a situation common to existing HCC risk scores. One of the possible reasons is that the cirrhosis diagnosis may 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) still needs further investigation. 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 continuous 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 five routine clinical and laboratory parameters without the inclusion of viral factors. This score will be a useful tool for realizing individualized HCC surveillance to improve early HCC detection and reduce mortality, ultimately helping to achieve WHO's ambitious goals by 2030.

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**Figure legends**

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

**Figure 2. Calibration curves of the aMAP score to predict hepatocellular carcinoma in each cohort.** (A) Search-B training cohort, (B) Search-B validation cohort, (C) REALM cohort, (D) Gilead Asian CHB cohort, (E) European PAGE-B cohort, (F) Gilead Caucasian CHB cohort, (G) Japanese HCV cohort, (H) UK SVR cirrhotic cohort, (I) Gilead SVR cirrhotic cohort, and (J) NVH cohort. CHB: chronic hepatitis B; HCV: hepatitis C virus; NVH: non-viral hepatitis; SVR: sustained virologic response.

**Tables**

**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 | 3688 |  | 2847 | 2548 | 1495 |  | 1938 | 572 |  | | 1077 | | 1230 | | 1259 | 720 |
| Male, n (%) | 2977  (80.7) |  | 2071  (72.7) | 2061  (80.9) | 977  (65.4) |  | 1369  (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) | 167/1466  (11.4) |  | 518/1892 (27.4) | 98/558  (17.6) |  | | 195  (18.1) | | 1230  (100) | | 1259  (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 |  | | NA | | 74 | | 23 | NA |
| IQR | 20, 43 |  | 18, 38 | 42, 139 | 56, 135 |  | 24, 88 | 69, 169 |  | | NA | | 48, 120 | | 17, 31 | NA |
| Total No. with data | 3670 |  | 2794 | 2547 | 1495 |  | 1830 | 572 |  | | NA | | 1230 | | 1259 | NA |
| Albumin, g/L |  |  |  |  |  |  |  |  |  | |  | |  | |  |  |
| Median | 45 |  | 46 | 47 | 43 |  | 44 | 43 |  | | NA | | 39 | | 44 | NA |
| IQR | 43, 47 |  | 43, 48 | 44, 49 | 41, 45 |  | 40, 46 | 40, 45 |  | | NA | | 35, 42 | | 41, 46 | NA |
| Total No. with data | 3670 |  | 2793 | 2547 | 1495 |  | 1797 | 572 |  | | NA | | 1230 | | 1259 | NA |
| Total bilirubin, μmol/L |  |  |  |  |  |  |  |  |  | |  | |  | |  |  |
| Median | 12.2 |  | 14.9 | 14.2 | 10.3 |  | 12.0 | 10.3 |  | | NA | | 13.0 | | 10.3 | NA |
| 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 |  | | NA | | 9.0, 19.0 | | 6.8, 17.1 | NA |
| Total No. with data | 3671 |  | 2790 | 2546 | 1495 |  | 1821 | 572 |  | | NA | | 1230 | | 1259 | NA |
| 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 | NA | NA |  | NA | NA |  | | NA | | NA | | 14.1 | NA |
| IQR | 5.5, 11.1 |  | 5.2, 12.0 | NA | NA |  | NA | NA |  | | NA | | NA | | 9.4, 21.3 | NA |
| Total No. with data | 3598 |  | 2451 | NA | NA |  | NA | NA |  | | NA | | NA | | 1063 | NA |
| 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 Supplementary Table 1.

ALBI: albumin-bilirubin; ALT: alanine aminotransferase; CHB: chronic hepatitis B; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; IQR: interquartile range; LSM: Liver stiffness measurement; NA: not applicable or not available; NVH: non-viral hepatitis; SVR: sustained virologic response; UK: United Kingdom;.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **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 log10 IU/mL | 0.917 | 0.812, 1.036 | 0.168 |  |  |  |  |  |
| HBeAg (Positive vs. Negative) | 0.382 | 0.226, 0.645 | <0.001 |  |  |  |  |  |
| HBsAg, per log10 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 103/mm3 | 0.983 | 0.980, 0.987 | <0.0001 |  | -0.012 | 0.988 | 0.985, 0.992 | <0.0001 |

**Table 2.** Cox regression analysis in the training cohort.

ALBI: albumin-bilirubin; ALT: alanine aminotransferase; CI: confidence interval; HBeAg: Hepatitis B e antigen; HBsAg: hepatitis B surface antigen; LSM: liver stiffness measurement.

**Table 3.** C-index (95% confidence interval) 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 cirrhosis SVR cohort | Gilead cirrhosis SVR 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; HCV: hepatitis C virus; NVH: non-viral hepatitis; UK: United Kingdom; SVR: sustained virologic response.

**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; CI: confidence interval; HCV: hepatitis C virus; NPV: Negative predictive value; NVH: non-viral hepatitis; PPV: Positive predictive value; SVR: sustained virologic response; UK: United Kingdom. | | | | | | | | | | | | | | | |

**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 liver stiffness measurement (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.

**Figures**

**Figure 1 (A and B)**



**Figure 2 (A, B, C)**

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**Supplementary Figures**

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