Received: 31 December 2020 | Accepted: 25 January 2021

DOI: 10.1002/ygh2.443

GastroHep WILEY

Assessing efficacy of hepatocellular carcinoma prediction scores to prioritise hepatitis B surveillance in the COVID-19 era

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Funding information
No funding bodies contributed to the development of this article.

Abstract

Objective: An estimated 250 million people worldwide are chronically infected with hepatitis B virus (HBV), the leading cause of hepatocellular carcinoma (HCC) globally. The novel *Sars-cov2* virus continues to spread at an alarming rate, and with guidance at the onset of the pandemic recommending the deferral of HCC surveillance, the implications on liver cancer care are now emerging and highlight the urgent need for reorganisation of services.

Methods: We analysed how five HCC risk prediction scores could aid stratification of patients with chronic HBV. We calculated scores using parameters measured from 3 years prior (where available, n = 17) and at the time of HCC diagnosis in all adult patients with chronic HBV diagnosed with HCC (n = 46), and controls (n = 100). We compared the number of patients requiring cancer surveillance according to each score and regional surveillance guidance.

Results: The aMAP score had the highest discriminatory performance in HCC risk prediction at 3 years (area under receiver-operating characteristic curve (auROC) of 0.824), followed by the mREACH B score (auROC of 0.719), and mPAGE B score (auROC of 0.742). However, only the mREACH B score had a negative predictive value (NPV) >99%. Applying the mREACH B score to our HBV cohort identified 11 patients requiring HCC surveillance, compared with 62 under current guidelines.

Conclusion: The use of HCC risk prediction scores could streamline the surveillance of patients with chronic HBV at a time of extremely limited resources. Overall, the mREACH B score had both a strong discriminatory performance and a high NPV, thus safely identifying low risk patients not requiring surveillance.

Abbreviations: AFP, alpha fetoprotein; aMAP, age-Male-Albumin-bilirubin-Platelets; auROC, area under receiver-operating characteristic curve; BMI, body mass index; GAG HCC, guide with age, gender, HBV DNA, core promotor mutations and cirrhosis; HBV, hepatitis B; HCC, hepatocellular carcinoma; IQR, inter-quartile range; mPAGE B, modified platelets, age, gender; mREACH B, modified risk estimation for hepatocellular carcinoma in chronic hepatitis B; REACH B, Risk estimation for hepatocellular carcinoma in chronic Hepatitis B; SD, standard deviation.

1 | INTRODUCTION

An estimated 250 million people worldwide are chronically infected with hepatitis B virus (HBV), the leading cause of hepatocellular carcinoma (HCC) globally.[1] HCC is now the third commonest cause of cancer-related deaths and UK-wide incidence rates are projected to rise by 38% by the year 2035.[2] Nine months since the first reports of the novel Sars-cov2 virus in China,[3] and 6 months after the imposition of the UK-wide lockdown, the virus has had an unprecedented impact on healthcare services. The pandemic has seen dramatic reductions in early cancer referrals, delayed treatment and the suspension of cancer surveillance programmes.[4] Guidance at the onset of the pandemic recommended the deferral of HCC surveillance to protect the most vulnerable patients, however, the implications on liver cancer care are now emerging and the need for reorganisation of services is becoming urgent.[5]

HBV is a partially double stranded DNA virus that exclusively infects hepatocytes. Increased cancer risk is the result of HBV DNA integration into the nuclei of infected cells, which leads to the promotion of hepatocyte clonal expansion. Importantly this process has been found to occur in all phases of chronic infection in those exposed to the virus perinatally or in childhood, regardless of severity of inflammation or liver fibrosis.[6] As HBV uses covalently closed circular DNA (cccDNA) in the nuclei of hepatocytes as a template for replication, it is unlikely that current or future therapies will eradicate all traces of the virus, and thus the risk for HCC occurrence remains in all patients with chronic HBV.

This risk is greatly increased in those with liver cirrhosis and indeed guidelines concur that this population should undergo HCC surveillance, by means of ultrasound scans and alpha fetoprotein (AFP) measurements, every 6 months. Guidelines are discordant, however, on the utility of viral and patient factors. Viral factors independently associated with increased HCC risk include HBV genotype[7] and hepatitis B E antigen.[8] Patient factors include male gender, age, alcohol excess, aflatoxin exposure, viral co-infection and metabolic syndrome.[9]

In the last decade, several HCC risk prediction scores have been developed, taking patient and viral factors into account, while more recent scores place more emphasis on liver fibrosis measurements. In the present study, we analysed how five HCC risk prediction scores could aid stratification of patients with HBV attending the East of England Hepatitis B Regional Service at Addenbrookes Hospital, Cambridge University Hospitals NHS Trust UK, to safely identify those at high risk of HCC who require surveillance and those at low risk, in whom surveillance might be unnecessary. Furthermore, we investigated how these scores compare to regional surveillance guidelines, to rationalise services that have been strained during this pandemic.

2 | METHODS AND MATERIALS

We retrospectively assessed the diagnostic performance of five validated HCC risk scores, namely: Guide with Age, Gender, HBV DNA, core promotor mutations and cirrhosis score (GAG HCC score),[10] Risk estimation for hepatocellular carcinoma in Chronic Hepatitis B (REACH B score),[11] Modified REACH B score (HBV DNA substituted for liver fibrosis measurements),[12] modified platelets, age, gender (mPAGE B score)[13] and the age-Male-ALBI-Platelets (aMAP) score.[14]

2.1 | Study subjects

The five HCC risk scores were calculated for all adult patients with chronic HBV diagnosed with HCC from 2007 to 2019 at Addenbrookes Hospital, Cambridge University Hospitals NHS Trust. One hundred consecutive patients with a diagnosis of chronic HBV but without HCC attending our outpatient clinic between March and April 2020 were selected as the control group. Two scores were calculated for each patient: one from parameters contemporaneous to the HCC diagnosis for the cancer group or the latest clinic review for the control group, and one score from parameters 3 years prior.

2.2 | Cirrhosis and HCC assessment

Chronic HBV was diagnosed in those who tested positive for hepatitis B surface antigen for ≥6 months. The diagnosis of cirrhosis was based on serum markers and radiological findings, transient liver elastography (FibroScan) or liver biopsy. The diagnosis of HCC was based on radiological findings of multiphasic computed tomography and dynamic contrast enhanced MRI. In cases where imaging was not diagnostic for HCC, liver biopsy was performed.

2.3 | HCC risk score calculation

HCC risk scores were calculated using previously published formulas.[10-14] Current local guidelines advise the surveillance of patients with chronic HBV if they are men over the age of 40 years, women over the age of 50 years, have cirrhosis or a family history of HCC.

2.4 | Statistical analysis

Analysis was performed using Prism GraphPad v.8.0 and R version 3.5.1. Normality was determined using the D'Agostino-Pearson test. Data were presented as mean ± standard deviation (±SD) if normally distributed, or median (IQR) for non-normal distribution. Two groups were compared by an unpaired t test if normally distributed, or by the Mann–Whitney U test if non-normally distributed. For multivariable analyses, logistic regression was used for binary outcomes. Receiver-operating characteristic curves were used to determine the ability of the scores to discriminate between patients with HCC from controls. Negative predictive values (NPVs) were calculated using optimal HCC risk score thresholds from validation studies to identify those at low risk of HCC. P values < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Study population

In total 46 patients with chronic HBV were diagnosed with HCC from 2007 to 2019 (Table 1). The control group comprised of 100 patients with chronic HBV without HCC. The mean age in the HCC group was 58.16 ± 12.60 years. The majority (39/46, 84.78%) of patients were male, and 24 were of Asian ethnicity (52.17%). The mean age of the control group was 46.54 ± 11.39 years, with 59 being male (59%) and 57 of Asian ethnicity (57%). There were significant differences in age, gender, liver biochemistry and viral markers

TABLE 1 Baseline characteristics of study participants using parameters at the time of HCC diagnosis and 3 years prior

	Contemporaneous parameters			Parameters 3 years prior to diagnosis		
	HCC n = 46	Controls n = 100	*P* value <0.05	HCC n = 17	Controls n = 17	*P* value <0.05
Age in years (Mean ± SD)	58.16 ± 12.60	46.54 ± 11.39	**<0.0001**	56.59 ± 11.97	55.35 ± 10.47	0.75
Gender n (%)						
M	39 (84.78%)	59 (59%)	**0.0022**	15 (88.24%)	15 (88.24%)	>0.99
F	7 (15.22%	41(41%)		2 (11.76%)	2 (11.76%)	
BMI in kg/m^2 Median (IQR)	24 (22,27)	26 (23,29)	0.12	25 (22, 27.50)	25 (23.50, 27)	0.88
Ethnicity n (%)						
Asian	24 (52.17%)	57 (57%)	0.60	8 (47.06%)	11 (64.70%)	0.65
Caucasian	16 (34.78%)	28 (28%)		7(41.18%)	3 (17.65%)	
Afro-Caribbean	6 (13.05%)	15 (15%)		2 (11.76%)	3 (17.65%)	
Mixed/other	0 (0%)	0(0%)		0(0%)	0 (0%)	
Liver disease fibrosis stage n (%)						
Cirrhosis	35 (79.55%)	6 (6.19%)		11 (64.71%)	3 (17.65%)	
Severe fibrosis	0 (0%)	2 (2.06%)		0 (0%)	0 (0%)	
Moderate fibrosis	1 (2.27%)	8 (8.25%)		1 (5.88%)	1 (5.88%)	
Mild fibrosis	7 (15.91%)	15 (15.46%)		5 (29.41%)	3 (17.65%)	
No fibrosis	1 (2.27%)	66 (68.04%)		0 (0%)	10 (58.82%)	
Child-Pugh Score (if cirrhotic, n%)						
A	23 (65.71%)	6 (100%)		6 (54.55%)	3 (100%)	
B	11 (31.43%)	0 (0%)		4(36.36%)	0 (0%)	
C	1 (2.86%)	0 (0%)		1 (9.09%)	0 (0%)	
First positive screening test n (%)						
AFP	11 (26.19%)					
Ultrasound	14 (33.33%)					
Clinical change (decompensation, biochemical change)	17 (40.48%)					
HBeAg positive n (%)	6 (14.29%)	9 (9%)	0.45	3 (17.65%)	1 (5.88%)	0.29
HBV DNA (IU/mL) Median, IQR	6500 (200, 340 000)	180 (31, 2050)	**0.0004**	6 (0, 1415)	180 (17, 117 400)	0.08
Platelets (10*9/L) Median, IQR	137.50 (89.25, 193.50)	214.50 (180.30, 270.80)	**<0.0001**	132 (66.50, 174.50)	207 (171.50, 305)	**0.0001**
Albumin (g/L) Median, IQR	35 (29.50, 40)	40 (38, 42)	**<0.0001**	38 (34, 42.50)	42 (40, 43)	**0.02**
ALT (U/L) Median, IQR	70 (46.50, 110)	28 (22.25, 38)	**<0.0001**	43 (30, 57.50)	24 (18, 31.50)	**0.001**
AFP (kU/L) Median, IQR	45.5 (4.75,493.80)	2 (1,3)	**<0.0001**	5 (3,10)	2 (1, 2)	**<0.0001**

Note: Mean ± SD presented for normally distributed data, median (IQR) for non-normally distributed data, and count (%) for categorical data. Groups were compared by unpaired t test, Mann–Whitney U test or Chi-squared test as appropriate. Bold indicates statistically significant values ($P < 0.05$).

between the HCC group and the control group, but no significant differences in ethnicity or BMI. Liver cirrhosis was present in 35 patients in the HCC group (79.55%), with 23 of those being staged as Child-Pugh score A (65.71%). In the control group, there were six patients with cirrhosis (6.19%), all of whom with Child-Pugh A stage disease.

Most cases of HCC were first identified due to a change in their clinical picture, presenting with either deteriorating liver biochemistry or decompensated liver disease (n = 17, 40.48%). HCC was identified by surveillance ultrasound scan in 14 patients (33.33%) and 11 cases were identified by an elevated AFP (26.19%). A raised AFP > 10kUl was found in 71% of patients with HCC. In four patients information pre-HCC diagnosis was incomplete.

Seventeen patients in the HCC group had data available 3 years prior to the cancer diagnosis. The mean age in this HCC subgroup was 56.59 ± 11.97 years and the majority (15) were male (88.24%). We also selected 17 patients from the control HBV group, that were matched for age, gender, BMI and ethnicity to act as a control subgroup (Table 1).

TABLE 2 Multi-level Logistic regression with all covariates (AFP categorised). *P* value is significance of the variable coefficients in the logistic regression model

Variable	Category	Log (OR)	*P* value < 0.05
Age (years)		0.065	0.321
Gender	Female	(reference)	
	Male	0.078	0.965
BMI (kg/m^2)		−0.206	0.188
Ethnicity	Caucasian	(reference)	
	Asian	0.917	0.524
	Afro-Caribbean	−3.255	0.190
Liver fibrosis[a]		1.947	**0.003**
AFP (kU/l)[b]		3.978	**0.002**
HBV DNA Log10		0.228	0.460
Platelets (10*9/L)		−0.007	0.363
Albumin (g/L)		0.039	0.814

Bold indicates statistically significant values ($P < 0.05$).

[a]Liver fibrosis is an ordinal categorical variable with categories: no fibrosis; mild fibrosis; moderate fibrosis; severe fibrosis; cirrhosis.

[b]AFP (k/UL) is an ordinal categorial variable with categories: 0; 1; 2; 3-7; >7.

3.2 | Multivariable analysis to model variables associated with the development of HCC in our cohort

A multivariable logistic regression model was applied to the whole study population to determine the variables associated with the development of HCC. When including the variables age, gender, body mass index (BMI), ethnicity, HBV DNA log, platelet count and albumin levels, a statistically significant relationship was observed between liver fibrosis ($P = 0.003$), AFP ($P = 0.002$) and HCC. As liver

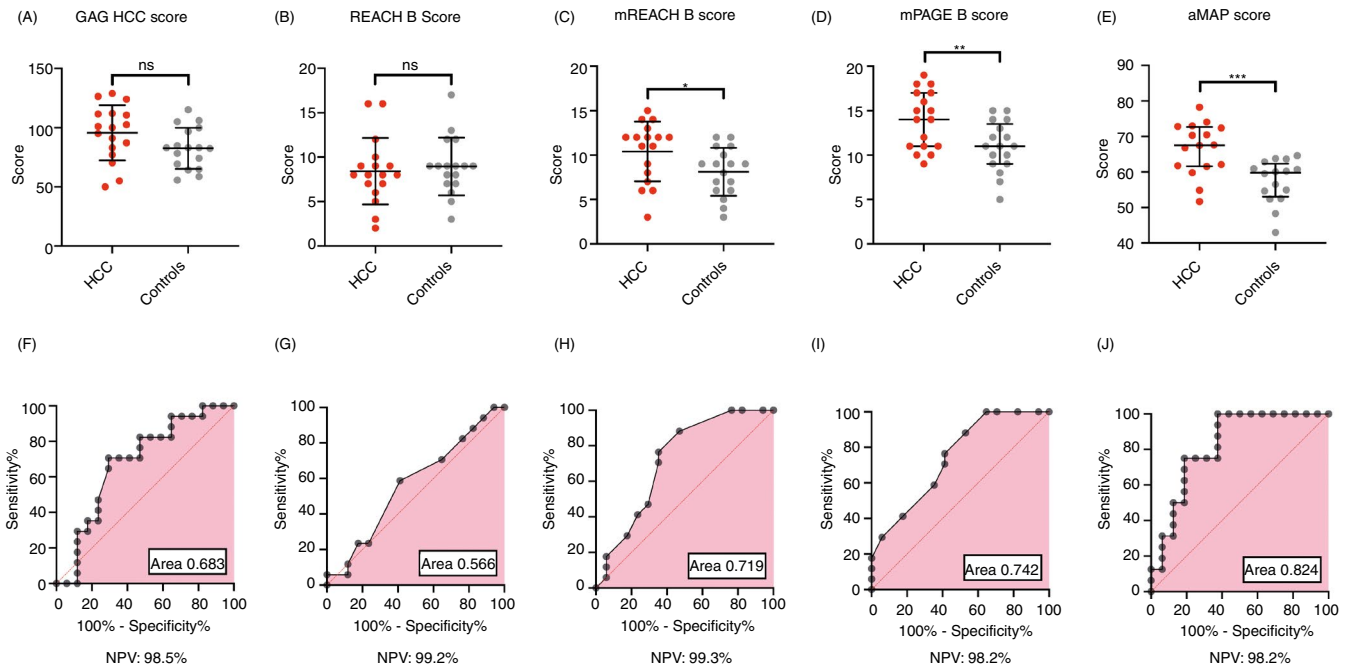

FIGURE 1 Predictive performance of HCC risk scores calculated using parameters 3 years prior to HCC diagnosis. Scatterplot of mean ± SD HCC scores in patients with HBV and HCC (n = 17, in red) and HBV controls (n = 17, in grey) calculated by the (A) GAG HCC score, (B) REACH B score, (C) mREACH B score, (D) mPAGE B score and (E) aMAP score; groups were compared by unpaired t test; ***$P = 0.0006$, **$P = 0.0071$, *$P = 0.0358$. Area under receiver-operating characteristic curve (auROC) for discriminative performance of (F) GAG HCC score, (G) REACH B score, (H) mREACH B score, (I) mPAGE B score and (J) aMAP score to differentiate diagnosis of HCC from HBV controls

fibrosis was used as an ordinal variable in our model, the risk of HCC was highest for cirrhosis than for other categories of fibrosis categories below (Table 2).

3.3 | Performance of HCC risk scores in discriminating between HCC and control group

There was a clear difference in the median scores between those with HCC and controls in all five scores (Figure S1A-E). The aMAP score had the highest discriminatory performance (area under receiver-operating characteristic curve (auROC) of 0.926) (Figure S1J), followed closely by the mREACH B (auROC of 0.893), GAG HCC (auROC of 0.894), mPAGE B (auROC of 0.867) and REACH B (auROC of 0.817) scores (Figure S1F-I). The REACH B, GAG HCC, aMAP and mREACH B scores had high NPVs (99.7%, 99.8%, 99.8%, 99.7% respectively), and thus accurately identified those without HCC.

3.4 | Performance of HCC risk scores in predicting 3-year HCC risk

Using parameters 3 years prior to HCC diagnosis to calculate each patient's HCC risk score revealed that only three scores (aMAP, mPAGE B and mREACH B) were able to significantly differentiate patients with HCC from those without (Figure 1H-J). This was reflected in the ROC curves, with the aMAP score having the highest discriminatory performance (auROC of 0.824), followed by the mPAGE B (auROC of 0.742) and mREACH B score (auROC of 0.719), whilst the performance of GAG HCC and REACH B scores was lower (auROCs of 0.683 and 0.566 respectively) (Figure 1F-G). The mREACH B was the only score with an NPV > 99%, thus demonstrating good ability to identify those at low risk for HCC at 3 years.

3.5 | Impact of HCC risk stratification on HCC surveillance

We used each score's optimal threshold derived from their respective validation studies (Table S1), to identify which patients in the HBV group required surveillance and compared how these differ to the 62 patients identified by current surveillance guidelines. Applying the scores to our control group identified significantly lower numbers of patients meeting criteria for surveillance when using the GAG HCC score (n = 16, $P < 0.0001$), the REACH B score (n = 26, $P < 0.0001$) and the mREACH B (n = 11, $P < 0.0001$). Use of the other two scores resulted in no-significant difference in those meeting criteria for surveillance compared to current guidelines (n = 59 for the mPAGE B, $P > 0.99$ and n = 72 for the aMAP score, $P = 0.754$) (Figure 2A). As mREACH B was the score with both high predictive performance and excellent NPV, we also calculated how many patients would require HCC surveillance using different cut-offs of this score. Unsurprisingly lower cut-offs resulted in more patients requiring surveillance, however, this did not affect the negative diagnostic performance of the score (Figure 2B).

4 | DISCUSSION

We demonstrate that the mREACH B, aMAP and mPAGE B scores show excellent 3-year predictive performance for the development of HCC in patients with chronic HBV. However, only the mREACH B score had an NPV > 99% to identify those at low risk of developing HCC. Applying the mREACH B score to our control HBV population and using a threshold score of <10 identified 11 patients requiring HCC surveillance, compared with 62 currently undergoing this under existing guidelines. Consequently, the use of HCC risk prediction scores could streamline the management of patients with chronic HBV, by accurately identifying those requiring surveillance, whilst also safely identifying those at low risk of HCC. These scores have the potential to significantly improve clinical effectiveness at a time of extremely limited resources.

We reviewed the ease of use of each score and whilst all were designed as bedside clinical tools, some were easier to calculate than others. The GAG HCC, REACH B, mPAGE B and aMAP scores use age and biochemical parameters that are easy to collect, however, the aMAP score uses a complex formula not easily calculated in the clinical setting. Furthermore, the mREACH B score substitutes HBV DNA levels (incorporated in the REACH B score) for fibrosis measurements, potentially raising issues with access, cost and operator variability in measurements.

The introduction of widespread anti-viral treatment has shaped the natural history of the virus. Scores developed in the era preceding anti-viral use, such as GAG HCC and REACH B, placed greater emphasis on viral factors, whereas more recent scores mPAGE, mREACH and aMAP are centred around the presence of fibrosis. Indeed, these scores demonstrated superior discriminative performance in our study population. Furthermore, in our cohort, which includes both treated and untreated patients, liver fibrosis and AFP were associated with an increased risk of developing HCC, while HBV DNA and other recognised risk factors for HCC such as BMI, were not found to be significant. This is in keeping with recent studies demonstrating that HBV DNA levels are not associated with increased incidence of HCC, especially in patients on anti-viral therapy.[15] Recent validation studies also suggest that HCC risk scores incorporating HBV DNA levels may have reduced predictive capacity.[16]

Whilst the performance of mREACH B, mPAGE B and aMAP scores remained similar when using parameters contemporaneous to the diagnosis and 3 years prior to this, the performance of the GAG HCC and REACH B score declined when using parameters 3 years prior to the cancer diagnosis. This might be due to the inclusion of inflammatory parameters (such as ALT) in the REACH B score, and the use of HBV DNA levels in both scores which are fluctuant and have previously shown to be associated with reduced predictive performance.[16]

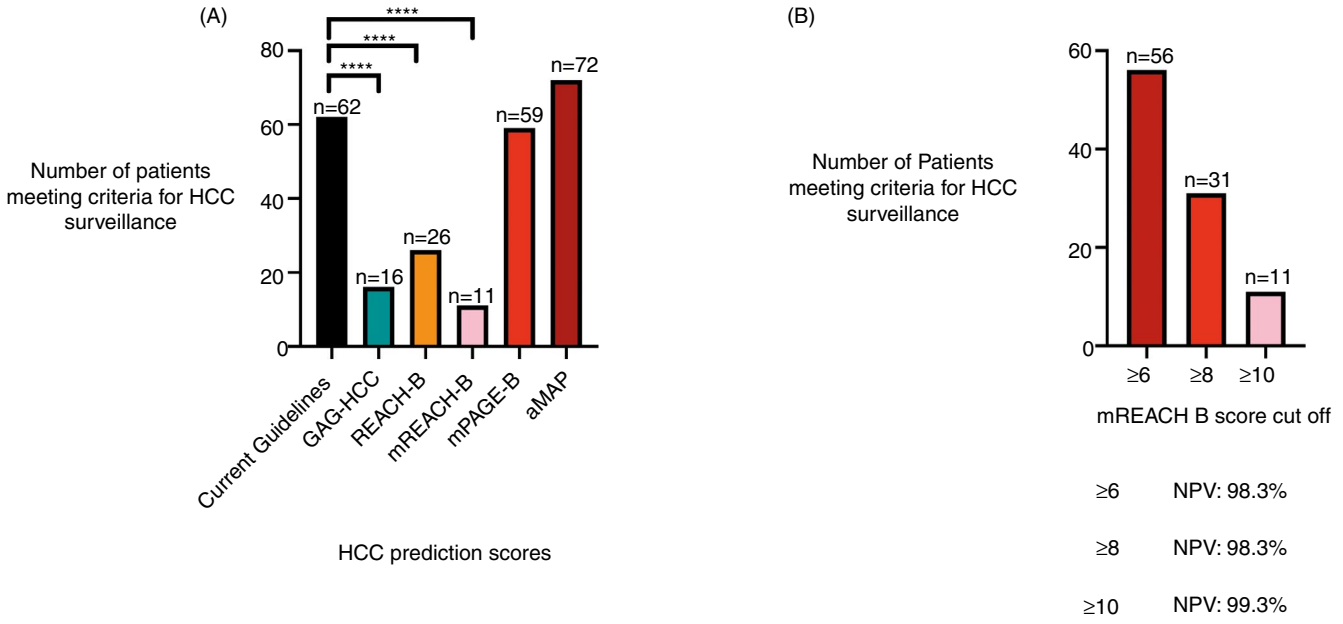

FIGURE 2 Impact of HCC risk stratification on HCC surveillance. (A) Histogram of the number of patients requiring HCC surveillance according to each HCC risk score and current local guidelines; comparison was made by Kruskal-Wallis test with multiple comparisons (where each column was compared to the first column); **** $P < 0.0001$. (B) Histogram of the number of patients requiring HCC surveillance according to the mREACH B score after using three cut-offs

Validation studies have shown variability in predictive performance, which was greatest with the REACH B score (auROCs of 0.60-0.81),[13,17-24] whereas the GAG HCC (auROCs of 0.75-0.82),[13,17-20,22,23] mREACH B (auROCs of 0.77-0.82),[20,21,25] mPAGE B (auROCs of 0.71-0.88)[24,25] and aMAP scores (0.82-0.87)[14] showed narrower performance ranges. All five HCC risk scores were internally and externally validated in Asian and Caucasian cohorts, however, none of them were specifically tested in Afro-Caribbean cohorts who have a higher risk of developing HCC, thus affecting the validity of the use of these scores in certain areas of the UK.[26] The predictive performance in patients with liver cirrhosis is suboptimal in all the scores, as patients with liver cirrhosis were often excluded in many derivation and validation studies.[11]

An effective HCC risk score requires distinct optimal cut-off scores based on cumulative risk of developing HCC while also retaining a high NPV in order to safely streamline cancer surveillance services. A GAG HCC score <82 had an NPV of 100% for 10-year risk prediction in its derivation study, however, an NPV < 99% was found in six out of seven validation studies.[13,17-20,22,23] Two out of nine validation studies of the REACH B score showed a NPV > 99% using a cut-off of 8.[13,17-24] The derivation study for the mREACH B score did not include thresholds, but a subsequent validation study identified an optimal cut-off score of <10 using the Youden Index.[20] An NPV > 99% was found in 1 of 3 subsequent validation studies.[20,21,25] Interestingly though, cumulative incidence rates of HCC in those with scores <7 were significantly lower than those with higher scores.[20] Patients with an mPAGE B score ≤8 had a 0.7% 5-year HCC risk with NPVs > 99%.[23,24] An aMAP score <50 had a 5-year cumulative risk of HCC of 0.8% and a NPV > 99%.[14]

Strengths of the study include the evaluation of the performance of each score in our specific HBV population. Indeed, regression analysis revealed that parameters associated with the development of HCC in our cohort were concordant with the best performing risk scores. Furthermore, we critically appraised the literature regarding the validation of each score, which can aid the selection of the most appropriate score in different population settings. As a result of COVID-19 there are significant delays in ultrasound scans and patients are unable or reluctant to attend appointments. Utilising these scores would give clinicians some reassurance during these delays. A second wave of COVID-19 infections is currently observed in Europe and it is our hope that this body of work will help streamline services in the near future by reducing the number of unnecessary tests.

Limitations of the study include a small retrospective study design. A large prospective study comparing the best performing scores to current practice would be of value to validate our conclusions. Using contemporaneous parameters to diagnosis of HCC to assess the performance of each score we used the scores outside their original study indications. For this reason, we utilised the scores' 3-year diagnostic performance when deciding which ones can be adopted henceforth.

In summary the mREACH B, aMAP and mPAGE B scores appear to have the strongest discriminatory performance in identifying chronic HBV patients at high risk of HCC, whilst the mREACH B score has a high NPV to identify those at low risk. Incorporating the mREACH B score in the management of patients with HBV, reduced the number requiring surveillance by more than five times. Consequently, the use of HCC risk prediction scores could have a considerable impact in the management of this patient population at a time of extremely limited resources.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. As we are reporting on routinely collected nonidentifiable clinical audit data, no approval from a research ethics committee was additionally required under the UK Policy Framework for Health and Social Care.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare. The research was conducted in the absence of any personal, professional, commercial or financial relationships that could be construed as a potential conflict of interest, and this applies to all authors.

AUTHOR CONTRIBUTIONS

RS, GM and WG designed the study, RS and AJG collected and analysed the data, RS and AJG performed the statistical analysis, RS prepared the manuscript and designed the figures and tables, RS, AJG, LR, RB, GM and WG reviewed and edited the final manuscript, WG was the project supervisor, and is the guarantor of this project. All authors have made a substantial, direct and intellectual contribution to the work and approved the manuscript prior to its submission.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/ygh2.443.

DATA AVAILABILITY STATEMENT

An anonymised dataset and data analysis code is available upon application to the corresponding author.

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SUPPORTING INFORMATION

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

How to cite this article: Sinharay R, Grant AJ, Rivett L, Blackwell R, Mells G, Gelson W. Assessing efficacy of hepatocellular carcinoma prediction scores to prioritise hepatitis B surveillance in the COVID-19 era. *GastroHep*. 2021;3:80–87. https://doi.org/10.1002/ygh2.443