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Mini review article

Current trends in the risk prediction for hepatitis B virus-related hepatocellular carcinoma

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Chronic hepatitis B related hepatocellular carcinoma (HCC) is a leading cause of cancer death in hepatitis B virus endemic areas including the Asia–Pacific region. The risk of HCC development can be reduced by antiviral therapy and surveillance programs. However, this would place a heavy fiscal burden on low- and middle-income countries, which are in these endemic areas. Therefore, there is a need for accurate prediction of HCC risk to prioritize patient care. Based on well-established host and viral risk factors, several HCC risk scores have been derived and validated: GAG-HCC, CU-HCC, and REACH-B for Asians and PAGE-B for white people of European ancestry. Each score has been shown to be accurate in predicting HCC up to 10 years into the future when applied to the appropriate patient group, especially with regards to their ethnicity and antiviral therapy status. Recently noninvasive tests of liver fibrosis have been integrated into existing HCC risk scores with encouraging results. As HCC risk prediction continues to evolve, the future promises a more individualized approach to HCC surveillance, ultimately leading to improved patient care and resource allocation.

Keywords: Albumin, antiviral therapy, cirrhosis, entecavir, transient elastography

Abbreviations
AFP = alpha fetoprotein
ALT = alanine aminotransferase
APRI = aspartate aminotransferase to platelet ratio
ASPRI = age-spleen-platelet ratio
AUROC = area under the receiver operating characteristic curve
CHB = chronic hepatitis B
ELF = Enhanced Liver Fibrosis
HBeAg = hepatitis B e antigen
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HCC = hepatocellular carcinoma
HCV = hepatitis C virus
HDV = hepatitis D virus
LSM = liver stiffness measurements
US = ultrasound scan

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and ninth most common in women globally [1]. The disease carries a high mortality rate and represents the second most frequent cause of cancer death worldwide (746,000 deaths in 2012). Chronic hepatitis B (CHB) infection is a major risk factor for HCC development and accounts for approximately 50% of cases worldwide and 70%–80% of cases in hepatitis B virus (HBV) endemic regions [2]. The majority of HCC disease burden (85%) is found in low- and middle-income countries with a high prevalence of HBV including the Asia–Pacific region [3]. This places a heavy financial burden in this area where resources for antiviral therapy, HCC surveillance, diagnosis, and treatment are limited. There is therefore a need to develop accurate risk calculators for HBV-related HCC to guide patient selection for antiviral therapy and HCC surveillance.

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Risk factors for HBV-related HCC

Patient factors

A variety of risk factors have been identified for the development of HCC, which can be divided into patient factors and viral factors (**Table 1**). Cirrhosis is the single most important risk factor for HCC

in patients with CHB even though HCC can develop in its absence. In both East Asian and Western populations, patients with CHB and cirrhosis have a more than a 5-fold increased incidence of HCC compared with CHB patients without cirrhosis [4]. As liver injury and fibrosis in patients with CHB accrues over time, the incidence of HCC also increases with age [5]. Other nonmodifiable risk factors include male sex [1] and a family history of HCC [6]. Additional liver insults from coinfection (e.g. hepatitis C, hepatitis delta) or concomitant liver disease (e.g. alcohol abuse, nonalcoholic fatty liver disease) can accelerate fibrosis progression and development of HCC [7]. Similarly, liver inflammation as evidenced either biochemically (high alanine aminotransferase) or histologically (necroinflammation) has been associated with increased risk of HCC [8].

Viral factors

Because HBV is a direct carcinogen to the liver, several viral factors augment the risk of HCC. Patients with active viral replication as demonstrated by hepatitis B e antigen (HBeAg) seropositivity [9] or high serum HBV DNA levels [10] are at increased risk of HCC compared with so-called "inactive carriers" (HBeAg negative, normal alanine aminotransferase [ALT], low level HBV DNA). The REVEAL-HBV study demonstrated a dose-response relationship between the incidence of HCC and baseline HBV DNA level with elevated HBV DNA levels ≥10,000 copies/mL (i.e. approximately 2,000 IU/mL) being a strong independent predictor of HCC [10]. Although a weaker predictor than HBV DNA, the clinical significance of quantitative hepatitis B surface antigen (HBsAg) has also become increasingly recognized. HBsAg levels can complement HBV DNA level in predicting HCC development, especially when HBV DNA <2,000 IU/mL, with high levels (≥1000 IU/mL) conferring greater risk than lower levels [11]. Patients with genotype C or certain mutations (e.g. A1762T/G1764A basal core promoter or pre-S deletion) are also contributors to HCC risk [12].

Effect of HBV treatment

Treatment of CHB with antiviral therapy has been shown to reduce, but not completely eliminate the risk of HCC [13]. While overall HCC risk scores can still be accurately applied to patients on treatment [14], some risk factors such as HBeAg status, HBV DNA, ALT, and cirrhosis may need to be refined or even omitted, because the natural history of the disease has been modified. For example, in treated patients, baseline HBV DNA is no longer a predictor of HCC, whereas failure to achieve and maintain viral suppression is associated with a higher risk of HCC [15-17].

Current recommendations on HCC surveillance

A challenge with HCC is that it can be rapidly progressive and present at an advanced stage in the absence of symptoms. Hence, there is a need to identify early tumors, which may have better prognosis and be amenable to effective treatment. However, only modest evidence supporting the efficacy of HCC surveillance in high-risk groups is found. Although observational and uncontrolled studies have demonstrated earlier detection (stage migration) and improved survival with surveillance [18, 19], they have been subject to lead-time bias and may not reflect a true reduction in cancer-specific mortality [20]. There is one large randomized controlled trial of 18,816 Chinese HBV positive patients that showed surveillance with 6-monthly ultrasound scan (US) and alpha-fetoprotein (AFP) was associated with a 37% reduction in mortality because of HCC [21]. Nonetheless, surveillance for patients at high risk of HCC is recommended in practical guidelines issued by American Association of the Study of Liver Diseases (AASLD), Asian Pacific Association for the Study of the Liver (APASL), and European Association for the Study of the Liver (EASL) (**Table 2**) [22-24].

All three key international guidelines support surveillance in cirrhotic patients, but differ on their definition of the at-risk population in noncirrhotic CHB patients. APASL acknowledges the need for further (randomized) studies in order to make recommendations in noncirrhotic patients [23]. AASLD guidelines target populations where the incidence of HCC exceeds 0.2% per year (the cut-off for cost-effectiveness in CHB) based on age, sex, ethnicity, and family history [22], while EASL recommends surveillance in HBV carriers with active hepatitis and patients with a family history of HCC [24]. All three guidelines support 6-monthly HCC surveillance with abdominal ultrasonography. The APASL recommends the addition of AFP to US for surveillance; however, this has not been adopted by EASL or AASLD because of its suboptimal performance as a serological test in this setting.

Table 1. Risk factors for HBV-related HCC

Patient factors	Viral factors
Cirrhosis	High serum HBV DNA
Older age	HBeAg seropositivity
Male	High serum HBsAg levels
Family history	Genotype C
Coinfection with HCV, HDV	Core promoter mutations
Concomitant liver disease (e.g. alcohol, fatty liver)	
High ALT	
Active necroinflammation on liver biopsy	

Table 2. Recommendations on HCC surveillance in HBV patients by liver associations

	APASL [25]	AASLD [26]	EASL-EORTC [27]
Population group	• Cirrhosis	• Cirrhosis • Males age >40 • Female age >50 • Family history of HCC • African/North American blacks	• Cirrhosis • HBV carrier with active hepatitis • Family history of HCC
Modality	US + AFP	US	US
Interval	6-monthly	6-monthly	6-monthly

US, ultrasound scan; AFP, alpha-fetoprotein; AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; EORTC, European Organisation for Research and Treatment of Cancer

HCC surveillance in resource-limited, high HBV-burden settings remains a challenge. While HCC surveillance has been demonstrated to be cost-effective in some countries (Egypt) [28], it has not in others (India) [29]. These differences reflect the variation in HCC prevalence and economic situation in each region, with greater cost-effectiveness of surveillance programs seen in countries with high prevalence [30]. Effective surveillance programs also require a means for implementing treatment for early HCC. Access to curative treatments such as liver transplantation or resection is limited, even in high-income countries. Therefore evaluation of low-cost treatment strategies including alcohol injection for small HCCs in low- and middle-income countries is a current research gap [31]. Furthermore, preventive measures that have been shown to reduce HCC incidence such as HBV vaccination [32] and antiviral therapy [13] have been hampered by poor access in developing countries with high endemicity [33].

Risk prediction for HBV-related HCC

Several published scoring systems have been developed to predict the risk of HCC in patients with CHB (**Table 3**). The development of all HCC risk scores follows a similar methodology. First, a collection of independent factors associated with HCC is derived from a (training) cohort of patients with CHB through multivariable analysis by Cox proportional hazards regression. The relative weighting assigned to each risk factor in the final score is determined by its regression coefficient. A scoring system is then formulated and must be validated with an independent (validation) cohort [5]. If an external validation cohort is not available then a leave-one-out cross validation is performed [34].

Risk scores for untreated patients

The three commonly applied HCC risk scores were derived from data on prospective Asian cohorts primarily untreated with antiviral therapy.

Table 3. Published risk scoring systems for HBV-related HCC

	GAG-HCC [52]		**CU-HCC [53]**		**REACH-B [54]**		**PAGE-B [55]**	
Patients (n)	820		1,005		3,584		1,325	
Training cohort (TC)	Chinese		Chinese		Chinese		Europeans	
Patients (n)	Leave one out cross validation		424		1505		490	
Validation cohort (VC)			Chinese		Chinese and Koreans		Italians	
Age (years)	40.6		48.0		45.7		52	
Antiviral therapy (%)	0		TC: 15.1		TC: 0		TC: 100	
			VC: 25		VC: 0		VC: 100	
Cirrhosis (%)	15.1		TC: 38.1		TC: 0.0		TC: 20.3	
			VC: 16.3		VC: 18.4		VC: 47.8	
Follow-up (years)	6.4		9.9		12.0		4.2	
HCC (n, %)	40 (4.9)		TC: 105 (10.4)		TC: 131 (3.7)		TC: 51 (3.8)	
			VC: 45 (10.6)		VC: 111 (7.4)		VC: 34 (6.9)	
Score	**Variable**	**Points**	**Variable**	**Points**	**Variable**	**Points**	**Variable**	**Points**
	Age	1 per year	Age >50 years	3	Age	1 per 5 years over 30	Age 16–29	0
	Male	16 (14*)	Albumin ≤3.5g/dL	20			30–39	2
	Cirrhosis	30 (33*)	Bilirubin >1.1mg/dL	1.5	Male	2	40–49	4
	HBV DNA	3 (3*) per log	Cirrhosis	15	ALT (U/L) 15–44	1	50–59	6
	BCP Mutation	19	HBV DNA		≥45	2	60–69	8
			4–6 log	1	HBeAg positive	2	≥70	10
			6 log	4	HBV DNA		Male	6
					<4 log	0	Platelets (/mm^3)	
					4– <5 log	3	≥200,000	0
					5– <6 log	5	100,000–199,999	6
					≥6 log	4	<100,000	9
Optimum cut-offs	**With inclusion of BCP Mutation:**		Low risk <5		17- point risk score		Low risk <10	
	Low risk <101		Intermediate risk 5–20				Intermediate 10–17	
	High risk ≥101		High risk >20				High risk ≥18	
	Without inclusion of BCP mutation:							
	5-year prediction							
	Low risk <100							
	High risk ≥101							
	10-year prediction							
	Low risk <82							
	High risk ≥82							

Table 3. Published risk scoring systems for HBV-related HCC (Cont)

	GAG-HCC [52]	CU-HCC [53]	REACH-B [54]	PAGE-B [55]
Performance	**Using a cut-off of 101:** *5-year prediction* AUROC 0.88 Sensitivity 87.9% Specificity 76.2% PPV 14.6% NPV 99.3% *10-year prediction* AUROC 0.89 Sensitivity 100% Specificity 79.1% PPV 25.7% NPV 100%	**Using a cut-off of 5:** *5-year prediction* AUROC 0.76 Sensitivity 78.3% Specificity 72.8% PPV 14.2% NPV 98.3% *10-year prediction* AUROC 0.78 Sensitivity 81.0% Specificity 75.7% PPV 26.8% NPV 97.3%	AUROC: 3 years 0.811 5 years 0.796 10 years 0.769	**Using cut-off of 10:** Harrell's c-index 0.82 *5-year prediction* Sensitivity 100% Specificity 19.6% PPV 10.3% NPV 100%

*Simplified GAG-HCC score without core promoter mutation. HBV DNA measured in $\log_{10}$ copies/mL.

GAG-HCC, Guide with age, gender; HBV DNA, Core promoter mutations and Cirrhosis-Hepatocellular Carcinoma; CU-HCC, Chinese University-Hepatocellular Carcinoma; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; TC, training cohort; VC, validation cohort; BCP, basal core promoter; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; AUROC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value

Guide with age, sex, HBV DNA, core promoter mutations and cirrhosis (GAG-HCC)

The GAG-HCC was one of the first published HCC risk scores in CHB [34]. It was derived from 820 untreated Chinese patients. Only 15% of the training population had cirrhosis as judged by aspartate aminotransferase to platelet ratio (APRI), ultrasound and hypoalbuminemia. As there was no external validation cohort, the leave-one-out statistical analysis was applied to validate the score. The five independent predictors of HCC which contributed to the GAG-HCC were sex, age, HBV DNA, the presence of core promoter mutations and cirrhosis. Because core promoter mutations are not typically tested in clinical practice, a reformulated score suggested a similar predictive capability without the core promoter mutation component. The score had a good area under the receiver operating characteristic curve (AUROC) of 0.88 and 0.89 for 5- and 10-year prediction of HCC development. The optimal cut-off found (for the 5-variable score) was 101 which gave the best sensitivity, specificity, and negative predictive values at 5 years (84.1%, 76.2% and 98.3%, respectively) and 10 years (88%, 78.7% and 100%, respectively). The chance of development of HCC increased exponentially once the score was ≥101.

Chinese University-HCC (CU-HCC)

The CU-HCC score evaluated 1,005 Chinese patients with CHB and 38% having cirrhosis as defined by ultrasound (small nodular liver with coarse echotexture or evidence of portal hypertension) [35]. There was a high rate of HCC in the study (10% of subjects in both training and validation cohorts). Five independent factors were found to predict HCC development: age, albumin, bilirubin, HBV DNA, and cirrhosis. These were then used to construct a score ranging from 0 to 44.5. Validation was performed on an independent cohort of 424 Chinese patients with CHB. While all patients were treatment na ve at baseline, 15.1% and 25% of patients from the training and validation cohorts subsequently received antiviral therapy during the median 10-year follow up. The authors proposed two cut-offs scores of 5 and 20 to stratify patients into low- (<5), medium- (5–20) and high-risk (>20) groups, which corresponded to 5-year HCC-free survival rates of 98.3%, 90.5% and 78.9%, respectively in the validation cohort.

Risk Estimation for HCC in CHB (REACH-B)

The large Taiwanese REVEAL-HBV [10] community-based cohort of 3,584 CHB patients was used as the training cohort to develop the REACH-B score [5]. Patients were treatment na ve for the duration of the study and none had cirrhosis at baseline (based on APRI, ultrasound and hypoalbuminemia). The score was validated on 1,505 Asian hospital-based patients with CHB in Hong Kong and South Korea of which 18.4% had cirrhosis. Variables included in the 17-point risk score were sex, age, serum alanine aminotransferase concentration, HBeAg status, and serum HBV DNA level. No cut-off scores were offered by the authors, but rather the REACH-B was left as a continuum of increasing cumulative risk from 0 points to 17 points to predict 3-, 5-, and 10 year HCC risk. The risks varied from 0–23.6% at 3 years, 0–47.4% at 5 years and 0–81.6% at 10 years. The score was designed for a community noncirrhotic population and indeed became more accurate (with higher AUROCs) when applied to the validation cohort after the exclusion of patients with cirrhosis.

Risk scores for treated patients

PAGE-B

Although the above HCC risk scores are versatile and have been successfully applied to patients receiving entecavir [14], their performance in CHB patients with European ancestry is poor to modest [36, 37]. This prompted Papatheodoridis et al. to develop PAGE-B, a HCC risk score for CHB patients with European ancestry treated with entecavir or tenofovir [15]. The score was derived from 1,325 patients across 8 European centers (Greece, Spain, Netherlands, and Turkey) who had received ≥12 months of entecavir or tenofovir. A fifth of patients in the training cohort had cirrhosis. The score was then externally validated on 490 patients from a ninth European center in Italy. The elements in the PAGE-B score were age, sex, and platelet count with a composite score ranging from 0 to 25. Interestingly, the addition of cirrhosis to the score did not improve its predictability. Patients with PAGE-B ≤9, 10–17, 18 had 5-year cumulative HCC incidence rates of 0%, 4%, and 16% in the validation dataset, respectively. A cut-off of >10 yielded an excellent negative predictive value of 100% (sensitivity 100%, specificity 19.6%), which could be used to identify a low-risk group who may safely avoid HCC surveillance.

Impact of ethnicity

The GAG-HCC, CU-HCC, and REACH-B scores were developed using Asian (mainly Chinese) populations. These scores have been tested on two large western multi-center CHB cohorts on treatment with entecavir or tenofovir and their predictability for HCC was demonstrated to be poor [36, 37]. It is difficult to know the magnitude of contributions from ethnicity versus the disease modifying effect of antiviral therapy to account for this difference in performance; however, as mentioned, the accuracy of these scores were not greatly affected by antiviral therapy alone [14]. Abu-Amara et al. in a cohort of 2,105 North American CHB patients (including 300 white patients with European ancestry and 114 black patients) found good predictability of GAG-HCC, CU-HCC, and REACH-B scores in non-Asians (AUROCs 0.77–0.91) [38]. However there were only 16 non-Asian patients with HCC in the study. Therefore, these studies and the development of the PAGE-B score [15] suggest that Asian HCC risk scores cannot be directly applied to people of other ethnicities.

There may be several reasons for this impact of ethnicity on HCC risk scores. Firstly, the mode of transmission of HBV varies geographically. Perinatal infection is the predominant mode of HBV transmission across Asia [39] whereas sexual and parenteral transmission in adolescence and adulthood remains the major mode of spread in developed countries [40]. Therefore Asians are typically younger at the time of infection and have experienced long periods of immune tolerance with high serum HBV DNA levels. By contrast, patients with European ancestry tend to acquire HBV infection acutely in adulthood and do not undergo the immune tolerance phase. Presented are two vastly different natural histories of CHB and hence predictive factors such as HBeAg status and HBV DNA in Asian populations may not carry the same significance in populations with European ancestry. Furthermore, age is a component in all HCC risk scores; however, at a given age Asians with perinatally acquired CHB will have a longer duration of infection compared with individuals of European ancestry with horizontally acquired CHB. This translates to different incidences of cirrhosis and HCC between Asian patients and those with European ancestry at the same age [4]. The prevalence of specific HBV genotypes also varies geographically [41]. Because patients with genotype C are at higher risk for HCC than others [12], risk factors derived from genotype C prevalent Asian populations may not accurately predict HCC in European populations where genotype A predominates. Finally, single nucleotide polymorphisms on chromosome 1p36.22 have been shown to be highly associated with HBV-related HCC in a Han Chinese population [42]. Although not yet studied in western populations, it is likely that genetic influences also contribute to differences in HCC risk across ethnicities.

How to improve accuracy of risk prediction

Current limitations of HCC risk scores

While HCC risk scores need to be re-evaluated in cohorts of European ancestry and refined in patients on antiviral therapy, another frontier for improvement is in the diagnosis of cirrhosis. Presence of cirrhosis has been assigned heavy weightings in the CU-HCC [35] and GAG-HCC [34] scores and was used to exclude patients in the study of the REACH-B score [5]. In the PAGE-B score [15], cirrhosis was strongly associated with HCC, but was less predictive than platelet count, a nonspecific marker. However, the diagnosis of cirrhosis in these studies was assessed using APRI, hypoalbuminemia, and presence of nodularity or portal hypertension on abdominal ultrasound. As these tests are insensitive markers of early cirrhosis [43, 44], a substantial number of patients may have been misclassified as having no cirrhosis. Despite being the most important risk factor for HBV-related HCC, cirrhosis has been diagnosed using relatively crude measures in major risk score studies thus far.

Optimization of HCC risk scores with liver stiffness measurement

The cohorts used in HCC risk score studies existed before the widespread use of transient elastography, a noninvasive test to evaluate liver stiffness measurements (LSM). Not only have LSM been widely validated to accurately diagnose cirrhosis in patients with CHB [45], it has also been shown to predict HBV-related HCC in a dose-dependent manner [46]. Therefore, it should be advantageous to integrate LSM into existing HCC risk scores. This was studied on a prospective cohort of 1,555 Chinese patients (1,035 in a training cohort, 520 in a validation cohort) with CHB referred for transient elastography [47]. Roughly a third of patients underwent antiviral therapy. Patients were assessed using the CU-HCC score with the original clinical diagnosis of cirrhosis (using

ultrasound features) substituted by LSM, thus creating a new LSM-HCC score. LSM cut-off values of 8.0 kPa and 12.0 kPa were chosen to stratify patients into three risk categories for HCC. Serum bilirubin from the CU-HCC score was no longer discriminatory after integration of LSM. The final components of the LSM-HCC score were age, albumin, HBV DNA, and LSM, which summate to a total score ranging from 0 to 30. The LSM-HCC score appeared superior to the CU-HCC score with higher AUROCs at 3 years (0.89 vs 0.71) and 5 years (0.83 vs 0.75), although this difference was not statistically significant. By applying a cut-off of score 11, the LSM-HCC was able to identify a low risk group with a 3- and 5- year HCC-free survival of 100% and 99.4%, respectively.

A small Korean study of 192 CHB patients with undetectable serum HBV DNA after treatment with entecavir evaluated a modified version of the REACH-B score (mREACH-B) on predicting HCC development [17]. In this model, LSM was incorporated into the REACH-B score in place of serum HBV DNA level, which proved to have no prognostic value in this treated cohort. The mREACH-B was found to have a better predictive performance for HCC at 3 years compared with the conventional score (AUROC 0.805–0.814 vs 0.629). The authors recently proceeded to validate the mREACH-B score in a larger cohort of 1,308 patients (17.8% cirrhosis, 65% commenced or continued antiviral therapy) and assessed its accuracy against other conventional HCC prediction models (CU-HCC, GAG-HCC, REACH-B, and LSM-HCC scores) [16]. The mREACH-B had significantly higher AUROCs for the prediction of HCC development at 3 and 5 years compared with other models, with the improvement seen primarily among patients receiving antiviral therapy. Interestingly, the exclusion of serum HBV DNA levels from the REACH-B score alone (without the addition of LSM) led to a paradoxical improvement in its predictive performance. This suggests the superior performance of the mREACH-B score is, in part, because of removal of HBV DNA level from the original score, rather than wholly from the addition of LSM. While results from studies of the LSM-HCC and mREACH-B scores are very promising, clearly more study on the role of incorporating LSM into HCC risk scores is warranted.

It is likely that other measurements of liver stiffness such as acoustic radiation force impulse, shear wave elastography and magnetic resonance elastography have predictive capabilities for HCC. However, they have not yet been extensively evaluated to allow for use in HCC risk scores.

Role of emerging biomarkers of liver fibrosis

Aside from LSM, other noninvasive indicators of liver fibrosis, such as serum biomarkers, have been evaluated in CHB [48], which can broadly be categorized as direct or indirect biomarkers of fibrosis.

Direct biomarkers

Direct biomarkers reflect the turnover of extracellular matrix within the liver. These include glycoproteins (hyaluronate, laminin, YKL-40), collagens (procollagen III N-peptide, type IV collagen), collagenases, and their inhibitors (matrix metalloproteases, tissue inhibitor of metalloprotease-1). The Enhanced Liver Fibrosis (ELF) test is a panel consisting of three direct biomarkers: hyaluronic acid, N-terminal propeptide of collagen type-III, and tissue inhibitor of metalloproteinase-1. Although first studied in hepatitis C patients, it has also proved to be useful in predicting ≥F2 fibrosis in Asian CHB patients [49]. The same authors then studied 170 Korean CHB patients who underwent liver biopsy, transient elastography and ELF testing and demonstrated that the ELF test was a good predictor of liver related events (hepatic decompensation, HCC and death) [50]. The ELF test consistently outperformed LSM and liver histology in predicting all liver related events with higher AUROC values, although the differences were not significant. In particular, for predicting the 31 HCCs in the study, ELF tests had the highest AUROC of 0.746, followed by LSM (0.708) and liver histology (0.686). The authors also showed by using cut-offs values of 8.10 and 10.40, the ELF test can risk stratifying patients into low-, intermediate-, and high-risk groups for HCC. These results suggest the prognostic utility of the ELF test (and potentially other direct biomarkers) is encouraging. However, further study is needed before it can be incorporated in future HCC risk scores.

Indirect biomarkers

Indirect markers are nonspecific measurements in blood, which reflect alterations in hepatic function. Examples include platelet count, aspartate to alanine aminotransferase ratio (AST/ALT), age-spleen-platelet ratio (ASPRI) and APRI. Biomarkers can also

be combined into larger panels and used as a diagnostic tool (e.g. Fibrotest). Practical advantages of using serum biomarkers to measure fibrosis include their high applicability, reproducibility, widespread availability, and low cost. In the setting of CHB, indirect biomarkers have been shown to predict significant fibrosis, cirrhosis, and even 5-year survival [45]. However, there is currently only limited data to suggest a correlation between these biomarkers and HCC. The aforementioned Korean study by Kim et al. revealed the performance of biomarkers such as ASPRI were suboptimal and inferior to LSM and ELF test for predicting liver related events, including HCC [50]. The role of indirect biomarkers in HCC prediction needs to be explored.

Conclusions

There is a need to develop accurate risk scores for HBV-related HCC to prioritize patient care, and current international guidelines vary widely on their definitions of high-risk patients. Risk prediction for HCC in CHB continues to be a dynamic and evolving field. Current risk scores can accurately predict HCC in specific populations. However, there is more work to be done to optimize risk scores in the non-Asian populations and patients on antiviral therapy. Improving the diagnosis of cirrhosis in risk scores by the integration of noninvasive markers of liver fibrosis such as transient elastography or serum biomarkers has shown promise and will continue to be an area of further study. Finally, the process of translating HCC risk into clinical practice by redefining surveillance intervals or modalities in patients with different risks to achieve survival benefit will also be a challenge.

Author Contributions

Ken Liu and Grace Wong drafted and critically revised the manuscript for important intellectual content.

Authors' declaration of personal interests

Ken Liu has no competing interests. Grace Wong has served as an advisory committee member for Otsuka and Gilead, and a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead, Janssen, Otsuka and Roche.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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