TOPIC HIGHLIGHT

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Risk calculators for hepatocellular carcinoma in patients affected with chronic hepatitis B in Asia

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Abstract

Risk calculators are widely used in many clinical fields, and integrate several important risk factors through the conversion of a risk function into a single measure of risk. Several studies have been carried out to create risk calculators for the prediction of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). Most of them were hospital-based, with limited sample sizes and insufficient external validation. These study groups collaborated to establish the REACH-B risk score, which incorporated five clinical variables to predict HCC risk. This risk score was then validated in international clinical cohorts. Evidence suggests that quantitative serum HBsAg level provides additional predictability of HCC, especially in patients with low levels of hepatitis B virus DNA. This novel marker was incorporated into a risk calculator and was internally validated. This tool will hopefully be externally validated in the near future. Risk calculators can be used to support clinical practice, and to establish preventive measures; several "off-label" extension usages have also been implemented. Albeit beneficial, several precautions and discussions should be noted in using the risk calculators. The future development of risk calculators for CHB patients can be extended by applying them to additional CHB-related outcomes, and by incorporating emerging risk parameters.

Key words: Chronic hepatitis B; Hepatocellular carcinoma; Risk calculator; Hepatitis B virus

Core tip: The risk calculator is a useful tool in many fields of medicine, including hepatology. This paper reviews the history of the development and validation of risk calculators of hepatocellular carcinoma (HCC) for patients with chronic hepatitis B (CHB). The rationale for using HCC risk calculators is first given, followed by a description of the course and pathway towards deriving HCC risk estimation tools for treatment-free CHB patients. Examples of the application of HCC risk prediction tools in clinical and public health settings is also shown. The paper also discusses several issues raised by the application of HCC risk scores.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most important adverse outcomes of chronic hepatitis B virus (HBV) infection, which affects more than 350 million people worldwide[1,2]. HCC causes poor quality of life and shortened survival, and is thus regarded as a major health challenge. The risk of chronic hepatitis B (CHB) progressing to HCC may be reduced by antiviral therapy[3], and surveillance with abdominal ultrasonography and serum alpha-fetoprotein tests can screen patients for early HCC treatment. Although the global number of individuals infected with CHB is extensive, especially in endemic areas such as Asian-Pacific and sub-Saharan African regions, only a small number of patients develop end-stage liver diseases. Therefore, the identification and triage of patients who are at high risk of HCC development is important. Several factors, such as gender, age, family history of HCC, presence of hepatic inflammation/fibrosis, alcohol consumption, elevated viral load, hepatitis B e antigen (HBeAg) positivity, and specific HBV genotypes (*e.g.*, genotype C), have been identified to be independently associated with elevated risk of HCC development (Figure 1)[4-8]. These factors, including patient, viral, and environmental factors, interact with one another and lead to HCC development in patients with chronic HBV infection. From the individualized medicine point of view, these factors should be used to reveal the future risk of HCC progression in patients with viral hepatitis so that preventive measures can be applied to those with high risk. Intuitively, a patient who has all of the risk factors for HCC can easily be categorized as very high risk (such as patient A in Table 1), whereas a patient without risk factors can be identified as very low risk (such as patient B in Table 1), despite not knowing the exact risk in these patients. However, the risk in patients with mixed risk profiles (patients C and D in Table 1) cannot easily be determined or compared. Thus, a tool that is evidence based and appropriately weights these risk predictors to provide a simple and accurate risk estimate for the interested outcome (*i.e.*, HCC) would be very helpful. Consequently, some investigators have responded accordingly to this demand.

RISK CALCULATORS FOR HEPATOCELLULAR CARCINOMA IN CHB PATIENTS WITHOUT ANTIVIRAL TREATMENT

By 2011, several study groups had established prediction models that incorporated several clinical variables to estimate HCC risk for CHB patients (Table 2)[9-12]. Most of those were hospital-based in study design with limited sample sizes. These HCC prediction models had diverse sets of risk predictors, although some common parameters were used. The most important issue was the lack of external validation to a satisfactory extent, which

Table 1 Scenario for chronic hepatitis B patients with various risk profiles

	Patient A	Patient B	Patient C	Patient D
Gender	Male	Female	Male	Female
Age (yr)	70	30	55	40
ALT (U/L)	100	15	25	40
HBeAg	Positive	Negative	Negative	Negative
HBV DNA (copies/mL)	> 10^6	< 300	10^4	10^5
Risk of HCC	Very high (but the exact risk is unknown)	Very low (but the exact risk is unknown)	Unknown	Unknown

ALT: Alanine transaminase; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma.

was common among those tools. To solve this problem, these study groups collaborated to established an HCC risk score (REACH-B) incorporating gender, age, serum alanine transaminase (ALT) concentration, HBeAg status, and serum HBV DNA level as the predicting parameters[13]. This study derived a 17-point risk model from 3584 treatment- and cirrhosis-free CHB patients in a community-based Taiwanese cohort (REVEAL-HBV), and validated its use in a composite hospital-based cohort (*n* = 1505) from Hong Kong and Korea. This risk score could predict HCC with a wide range of risks, ranging from 0.0% to 23.6% at 3 years, 0.0% to 47.4% at 5 years, and 0.0% to 81.6% at 10 years for patients with the lowest through the highest scores. Although the derivation and validation cohorts were quite different in their distributions of sex, age, HBeAg serostatus, ALT concentration, HBV DNA level, and cirrhosis, the risk score developed from the derivation cohort accurately and reliably estimated the HCC risk at 3, 5 and 10 years of follow-up in the validation cohort. The area under the receiver operating characteristic curve (AUROC) and the corresponding 95%CI were 0.811 (0.790-0.831), 0.796 (0.775-0.816), and 0.769 (0.747-0.790), respectively, in predicting 3-, 5- and 10-year HCC risk, which indicate a fair discriminatory capability. The performance of the risk score was improved when cirrhotic patients were excluded from the validation cohort[13]. Moreover, the predicted risks were similar to the observed risks as estimated by the Kaplan-Meier method, which indicate good calibration. This is the first study to provide firm external validation of the use of a HCC risk prediction tool in a group of clinical CHB patients.

Recently, several lines of evidence have suggested that quantitative serum HBsAg levels provide additional predictability of HCC, especially in patients with low levels of HBV DNA[14-16]. This novel marker features high reproducibility and relatively low cost. Thus, the original REVEAL nomograms were then upgraded by incorporating this novel risk predictor into the HCC risk prediction model[16]. In addition to HCC, this study also provided a prediction model for predicting the long-
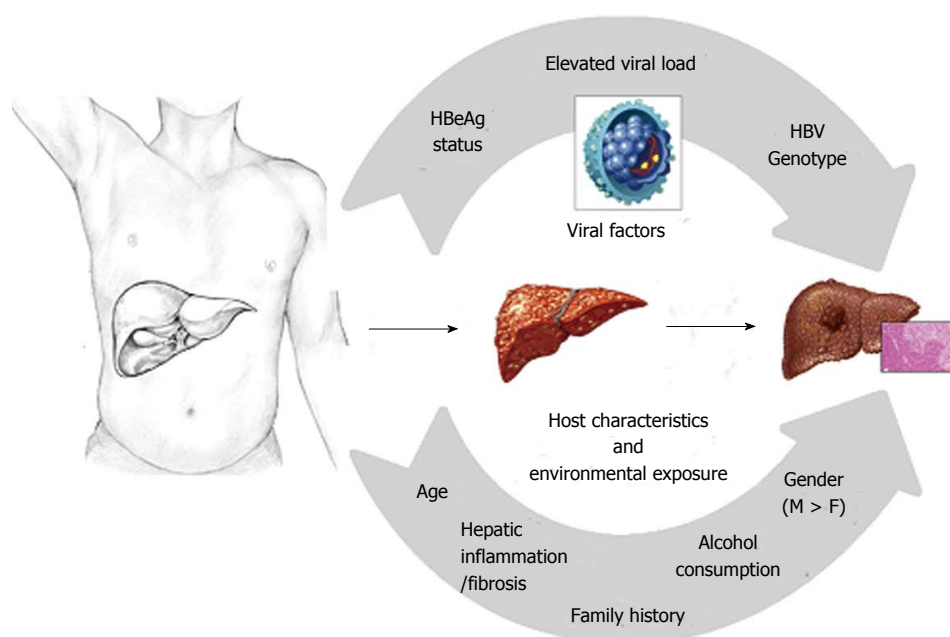
Figure 1 Known risk factors for hepatocellular carcinoma disease progression for chronic hepatitis B. M: Male; F: Female; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

	IPM[12]	GAG-HCC risk score[11]	CUHK clinical scoring system[10]	REVEAL nomograms[9]
Table 2 The hepatocellular carcinoma risk calculators for patients with chronic hepatitis B which have been developed before 2011				
Area	Korea	Hong Kong	Hong Kong	Taiwan
Origin of subjects	Hospital-based	Hospital-based	Hospital-based	Community-based
No. of subjects for derivation	2020	820	1005	2435
Feature of subjects	Not limited to CHB	CHB	CHB	CHB
No. of model	1	1	1	3
Risk predictors	Gender	Gender	Age	Gender
	Age	Age	Albumin	Age
	HCV infection	HBV DNA level	Bilirubin	ALT level
	HBV infection	CP mutations	HBV DNA level	Family history of HCC
	AFP level	Cirrhosis	Cirrhosis	Alcohol consumption
	Chronic hepatitis			HBeAg
	Cirrhosis			HBV DNA level
	Heavy alcoholics			HBV genotype
	ALT level			
Risk function	Logistic regression	Cox regression	Cox regression	Cox regression
Predicted outcomes	HCC risk	5-yr and 10-yr HCC risk	5-yr and 10-yr HCC risk	5-yr and 10-yr HCC risk
Validation (No. of subjects for validation)	2-yr prospective validation (n = 833)	Leave-one-out cross-validation	External validation (n = 424)	External validation with data splitting (n = 1218)

ALT: Alanine transaminase; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; CHB: Chronic hepatitis B.

term development of cirrhosis as well. The risk prediction model for HCC included age, sex, family history of HCC, and a combined variable encompassing HBeAg serostatus, serum HBV DNA and ALT levels, quantitative serum HBsAg level, and HBV genotype as the predicting parameters (Table 3; all parameters were included in the REVEAL nomogram except for quantitative serum HBsAg level). The projected 5-, 10-, and 15-year HCC risk for each score was pre-calculated and depicted in a nomogram (Figure 2). This upgraded HCC risk calculator was internally validated using a third of the population from which the model was derived from, and showed excellent prediction accuracy and discriminatory ability.

Taking the REACH-B score as a precedent, this upgraded version may hopefully be validated externally using clinical CHB patients to prove its accuracy, reliability, and added predictive capability over the original version in the near future. In addition to this, because testing serum HBV DNA levels is relatively costly compared to all other risk predictors in the risk calculator, a model/score might be generated in which quantitative serum HBsAg levels can be used in lieu of serum HBV DNA levels. This score/model, once generated and validated, can be used as a first-line risk prediction instrument by general practitioners and CHB patients who are interested in knowing their long-term risk, thereby largely extending
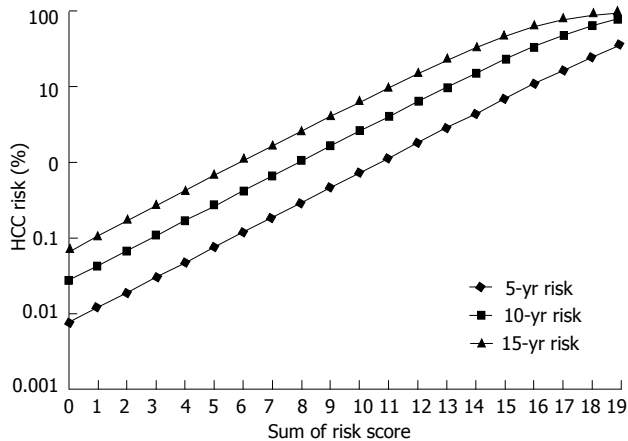
Figure 2 The updated REVEAL nomogram for the prediction of hepatocellular carcinoma risk. HCC: Hepatocellular carcinoma.
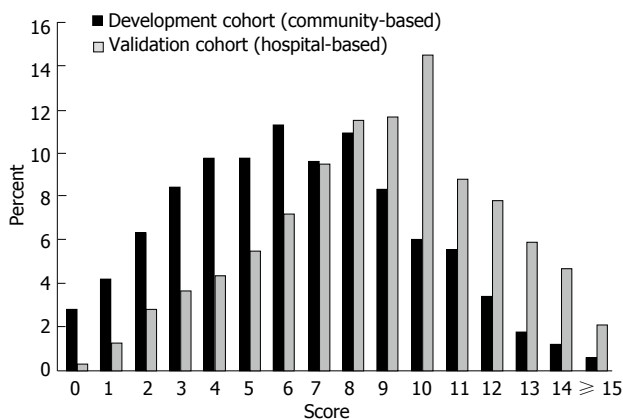

Figure 3 The distributions of score in the derivation cohort (from community) and the validation cohort (from clinical settings) used in the REACH-B study[13].

Table 3 The most updated hepatocellular carcinoma risk score for chronic hepatitis B patients upgraded from the REVEAL nomogram

Baseline hepatocellular carcinoma predictor	Risk score
Age (yr)	
30-34	0
35-39	1
40-44	2
45-49	3
50-54	4
55-59	5
60-65	6
Sex	
Female	0
Male	2
Levels of ALT (IU/L)	
< 15	0
15-44	1
$\geqslant$ 45	2
Family history of hepatocellular carcinoma	
No	0
Yes	2
HBeAg/HBV DNA/HBsAg/genotype	
Negative/< 10^4/< 100/any type	0
Negative/< 10^4/100-999/any type	2
Negative/< 10^4/$\geqslant$ 1000/any type	2
Negative/10^4-10^6/< 100/any type	3
Negative/10^4-10^6/100-999/any type	3
Negative/10^4-10^6/$\geqslant$ 1000/any type	4
Negative/$\geqslant$ 10^6/any level/B or B + C	5
Negative/$\geqslant$ 10^6/any level/C	7
Positive/any level/any level/B or B + C	6
Positive/any level/any level/C	7

ALT: Alanine transaminase; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen.

the application of this tool into the community.

IMPLICATIONS OF HCC RISK CALCULATORS FOR CLINICS AND PUBLIC HEALTH

As a useful risk estimation tool, the HCC risk calculator can be used to support clinical practice as well as derive preventive measures. The risk score helps to create a gauge for HCC risk assessment that can be used for evidence-based decisions during clinical management of chronic HBV carriers. Based on patients' personalized HCC risks, their follow-up intervals, surveillance patterns, and referral strategies can be tailored. Furthermore, as antiviral therapy has been shown to improve histology[17], timely antiviral therapy in high-HCC-risk patients may lead to improvement in quality of life and prolonged survival. The risk score also provides an appropriate platform for physician-patient communication, which may help to raise patients' awareness of HCC and assist in imparting knowledge to high-risk patients. Patients' willingness to receive antiviral therapies may hopefully be motivated by

understanding their own risk. The risk prediction score might also complement clinical practice guidelines by functioning as a risk stratification system. From a public health viewpoint, the risk calculator can bridge the gap between personal risk profiles and population health impact resulting from HCC, and may help in proper allocation of health care resources. For example, by knowing the distributions of scores from community and clinical settings used in the REACH-B paper (shown in Figure 3)[13], one can try to estimate the impact of HCC according to different risk scores in specific time frames. Further analyses on its cost-effectiveness can be conducted in order to guide public health intervention plans.

A key question that has been raised about the usage of the risk calculator is, how will patients with diverse predicted risks be managed differently? An argument was also brought up that it may instead be more important to identify a group of patients with a zero risk for HCC within a specific time frame. As Figure 2 shows, the HCC risk that can be predicted by the risk score is a risk continuum. The risk is never zero, even in patients with the lowest scores. The potential cut-off risk and corresponding management strategies is an issue. However, the risk calculator only deals with risk estimation of HCC. The management of CHB patients should take other information into consideration such as benefits, adverse

effects, as well as the cost-effectiveness of management strategies. International guideline development committees may integrate all of these factors when setting up threshold scores for beginning various clinical interventions.

EXTENDING THE USE OF HCC RISK SCORES IN TREATMENT RESEARCH

The REACH-B scoring system has been used to classify anti-viral treatment eligibility of CHB patients according to the 2012 Asian Pacific Association for the Study of the Liver (APASL) treatment guidelines[18]. In this study, a total of 904 noncirrhotic CHB patients were enrolled, and their age, gender liver biochemistry, HBeAg status, and HBV DNA levels were recorded. This study showed that for patients to be eligible for anti-viral treatment, the minimal REACH-B score should be 7 and 6, respectively, for HBeAg-seropositive and -negative patients. Additionally, in HBeAg-seronegative patients, the REACH-B score could predict treatment eligibility, with an adjusted OR (95%CI) of 1.78 (1.61-1.98). In HBeAg-seropositive patients, however, this same score-dependent eligibility of treatment was not observed. In this study, the authors also showed that the REACH-B score was excellent in discriminating treatment eligibility for young (< 40 years) HBeAg-seropositive patients (AUC: 0.903) and in both young (< 45 years; AUC: 0.907) and older (≥ 45 years; AUC: 0.883) HBeAg-seronegative patients; but the discriminatory capability for older (≥ 40 years) HBeAg-seropositive patients was poor (AUC: 0.664). After an in depth investigation, they found that 46.4% of HBeAg-seropositive patients older than 40 years of age with high risk of HCC, as estimated by a REACH score ≥ 11, would be erroneously excluded from treatment, mainly because their ALT levels never exceeded 2 × ULN, even after frequent blood tests during follow up. In other words, these patients were excluded from treatment, despite the fact that all these patients were significantly viraemic. The authors suggested that the severity of liver fibrosis in these high-risk patients be evaluated through liver biopsy or complementary noninvasive tools such as liver stiffness measurements, rather than exclude them from treatment.

The accuracy of HCC risk scores that were derived from treatment-naïve CHB patients has been evaluated in 1531 patients treated with entecavir[19]. These patients were treated with entecavir 0.5 mg daily for at least 12 mo, and were assessed once every 3-6 mo for symptoms, drug history, and adherence, in addition to collecting blood samples for biochemical analyses. Three HCC risk scores, including the CU-HCC, GAG-HCC, and REACH-B scores were used based on profiles at the start of treatment and 2 years later after treatment. The AUROCs for utilizing the CU-HCC, GAG-HCC, and REACH-B scores for predicting HCC were 0.80 (95%CI: 0.75-0.86), 0.76 (95%CI: 0.70-0.82), and 0.71 (95%CI: 0.62-0.81), respectively. This study also evaluated the on-

treatment performance of HCC risk scores, as well as the change in HCC risk scores from baseline to 2 years after treatment with entecavir. Interestingly, the CU-HCC, GAG-HCC, and REACH-B scores, which were originally developed in treatment-naïve patients, can be applicable to predict subsequent development of HCC in patients treated with entecavir. However, because all of these scores were derived from and validated in treatment-free cohorts, and many potential predictors related to therapy and responses during and after treatment could not be collected, they may not be the optimal prediction tools for CHB patients under antiviral treatment. A risk calculator derived from treated patients, which includes pre-treatment, on-treatment, and post-treatment parameters, might best fit this purpose.

Recently, the REACH-B score has been used as a natural history counterpart to evaluate the long-term effect of antiviral therapy using tenofovir on HCC incidence over time[20]. The analysis included more than 600 patients from two multinational Phase 3, placebo-controlled tenofovir trials (one for HBeAg-seronegative patients and the other for HBeAg positive patients). Participants in both trials were randomly assigned to tenofovir treatment or placebo for 1 year, after which the patients could opt to continue on open-label tenofovir for 8 years. The REACH-B scores were estimated using patients' baseline data. The standardized incidence ratio (SIR) of observed versus expected number of HCC cases, which was estimated according to the REACH-B score, was calculated. The analysis showed that by year 6, the SIR (95%CI) was 0.50 (0.29-0.84), which meant a 50% decrease from the predicted number of HCC cases. The effect of tenofovir was noticeable in non-cirrhotic patients (75% of study patients), in which a SIR (95%CI) of 0.45 (0.23-0.91) could be observed at 6 years of therapy. The authors concluded that the incidence of HCC in patients on tenofovir in both trials was lower than what was predicted by the REACH-B model, and that potent antiviral therapy may reduce the risk of HCC. Of note, among patients with cirrhosis (25% of study patients), the observed numbers of HCC were closer to the curve of expected cases predicted by REACH-B. This result, however, does not necessarily rule out the long-term benefits of tenofovir, because the REACH-B score was generated from non-cirrhotic patients, which may have underestimated actual HCC risk in cirrhotic patients without treatment.

It has been stated in the conclusion of the National Institutes of Health Consensus Development's statement on the management of hepatitis B[21] that the major goals of anti-HBV therapy are to prevent the development of progressive disease, specifically cirrhosis and liver failure, as well as HCC and subsequent death. However, to date, no randomized clinical trials (RCTs) of anti-HBV therapies have demonstrated a beneficial impact on overall mortality, liver-specific mortality, or development of HCC. Most published reports of hepatitis therapy use changes in short-term virologic, biochemical, and histologic parameters to infer the likelihood of long-term benefit. Approved therapies are associated with improve-

ments in intermediate biomarkers, including suppressed HBV DNA levels, HBeAg loss or seroconversion, decreases in ALT levels, and improvement in liver histology. According to this statement[21], the most important research needs include representative prospective cohort studies to define the natural history of the disease, and large RCTs of monotherapy and combined therapies, including placebo-controlled trials, that measure the effects on clinical health outcomes.

The aforementioned study was a good example in using the risk score developed from a natural history cohort as a scale to quantify the effect of antiviral therapy. For the time being, it is no longer feasible to conduct placebo-controlled RCTs to prove the efficacy of antiviral drugs on long-term outcomes, because they need large populations and a very long time to observe enough patients with outcomes. In addition, when treatments began showing their initial benefits, not treating patients for the sake of an arm of a clinical trial was no longer ethical. In this case, comparing outcomes from treatment cohorts with an existing natural history cohort is much more feasible. In adopting this approach, a difficulty may be encountered - CHB patients who are eligible for antiviral treatment should typically have worse risk profiles. When comparing the long-term risk of disease progression between CHB treatment cohorts and CHB natural history cohorts, it is crucial to take patients' risk profiles (such as gender, age, ALT, HBeAg, and HBV DNA level) into consideration because these are all important risk predictors of long-term clinical health outcomes. This issue can be overcome by introducing the natural history risk score, as shown by Kim *et al*[20] which was used as a risk scale to be contrasted with treatment cohorts.

PRECAUTION AND DISCUSSION OF USING THE RISK SCORES

Although the risk calculators are easy-to-use and the REACH-B predictive score was externally validated to be an applicable tool for HCC risk estimation, several precautions and discussions should be taken. Because surveillance strategies derived from a Taiwanese population might not apply globally, further validation is still needed in patients of different ethnicities, geographical areas, ages at infection, genetic background, HBV genotypes or species, comorbidities, and exposures to environmental factors such as aflatoxin and alcohol[13,22,23].

Another key question for the REACH-B score is whether this particular risk calculator is suitable for cirrhotic patients. We know that cirrhosis occurs at a relatively late stage in the spectrum of liver disease, and studies indicate that the annual risk of developing HCC among these patients is extremely high[24]. However, to date, there is no HCC risk prediction tool for patients with severe fibrosis and cirrhosis. As the carcinogenesis of HCC is a multistage and multi-factorial process, the risk predictors for developing HCC in cirrhotic patients, in which CHB has already progressed to a relatively late stage, should be very different from those patients without cirrhosis. A universal risk prediction tool for the whole spectrum of patients is thus not reasonable. The predictability of the REACH-B risk score in cirrhotic patients is limited because the derivation cohort did not include CHB patients with this complication. The original REACH-B article showed that the accuracy and values of prediction diminished when applying the risk score to cirrhotic carriers[13]. However, for those in the early stages of liver disease, its accuracy was quite satisfactory. We should also bear in mind that cirrhosis itself is an important predictor for future HCC development. Therefore, patients with existing cirrhosis need close monitoring and timely initiation of antiviral therapy. Risk assessment in this group of patients, or the use of cirrhosis as a variable might therefore be pointless.

The concern has been raised on whether the risk score is suitable to be used for changing risk profiles during follow-up, either spontaneously or as a result of antiviral treatment. Because current HCC risk prediction tools were generated from a natural history cohort without history of antiviral therapy, the inference of predicted risks under circumstances of antiviral therapy should theoretically be inappropriate. Furthermore, current HCC prediction tools are based on one-shot baseline measurements; further validation studies are required to evaluate whether this risk score is applicable for changing risk profiles during follow-up, either changing spontaneously or through antiviral therapy. A risk calculator, which incorporates not only the baseline risk parameters but also the repeated measurements of patients' risk profiles, would be expected to solve this problem, and thus deserves further efforts.

The risk calculator is a practical tool for managing various phases of a specific disease. Therefore, several other clinical outcomes and milestones of CHB, such as cirrhosis, liver-related mortality, as well as the seroclearance of HBeAg, HBsAg, and HBV DNA, can also be suitable for the development of risk or probability prediction tools. One example is a predictive scoring system for the spontaneous seroclearance of HBsAg in HBeAg-seronegative CHB patients[25]. Besides focusing on outcomes, some emerging clinical parameters might hopefully be incorporated into the current HCC risk score[26-29]. The incorporation of serum quantitative HBsAg titers is a good example; other factors such as host genetic and immunologic markers might also be candidates once their independent predictability are proved, even after taking known risk predictors into consideration. The realization of these prediction tools may benefit CHB patients by providing comprehensive and individualized management instruments, which have been developed based on scientific evidence of risk.

REFERENCES

1   **World Health Organization**. Fact Sheet: Hepatitis B. 2008. Available from : URL: http://www.who.int/mediacentre/factsheets/fs204/en/

2   **Lavanchy D**. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004; **11**: 97-107 [PMID: 14996343 DOI: 10.1046/j.1365-2893.2003.00487.x]

3   **Sung JJ**, Tsoi KK, Wong VW, Li KC, Chan HL. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2008; **28**: 1067-1077 [PMID: 18657133 DOI: 10.1111/j.1365-2036.2008.03816.x]

4   **Chen CJ**, Yu MW, Liaw YF. Epidemiological characteristics and risk factors of hepatocellular carcinoma. *J Gastroenterol Hepatol* 1997; **12**: S294-S308 [PMID: 9407350 DOI: 10.1111/j.1440-1746.1997.tb00513.x]

5   **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65-73 [PMID: 16391218 DOI: 10.1001/jama.295.1.65]

6   **Yang HI**, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, Hsiao CK, Chen PJ, Chen DS, Chen CJ. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002; **347**: 168-174 [PMID: 12124405 DOI: 10.1056/NEJM200211213472119]

7   **Kao JH**, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. *Gastroenterology* 2000; **118**: 554-559 [PMID: 10702206]

8   **Yang HI**, Yeh SH, Chen PJ, Iloeje UH, Jen CL, Su J, Wang LY, Lu SN, You SL, Chen DS, Liaw YF, Chen CJ. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. *J Natl Cancer Inst* 2008; **100**: 1134-1143 [PMID: 18695135 DOI: 10.1093/jnci/djn243]

9   **Yang HI**, Sherman M, Su J, Chen PJ, Liaw YF, Iloeje UH, Chen CJ. Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. *J Clin Oncol* 2010; **28**: 2437-2444 [PMID: 20368541 DOI: 10.1200/JCO.2009.27.4456]

10   **Wong VW**, Chan SL, Mo F, Chan TC, Loong HH, Wong GL, Lui YY, Chan AT, Sung JJ, Yeo W, Chan HL, Mok TS. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. *J Clin Oncol* 2010; **28**: 1660-1665 [PMID: 20194845 DOI: 10.1200/JCO.2009.26.2675]

11   **Yuen MF**, Tanaka Y, Fong DY, Fung J, Wong DK, Yuen JC, But DY, Chan AO, Wong BC, Mizokami M, Lai CL. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol* 2009; **50**: 80-88 [PMID: 18977053 DOI: 10.1016/j.jhep.2008.07.023]

12   **Han KH**, Ahn SH. How to predict HCC development in patients with chronic B viral liver disease? *Intervirology* 2005; **48**: 23-28 [PMID: 15785086 DOI: 10.1159/000082091]

13   **Yang HI**, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY, Ahn SH, Chen CJ, Wong VW, Seto WK. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011; **12**: 568-574 [PMID: 21497551 DOI: 10.1016/S1470-2045(11)70077-8]

14   **Tseng TC**, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, Hsu CA, Kuo SF, Liu CH, Chen PJ, Chen DS, Kao JH. Serum hepatitis B surface antigen levels help predict disease progression in patients with low hepatitis B virus loads. *Hepatology* 2013; **57**: 441-450 [PMID: 22941922 DOI: 10.1002/hep.26041]

15   **Tseng TC**, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, Kuo SF, Liu CH, Chen PJ, Chen DS, Kao JH. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. *Gastroenterology* 2012; **142**: 1140-1149.e3; quiz e13-14 [PMID: 22333950 DOI: 10.1053/j.gastro.2012.02.007]

16   **Lee MH**, Yang HI, Liu J, Batrla-Utermann R, Jen CL, Iloeje UH, Lu SN, You SL, Wang LY, Chen CJ. Prediction models of long-term cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: risk scores integrating host and virus profiles. *Hepatology* 2013; **58**: 546-554 [PMID: 23504622 DOI: 10.1002/hep.26385]

17   **Mommeja-Marin H**, Mondou E, Blum MR, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. *Hepatology* 2003; **37**: 1309-1319 [PMID: 12774009 DOI: 10.1053/jhep.2003.50208]

18   **Chen TM**, Chang CC, Huang PT, Wen CF, Lin CC. Performance of risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B) score in classifying treatment eligibility under 2012 Asian Pacific Association for the Study of the Liver (APASL) guideline for chronic hepatitis B patients. *Aliment Pharmacol Ther* 2013; **37**: 243-251 [PMID: 23171385 DOI: 10.1111/apt.12144]

19   **Wong GL**, Chan HL, Chan HY, Tse PC, Tse YK, Mak CW, Lee SK, Ip ZM, Lam AT, Iu HW, Leung JM, Wong VW. Accuracy of risk scores for patients with chronic hepatitis B receiving entecavir treatment. *Gastroenterology* 2013; **144**: 933-944 [PMID: 23415803 DOI: 10.1053/j.gastro.2013.02.002]

20   **Kim WR**, Berg T, Loomba R, Schall RA, Dinh P, Yee LJ, Martins EB, Flaherty JF, Gurel S, Buti M, Marcellin P. Long Term Tenofovir Disoproxil Fumarate (Tdf) Therapy and the Risk of Hepatocellular Carcinoma. *J Hepatol* 2013; **58**: S19-S19

21   **Sorrell MF**, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi JM, Kern ER, McHugh JA, Petersen GM, Rein MF, Strader DB, Trotter HT. National Institutes of Health consensus development conference statement: management of hepatitis B. *Hepatology* 2009; **49**: S4-S12 [PMID: 19399804 DOI: 10.1002/hep.22946]

22   **Sarin SK**, Kumar M. Predictive scores for hepatocellular carcinoma development in chronic hepatitis B virus infection: "does one size fit all?" *Gastroenterology* 2012; **142**: 1038-1040 [PMID: 22361059 DOI: 10.1053/j.gastro.2012.02.024]

23   **Keeffe EB**. Risk score for development of HCC: ready for use in practice? *Lancet Oncol* 2011; **12**: 517-518; discussion 518-519 [PMID: 21497552 DOI: 10.1016/S1470-2045(11)70085-7]

24   **Llovet JM**, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917 [PMID: 14667750 DOI: 10.1016/S0140-6736(03)14964-1]

25   **Liu J**, Lee MH, Batrla-Utermann R, Jen CL, Iloeje UH, Lu SN, Wang LY, You SL, Hsiao CK, Yang HI, Chen CJ. A predictive scoring system for the seroclearance of HBsAg in HBeAg-seronegative chronic hepatitis B patients with genotype B or C infection. *J Hepatol* 2013; **58**: 853-860 [PMID: 23246508 DOI: 10.1016/j.jhep.2012.12.006]

26   **Zhang HX**, Zhai Y, Hu ZB, Wu C, Qian J, Jia WH, Ma FC, Huang WF, Yu LX, Yue W, Wang ZF, Li PY, Zhang Y, Liang RX, Wei ZL, Cui Y, Xie WM, Cai M, Yu XS, Yuan YF, Xia X, Zhang XM, Yang H, Qiu W, Yang JM, Gong F, Chen MS, Shen HB, Lin DX, Zeng YX, He FC, Zhou GQ. Genome-wide association study identifies 1p36.22 as a new susceptibility locus for hepatocellular carcinoma in chronic hepatitis B virus carriers. *Nat Genet* 2010; **42**: 755-U739 [DOI: 10.1038/Ng.638]

27   **Mbarek H**, Ochi H, Urabe Y, Kumar V, Kubo M, Hosono N, Takahashi A, Kamatani Y, Miki D, Abe H, Tsunoda T, Kamatani N, Chayama K, Nakamura Y, Matsuda K. A genome-wide association study of chronic hepatitis B identified novel risk locus in a Japanese population. *Hum Mol Genet* 2011; **20**: 3884-3892 [PMID: 21750111 DOI: 10.1093/hmg/ddr301]

28   **Jiang DK**, Sun J, Cao G, Liu Y, Lin D, Gao YZ, Ren WH, Long XD, Zhang H, Ma XP, Wang Z, Jiang W, Chen TY, Gao Y, Sun LD, Long JR, Huang HX, Wang D, Yu H, Zhang P, Tang LS, Peng B, Cai H, Liu TT, Zhou P, Liu F, Lin X, Tao S, Wan B, Sai-Yin HX, Qin LX, Yin J, Liu L, Wu C, Pei Y, Zhou YF, Zhai Y, Lu PX, Tan A, Zuo XB, Fan J, Chang J, Gu X, Wang NJ, Li Y, Liu YK, Zhai K, Zhang H, Hu Z, Liu J, Yi Q, Xiang Y, Shi R, Ding Q, Zheng W, Shu XO, Mo Z, Shugart YY, Zhang XJ, Zhou G, Shen H, Zheng SL, Xu J, Yu L. Genetic variants in STAT4 and HLA-DQ genes confer risk of

hepatitis B virus-related hepatocellular carcinoma. *Nat Genet* 2013; **45**: 72-75 [PMID: 23242368 DOI: 10.1038/ng.2483]

29   **Li S**, Qian J, Yang Y, Zhao W, Dai J, Bei JX, Foo JN, McLaren PJ, Li Z, Yang J, Shen F, Liu L, Yang J, Li S, Pan S, Wang Y, Li W, Zhai X, Zhou B, Shi L, Chen X, Chu M, Yan Y, Wang J, Cheng S, Shen J, Jia W, Liu J, Yang J, Wen Z, Li A, Zhang Y, Zhang G, Luo X, Qin H, Chen M, Wang H, Jin L, Lin D, Shen H, He L, de Bakker PI, Wang H, Zeng YX, Wu M, Hu Z, Shi Y, Liu J, Zhou W. GWAS identifies novel susceptibility loci on 6p21.32 and 21q21.3 for hepatocellular carcinoma in chronic hepatitis B virus carriers. *PLoS Genet* 2012; **8**: e1002791 [PMID: 22807686 DOI: 10.1371/journal.pgen.1002791]

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