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# Risk prediction of hepatitis B virus-related hepatocellular carcinoma in the era of antiviral therapy

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## Abstract

Chronic hepatitis B (CHB)-related hepatocellular carcinoma (HCC) is a major health problem in Asian-Pacific regions. Antiviral therapy reduces, but does not eliminate the risk of HCC. It would be a heavy financial burden in most low and middle economic countries if all CHB patients received antiviral therapy and HCC surveillance. Thus, there is a need for accurate risk prediction to assist prognostication, decisions on the need for antiviral therapy and HCC surveillance. A few well-established risk factors for HCC, namely advanced age, male gender, high viral load, cirrhosis *etc.*, are the core components of three HCC risk scores: CU-HCC, GAG-HCC and REACH-B scores. These 3 scores were confirmed to be accurate in predicting HCC up to 10 years in treatment-naïve patients. Their validity and applicability have recently been demonstrated in a large cohort of entecavir treatment patients. A decrease in risk scores after antiviral therapy translates to a lower risk of HCC. These findings support the application of HCC risk scores in all CHB patients. Different levels of care and different intensities of HCC surveillance should be offered according to the risk profile of patients. Patients at risk of HCC should undergo regular HCC surveillance,

even when they are receiving antiviral treatment.

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**Key words:** Antiviral therapy; Cirrhosis; Hepatitis B virus DNA; Hepatocellular carcinoma; Risk prediction score; Transient elastography

**Core tip:** CU-hepatocellular carcinoma (HCC), GAG-HCC and REACH-B scores accurately predict subsequent HCC development in both treatment-naïve patients with chronic hepatitis B and those receiving antiviral therapy. At the recommended cutoff values, baseline CU-HCC and REACH-B scores had high sensitivity, while the GAG-HCC score had high specificity in predicting HCC. Patients persistently in the low-risk category have the lowest risk of HCC; those "downgraded" in risk category have significantly lower, but a small risk of HCC compared to those in the high-risk category. Patients in the high-risk category either at baseline or after treatment should undergo HCC surveillance.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer death in men worldwide<sup>[1]</sup>. Chronic hepatitis B virus (HBV) infection is one of the major causes of HCC, and it is estimated that over 350 million people are chronically infected with HBV worldwide<sup>[2]</sup>. Globally, HBV accounts for 53% of all cases of HCC<sup>[3]</sup>. Due to the high preva-

lence of HBV infection, the incidence of HCC in Eastern Asia and Southeast Asia is the highest in the world<sup>[4]</sup>.

In the last two decades, the development of antiviral therapy was a major breakthrough in the management of chronic hepatitis B (CHB), which modifies the natural history of the disease and reduces the risk of HCC<sup>[5-7]</sup>. Nonetheless, there is still a low, but clinically relevant risk of HCC in patients receiving antiviral therapy. It would be a heavy financial burden, particularly in low and middle economic countries, if all CHB patients received antiviral therapy and HCC surveillance. Thus, there is a need for accurate risk prediction to assist prognostication, decisions on the need for antiviral therapy and HCC surveillance.

## RISK FACTORS FOR HBV-RELATED HCC

### Treatment-naïve patients

A handful of factors have been repeatedly shown to increase the risk of HCC when studying the natural history of chronic HBV infection. In general the risk factors can be categorized into host factors, liver factors and viral factors (Table 1). Host factors include advanced age<sup>[8-10]</sup>, male gender<sup>[9,10]</sup>, family history of HCC<sup>[11]</sup>, and possibly single-nucleotide polymorphisms at different human genomic loci [*e.g.*, chromosome 1p36.22, chromosome 6 of human leukocyte antigen (HLA)-DP and HLA-DQ loci, and chromosome 8p12]<sup>[12,13]</sup>. Immunosuppressed conditions like human immunodeficiency virus co-infection is another risk factor<sup>[14]</sup>. Liver factors consist of advanced fibrosis and cirrhosis<sup>[11]</sup>, poor liver function as evidenced by hypoalbuminemia and hyperbilirubinemia<sup>[8]</sup>, active hepatitis as evidenced by high alanine aminotransferase (ALT) and active necroinflammation demonstrated on liver biopsy<sup>[9]</sup>, and other concomitant liver diseases such as co-infection with hepatitis C virus or hepatitis delta virus, alcoholic liver disease and nonalcoholic fatty liver disease<sup>[11]</sup>. Viral factors include high serum HBV DNA level<sup>[8,15]</sup>, hepatitis B virus e antigen (HBeAg) seropositivity<sup>[16]</sup>, HBV genotype C<sup>[17]</sup> and subgenotype Ce<sup>[18]</sup>, core promoter mutations<sup>[10]</sup> and probably high serum hepatitis B surface antigen (HBsAg) level<sup>[19]</sup>.

### Patients receiving antiviral therapy

The natural history of chronic HBV infection is altered by antiviral therapy. Therefore, the risk factors for HCC may be different in treated patients compared to untreated patients. The landmark Asian lamivudine trial did not specifically determine the risk factors for HCC, however, baseline Child-Pugh and Ishak fibrosis score, as well as genotypic resistance YMDD mutation were risk factors for disease progression<sup>[6]</sup>. The drug-resistant mutant did not increase the risk of HCC (both 4% in patients with or without YMDD mutation). Nonetheless, the significance of YMDD mutation might be masked by the short follow-up duration (study prematurely terminated at 32 mo) and the unspecified interval between emergence of drug resistance and HCC development.

**Table 1 Risk factors for hepatitis B virus-related hepatocellular carcinoma**

Host factors	Liver factors	Viral factors
Advanced age	Advanced fibrosis	High serum HBV DNA
Male gender	Cirrhosis	Positive HBeAg
Family history of HCC	Hypoalbuminemia	HBV genotype C
SNP at human genomic loci, <i>e.g.</i> , Chromosome 1p36.22	Hyperbilirubinemia	HBV subgenotype Ce
	High ALT	Core promoter mutations
Chromosome 6 of HLA-DP/Q loci	Active necroinflammation	High serum HBsAg level
Chromosome 8p12	Concomitant liver diseases, <i>e.g.</i> , Hepatitis C virus co- infection	
Immunosuppressed condition, <i>e.g.</i> , Human immunodeficiency virus co-infection	Hepatitis delta virus co-infection	
	Alcoholic liver disease	
	Nonalcoholic fatty liver disease	

ALT: Alanine aminotransferase; HBeAg: Hepatitis B virus e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HLA: Human leukocyte antigen; SNP: Single-nucleotide polymorphism.

In a retrospective study of 2795 Japanese CHB patients (657 lamivudine-treated *vs* 2138 untreated patients), the absence of treatment, male gender, family history of HBV carriage, age greater than 40 years, fibrosis more than grade 2 of 4, albumin level below 40 g/L, and platelet count of < 150000/mm<sup>3</sup> were independent risk factors for HCC<sup>[20]</sup>. The risk factors identified in this study appeared to be no different from those identified from studies on the natural history, probably because more than 75% of patients were untreated.

In a nationwide study from Greece retrospectively analyzing 818 HBeAg-negative patients treated with lamivudine, advanced age and cirrhosis were risk factors for HCC<sup>[21]</sup>. On-therapy virologic remission (*i.e.*, undetectable on-treatment serum HBV DNA level) did not significantly affect the incidence of HCC (although there was a trend for lower risk of HCC in the absence of cirrhosis). As all patients with on-therapy virologic remission who developed HCC (8 of 228; 3.6%) occurred within 30 mo of lamivudine treatment, some of these tumors might have been pre-existing HCC.

A recent large-scale cohort study of 1531 entecavir treatment CHB patients demonstrated the importance of maintained virologic response<sup>[22]</sup>. Old age, cirrhosis, and virologic remission for 24 mo or more were independent factors associated with HCC in the entire cohort; whereas advanced age and hypoalbuminemia were predictors in non-cirrhotic patients. Although maintained virologic response was important, 30 out of 47 patients (64%) who achieved this virologic target still developed HCC. This can be explained by the early integration of HBV into the host genome and the presence of cirrhosis, such that

even with very effective suppression of viral replication with antiviral agents, HCC may still develop<sup>[23]</sup>.

Summarizing the findings of these studies, advanced age and cirrhosis are the two major risk factors consistently demonstrated in patients receiving antiviral therapy. While maintained virologic response is likely a protective factor, baseline HBV DNA level is no longer important in these treated patients as it is usually much reduced after treatment. Theoretically HBsAg level, which reflects the amount and transcriptional activity of covalently closed circular DNA inside the liver, might have a role in predicting HCC in treated patients when serum HBV DNA is no longer detectable<sup>[24]</sup>. However, this was not confirmed in patients receiving entecavir<sup>[22]</sup>. The probable reason for this is that these patients had active disease to start with; those with lower HBsAg levels were more likely to be cirrhotic. In other words, there were no “inactive HBV carriers” at very low risk of HCC as in untreated natural history cohorts<sup>[19]</sup>.

## APPROACHES TO DEVELOP RISK SCORES

There are different approaches to developing a risk score for HCC, however, the first common step is to identify important independent factors associated with HCC in a training cohort. After statistical analysis, scores are assigned to different parameters in the equation to make up the final score. In order to demonstrate the applicability and reproducibility of the score, it should be validated in an independent cohort. If this independent cohort is not available, the leave-one-out cross-validation can be applied to assess the performance of the score in new data<sup>[25]</sup>. This validation involves using a single observation from the original sample as the validation data, and the remaining observations as the training data. This is repeated such that each observation in the sample is used once as the validation data.

Take the CU-HCC score as an example, significant variables were first identified in the multivariable Cox proportional hazards model<sup>[8]</sup>. A score was attributed to each variable according to its relative contribution in the model, as determined by the  $\chi^2$  score. Furthermore, different cutoff values of the score were determined to categorize patients into different levels of risk (*i.e.*, low-, medium-, and high-risk categories). The performance of the cutoff can be assessed in terms of discriminatory ability and monotonicity by the linear trend  $\chi^2$  test<sup>[26]</sup>.

Validation of the score usually involves two steps: discrimination and calibration. Discrimination can be assessed with the receiver operating characteristic (ROC) curve, *i.e.*, area under ROC (AUROC) curves, sensitivity, and specificity. Calibration is evaluated by estimating the observed HCC risk using the Kaplan-Meier method with the same cumulative risk scores. A combination of neighboring groups of cumulative risk scores will be performed if the observed HCC risk in a group with the same cumulative risk score is low<sup>[9]</sup>.

## EXISTING PREDICTION SCORES FOR HCC

The three most commonly applied HCC risk scores are described below (Tables 2 and 3).

### CU-HCC score

The CU-HCC score<sup>[8]</sup> was first derived from a cohort of 1005 Chinese CHB patients from a prospective study on the surveillance of HCC in chronic HBV carriers from The Chinese University of Hong Kong (abbreviated as CU in the name of the score)<sup>[18]</sup>. It was validated in an independent cohort of 424 Chinese CHB patients<sup>[27]</sup>. Both cohorts were from tertiary referral clinics. While all patients were treatment-naïve at baseline, 15.1% and 25.0% of patients from the training and validation cohort, respectively, received antiviral therapy during the long-term follow up to 10 years. The CU-HCC score is composed of 5 parameters: age, albumin, bilirubin, HBV DNA, and cirrhosis; it ranges from 0 to 44.5 (Table 2). The investigators identified two cutoff values (5 and 20) which best discriminated HCC risk into three categories. The 5-year HCC-free survival rates were 98.3%, 90.5%, and 78.9% in the low-, medium-, and high-risk groups, respectively. By applying the lower cutoff value, this score has high negative predictive value of 97.8% to exclude future HCC development.

### GAG-HCC score

The GAG-HCC score<sup>[10]</sup> was first developed from a cohort of 820 Chinese CHB patients from tertiary referral clinics. The name was abbreviated from “Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis”. All patients were treatment-naïve at baseline and censored at the time of initiation of antiviral therapy. As an independent cohort was not included, the investigators adopted the leave-one-out cross-validation mentioned above<sup>[25]</sup>. There are two versions of the score. The original version is composed of gender, age, core promoter mutations, HBV DNA level and cirrhosis. There is a simplified version which omits core promoter mutations, as they may not be easily available in some centers. The score ranges widely to above 100, as age (in years) is one of the components in the formula. A cutoff value of 101 was found to have good sensitivity and specificity of 84.1% and 76.2% for 5-year prediction, and 88.0% and 78.7% for 10-year prediction, respectively. The negative predictive values were as high as 98.3% to 100% to exclude future HCC development.

### REACH-B score

The REACH-B score<sup>[9]</sup> was first derived from a cohort of 3584 Chinese CHB patients from the community-based prospective Taiwanese REVEAL-HBV study<sup>[15]</sup>, and then validated in a cohort of 1505 patients from three hospitals in Hong Kong and South Korea tertiary referral clinics. The name was the abbreviation of “Risk Estimation for HCC in CHB”. All patients in the training

Table 2 Components of the risk scores

Factor	Risk score		
	CU-HCC	GAG-HCC (yr)	REACH-B
Age (yr)	≤ 50: 0 >50: 3		30-34: 0
			35-39: 1
			40-44: 2
			45-49: 3
			50-54: 4
			55-59: 5
Sex	NA	Male: 16	Male: 2
		Female: 0	Female: 0
Albumin (g/L)	≤ 35: 20 > 35: 0	NA	NA
Bilirubin (mmol/L)	≤ 18: 0 > 18: 1.5	NA	NA
ALT (U/L)	NA	NA	< 15: 0 15-44: 1 ≥ 45: 2
HBeAg	NA	NA	Positive: 2 Negative: 0
HBV DNA (copies/mL)	< 4 log: 0 4-6 log: 1 > 6 log: 4 (lack of maintained virologic suppression: 4)	3 × in log	< 4 log: 0
			4-5 log: 3
			5-6 log: 5
			≥ 6 log: 4
Cirrhosis	Presence: 15 Absence: 0	Presence: 33 Absence: 0	(lack of maintained virologic suppression: 4) NA

ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; NA: Not applicable; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus.

cohort did not have cirrhosis according to ultrasonography at the time of recruitment, and remained treatment-naïve throughout the follow-up period which was as long as 12 years. In contrast, 18.4% (277/1505) of patients in the validation cohort had cirrhosis. The REACH-B score consists of 5 parameters: gender, age, ALT level, HBeAg status and HBV DNA level. The score ranges from 0 to 17 and is primarily designed for patients without cirrhosis. The authors did not categorize patients into different risk levels, instead the 3-, 5- and 10-year risk of HCC was determined for each particular risk score. The HCC risk ranged from 0% to 23.6% at 3 years, 0% to 47.4% at 5 years, and 0% to 81.6% at 10 years for patients with the lowest (0 point) and highest HCC risk (17 points), respectively. As the risk increased significantly starting at 8 points, it could be used as an arbitrary cutoff value to categorize patients into different level of risks.

## IMPACT OF ANTIVIRAL THERAPY ON RISK PREDICTION

Most of the patients involved in the development of the risk scores did not receive antiviral therapy. This raised a concern regarding their validity and applicability to patients receiving treatment. This is particularly relevant to

Table 3 Comparison of the CU-hepatocellular carcinoma, GAG-hepatocellular carcinoma and REACH-B scores

Score	Patients	Components	Cutoff value	Performance
CU-HCC	Clinic patients: 1005 in training cohort, 424 in validation cohort	Age, albumin, bilirubin, HBV DNA, cirrhosis	5	97% NPV at 10 yr
GAG-HCC	820 clinic patients (leave-one-out cross-validation method)	Age, gender, HBV DNA, cirrhosis	101	99% NPV at 10 yr
REACH-B	Non-cirrhotic patients: 3584 in training cohort, 1505 in validation cohort	Age, gender, ALT, HBV DNA, HBeAg	8	98% NPV at 10 yr

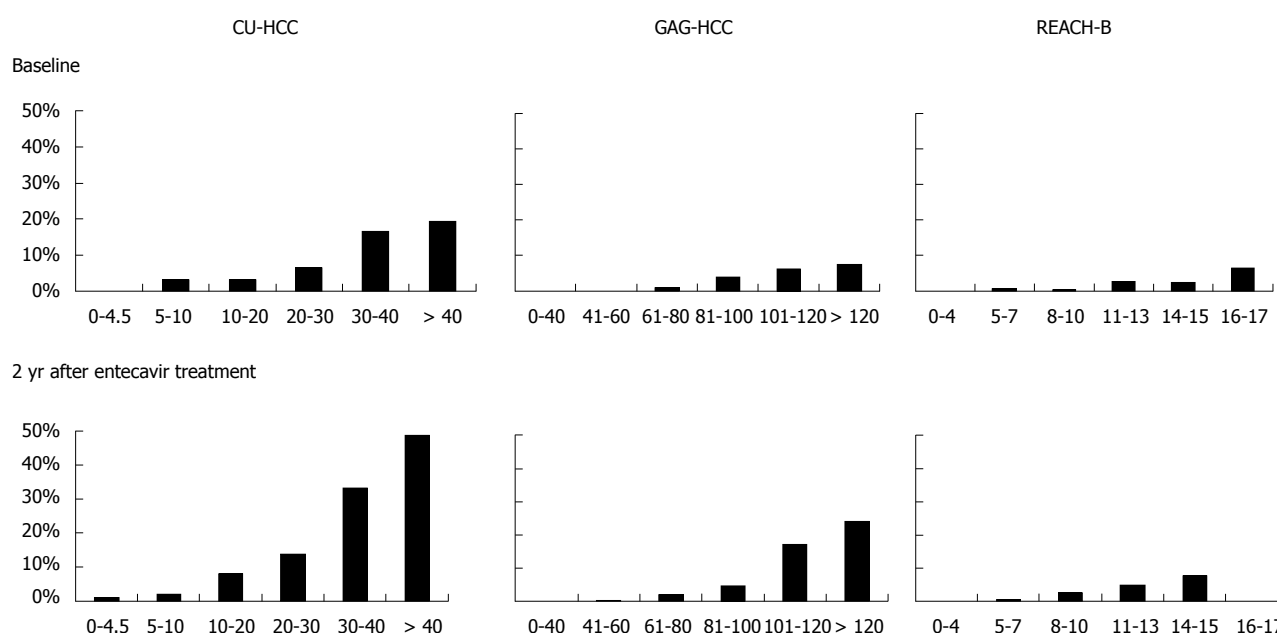
ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; NPV: Negative predictive value.

those at risk of HCC as they most often receive antiviral therapy. Antiviral therapy modifies the natural history of CHB by decreasing the serum HBV DNA levels, and altering other laboratory parameters (*e.g.*, lowering ALT, raising albumin and lowering bilirubin level). This leads to another question on the clinical significance of dynamic changes in the risk scores during longitudinal follow-up.

These important concerns have been addressed in a recent cohort study of 1531 entecavir treatment CHB patients followed up for  $42 \pm 13$  mo<sup>[22]</sup>. All patients received entecavir 0.5 mg daily for at least 12 mo. The importance of maintained viral suppression was emphasized in this study as virologic remission for 24 mo or more, together with advanced age and cirrhosis, were independent factors associated with HCC in this cohort. The CU-HCC, GAG-HCC and REACH-B scores were found to be accurate in predicting HCC in 3 and 5 years. Of these scores, the CU-HCC score had the highest AU-ROC at baseline (0.80 *vs* 0.76 and 0.71, respectively). At the recommended cutoff values, baseline CU-HCC and REACH-B scores had high sensitivity (93.6% and 95.2%, respectively), while the GAG-HCC score had high specificity (78.9%) in predicting HCC.

After antiviral therapy, the risk scores change due to decreased viral load (*i.e.*, lower HBV DNA) and even HBeAg-seroconversion, improvement in liver function (high albumin, lower bilirubin) and necroinflammation (lower ALT). Therefore, a significant proportion of patients would have decreased risk scores following treatment. From this cohort study, 14.0%, 8.2% and 38.3% of patients had their risk category changed from high risk to low risk as defined by the CU-HCC, GAG-HCC and REACH-B score, respectively, after 2 years of entecavir<sup>[22]</sup>. One unresolved issue is the regression of cirrhosis, which may occur after long-term antiviral therapy<sup>[28,29]</sup>. However, as this regression takes years to happen, its effect on the dynamic change in risk level can only be evaluated in a study with at least 8 to 10 years of follow up.





**Figure 1** Risk of hepatocellular carcinoma in the next 3 years by risk scores. Results adopted from Wong *et al*<sup>[22]</sup>. HCC: Hepatocellular carcinoma.

**Table 4** Dynamic changes in risk scores and 5-year risk of hepatocellular carcinoma

Risk score		HCC in 5 yr		
		CU-HCC	GAG-HCC	REACH-B <sup>1</sup>
Low	Low	0.4%	1.4%	0.0%
Low	High	0.0%	NA	0.0%
High	Low	2.1%	5.1%	0.0%
High	High	12.9%	26.4%	2.1%

<sup>1</sup>Only patients without cirrhosis were analyzed for the REACH-B score. Results adopted from Wong *et al*<sup>[22]</sup>. HCC: Hepatocellular carcinoma; NA: Not available.

The dynamic changes in risk scores after antiviral therapy had a significant meaning on HCC risk. For all three risk scores, patients persistently in the low-risk category had the lowest risk of HCC; those “downgraded” in risk category had a significantly lower risk of HCC compared to those in the high-risk category (Table 4)<sup>[22]</sup>. Only 0.4% of patients who remained at low risk at baseline and 2 years according to the CU-HCC score would develop HCC in 5 years; the corresponding figures were 2.1% and 12.9% in those who changed from high risk to low risk, and those who remained at high risk at both time points, respectively. With the GAG-HCC score, 1.4%, 5.1% and 26.4% of patients who remained at low risk, changed from high to low risk, and remained at high risk developed HCC in 5 years, respectively. The results from both the CU-HCC and GAG-HCC score showed that downgrading of risk score reduces, but does not eliminate the risk of HCC (Figure 1).

## CLINICAL APPLICATION OF RISK SCORES

The risk scores discussed above are simple to use as they combine a few widely available clinical variables for the estimation of HCC risk within a specific timeframe. However, the version of the GAG-HCC score which includes core promoter mutations as a component may not be preferred by clinicians, as tests for these mutations are not easily accessible in the primary care setting and general practitioners taking care of the majority of CHB patients. The simple calculations in these scores facilitate implementation in routine clinical use. However, the complexity of these calculations is less of a concern as web-based or smart phone apps which include calculators for some of these scores are now available<sup>[30,31]</sup>. The major limitation of these scores is that all studies only involve Asian (mostly Chinese) patients, therefore, the validity and applicability in other ethnic groups remain uncertain. These risk scores can potentially be incorporated into a clinical risk-prediction instrument that could improve patient management through appropriate and timely intervention. Clinicians could use the scores to assess the risk of progression, and subsequently make evidence-based decisions about the clinical management of these patients. A recent Japanese study showed that patients in the high-risk categories according to these risk scores would benefit most from entecavir<sup>[5]</sup>. Another long-term follow-up study of 641 patients receiving tenofovir for 6 years showed that the observed incidence of HCC was lowered compared to the predicted risk us-

ing the REACH-B score<sup>[32]</sup>. This is indirect evidence that antiviral therapy reduces the risk of HCC.

We advocate estimating the risk scores for all CHB patients. For treatment-naïve patients, the results of these scores may guide the need for antiviral therapy complementary to the treatment guidelines. The scores should be monitored regularly every 1 to 2 years. Patients remaining at low risk are suitable for regular monitoring in the primary care setting. Those at high risk should be referred for specialist care and appropriate treatment should be considered.

For patients receiving antiviral therapy, the risk scores should be monitored yearly. Those who respond well to treatment, *i.e.*, achieve maintained virologic remission, and remain in the low-risk category have a minimal risk of HCC. Therefore, they may also be referred to family physicians who are experienced in monitoring such patients. Patients with risk downgraded after treatment would have a lower, but 2% to 5% risk of HCC in 5 years. Therefore, they should undergo regular HCC surveillance<sup>[33]</sup>. Those in the high-risk category despite antiviral therapy may require more intensive HCC surveillance, as the risk of HCC can be as high as 12.9% to 26.4% in 5 years (Table 3). On the other hand, patients who fail to achieve maintained viral suppression should consider alternative treatment regimes in order to reduce the risk of HCC<sup>[34]</sup>.

## FUTURE DIRECTION

One potential problem with these risk scores is that heavy weighting is assigned to cirrhosis in CU-HCC and GAG-HCC. In the study of the REACH-B score, liver cirrhosis was excluded by ultrasonography. As early cirrhosis may be missed by ultrasonography, this limitation may lead to substantial prediction errors if the presence or absence of cirrhosis is misclassified<sup>[35]</sup>. Transient elastography is one of the most widely validated non-invasive tools to detect early liver cirrhosis in various chronic liver diseases<sup>[36]</sup>. Liver stiffness measurement (LSM) with this tool may be useful to refine the diagnosis of cirrhosis and substitute clinical cirrhosis as a component in the risk score to predict HCC. There is evidence that LSM can predict HCC<sup>[37]</sup>, patient survival<sup>[38]</sup> as well as complications after hepatic resection<sup>[39]</sup>. Therefore, it is reasonable to believe that LSM would be an important parameter in a HCC risk score.

A recent Korean study of 1250 CHB patients developed a predictive model for HCC using four clinical parameters, which included age, gender, HBV DNA and LSM value<sup>[40]</sup>. The probability equals  $1 - P^A$ ; where  $A = \exp(0.05306 \times \text{age} + 1.106 \times \text{male gender} + 0.04858 \times \text{LSM values} + 0.50969 \times \text{HBV DNA} \geq 20000 \text{ IU/L})$ . This model was found to have a moderately good discrimination capability, with an AUROC of 0.81. The predicted risk of HCC development correlated fairly well with the observed risk ( $r = 0.91$ ). More data concerning the role of LSM in the HCC risk score is now evolving<sup>[41]</sup>.

## CONCLUSION

In conclusion, HCC risk scores can accurately predict subsequent HCC development in both treatment-naïve patients and in those receiving antiviral therapy. Different levels of care and different intensities of HCC surveillance should be offered according to the risk profile of patients. Patients in the high-risk category should be one of the indications for antiviral therapy, as well as appropriate HCC surveillance. For patients receiving antiviral therapy, maintained virologic response should be the treatment target, particularly in patients with cirrhosis. Patients at risk of HCC should undergo regular HCC surveillance, even when they are receiving antiviral treatment.

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