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.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer death in men worldwide[1]. 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[2]. Globally, HBV accounts for 53% of all cases of HCC[3]. 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[9].

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[6-7]. 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[8-10], male gender[9,10], family history of HCC[11], 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][12,13]. Immunosuppressed conditions like human immunodeficiency virus co-infection is another risk factor[6]. Liver factors consist of advanced fibrosis and cirrhosis[11]; poor liver function as evidenced by hypoalbuminemia and hyperbilirubinemia[11]; active hepatitis as evidenced by high alanine aminotransferase (ALT) and active necroinflammation demonstrated on liver biopsy[6]; 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[11,13]. Viral factors include high serum HBV DNA level[8,13], hepatitis B virus e antigen (HBeAg) seropositivity[6], HBV genotype C[17] and subgenotype Ce[18], core promoter mutations[10] and probably high serum hepatitis B surface antigen (HBsAg) level[9].

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[6]. 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 | Hypoalbuninemia | HBV genotype C |
| SNP at human genomic loci, e.g. | Hyperbilirubinemia | HBV subgeno-type Ce |
| Chromosome 1p36.22 | High ALT | Core promoter mutations |
| Chromosome 6 of HLA-DP/Q loci | Active necroinflammation | High serum HBsAg level |
| Chromosome 8p12 | Concomitant liver diseases, e.g. | |
| Immunosuppressed condition, e.g. | Hepatitis C virus co-infection | |
| Human immunodeficiency virus co-infection | Hepatitis delta virus co-infection | |
| Family history of HCC | Alcoholic liver disease | |
| Male gender | 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; SNV: 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/mm³ were independent risk factors for HCC[21]. 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[21]. 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[22]. 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
SUMMARIZING THE FINDINGS OF THESE STUDIES, ADVANCED
AGE AND CIRRHOsis ARE THE TWO MAJOR RISK FACTORS CONSIS-
TENTLY DEMONSTRATED IN PATIENTS RECEIVING ANTIVIRAL THERAPY.
WHile MAINTAINED VIROLOGIC RESPONSE IS LIKELY A PROTECTIVE
FACTOR, BASELINE HBV DNA LEVEL IS NO LONGER IMPORTANT IN
THEREOF PATIENTS AS FUNDAMENTALLY 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. However, THIS WAS NOT
CONFIRMED IN PATIENTS RECEIVING ENTECAVIR. The PROBABLE
REASON FOR THIS IS THAT THESE PATIENTS HAD ACTIVE DISEASE TO
START WITH; THOSE WITH LOW HBsAg LEVELS WERE MORE LIKELY TO
BE CIRRHOTIC. In OTHER WAYS, THERE WERE NO “INACTIVE
HBV CARRIERS” AT VERY LOW RISK OF HCC AS IN TREATED
NATURAL HISTORY COHORTS.

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 as-
nigned 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.
This validation involves using a single observation from
the original sample as the validation data, and the remain-
ing observations as the training data. This is repeated
such that each observation in the sample is used
only as the validation data.

Take the CU-HCC score as an example, significant
variables were first identified in the multivariable Cox
proportional hazards model. 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.

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, sensitiv-
ity, 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.

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 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
hong Kong University (abbreviated as CU in the name of the score). It was validated in an in-
dependent cohort of 424 Chinese CHB patients. Both
cohorts were from tertiary referral clinics. While all pa-
ents 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 investiga-
gors 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 was first developed from a co-
hort of 820 Chinese CHB patients from tertiary referral
clinics. The name was abbreviated from “Guide with Age,
Gender, HBV DNA, Core promoter mutations and Cirrhi-
sis”. 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 investi-
gators adopted the leave-one-out cross-validation men-
tioned above. There are two versions of the score. The
original version is composed of gender, age, core pro-
moter mutations, HBV DNA level and cirrhosis. There
is a simplified version which omits core promoter muta-
tions, 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 high 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 ex-
clude future HCC development.

REACH-B score

The REACH-B score was first derived from a cohort of
3584 Chinese CHB patients from the community-
based prospective Taiwanese REVEAL-HBV study, 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

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cohort did not have cirrhosis according to ultrasonography at the time of recruitment, and remained treatment-naive 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 was found to be accurate in predicting HCC in 3 and 5 years. Of these scores, the CU-HCC score had the highest AUROC 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 scores, respectively, after 2 years of entecavir[22]. One unresolved issue is the regression of cirrhosis, which may occur after long-term antiviral therapy[28,29]. However, as this regression takes years to happen, its effect on the 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 ± 13 mo[22]. 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 AUROC 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.

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### 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 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.

### Table 2  Components of the risk scores

| Factor |CU-HCC | GAG-HCC (yr) | REACH-B |
|--------|-------|-------------|---------|
| Age (yr) |≤ 50: 0 | 30-34: 0 | 35-39: 1 |
| | >50: 3 | 40-44: 2 | 45-49: 3 |
| | | 50-54: 4 | 55-59: 5 |
| | | 60-65: 6 | > 6 log: 4 |
| Sex |NA | Male: 16 | Female: 0 |
| | | Male: 2 | Female: 0 |
| Albumin (g/L) | < 35: 20 | NA | NA |
| | > 35: 0 | NA | NA |
| Bilirubin (mmol/L) | < 18: 1.5 | NA | NA |
| | | < 15: 0 | 15-44: 1 |
| | | ≥ 45: 2 | (lack of maintained virologic suppression: 4) |
| ALT (U/L) | NA | NA | Positive: 2 |
| | | | Negative: 0 |
| HBeAg | NA | NA | (lack of maintained virologic suppression: 4) |
| HBV DNA (copies/mL) | < 4 log: 0 | 3 × in log | < 4 log: 0 |
| | 4-6 log: 1 | 4-5 log: 3 | 4-5 log: 3 |
| | > 6 log: 4 | 5-6 log: 5 | ≥ 6 log: 4 |
| Cirrhosis | Presence: 15 | Presence: 33 | NA |
| | Absence: 0 | Absence: 0 | Absence: 0 |

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

| Score | Patients | Components | Cutoff value | Performance value |
|-------|---------|------------|--------------|------------------|
| 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.

ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; NPV: Negative predictive value.
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)\(^{22}\).

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).

### 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\(^1\) |
|------------|------------|--------|---------|----------------|
| Baseline   | 2 yr       |        |         |                |
| 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%           |

\(^1\)Only patients without cirrhosis were analyzed for the REACH-B score. Results adopted from Wong et al\(^{22}\). HCC: Hepatocellular carcinoma; NA: Not available.

The 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\(^{30,31}\). 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\(^5\). 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\[33\]. This is indirect evidence that antiviral therapy reduces the risk of HCC.

We advocate estimating the risk scores for all CHB patients. For treatment-naive 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\[38\]. 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\[34\].

**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 absence of cirrhosis is misclassified\[39\]. Transient elastography is one of the most widely validated non-invasive tools to detect early liver cirrhosis in various chronic liver diseases\[40\]. 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\[41\], patient survival\[42\] as well as complications after hepatic resection\[9\]. 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\[43\]. The probability equals 1 - P; where $\Lambda = \exp (0.05306 \times age + 1.106 \times male gender + 0.04858 \times LSM values + 0.50969 \times HBV DNA \geq 30000 IU/L)$. 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\[41\].

**CONCLUSION**

In conclusion, HCC risk scores can accurately predict subsequent HCC development in both treatment-naive 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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