강력한 항바이러스 치료가 보편적으로 가능한 시대에서 만성 B형간염 환자의 간암 발생 예측 모델

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Hepatocellular Carcinoma Prediction Models for Patients with Chronic Hepatitis B Virus Infection in the Era of Potent Antiviral Therapy

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Appropriate prediction of hepatocellular carcinoma (HCC) development is of paramount importance in terms of decision on antiviral therapy and HCC surveillance. To date, many HCC risk prediction models had been derived based on well-known risk factors such as age, male gender, the degree of fibrosis, and serum hepatitis B virus (HBV)-DNA load. Overall, such models showed high negative predictive values of approximately >90%, excluding the possibility of HCC development in 3 to 10 years with considerable accuracy. On the other hands, on the basis that potent antiviral therapy can substantially reduce the risk of HCC, its indications are steadily getting expanded for prevention of disease progression. Since antiviral therapy is a very strong disease modifier, the uniform application of HCC risk scores developed before the era of potent antiviral therapy would overestimate the risk of HCC. Furthermore, the tools to assess the fibrotic burden have remarkably evolved, from subjective determination based upon clinical symptom sign and ultrasonographic finding to more objective and delicate non-invasive tests based upon imaging and/or serological methods. Therefore, in the current era of potent antiviral therapy, the clinical significance of recently developed HCC risk models for patients with chronic HBV infection should be reappraised further. (*J Liver Cancer* 2018;18:87-93)

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INTRODUCTION

It is critically important to identify a certain subgroup at

high risk for hepatocellular carcinoma (HCC) occurrence among patients with chronic hepatitis B virus (HBV) infection, since chronic HBV infection is the leading cause of liver cirrhosis and HCC, affecting over 350 million people worldwide.¹⁻³ To date, the factors associated with HCC occurrence among a population with chronic HBV infection, including male gender, old age, advanced liver fibrosis or cirrhosis, and a high serum HBV-DNA level, have been extensively studied.⁴⁻⁷ Based upon these findings, several HCC risk predic-

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tion models composed of multiple parameters have been developed recently, with promising results.⁸⁻¹² On the other hands, on the basis that potent antiviral therapy can substantially reduce HCC risk, its indications are steadily getting expanded for prevention of disease progression.¹³⁻¹⁵ Since antiviral therapy is a very strong disease modifier, the uniform application of HCC risk scores developed before the era of potent antiviral therapy in a current real clinical setting without appropriate consideration of virological characteristics would provide the information out of touch with reality. Furthermore, the development of new biomarkers based upon serological and imaging studies would facilitate the more precise prognostification in each individual. Here, this review discusses the development and application of HCC risk scores (Table 1) and highlights their current status in the era of potent antiviral therapy.

HCC RISK PREDICTION MODELS IN THE UNTREATED NATURAL HISTORY COHORTS

1. The guide with age, gender, HBV-DNA, core promoter mutations and cirrhosis (GAG-HCC)

The guide with age, gender, HBV-DNA, core promoter mutations and cirrhosis (GAG-HCC) score was developed from a cohort of 820 Chinese patients with chronic HBV infection.^{11,16} The original version used five parameters: gender, age, serum HBV-DNA level, and the presence of cirrhosis and core promoter mutations. However, the test for core promoter mutations was not available in some centers, and the score was thus simplified to omit these mutations. The score can exceed 100, because age is one of the components. A cutoff value of 101 had a respective sensitivity and a specificity of 84.1% and 76.2% for 5-year prediction and 88.0% and 78.7% for 10-year prediction. The negative predictive values for excluding HCC development in the future were 98.3-100%.

Table 1. Summary of HCC prediction models

	GAG-HCC	REACH-B	CU-HCC	LSM-HCC	mREACH-B	PAGE-B	mPAGE-B
No. of patients	820	3,584	1,005	1,035	1,308	1,619	2,001
Country	Hong Kong	Taiwan	Hong Kong	Hong Kong	Korea	Europe	Korea
Race	Asian	Asian	Asian	Asian	Asian	Caucasian	Asian
Age (years)	40.6	45.7	48	46	50	53	50
HBeAg-negative (%)	56.6	84.8		75	60.3	84	66.1
Cirrhosis (%)	15.1	0	38.1	32	17.8	30	19.1
Follow-up (years)	5.62	12	9.94	5.8	6.3	3.3	4.1
Antiviral therapy (%)	0	0	15.1	38	64.8	100	100
HCC development, n (%)	40 (4.9)	131 (3.7)	105 (10.4)	38 (3.7)	125 (9.6)	56 (3.5)	131 (6.5)
Components of risk model	Age Male BCP mutation Cirrhosis HBV DNA	Age Male ALT HBeAg-positive HBV DNA	Age Albumin Bilirubin Cirrhosis HBV DNA	Age Albumin HBV DNA LSM value	Age Male ALT HBeAg-positive LSM value	Age Male Platelet	Age Male Platelet Albumin
Risk stratification	Low (<101) High (≥101)	Low (<8) High (≥8)	Low (≤4) Intermediate (5-20) High (≥21)	Low (<11) High (≥11)	Low (<10) High (≥10)	Low (≤9) Intermediate (10-17) High (≥18)	Low (≤8) Intermediate (9-12) High (≥13)
NPV (%)	99% at 10 years	98% at 10 years	97% at 10 years	99.4% at 5 years	96.8% at 5 years	100% at 5 years	96.3% at 5 years

HCC, hepatocellular carcinoma; HBeAg, hepatitis B e antigen; BCP, basal core promoter; HBV, hepatitis B virus; ALT, alanine aminotransferase; LS, liver stiffness; NPV, negative predictive value.

2. Nomogram (NGM) 1-HCC and NGM2-HCC

The risk evaluation of viral load elevation and associated liver disease (REVEAL)-HBV investigators first suggested easy-to-use nomograms based on noninvasive clinical characteristics.⁹ Previously confirmed risk predictors were as follows; gender, age, family history of HCC, alcohol consumption habit, serum alanine aminotransferase (ALT) level, hepatitis B e antigen (HBeAg) serostatus, serum HBV-DNA level, and HBV genotype. Regression coefficients were rounded to yield integer risk scores, and the predicted risk over 5- and 10-year periods for each risk score was calculated and depicted as nomograms. NGM1-HCC and NGM2-HCC were used to calculate individual baseline risk scores for each patient. The patients were categorized into low-, medium-, and high-risk groups to facilitate comparison of the risk scores of the different prediction models, and to simplify their use.

3. The risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B)

The REACH-B score was derived from the Taiwanese REVEAL cohort, and validated in 1,505 patients with chronic HBV infection in Hong Kong and the Republic of Korea.^{10,16} This model included variable included sex, age, serum ALT level, HBeAg status, and HBV-DNA level. During follow-up, HCC developed in 131 patients (3.7%) in the training cohort and 111 patients (7.4%) in the validation cohort. A 17-point risk score was developed and the HCC risk ranged from 0-23.6%, 0-47.4%, and 0-81.6% at 3, 5, and 10 years, respectively. Because the risk of HCC increased significantly at 8 points, this was used as a cutoff value to categorize the level of risk.

HCC RISK PREDICTION MODELS IN THE POTENT ANTIVIRAL THERAPY ERA

While above mentioned models, GAG-HCC, NGM1-HCC, NGM2-HCC, and REACH-B included only untreated patients with chronic HBV infection, several recently devel-

oped models included in part patients undergoing antiviral therapy in their cohorts. Nowadays, the practice guidelines recommend entecavir or tenofovir, which have high genetic barriers to resistance, as the first-line treatment option.^{15,17} Therefore, the prognostic significance of a biological gradient of serum HBV-DNA level measured at given time points during the disease course has substantially diminished, because most treated patients will eventually achieve virological response. Consequently, there might be a considerable concern over whether the earlier risk prediction models heavily relying on serum HBV-DNA level at a particular time point can accurately determine the risk of HCC development in the future. Considering that antiviral therapy is a very strong disease modifier, the universal application of HCC risk scores developed before the era of potent antiviral therapy would overestimate the risk of HCC.

1. The Chinese University (CU)-HCC

The CU-HCC score was derived using a cohort of Chinese patients with chronic HBV infection undergoing HCC surveillance at the Chinese University of Hong Kong.^{8,16} During follow-up, antiviral therapy was given to 15.1% patients in the training cohort and 25.0% in the validation cohort. The CU-HCC score is composed of five factors: age, serum albumin level, serum bilirubin level, serum HBV-DNA level, and cirrhosis; it ranges from 0 to 44.5. Two cutoff values of 5 and 20 were used to classify HCC risk into three categories. HCC developed in 105 patients (10.4%) in the training cohort and 45 patients (10.6%) in the validation cohort. The 5-year HCC-free survival rates were 98.3%, 90.5%, and 78.9% in the low-, medium-, and high-risk groups, respectively. Using the lower cutoff of 5 points, this score has a high negative predictive value (97.8%) for excluding HCC development in the future.

2. The liver stiffness measurement (LSM)-HCC score

The LSM-HCC score is composed of LSM by transient elastography (TE), age, serum albumin, and HBV-DNA lev-

el.¹² Because a diagnosis of cirrhosis based on ultrasonography may be incorrect, LSM replaced a diagnosis of cirrhosis as a factor in the CU-HCC score. After a mean follow-up of 69 months, 38 patients (3.7%) in the training cohort and 17 patients (3.4%) in the validation cohort developed HCC. The LSM-HCC score ranged from 0 to 30. Using 11 as the cutoff value, 706 (68.2%) and 329 (31.8%) patients were in the low- and high-risk categories, respectively, and four (0.6%), and 29 (8.8%) of these patients developed HCC over 5 years.

3. Modified REACH-B (mREACH-B)

As a pilot study, mREACH-B model was developed, where serum HBV-DNA level was substituted for LSM value by TE among patients who achieved complete virological response through entecavir therapy.¹⁸ As a result, the better overall predictive performances of mREACH-B model, compared to the area under the receiver operating characteristic curve (AUROC) 0.629 (95% confidence interval [CI], 0.500-0.786) of original REACH-B scoring system, were observed; the AUROC value for risk of HCC at the 3-year follow-up was 0.805 (95% CI, 0.678-0.925) when 0, 1, and 2 points were assigned to LS values of <8.0, 8.0-13.0, and >13.0 kPa, respectively (mREACH-B I) and that was 0.814 (95% CI, 0.709-0.912) when 0, 2, and 4 points were assigned to LS values of <8.0, 8.0-13.0, and >13.0 kPa, respectively (mREACH-B II). In a subsequent validation study based upon a large population which enrolled a total of 1308 patients with chronic HBV infection, mREACH-B model (more exactly, mREACH-B II model) had consistently higher AUROCs for prediction of HCC development at 3- and 5-years, compared to LSM-HCC, GAG-HCC, REACH-B, and CU-HCC scores.¹⁹ Notably, in this study, authors tried to re-calculate AUROCs after excluding serum HBV-DNA level from the formula of REACH-B score, using only 4 variables, gender, age, serum ALT level, and HBeAg status, to find the trend toward the paradoxically better AUROCs in comparison with those by the original REAH-B score. As a matter of fact, all of the established scoring systems (LSM-HCC, GAG-HCC, REACH-B, and CU-HCC scores) included serum

HBV-DNA level in their equations, however, it might paradoxically compromise the predictive performances of the risk prediction models among entire population and in particular, those undergoing antiviral therapy. Therefore, we can cautiously speculate that incorporating a high serum HBV-DNA level measured at particular time points before the commencement of antiviral therapy into the equations might be inappropriate and that serum HBV-DNA level should be handled cautiously in accordance with status of viral activity and antiviral therapy of each individual.

4. PAGE-B

A new score named PAGE-B was developed for Caucasian patients with chronic HBV infection.²⁰ This was the first HCC risk score developed for Caucasian patients and patients treated with currently recommended first-line antivirals with a high genetic barrier. A nine-center cohort study included 1,815 patients with chronic HBV infection treated with entecavir or tenofovir for more than 1 year. The PAGE-B score was developed based on age, gender, and platelet count. During follow-up, HCC developed in 51 patients (3.8%) in the derivation group and 34 patients (6.9%) in the validation group. Patients with PAGE-B scores of ≤ 9 , 10-17, and ≥ 18 had 5-year cumulative HCC incidences of 0%, 3% and 17%, respectively. In the validation cohort, the negative predictive value for excluding HCC using a cut-off of 10 points approached 100%. Notably, PAGE-B model do not include serum HBV-DNA level measured at a given point, however, it showed the acceptable predictive performance (c-index=0.82, 0.81 after bootstrap validation in training cohort and 0.82 in the validation dataset).

5. Modified PAGE-B (mPAGE-B)

The mPAGE-B recently suggested predicting HCC development during the first 5 years of antiviral treatment in Asian patients with CHB.²¹ The mPAGE-B score was developed based on age, gender, platelet counts, and albumin levels (time-dependent AUROC 0.82). The 5-year cumulative HCC incidence rates were 6.5% and 7.2% in the derivation (n=2,001)

and validation datasets (n=1,000) after entecavir/tenofovir onset. In the validation set, the AUROC of mPAGE-B at 5 years was 0.82 significantly higher than the other models (PAGE-B, Toronto HCC risk index, CU-HCC, GAG-HCC, and REACH-B). With a scoring range from 0 to 21 points, a modified PAGE-B score differentiates the HCC risk. A modified PAGE-B score significantly differentiates the 5-year HCC risk: low ≤ 8 points and high ≥ 13 points. The 5-year cumulative probabilities of HCC development in the patients in the low (≤ 8), intermediate (9-12), and high (≥ 13) mPAGE-B score groups were 0.7%, 5.1%, and 18.4%, respectively

6. Other TE-based prediction model of HCC occurrence at 3 years

Another novel TE-based predictive model for the occurrence of HCC at 3 years was devised based on a single tertiary hospital-based cohort in the Republic of Korea.²² Among 1,250 patients with chronic HBV infection, HCC occurred in 56 (4.5%) during a median follow-up of 30.7 months. The predictive model for HCC occurrence was determined based on a Cox proportional hazards model. The authors developed a predictive model for HCC occurrence at 3 years using the objective variables (age, male gender, LSM value, and HBV-DNA level $\geq 20,000$ IU/L). The suggested formula for 3-year probability of HCC occurrence is as follows: probability = $1 - P^A$ ($A = \exp [0.05306 \times \text{age} + 1.106 \times \text{male gender} + 0.04858 \times \text{LS values} + 0.50969 \times \text{serum HBV-DNA level} \geq 20,000 \text{ IU/L}]$). The correlation coefficient between predicted risk and observed risk of HCC occurrence was 0.905 with a good discrimination capability of an AUROC of 0.806 (95% CI, 0.738-0.874). However, external validation in different populations with different virological status is still needed.

CANDIDATES AS NEW SEROLOGICAL BIOMARKERS IN THE FUTURE TO PREDICT RISK OF HCC DEVELOPMENT

The clinical significance of quantitative hepatitis B surface antigen (qHBsAg) as a new biomarker to assess the viral activity became increasingly recognized. Since hepatitis B sur-

face antigen (HBsAg) originates from both mature virions and defective particles, serum qHBsAg level indicates not only cccDNA transcription or mRNA translation, but also host immune control over HBV infection.⁷ Furthermore, qHBsAg was better than serum HBV-DNA level in terms of prediction of spontaneous HBsAg loss in HBeAg-negative carriers with a low viral load ($< 2,000$ IU/mL) and qHBsAg level < 10 IU/mL was the strongest predictor of HBsAg loss in patients with a low viral load.²³ The potential role of qHBsAg to predict the risk of HCC was demonstrated in the subsequent studies.^{24,25} In HBeAg-negative patients with low viral loads and genotype B or C virus infection, HBsAg $< 1,000$ IU/mL in combination with low levels of HBV DNA and ALT help define minimal-risk HBV carriers. More recently, serum HBV core-related antigen (HBcrAg) level has been shown to be associated with HCC development.²⁶⁻²⁸ For untreated patients, Tada et al.²⁶ indicated that serum HBcrAg $> 2.9 \log \text{ U/mL}$ was an independent predictor of HCC development with hazard ratio of 5.05 and that its time-dependent AUROCs were superior to serum HBV-DNA level. More importantly, for patients undergoing oral antiviral therapy for at least 2 years, HBcrAg positivity also proved to be an independent risk factor for HCC.²⁹

On the other hands, genetic variations in HBV genome are closely associated with molecular mechanisms of carcinogenesis. First, molecular variants in HBV genome occur due to spontaneous errors during replication, or as the consequence of selection pressure by the host immune system and/or by exogenous factors. Variations in pre-core, core promoter, X and pre-S/S genes have been reported to be associated with the disease progression such as development of cirrhosis and HCC.³⁰⁻³³ For example, Yuen et al.¹¹ incorporated core promoter mutations into a predictive score. Furthermore, HBV genotypes may influence the long-term prognosis of patients with chronic HBV infection.^{34,35} HBV genotype C, D, and F were more associated with an increased risk of HCC.^{31,36} In contrast, patients with HBV genotype A and B are less susceptible to HCC development.³³ It should be noted that HBV genotypes usually have specific geographic distribution and that some sub-genotypes had specific patterns of HBV genomic mutation. Therefore, comprehensive analysis between

HBV molecular variations and risk of HCC should be further required.

CONCLUSIONS

HCC risk prediction models generally demonstrate high negative predictive values to exclude HCC development in the next 3 to 10 years. In the current era of potent antiviral therapy, the uniform application of HCC risk scores without appropriate consideration of virological characteristics would hinder an optimal risk assessment. A more accurate risk model that incorporates newly identified serological and molecular biomarkers will facilitate more precise estimation of an individual risk. Furthermore, from the perspective of cost-effectiveness, different levels of care and different intensities of HCC surveillance could be offered on the basis of the patient's individual risk profile.

Conflicts of Interest

The authors have no conflicts to disclose.

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