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**Prediction models of hepatocellular carcinoma development in chronic hepatitis B patients**

Lee HW *et al*. Prediction of HCC development

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**Abstract**

Chronic hepatitis B virus (HBV) infection is a major cause of cirrhosis and hepatocellular carcinoma (HCC). Applying the same strategies for antiviral therapy and HCC surveillance to all chronic hepatitis B (CHB) patients would be a burden worldwide. To properly manage CHB patients, it is necessary to identify and classify the risk for HCC development in such patients. Several HCC risk scores based on risk factors such as cirrhosis, age, male gender, and high viral load have been used, and have negative predictive values of ≥ 95%. Most of these have been derived from, and internally validated in, treatment-naïve Asian CHB patients. Herein, we summarized various HCC prediction models, including IPM (Individual Prediction Model), CU-HCC (Chinese University-HCC), GAG-HCC (Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis-HCC), NGM-HCC (Nomogram-HCC), REACH-B (Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B), and Page-B score. To develop a noninvasive test of liver fibrosis, we also introduced a new scoring system that uses liver stiffness values from transient elastography, including an LSM (Liver Stiffness Measurement)-based model, LSM-HCC, and mREACH-B (modified REACH-B).

**Key words:** Chronic hepatitis B; hepatocellular carcinoma; development; prediction models

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**Core tip:** This is the summary about prediction models of hepatocellular carcinoma development in chronic hepatitis B patients.

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**Introduction**

Chronic hepatitis B virus (HBV) infection is the main cause of cirrhosis, hepatic failure, and hepatocellular carcinoma (HCC) globally[[1](#_ENREF_1)]. Of chronic HBV carriers, approximately 15%-40% develop chronic hepatitis B (CHB)[[2](#_ENREF_2)]. Around 90% of CHB patients undergo seroconversion of HBeAg to anti-HBe and become inactive carriers. However, approximately 10% of CHB patients have chronic active hepatitis and develop liver cirrhosis at a rate of 2% per year. Because progression of liver disease in CHB patients is closely associated with active viral replication, a high level of HBV DNA has been known as an independent risk factor for disease progression. Therefore, suppression of HBV with antiviral therapy could reduce the risk of developing cirrhosis and HCC.

The development of potent antiviral drugs has an important role in the management of patients with CHB. The natural course of the disease could be modified by HBV therapy and risk for HCC could be reduced[[3-5](#_ENREF_3)]. Antiviral therapy reduces, but does not completely eliminate risk for HCC[[6](#_ENREF_6),[7](#_ENREF_7)]. The annual incidence of HCC range from 0.01% to 5.4% in CHB patients treated with entecavir or tenofovir[[8](#_ENREF_8)]. Therefore, applying a standardized policy for antiviral therapy and HCC surveillance to all CHB patients may not be cost-effective[[9](#_ENREF_9)]. Thus, stratification of the risk for HCC development is important for the management of CHB patients.

This review summarizes the prediction models of HCC development in CHB patients.

**Risk factors for HBV-related HCC**

Risk factors for disease progression in CHB can be classified into three categories: host factors, viral factors and liver factors[[4](#_ENREF_4),[10](#_ENREF_10),[11](#_ENREF_11)]. Host factors include older age, male gender, family history of HCC, obesity, genetic susceptibility such as single-nucleotide polymorphisms, cirrhosis, smoking, alcohol, diabetes mellitus and immune status[[11-16](#_ENREF_11)]. Viral factors include a high level of HBV DNA, positive hepatitis B virus e antigen (HBeAg), HBV genotype, HBV mutants, and a high serum level of hepatitis B surface antigen (HBsAg)[[16-22](#_ENREF_16)]. Particularly, an increasing viral load is a strong predictor of the risk for HCC independent of HBeAg, aminotransferase, and cirrhosis[[12](#_ENREF_12),[13](#_ENREF_13),[18](#_ENREF_18),[23](#_ENREF_23)]. Liver factors consist of advance fibrosis and cirrhosis, poor liver function, active hepatitis, and other concomitant liver diseases such as co-infection with hepatitis C virus or, alcoholic and nonalcoholic fatty liver diseases[[11-13](#_ENREF_11),[24-26](#_ENREF_24)].

The progression of liver disease in chronic HBV infection is mediated by active virus replication. The annual incidence of cirrhosis in the overall population with CHB is 2-7%, depending on viral replication status[[27](#_ENREF_27)]. In particular, disease progression is markedly accelerated in patients with active viral replication by up to 15-20%. Currently, a complete virological response (CVR) can be achieved even in CHB patients using potent antiviral therapy. Thus, the prognostic value of the baseline level of HBV DNA, which was suggested by large-scale studies to be a robust prognostic indicator of the “natural” course of chronic HBV infection before the era of antiviral treatment, is limited[[28](#_ENREF_28)]. In the era of antiviral therapy, the prognostic significance of serum levels of HBV DNA has substantially diminished, because most treated patients achieve a virological response[[28](#_ENREF_28)]. More importantly, the risk for developing liver-related events cannot be completely eliminated even in those who achieve a complete virological response; thus, caution is required in so-called “high-risk” patients who may experience disease progression.

**Approaches to developing risk scores**

Factors independently associated with HCC are first identified in a training or derivation cohort[[4](#_ENREF_4),[16](#_ENREF_16)]. Second, scores are assigned to different parameters in the equation to generate the final score. This score is validated in a validation cohort to demonstrate its applicability and reproducibility. If no independent cohort is available, external 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 remaining observations as the training data. This is repeated such that each observation is used as training and validation data.

Validation of the score usually includes discrimination and calibration. Discrimination can be assessed using a receiver operating characteristic (ROC) curve, sensitivity, and specificity[[29](#_ENREF_29),[30](#_ENREF_30)]. 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[[4](#_ENREF_4),[13](#_ENREF_13)].

**HCC risk scores**

Until now, several HCC risk prediction scoring systems have been derived to estimate the risk for HCC development in CHB from baseline parameters[[11-13](#_ENREF_11),[31](#_ENREF_31)]. Almost all the scores were derived from and internally validated in treatment-naïve Asian CHB patients[[23](#_ENREF_23)]. Besides, external validation has been limited to Asian CHB patients or those undergoing treatment with entecavir. Studies including European Caucasian and American patients have shown the models to be somewhat less predictive; however, rates of HCC were very low, significantly limiting the conclusions[[6](#_ENREF_6),[32](#_ENREF_32)].

***Individual prediction model***

Based on the risk factors of 4339 Korean patients, the individual prediction model (IPM) was developed by calculating the relative weights of risk factors, and a screening program for HCC was established[[33](#_ENREF_33)]. Old age, male gender, initial serum AFP level, platelet count, serum albumin, severe liver parenchymal echogenic pattern in ultrasonography and heavy alcohol consumption were significant risk factors for HCC. Based on these risk factors, the IPM was calculated using the following formula: Risk Index (RI) for HCC = eA, A = -6.2543 + (1.7219 × liver cirrhosis) + (1.3145 × old age over 40 years) + (1.2631 × chronic HCV infection) + (0.8257 × AFP > 20 ng/mL) + (0.7754 × chronic HBV infection) + (0.7339 × chronic hepatitis) + (0.5840 × heavy alcoholics) + (0.3 × man) + (0.2830 × ALT > 40 IU/L) + (0.221 × unknown alcohol history). Probability for HCC = RI/(1 + RI). The authors prospectively applied the screening program to 833 patients with chronic liver disease stratified into three groups [a low-risk group (< 5% probability), an intermediate group (5%-15% probability), and high-risk group (> 15% probability)] by IPM. The patients were followed, at intervals that varied according to the risk index. According to IPM, 2 of 324 patients in the low-risk group (0.62%), 20 of 413 patients in the intermediate-risk group (4.8%), and 22 of 96 patients in the high-risk group (22.9%) were diagnosed with HCC. Thus, the screening program based on IPM enabled cost-effective prediction of the risk of developing of HCC by focusing on the high-risk group.

***CU-HCC score***

The Chinese University (CU)-HCC score was first derived using a cohort of 1,005 Chinese CHB patients that had undergone HCC surveillance at the Chinese University of Hong Kong[[4](#_ENREF_4),[12](#_ENREF_12),[25](#_ENREF_25)]. It was validated in an independent cohort of 424 Chinese CHB patients[[34](#_ENREF_34)]. All patients were treatment-naïve at baseline. Among the patients in the training and validation cohort, 15.1% and 25.0%, respectively, received antiviral therapy during the long-term follow-up. The CU-HCC score is composed of five factors: age, albumin, bilirubin, HBV DNA, and cirrhosis; it ranges from 0 to 44.5. Two cutoff values (5 and 20) discriminated HCC risk into three categories. In all, 105 (10.4%) patients in the training cohort and 45 (10.6%) patients in the validation cohort developed HCC during a median of 10 years of follow-up. 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 future HCC development.

***GAG-HCC score***

The Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis (GAG-HCC) score was developed from a cohort of 820 Chinese CHB patients from tertiary referral clinics[[4](#_ENREF_4),[13](#_ENREF_13)]. All patients were treatment-naïve at baseline and followed-up for a median of 77 months. There are two versions of the score. The original version is composed of five parameters: gender, age, core promoter mutations, levels of HBV DNA, and cirrhosis. Because the test for core promoter mutations may not be available in some centers, the score was simplified to omit such mutations. The score can be above 100, as age is one of the components. A cutoff value of 101 had a 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 for excluding future HCC development were 98.3%-100%.

***NGM1-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 using data from 3653 patients[[31](#_ENREF_31)]. Previously confirmed independent risk predictors were sex, age, family history of HCC, alcohol consumption habit, ALT level, HBeAg serostatus, levels of HBV DNA, and HBV genotype. Regression coefficients were rounded to integer risk scores, and the predicted risk over 5- and 10-year periods for each risk score was calculated and depicted as nomograms. Nomogram 1 and Nomogram 2 hepatocellular carcinoma (NGM1-HCC and NGM2-HCC) were used to calculate individual baseline risk scores for each patient[[31](#_ENREF_31)]. The patients were categorized into low-, medium- and high-risk groups to facilitate comparison of the risk scores using the different prediction models, and to simplify their use in the clinical setting. The correlation coefficients between observed HCC risk and the nomogram-predicted risk were greater than 0.90.

***REACH-B score***

The risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B) score was derived using 3584 Chinese CHB patients from the Taiwanese REVEAL cohort, and validated in a cohort of 1505 patients from three tertiary referral clinics in Hong Kong and South Korea[[4](#_ENREF_4),[11](#_ENREF_11)]. The patients in the training cohort did not have cirrhosis at the time of recruitment, and remained treatment-naïve throughout the 12-year follow-up period. Variables included in the risk score were sex, age, serum levels of alanine aminotransferase, HBeAg status, and levels of HBV DNA level. In all, 131 (3.7%) patients in the training cohort and 111 (7.4%) patients in the validation cohort were developed HCC. A 17-point risk score was developed and 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 and highest HCC risks, respectively. The score accurately estimated the risk for developing HCC at 3, 5, and 10 years in patients with CHB. As the risk increased significantly starting at 8 points, this could be used as an arbitrary cutoff value to categorize levels of risk. A revised version of REACH-B that includes serum levels of qHBsAg is also available[[35](#_ENREF_35)].

***PAGE-B score***

Previous risk scores have been developed mainly in Asians. Therefore, these scores may not be suitable for Caucasian patients with CHB. A new score named PAGE-B has recently been developed for Caucasian CHB patients[[36](#_ENREF_36)]. A nine-center cohort study was performed in Caucasian CHB patients treated with oral antivirals[[36](#_ENREF_36)]. They included 1815 adult CHB patients without baseline HCC who received entecavir or tenofovir for more than 1 year. The PAGE-B score was developed based on age, gender, and platelets. During a median of 50 months of follow-up, 51 (3.8%) patients in the derivation group and 34 (6.9%) patients in the validation group developed HCC. 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 to exclude HCC using at a cut-off of 10 points approached 100%. This was the first study to develop an HCC risk score for Caucasian CHB patients and was the first score for patients treated with current first-line antiviral therapies.

**Liver stiffness measurement-based models**

The degree of liver fibrosis is significantly related to risk for HCC development[[37](#_ENREF_37),[38](#_ENREF_38)]. To date, the gold standard for evaluating the degree of fibrosis is liver biopsy. However, liver biopsy cannot be performed in all CHB patients in a clinical setting due to its invasiveness and complications[[39](#_ENREF_39)]. Transient elastography (TE, FibroScan®, Echosens, Paris, France) has been validated as a noninvasive method for assessing fibrosis in chronic liver disease[[40](#_ENREF_40)]. The advantage of TE include its noninvasiveness, highly reproducibility, and accuracy. TE is used as a reliable surrogate for liver biopsy to detect early cirrhosis in patients with CHB[[41](#_ENREF_41)].

For patients with ascites or high BMI, the use of XL probe could be helpful to check liver stiffness[[42](#_ENREF_42),[43](#_ENREF_43)]. Especially, the presence of nonhepatic ascites does not affect underlying liver stiffness by TE[[42](#_ENREF_42)]. A liver stiffness value > 12 kPa or 13 kPa by TE can be used to detect histologic cirrhosis in patients with CHB[[44](#_ENREF_44),[45](#_ENREF_45)]. Furthermore, recent studies have reported TE can predict the development of portal hypertension-related complications and HCC[[46-48](#_ENREF_46)].

***Liver stiffness measurement-based Model***

Stratified baseline liver stiffness values in patients with CHB are independent predictors of HCC development[[38](#_ENREF_38)]. The 3-year cumulative incidence of HCC is significantly higher in patients with a higher liver stiffness value[[38](#_ENREF_38)]. Kim *et al*[[49](#_ENREF_49)] prospectively analyzed 1110 patients with CHB who received a transient elastography and were available for inclusion criteria from May 2005 to December 2007.

A previous multivariate analysis showed that age, male gender, and liver stiffness values independent predictors of HCC (all *P* < 0.05). In addition, HBV DNA levels ≥ 20000 IU/L showed borderline significance. Using these four variables, a predictive model was developed (AUROC 0.806, 95%CI: 0.738-0.874). The formula for a 3-year probability of HCC occurrence is as follows: Probability = 1 - PA [A = exp (0.05306 × age + 1.106 × male gender + 0.04858 × liver stiffness values + 0.50969 × HBV DNA ≥ 20000 IU/L)]. In bootstrap analyses, the AUROC remained largely unchanged between iterations, with an average value of 0.802 (95%CI: 0.791-0.812). The predicted risk for HCC development calibrated well with the observed risk, with a correlation coefficient of 0.905 (*P* < 0.001).

***LSM-HCC score***

Wong *et al*[[50](#_ENREF_50)] developed a new liver stiffness measurement (LSM)-HCC score composed of LSM, age, serum albumin, and levels of HBV DNA. Because diagnosis of cirrhosis based on ultrasonography may be incorrect, cirrhosis as a factor of CU-HCC score was substituted by LSM. Among 1555 CHB patients, 1035 and 520 were assigned to the training and validation cohort, respectively. During a mean of 69 months of follow-up, 38 (3.7%) patients in the training cohort and 17 (3.4%) patients 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; 4 (0.6%), and 29 (8.8%) patients developed HCC over 5 years. The AUROCs of the LSM-HCC score were higher than those of the CU-HCC score (0.83-0.89 *vs* 0.75-0.81). The sensitivity for identifying HCC was 87.9% and the NPV was 99.4% at 5 years.

***Modified REACH-B score***

The REACH-B scoring system, which was developed and validated as a simple HCC prediction model prior to the era of antiviral therapy, showed suboptimal predictive performance. Therefore, an alternative predictor of long-term prognosis is required particularly in CHB patients who had achieved CVR from antiviral treatment, because levels of HBV DNA are no longer useful at the time of CVR.

In the modified REACH-B model (mREACH-B model), the serum levels of HBV DNA were substituted for the LS value, and had better predictive performance among patients who were at CVR following entecavir therapy[[28](#_ENREF_28)]. The authors reassessed the scores at CVR, using LS values instead of suppressed HBV DNA. The AUROC value for risk at the 3-year follow-up was 0.805, compared to 0.629 using the original REACH-B scoring system, when 0, 1, and 2 points were assigned to LS values of < 8.0, 8.0-13.0, and > 13.0 kPa, respectively (referred to as the modified REACH-B I), and 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 (referred to as the modified REACH-B II).

The performance of conventional HCC prediction models (CU-HCC, GAG-HCC, REACH-B, and LSM-HCC scores) and the mREACH-B score has been assessed[[51](#_ENREF_51)]. During the follow-up (median, 75.3 mo), HCC developed in 125 (9.6%) of 1,308 subjects. The mREACH-B score had a significantly higher AUROC for prediction of HCC development at 3/5 years (0.828/0.806), compared to the LSM-HCC (0.777/0.759), GAG-HCC (0.751/0.757), REACH-B (0.717/0.699), and CU-HCC (0.698/0.700) scores (all *P* values < 0.05 *vs* mREACH-B). Thus, the prognostic performance of the mREACH-B score was superior to that of the conventional models.

**Other HCC risk models**

Existing prediction models were mostly developed in Asia. There were limited data about HCC risk models for people at high risk in the United States or European countries. France group suggested *PNPLA3* rs738409 (GG) genotype had an effect on the occurrence of HCC[[52](#_ENREF_52)]. They created the following model: age × 0.05085 - 1.88790 × female gender + BMI × 0.09712 + rs738409 (GG) × 0.78377.

When applied to 250 patients with alcoholic cirrhosis, scores ranged from 2.20-9.25. The cut-off values for calculated score were below 5, between 5 and 7, and above 7, respectively. 6-year incidence of HCC increased according to stratification of three risk groups.

There was another risk prediction model suggested from United States[[53](#_ENREF_53)]. By Cox proportional hazards regression model, clinical and demographic data (including age, sex, smoking status, alkaline phosphatase level, and platelet count) and Epidermal Growth Factor Gene genotype (GG) was used to predict HCC risk. The cohort was stratified into three groups depending on the risk of HCC development.

**Conclusion**

This review summarizes prediction models of HCC development in CHB patients. HCC risk scores can accurately predict subsequent HCC development in CHB patients. Different levels of care and different intensities of HCC surveillance should be offered according to the patient’s risk profile. Patients in the high-risk category should be offered antiviral therapy, as well as appropriate HCC surveillance. Effective suppression of HBV replication by antiviral therapy can reduce risk for HCC development. However, antiviral therapy does not eliminate the HCC risk completely, because of the presence of virus integrated into the host genome. The HCC risk is higher in cirrhotic than non-cirrhotic patients. Antiviral therapy with no risk of resistance such as ETV or TDF should be initiated before cirrhosis occurs.

HCC prediction models can help optimize antiviral therapy based on the level of HCC risk. It should be adjusted for patients who are already on treatment. Decisions regarding who needs treatment and regular surveillance should be individualized using HCC risk prediction models.

**Future perspectives**

In the future, a more accurate risk model that incorporates newly identified risk factors and somatic and inherited biomarkers (e.g., single-nucleotide polymorphisms proteomics) is required for more accurate estimation of risk. Various plasma proteins have been proposed as new biomarkers of genetic background to predict development of HCC. These biomarkers are expected to guide individual surveillance or treatment for CHB patients. However, further functional studies are needed to validate these biomarkers. In addition, simple, user-friendly models for primary care providers would facilitate referral of high-risk patients.

**References**

1 **Fattovich G**, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 2008; **48**: 335-352 [PMID: 18096267 DOI: 10.1016/j.jhep.2007.11.011]

2 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]

3 **Hosaka T**, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, Akuta N, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Kumada H. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology* 2013; **58**: 98-107 [PMID: 23213040 DOI: 10.1002/hep.26180]

4 **Wong GL**, Wong VW. Risk prediction of hepatitis B virus-related hepatocellular carcinoma in the era of antiviral therapy. *World J Gastroenterol* 2013; **19**: 6515-6522 [PMID: 24151375 DOI: 10.3748/wjg.v19.i39.6515]

5 **Liaw YF**, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, Dixon JS, Gray DF, Sabbat J. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; **351**: 1521-1531 [PMID: 15470215 DOI: 10.1056/NEJMoa033364]

6 **Arends P**, Sonneveld MJ, Zoutendijk R, Carey I, Brown A, Fasano M, Mutimer D, Deterding K, Reijnders JG, Oo Y, Petersen J, van Bömmel F, de Knegt RJ, Santantonio T, Berg T, Welzel TM, Wedemeyer H, Buti M, Pradat P, Zoulim F, Hansen B, Janssen HL. Entecavir treatment does not eliminate the risk of hepatocellular carcinoma in chronic hepatitis B: limited role for risk scores in Caucasians. *Gut* 2015; **64**: 1289-1295 [PMID: 25011935 DOI: 10.1136/gutjnl-2014-307023]

7 **Vlachogiannakos J**, Papatheodoridis G. Hepatocellular carcinoma in chronic hepatitis B patients under antiviral therapy. *World J Gastroenterol* 2013; **19**: 8822-8830 [PMID: 24379605 DOI: 10.3748/wjg.v19.i47.8822]

8 **Papatheodoridis GV**, Chan HL, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. *J Hepatol* 2015; **62**: 956-967 [PMID: 25595883 DOI: 10.1016/j.jhep.2015.01.002]

9 **Nouso K**, Tanaka H, Uematsu S, Shiraga K, Okamoto R, Onishi H, Nakamura S, Kobayashi Y, Araki Y, Aoki N, Shiratori Y. Cost-effectiveness of the surveillance program of hepatocellular carcinoma depends on the medical circumstances. *J Gastroenterol Hepatol* 2008; **23**: 437-444 [PMID: 17683496 DOI: 10.1111/j.1440-1746.2007.05054.x]

10 **Chen CJ**, Yu MW, Liaw YF. Epidemiological characteristics and risk factors of hepatocellular carcinoma. *J Gastroenterol Hepatol* 1997; **12**: S294-S308 [PMID: 9407350]

11 **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]

12 **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]

13 **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]

14 **Chan KY**, Wong CM, Kwan JS, Lee JM, Cheung KW, Yuen MF, Lai CL, Poon RT, Sham PC, Ng IO. Genome-wide association study of hepatocellular carcinoma in Southern Chinese patients with chronic hepatitis B virus infection. *PLoS One* 2011; **6**: e28798 [PMID: 22174901 DOI: 10.1371/journal.pone.0028798]

15 **Zhang H**, Zhai Y, Hu Z, Wu C, Qian J, Jia W, Ma F, Huang W, Yu L, Yue W, Wang Z, Li P, Zhang Y, Liang R, Wei Z, Cui Y, Xie W, Cai M, Yu X, Yuan Y, Xia X, Zhang X, Yang H, Qiu W, Yang J, Gong F, Chen M, Shen H, Lin D, Zeng YX, He F, Zhou G. 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**: 755-758 [PMID: 20676096 DOI: 10.1038/ng.638]

16 **Wong VW**, Janssen HL. Can we use HCC risk scores to individualize surveillance in chronic hepatitis B infection? *J Hepatol* 2015; **63**: 722-732 [PMID: 26026875 DOI: 10.1016/j.jhep.2015.05.019]

17 **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/NEJMoa013215]

18 **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]

19 **Andreani T**, Serfaty L, Mohand D, Dernaika S, Wendum D, Chazouillères O, Poupon R. Chronic hepatitis B virus carriers in the immunotolerant phase of infection: histologic findings and outcome. *Clin Gastroenterol Hepatol* 2007; **5**: 636-641 [PMID: 17428739 DOI: 10.1016/j.cgh.2007.01.005]

20 **Wong VW**, Sung JJ. Diagnosis and personalized management of hepatitis B including significance of genotypes. *Curr Opin Infect Dis* 2012; **25**: 570-577 [PMID: 22903232 DOI: 10.1097/QCO.0b013e328357f2f8]

21 **Kao JH**, Chen PJ, Lai MY, Chen DS. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. *Gastroenterology* 2003; **124**: 327-334 [PMID: 12557138 DOI: 10.1053/gast.2003.50053]

22 **Chan HL**, Thompson A, Martinot-Peignoux M, Piratvisuth T, Cornberg M, Brunetto MR, Tillmann HL, Kao JH, Jia JD, Wedemeyer H, Locarnini S, Janssen HL, Marcellin P. Hepatitis B surface antigen quantification: why and how to use it in 2011 - a core group report. *J Hepatol* 2011; **55**: 1121-1131 [PMID: 21718667 DOI: 10.1016/j.jhep.2011.06.006]

23 **Abu-Amara M**, Cerocchi O, Malhi G, Sharma S, Yim C, Shah H, Wong DK, Janssen HL, Feld JJ. The applicability of hepatocellular carcinoma risk prediction scores in a North American patient population with chronic hepatitis B infection. *Gut* 2016; **65**: 1347-1358 [PMID: 25934760 DOI: 10.1136/gutjnl-2014-309099]

24 **Wong GL**, Chan HL, Yiu KK, Lai JW, Chan VK, Cheung KK, Wong EW, Wong VW. Meta-analysis: The association of hepatitis B virus genotypes and hepatocellular carcinoma. *Aliment Pharmacol Ther* 2013; **37**: 517-526 [PMID: 23305043 DOI: 10.1111/apt.12207]

25 **Chan HL**, Tse CH, Mo F, Koh J, Wong VW, Wong GL, Lam Chan S, Yeo W, Sung JJ, Mok TS. High viral load and hepatitis B virus subgenotype ce are associated with increased risk of hepatocellular carcinoma. *J Clin Oncol* 2008; **26**: 177-182 [PMID: 18182659 DOI: 10.1200/jco.2007.13.2043]

26 **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 e13-4 [PMID: 22333950 DOI: 10.1053/j.gastro.2012.02.007]

27 **Hsu YS**, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology* 2002; **35**: 1522-1527 [PMID: 12029639 DOI: 10.1053/jhep.2002.33638]

28 **Lee HW**, Yoo EJ, Kim BK, Kim SU, Park JY, Kim do Y, Ahn SH, Han KH. Prediction of development of liver-related events by transient elastography in hepatitis B patients with complete virological response on antiviral therapy. *Am J Gastroenterol* 2014; **109**: 1241-1249 [PMID: 24957159 DOI: 10.1038/ajg.2014.157]

29 **Hung YC**, Lin CL, Liu CJ, Hung H, Lin SM, Lee SD, Chen PJ, Chuang SC, Yu MW. Development of risk scoring system for stratifying population for hepatocellular carcinoma screening. *Hepatology* 2015; **61**: 1934-1944 [PMID: 25418332 DOI:10.1002/hep.27610]

30 **Wen CP**, Lin J, Yang YC, Tsai MK, Tsao CK, Etzel C, Huang M, Hsu CY, Ye Y, Mishra L, Hawk E, Wu X. Hepatocellular carcinoma risk prediction model for the general population: the predictive power of transaminases. *J Natl Cancer Inst* 2012; **104**: 1599-1611 [PMID: 23073549 DOI: 10.1093/jnci/djs372]

31 **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]

32 **Papatheodoridis GV**, Dalekos GN, Yurdaydin C, Buti M, Goulis J, Arends P, Sypsa V, Manolakopoulos S, Mangia G, Gatselis N, Keskın O, Savvidou S, Hansen BE, Papaioannou C, Galanis K, Idilman R, Colombo M, Esteban R, Janssen HL, Lampertico P. Incidence and predictors of hepatocellular carcinoma in Caucasian chronic hepatitis B patients receiving entecavir or tenofovir. *J Hepatol* 2015; **62**: 363-370 [PMID: 25195548 DOI: 10.1016/j.jhep.2014.08.045]

33 **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]

34 **Chan HL**, Hui AY, Wong ML, Tse AM, Hung LC, Wong VW, Sung JJ. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. *Gut* 2004; **53**: 1494-1498 [PMID: 15361502 DOI: 10.1136/gut.2003.033324]

35 **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]

36 **Papatheodoridis G**, Dalekos G, Sypsa V, Yurdaydin C, Buti M, Goulis J, Calleja JL, Chi H, Manolakopoulos S, Mangia G, Gatselis N, Keskin O, Savvidou S, de la Revilla J, Hansen BE, Vlachogiannakos I, Galanis K, Idilman R, Colombo M, Esteban R, Janssen HL, Lampertico P. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. *J Hepatol* 2016; **64**: 800-806 [PMID: 26678008 DOI: 10.1016/j.jhep.2015.11.035]

37 **Park BK**, Park YN, Ahn SH, Lee KS, Chon CY, Moon YM, Park C, Han KH. Long-term outcome of chronic hepatitis B based on histological grade and stage. *J Gastroenterol Hepatol* 2007; **22**: 383-388 [PMID: 17295771 DOI: 10.1111/j.1440-1746.2007.04857.x]

38 **Jung KS**, Kim SU, Ahn SH, Park YN, Kim DY, Park JY, Chon CY, Choi EH, Han KH. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). *Hepatology* 2011; **53**: 885-894 [PMID: 21319193 DOI: 10.1002/hep.24121]

39 **McGill DB**, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology* 1990; **99**: 1396-1400 [PMID: 2101588]

40 **Kim JH**, Kim MN, Han KH, Kim SU. Clinical application of transient elastography in patients with chronic viral hepatitis receiving antiviral treatment. *Liver Int* 2015; **35**: 1103-1115 [PMID: 24976523 DOI: 10.1111/liv.12628]

41 **Wong GL**. Transient elastography: Kill two birds with one stone? *World J Hepatol* 2013; **5**: 264-274 [PMID: 23717737 DOI: 10.4254/wjh.v5.i5.264]

42 **Kohlhaas A**, Durango E, Millonig G, Bastard C, Sandrin L, Golriz M, Mehrabi A, Büchler MW, Seitz HK, Mueller S. Transient elastography with the XL probe rapidly identifies patients with nonhepatic ascites. *Hepat Med* 2012; **4**: 11-18 [PMID: 24367229 DOI: 10.2147/hmer.s30256]

43 **Sasso M**, Audière S, Kemgang A, Gaouar F, Corpechot C, Chazouillères O, Fournier C, Golsztejn O, Prince S, Menu Y, Sandrin L, Miette V. Liver Steatosis Assessed by Controlled Attenuation Parameter (CAP) Measured with the XL Probe of the FibroScan: A Pilot Study Assessing Diagnostic Accuracy. *Ultrasound Med Biol* 2016; **42**: 92-103 [PMID: 26386476 DOI: 10.1016/j.ultrasmedbio.2015.08.008]

44 **Chan HL**, Wong GL, Choi PC, Chan AW, Chim AM, Yiu KK, Chan FK, Sung JJ, Wong VW. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. *J Viral Hepat* 2009; **16**: 36-44 [PMID: 18673426 DOI: 10.1111/j.1365-2893.2008.01037.x]

45 **Wong GL**, Wong VW, Choi PC, Chan AW, Chan HL. Development of a non-invasive algorithm with transient elastography (Fibroscan) and serum test formula for advanced liver fibrosis in chronic hepatitis B. *Aliment Pharmacol Ther* 2010; **31**: 1095-1103 [PMID: 20180785 DOI: 10.1111/j.1365-2036.2010.04276.x]

46 **Park MS**, Han KH, Kim SU. Non-invasive prediction of development of hepatocellular carcinoma using transient elastography in patients with chronic liver disease. *Expert Rev Gastroenterol Hepatol* 2014; **8**: 501-511 [PMID: 24939348 DOI: 10.1586/17474124.2014.898563]

47 **Kim BK**, Fung J, Yuen MF, Kim SU. Clinical application of liver stiffness measurement using transient elastography in chronic liver disease from longitudinal perspectives. *World J Gastroenterol* 2013; **19**: 1890-1900 [PMID: 23569334 DOI: 10.3748/wjg.v19.i12.1890]

48 **Seijo S**, Reverter E, Miquel R, Berzigotti A, Abraldes JG, Bosch J, García-Pagán JC. Role of hepatic vein catheterisation and transient elastography in the diagnosis of idiopathic portal hypertension. *Dig Liver Dis* 2012; **44**: 855-860 [PMID: 22721839 DOI: 10.1016/j.dld.2012.05.005]

49 **Kim do Y**, Song KJ, Kim SU, Yoo EJ, Park JY, Ahn SH, Han KH. Transient elastography-based risk estimation of hepatitis B virus-related occurrence of hepatocellular carcinoma: development and validation of a predictive model. *Onco Targets Ther* 2013; **6**: 1463-1469 [PMID: 24204161 DOI: 10.2147/ott.s51986]

50 **Wong GL**, Chan HL, Wong CK, Leung C, Chan CY, Ho PP, Chung VC, Chan ZC, Tse YK, Chim AM, Lau TK, Wong VW. Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. *J Hepatol* 2014; **60**: 339-345 [PMID: 24128413 DOI: 10.1016/j.jhep.2013.09.029]

51 **Jung KS**, Kim SU, Song K, Park JY, Kim do Y, Ahn SH, Kim BK, Han KH. Validation of hepatitis B virus-related hepatocellular carcinoma prediction models in the era of antiviral therapy. *Hepatology* 2015; **62**: 1757-1766 [PMID: 26249025 DOI: 10.1002/hep.28115]

52 **Guyot E**, Sutton A, Rufat P, Laguillier C, Mansouri A, Moreau R, Ganne-Carrié N, Beaugrand M, Charnaux N, Trinchet JC, Nahon P. PNPLA3 rs738409, hepatocellular carcinoma occurrence and risk model prediction in patients with cirrhosis. *J Hepatol* 2013; **58**: 312-318 [PMID: 23069476 DOI: 10.1016/j.jhep.2012.09.036]

53 **Abu Dayyeh BK**, Yang M, Fuchs BC, Karl DL, Yamada S, Sninsky JJ, O'Brien TR, Dienstag JL, Tanabe KK, Chung RT. A functional polymorphism in the epidermal growth factor gene is associated with risk for hepatocellular carcinoma. *Gastroenterology* 2011; **141**: 141-149 [PMID: 21440548 DOI: 10.1053/j.gastro.2011.03.045]

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| **Table 1** **Summary of hepatocellular carcinoma prediction models** |
| 　 | **IPM** | **CU-HCC** | **GAG-HCC** | **REACH-B** | **LSM-HCC** | **mREACH-B** | **PAGE-B** |
| Full name | Individual Prediction Model | Chinese University-HCC | Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis-HCC | Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B | Liver Stiffness Measurement-HCC | Modified Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B |  |
| Calculation | Risk Index (RI) for HCC = eA, A = -6.2543 + (1.7219 × liver cirrhosis) + (1.3145 × old age over 40 yr) + (1.2631 × chronic HCV infection) + (0.8257 × AFP > 20 ng/mL) + (0.7754 × chronic HBV infection) + (0.7339 × chronic hepatitis) + (0.5840 × heavy alcoholics) + (0.3 × man) + (0.2830 × ALT > 40 IU/L) + (0.221 × unknown alcohol history) | Age (> 50 yr = 3; ≤ 50 = 0) + albumin (≤ 25 g/L = 20; > 35 = 0) + bilirubin (> 18 µmol/L = 1.5; < 18 = 0) + HBV DNA (< 4 log copies/mL = 0; 4-6 = 1; > 6 = 4) + cirrhosis (yes = 15; no = 0) | 14 × sex (male = 1; female = 0) + age (in years) + 3 × HBV DNA (log copies/mL) + 33 × cirrhosis presence =1; absence =0) | Male sex: 2 pointsAge: 1 point for every 5 yr from 35 to 65 yr of age (0-6 points)ALT (IU/L): 15-44 (1 point), ≥45 (2 points)Positive HBeAg: 2 pointsHBV DNA (log copies/mL): 4-5 (3 points), 5-6 (5 points), ≥ 6 (4 points) | Age (> 50 yr = 10; < 50 = 0) + albumin (≤ 35 g/L = 1; > 35 = 0) + HBV DNA (> 200000 IU/mL = 5; ≤ 200000 = 0) + liver stiffness (≤ 8.0 kPa = 0; 8.1-12.0 = 8; > 12.0 = 14) | Male sex: 2 pointsAge: 1 point for every 5 yr from 35 to 65 yr of age (0-6 points)ALT (IU/L): 15-44 (1 point), ≥ 45 (2 points)Positive HBeAg: 2 pointsLiver stiffness values: < 8.0 kPa (0 point), 8.0-13.0 (2 points), > 13.0 kPa (4 points) | Age;< 30 (-4 points),30-39 (-2 points),40-49 (0 point),50-59 (2 points),60-69 (4 points),≥ 70 (6 points)Male sex:5 pointsPlatelets (mm3):≥ 200 × 103 (0 point),100× 103-200 × 103(6 points),< 100 × 103 (1 point) |
| HCC: hepatocellular carcinoma; HBV: hepatitis B virus; ALT: alanine aminotransferase. |

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| **Table 2** **Comparisons of published hepatocellular carcinoma prediction models** |
| 　 | **IPM** | **CU-HCC** | **GAG-HCC** | **REACH-B** | **LSM-HCC** | **mREACH-B** | **PAGE-B** |
| Number of patients | 833 | 1005 | 820 | 3584 | 1035 | 1308 | 1619 |
| Place of development | South Korea | Hong Kong | Hong Kong | Taiwan | Hong Kong | South Korea | Europe |
| Race | Asian | Asian | Asian | Asian | Asian | Asian | Caucasian |
| Age, years |  | 48.0 | 40.6 | 45.7 | 46.0 | 50.0 | 53.0 |
| HBeAg-negative (%) |  |  | 56.6 | 84.8 | 75.0 | 60.3 | 84 |
| Cirrhosis (%) |  | 38.1 | 15.1 | 0 | 32.0 | 17.8 | 30 |
| Follow-up (years) | 3.0 | 9.94 | 5.62 | 12.0 | 5.8 | 6.3 | 3.3 |
| Antiviral therapy (%) |  | 15.1 | 0 | 0 | 38.0 | 64.8 | 100 |
| HCC (%) | 44 (5.3) | 105 (10.4) | 40 (4.9) | 131 (3.7) | 38 (3.7) | 9.6 | 56 (3.5) |
| Components of the risk scores | age | age | age | age | age | age | age |
|  | male | albumin | male | male | albumin | male | male |
|  | platelet | bilirubin | BCP mutation | ALT | HBV DNA | ALT | platelet |
|  | cirrhosis | cirrhosis | cirrhosis | HBeAg-positive | LS value | HBeAg-positive |  |
|  | albumin | HBV DNA | HBV DNA | HBV DNA |  | LS value |  |
|  | AFP |  |  |  |  |  |  |
|  | heavy alcoholics |  |  |  |  |  |  |
| Risk scores | Low (< 5) | low (< 5) | low (< 101) | low (< 8) | low (< 11) | low (< 10) | low (< 6) |
|  | Intermediate (5-15) | intermediate (5-20) |  |  |  |  | intermediate (6-10) |
|  | High (> 15) | high (> 20) | high (≥ 101) | high (≥ 8) | high (≥ 11) | high (≥ 10) | high (> 10) |
| NPV (%) |  | 97% at 10 yr | 99% at 10 yr | 98% at 10 yr | 99.4% at 5 yr | 96.8% at 5 yr | 100% 5 yr |
| HCC: hepatocellular carcinoma; HBeAg: hepatitis B e antigen; ALT: alanine aminotransferase; HBV: hepatitis B virus; LS: liver stiffness; AFP: α-fetoprotein; NPV: negative predictive value. |