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EDITORIAL

Prediction and prophylaxis of hepatocellular carcinoma occurrence and postoperative recurrence in chronic hepatitis B virus-infected subjects

Yan Du, Xue Han, Yi-Bo Ding, Jian-Hua Yin, Guang-Wen Cao

Yan Du, Office of Clinical Epidemiology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai 200011, China

Xue Han, Division of Chronic Disease Control, Center for Diseases Control and Prevention of Yangpu District, Shanghai 200090, China

Yi-Bo Ding, Jian-Hua Yin, Guang-Wen Cao, Department of Epidemiology, Second Military Medical University, Shanghai 200433, China

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Correspondence to: Guang-Wen Cao, MD, PhD, Professor, Chairman, Department of Epidemiology, Second Military Medical University, 800 Xiangyin Rd., Shanghai 200433, China. gcao@smmu.edu.cn
Telephone: +86-21-81871060
Fax: +86-21-81871060

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common and highly fatal malignancies worldwide. Chronic infection with hepatitis B virus (HBV) is a major cause of HCC. High HBV replication rate and related non-resolving inflammation are the major risk factors of HCC occurrence and postoperative recurrence. Early prophylactic options are effective in reducing HCC occurrence and improving survival. Therefore, it is important to identify HBV-infected patients who are at a higher risk of developing HCC and HBV-HCC patients who are more likely to relapse after surgery, thus providing them with more precise prophylactic strategies. Several prediction models of HCC occurrence have been constructed, with satisfactory predictive accuracy and discriminatory ability. However, there is a lack of consensus for their clinical implementation. Several staging systems have been proposed for HCC prognosis. However, the accuracy of these staging systems based on demographic characteristics and clinical measurements needs to be further improved, possibly by systematically incorporating viral and inflammatory factors. Since antiviral treatments are effective in promoting liver function reserve, reducing HCC occurrence and prolonging postoperative survival in some HBV-infected subjects, it is very important to

identify subgroups of HBV-infected patients who would most benefit from antiviral treatment.

Key words: Hepatocellular carcinoma; Chronic hepatitis B; Incidence; Prognosis; Prediction

Core tip: Early prophylactic options are effective in reducing hepatitis B virus (HBV)-hepatocellular carcinoma (HCC) occurrence and improving survival. Therefore, it is important to identify HBV-infected patients who are at a higher risk of developing HCC and HBV-HCC patients who are more likely to relapse after surgery. Several prediction models of HCC occurrence have been constructed, with satisfactory predictive accuracy and discriminatory ability. However, there is a lack of consensus for their clinical implementation. Several staging systems have been proposed for HCC prognosis but none have been universally accepted. We discuss important features when translating risk prediction scores derived from academic studies to clinical practice.

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HEPATITIS B VIRUS RELATED HEPATOCELLULAR CARCINOMA IS AN IMPORTANT PUBLIC HEALTH PROBLEM

Hepatocellular carcinoma (HCC) is one of the most common and highly fatal malignancies worldwide. Globally, there are about 782500 cases of HCC, with 745500 deaths annually[1]. Chronic infection with hepatitis B virus (HBV) is the most common cause of HCC worldwide[2,3]. More than 80% of new cases and related deaths occur in the developing world, such as in East Asia and Sub-Saharan Africa where chronic HBV infection is endemic[1-3]. Meanwhile, western countries are also experiencing an increasing trend of liver cancer incidence because of increased worldwide travel and immigration of people from HBV-endemic countries[4]. Thus, HBV-caused HCC (HBV-HCC) is an international public health issue. There are at least 8 genotypes (A-H) of HBV with a nucleotide sequence divergence greater than 8% in the entire genome[5]. HBV genotypes have distinct geographical distributions and differ in hepatitis B e antigen (HBeAg) seroconversion, clinical outcomes, prognosis and response to interferon-α treatment[5]. It is important to profile an individual's HCC risk among the HBV-infected population in order to provide more rigorous surveillance and active intervention for those at higher risk.

EXTREMELY POOR PROGNOSIS INDICATES THE NECESSITY OF PREDICTING HCC OCCURRENCE IN HBV-INFECTED SUBJECTS

HCC is a highly fatal disease, with its mortality almost the same as its incidence[1]. So far, the main treatments for HCC are surgical resection and liver transplantation. However, only a small proportion of patients are eligible for surgical treatment[6]. It is reported that the 5-year survival rate was 30%-35% after surgical procedures[7]. In addition, most HCC patients present at the late stages and with serious liver cirrhosis, missing the best window for surgical treatment[8]. Thus, it is necessary to predict HCC occurrence in chronic HBV-infected subjects so that timely effective prophylactic measures can be used to decrease or postpone HCC occurrence.

CONSTRUCTION OF PREDICTION MODELS OF HCC OCCURRENCE USING DATA FROM COHORT STUDIES

Strategic screening and treatment allocation require assessment and counseling of chronic hepatitis B (CHB) patients based on their predicted risks of disease progression. Regular HCC surveillance with ultrasonography and/or α-fetoprotein (AFP) assay is cost-effective in identifying HCC[9]. Epidemiological studies have shown that in chronically HBV-infected subjects, active hepatic inflammation status, HBV genotype C (*vs* genotype B), high serum HBV DNA level (> 1 × 10^4 copies/mL), HBeAg positivity and some viral mutations in the enhancer Ⅱ/basal core promoter/precore (EnhII/BCP/PC) and the preS regions of the HBV genome are significantly associated with an increased risk of HCC[10-13]. Prospective studies have shown that a continuing high viral load and/or HBeAg expression are significantly associated with an increased risk of HCC in CHB patients[14]. However, viral load fluctuates during the chronic course of HBV infection, especially after HBeAg seroconversion[15]. HBeAg seroconversion occurs during the natural course of chronic HBV infection, which reflects viral mutations in the HBV genome, especially in the EnhII/BCP/PC and preS regions[16]. Thus, HBeAg status should be considered if the HBV mutations are included in the HCC prediction system. Other risk factors include male gender, increasing age, family history of HCC, exposure to aflatoxin B1 and binge drinking, as well as disease factors including alanine aminotransferase

(ALT) level and the presence of cirrhosis[17]. Some of these risk factors have been used in clinical guidelines to triage patients[18-20]. Moreover, a number of studies have attempted to integrate important risk factors and construct prediction models of HBV-HCC occurrence using the data of cohort studies (Table 1)[17,21-27].

Three prediction models were developed in Hong Kong[17,21,22], another four were derived from the REVEAL-HBV study in Taiwan[23-26] and the Kim-HCC score was built from a cohort in Korea[27]. Most of the prediction scores include age, sex, ALT and HBV DNA levels. The sample sizes for all studies are relatively large. The REACH-B score enrolled the largest cohort of 3548 patients for model derivation and another 1505 for validation[24]. All the studies except the Kim score have a relatively long period of follow-up time, allowing adequate time for HCC development. Studies from Hong Kong[17,21,22] and South Korea[27] derived models from hospital-based cohorts, while prediction models developed in Taiwan were from a population-based cohort, thus with less selection bias and more generalizability. All lacked external validation except the REACH-B score, which was validated in a hospital-based cohort from Hong Kong and South Korea[24]. This risk score accurately estimated HCC risk at 3, 5 and 10 years. The overall model showed a fairly good discriminatory capability and the predicted risk was well calibrated with observed risk[24]. Five HCC risk prediction models were developed in CHB patients without antiviral treatment that may reduce HCC risk[17,23-26] and the other three models derived from cohorts had an antiviral treatment rate less than 40%[21,22,27]. It is very important to calculate the risk score in a treated cohort to evaluate whether the risk is modified after initiation of antiviral therapy. Furthermore, none of the risk algorithms have been extensively validated and widely used in the clinical setting for decision making. In addition, all these models were developed and validated in Asian patients (infected predominantly with genotypes B and C HBV and presumably infected early in life). Discriminatory performance of HCC risk scores established in Asian HBV-infected patients was limited in Caucasians[28]. Therefore, further independent validations are needed for other ethnic groups with a diverse genetic background, infection profile, HBV genotypes or quasispecies and exposure to environmental factors[29]. Caution is also needed for using these prediction models in patients with HIV or HCV co-infection.

CONSTRUCTION OF PREDICTION MODELS OF HCC RECURRENCE/DEATH USING DATA FROM COHORT STUDIES

The high recurrence rate is a major obstacle to improving HCC prognosis as about 70% of those patients will relapse within 5 years after hepatectomy[30]. The most significant prognostic factor of HCC is vascular invasion. Other predictive factors include tumor size, number of nodules, AFP level, degree of differentiation, satellites and gene expression profiling in the surgically removed specimens[31,32]. So far, a number of staging systems have been proposed to predict the outcome of HCC patients[33]. Studies have prospectively evaluated different staging systems in predicting long-term prognosis of HCC but the results are inconsistent[34-37]. The inconsistencies may be explained by the different variables included, such as the relative score weighting for each variable, pattern of patient referral, different treatment modality, cohort sample size and variation in populations. The choice of a prognostic staging system in clinical practice should be based on the characteristics of the individual patient, such as ethnic origin, disease stages and treatment strategies. It should also take into account time-varying predictors, including viral load and HBeAg status.

The natural history of HCC is extremely complex. HCC is not a single disease at the molecular level. A number of studies have developed gene expression signatures to predict HCC prognosis, which may have functional implications and reflect highly relevant biological functions to point to possible pathways to search for biomarkers and therapeutic targets[31]. On the other hand, there are few overlap genes among the signatures in different studies. To improve outcome prediction, Villanueva *et al*[38] incorporated genomic data with clinicopathological data and developed an HCC prognostic model. The multivariate analysis showed that the tumor-associated signature "G3-proliferation", an adjacent "poor-survival" signature, and satellites were significantly associated with HCC recurrence. Another important study demonstrated that gene expression profiles of tumor tissue failed to yield a significant association with survival; in contrast, gene expression profiles of the adjacent hepatic tissue were highly correlated with survival[39]. These studies introduced a novel and effective approach to systematically integrate different types of data to improve HCC prognosis prediction. Further validations in different ethnic populations are necessary to verify the robustness of these signatures for the prediction of HCC postoperative prognosis.

PROPHYLAXIS OF HCC IN HIGH RISK HBV-INFECTED SUBJECTS

There are currently two main categories of antiviral treatment approved for the treatment of CHB: interferon-α and nucleos(t)ide analogs (NAs). Meta-analyses have shown that the risk of progression from chronic CHB to HCC can be reduced by antiviral treatment[40,41]. It is reported that controlling sustained viral loads (serum HBV DNA level < 10^4 copies/mL) using NAs during follow-up can reduce long-term risk of HCC[42]. Hosaka *et al*[43] examined the effect of long-term entecavir (ETV) treatment in Japanese

Table 1 Hepatocellular carcinoma risk prediction scores using data from hepatitis B virus-infected cohorts

Ref.	Population and follow-up	Parameters	Validity and reliability (AUROC, sensitivity, specificity)	Advantages and disadvantages
Yuen *et al*[17], 2009 Hong Kong	*n* = 820, mean 76.8 mo	Age, sex, HBV DNA, core promoter mutations, cirrhosis	Leave-one-out cross-validation Optimal cut-off was 101 for 5-yr (sensitivity = 87.9% and specificity = 76.2%) and 10-yr (sensitivity = 100% and specificity = 79.1%) development of HCC	Highlighted the importance of prevention and treatment of remediable cirrhosis with antiviral treatment Developed from a hospital population without external validation, thus may have limited generalizability. HBV mutations may not be easily available in some clinics
Wong *et al*[21], 2010 Hong Kong	*n* = 1005 (training cohort, median 9.94 yr); *n* = 424 (validation cohort, median 10.53 yr)	Age, albumin, bilirubin, HBV DNA, cirrhosis	Internal validation The score ranged from 0 to 44.5, with the best discriminatory cutoff points of 5 and 20 to categorize patients into the low-, medium-, and high-risk groups. Sensitivity and NPV: 88.6% and 97.8% in the training cohort; 82.2% and 97.3% in the validation cohort	Included commonly measured parameters in the score, which could facilitate its routine clinical implementation Derived from a hospital-based cohort with internal validation, thus cannot be readily applied to populations with very different characteristics
Wong *et al*[22], 2014 Hong Kong,	*n* = 1035 (training cohort); *n* = 520 (validation cohort). mean 69 mo	Age, LSM, albumin, HBV DNA	Internal validation The score ranged from 0-30, best cut-off value was 11. For 5-yr HCC risk prediction, the sensitivity was 87.9%, and NPV was 99.4% in the training cohort. In the validation cohort, sensitivity was 100% and NPV was 100% at year 3, and sensitivity was 92.3% and NPV was 99.7% at year 5 AUROC was 0.89 at 3 yr and 0.83 at 5 yr in the validation cohort	Indicated the importance of complete viral suppression in the clinical management. Did not measure LSM in the follow-up, and had relatively small number of events. There was no external validation, thus the results cannot be generalized to other populations with different characteristics
Yang *et al*[23], 2010 Taiwan	*n* = 2435 (model derivation); *n* = 1218 (model validation). About 12 yr (REVEL-HBV cohort)	All three models included: sex, age in 5-yr increments, family history of HCC, alcohol consumption, ALT. Model 1: + HBeAg; Model 2: HBeAg + HBV DNA; Model 3: HBeAg + HBV DNA + HBV genotype	Internal validation The range of score was 0 to 17 in model 1, 0 to 20 in model 2 and model 3 The discrimination capability was satisfactory (AUROC > 80%). The calibration capability was excellent (correlation coefficients between observed risk and estimated mean predicted risk greater than 0.9)	Risk profiling allows accurate estimation of future HCC risk and appropriate recognition of patients with several seemingly marginal risk factors but may overall have high risk of HCC occurrence and thus need clinical awareness. Developed prediction models for various clinical settings with reasonably satisfactory performances Need extra caution when applied to patients with different characteristics
Yang *et al*[24], 2011 Taiwan	*n* = 3584 (development cohort, median 12 yr, REVEL-HBV cohort); *n* = 1505 (validation cohort, mean 7.3 yr)	Age, sex, ALT, HBeAg, HBV DNA	External validation (Hong Kong, South Korea) A 17-point risk score. AUROCs were 81.1% at 3 yr, 79.6% at 5 yr, and 76.9% at 10 yr in the validation cohort; and 90.2%, 78.3%, and 80.6%, respectively in the validation cohort excluding cirrhosis patients. The predicted risk was well calibrated with observed risk, with a correlation coefficient of 0.975 at 3 yr, 0.991 at 5 yr, and 0.999 at 10 yr in the non-cirrhotic model	This risk score can be used to guide treatment for the group of patients who do not meet existing treatment initiation recommendation by focusing on the long-term outcome. It allows the determination of risk at different time points. It provides a possibility to assess the change in risk after therapy initiation This risk score might be inappropriate in immune-tolerant patients, or those with ALT flares, and patients with evidence of cirrhosis
Lin *et al*[25], 2013 Taiwan	*n* = 1822, median 5.9 yr (REVEL-HBV cohort)	Model 1: Age, sex, ALT, HBV seromarkers Model 2: Age, sex, ALT, AAR, ALT, AFP, GGT, albumin, alpha-1 globulin Model 3: Model 2+ HBV seromarkers	The best cutoff score: 6 for Model 1, 22 for Model 2, 19 for Model 3. Sensitivity and specificity: 0.93 and 0.57 for Model 1, 0.70 and 0.93 for Model 2, 0.80 and 0.88 for Model 3. For the 6-yr prediction, the AUROC, best Youden index, LR+, LR- were 0.83, 0.50, 2.17, and 0.11 for Model 1; 0.89, 0.63, 10.38, and 0.33 for Model 2; 0.91, 0.68, 6.52, 0.22 for Model 3	The findings suggest interventions to reverse fibrosis and cirrhosis are also important to reduce HCC risk. Provide an estimate of 6-yr HCC risk, allowing clinicians give clinical advice. Application in patients infected in adulthood, younger chronic HBV carriers, infected with other HBV genotypes (not B/C) needs further validation

Lee *et al*[26], 2013 Taiwan	*n* = 3340 (derivation: validation = 2:1), 53551 person-years (revel-HBV cohort)	Age, sex, ALT, HBeAg, HBV DNA, HBsAg, HBV genotype, family history of HCC	Internal validation Risk score < 9 (low-risk), 9-12 (medium-risk), ⩾ 13 (high-risk). The AUROC was 0.89, 0.85, and 0.86 for the 5-yr, 10-yr, 15-yr predicted risk in the derivation set and 0.84, 0.86, and 0.87 for the 5-yr, 10-yr, 15-yr predicted risk.	Incorporating both baseline and follow-up values into the model may increase the predictability, but may not be practical at the one-shot clinical consultation. The generalizability to younger and older patients needs further evaluation.
Kim *et al*[27], 2013 South Korea	*n* = 1110, median 30.7 mo	Age, sex, liver stiffness, HBV DNA	Bootstrap to assess discrimination Average AUROC = 0.802 (95%CI: 0.791-0.812). Correlation coefficient of predicted and observed risk = 0.905	Included simple, not exhaustive, non-invasive, obtainable and objective variables. Adjusted the influence of antiviral treatment. The use of transient elastography is limited. No long-term follow-up and no external validation

AAR: AST/ALT ratio; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AUROC: Areas under receiver operating curve; GGT: Gamma-glutamyl transferase; HBeAg: Hepatitis B e antigen; HBsAg: HBV surface antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; LSM: Liver stiffness measurements; NPV: Negative predictive value.

HBV-infected patients. They compared HCC incidence in ETV-treated patients with NA-naive patients and reported that the 5-year cumulative incidence rates were 3.7% for the ETV group and 13.7% for the control group ($P < 0.001$)[43]. They further examined HCC incidence using three previously published risk scores[17,21,24]. All three risk score scales consistently showed that ETV significantly reduced HCC incidence in patients at higher risk, suggesting that active prophylaxis in HBV-infected patients is an effective option to reduce HCC incidence. However, current NA treatments do not completely eradicate HBV[44]. Besides, long-term treatment is associated with risks of drug resistance, high costs, potential adverse events and non-adherence. Therefore, it is important to identify patients who will most benefit from antiviral therapy.

During the evolutionary process of hepatocarcinogenesis, HBV accumulates HCC-risk mutations. A number of HBV mutations in the EnhII/BCP and preS regions are reported to be associated with HCC occurrence[10-13,45]. Of these mutations, A1762T/G1764A has been shown to independently predict HCC risk in prospective studies[45]. Incorporating viral mutation information into risk scores may improve the predictive power and select the most appropriate CHB patients for HCC prophylaxis. We conducted a study with a total of 2114 HBV-infected Chinese patients to elucidate whether baseline HBV mutation information could predict the outcome of HBV-infected patients and whether antiviral treatment can selectively reduce HCC risk contributed by the HBV mutations[46]. The entire cohort was followed up for a total of 18406 person-years and multivariate Cox regression analyses showed that age, male gender, cirrhosis and HBV mutations (C1653T, T1753V and A1762T/G1764A) were associated with increased risk of HCC. In untreated patients carrying the A1762T/G1764A mutation, adding information of other baseline HBV mutations in the EnhII/BCP region (C1653T and T1753V) improved the validity of HCC prediction using age, male gender, and cirrhosis. To date, this is the first attempt to categorize the effects of active prophylaxis in HBV-infected patients based on their viral mutation profile. These data are helpful and point the way for individually evaluating a patient's risk and providing tailored therapy.

Active prophylaxis is also effective in preventing HCC recurrence and death. A large, retrospective study based on the health insurance research database in Taiwan indicated that antiviral treatment with NAs was associated with a lower risk of HCC recurrence among patients with HBV-related HCC after liver resection[47]. We conducted a two-stage longitudinal clinical study to evaluate the effect of NA treatment on postoperative prognosis of HBV-HCC. In the non-randomized cohort of 617 patients, high viral load ($\geqslant 10^4$ copies/mL) significantly predicted unfavorable overall survival (OS) and recurrence-free survival (RFS), while NA treatment significantly improved both types of survivals. In the randomized clinical trial that initially included 90 patients in each arm with a median follow-up time of 39.93 mo, the NA treatment significantly decreased HCC recurrence and HCC-related death in multivariate Cox analyses. The presence of carboxylic acid-terminal truncated HBV X protein (Ct-HBx) integration in adjacent hepatic tissues independently predicted a worse RFS in the NA treatment group ($P < 0.001$), suggesting NAs may not have any effects on the survival of patients with Ct-HBx integration[48]. The Ct-HBx is more potent in enhancing the invasiveness and metastasis in HCC cells than the full-length HBx[49]. Although our results need to be validated in future multicenter randomized phase Ⅱ-Ⅲ trials, we believe that NA treatment is effective in reducing recurrence and improving survival of HBV-HCC patients who are seropositive for HBV DNA.

FUTURE CHALLENGES

Since the prognosis of late stage HCC is extremely poor, it is important to detect HCC at an earlier stage for potential curative treatment, such as resection, liver transplantation or local ablation therapy. From a public health perspective, it is important to categorize

patients for better resource allocation: for low-risk patients, avoiding over-treatment and unnecessary emotional stress; and for high-risk patients, more intensive follow-up, rigorous HCC surveillance and administration of antiviral treatment. Several risk score prediction models have been established to estimate HCC risk in HBV-infected patients and to classify those patients into different risk groups. These models have reasonable accuracy and reliability. However, current prediction models have not been widely used in clinical practice. There are a number of established HCC risk factors. It is challenging to systematically evaluate these variables and decide which variables and what combination of variables should be included in the HCC risk prediction model. None of the models included the exact same risk factors, although all attempted to incorporate the most robust ones. To achieve the goal of reducing HCC incidence, special attention, including prophylaxis, should be given to patients with major and remediable/preventable risk factors, such as viral replication and cirrhosis. However, some risk scores do not include patients with cirrhosis and are therefore missing an important component of the equation. Another important element in constructing a risk prediction model is HCC case ascertainment as the rate of HCC occurrence might have been underestimated in some studies. Before wide implementation in clinical settings, external validation needs to be performed in independent populations to measure the accuracy of prediction scores. Last but not least, all these predictive models have been established in Asian patients and need to be generalized to other ethnic groups.

Even though based on cohort data, the above mentioned prediction models derived from academic studies might not be readily suitable for clinical application. For a risk prediction score to be clinically useful, it needs high reliability and accuracy and easy accessibility of risk factors. Risk factors included in the risk prediction score should be simple and easily obtained using non-invasive and cost-effective tests. Risk factors should also have standard definitions and measurements. To make a risk prediction model more widely applicable, it should be constructed in a way that can be modified according to different settings with varying available resources. It should not require complex calculations and visual tracing. Instead, it should be simple to use and easy to understand so that it can be used to communicate with patients to achieve better acceptance and compliance. Another crucial step before clinical application is to be validated in a large community-based cohort. The goal of constructing an HCC risk prediction score is to achieve early diagnosis and early treatment, thereby providing HBV-infected patients with a tailored screening program and personalized therapy.

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