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TOPIC HIGHLIGHT

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

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Abstract

Hepatocellular carcinoma (HCC) is a grave primary liver cancer that has a limited therapeutic option because it is generally diagnosed later in an advanced stage due to its aggressive biologic behavior. The early detection of HCC has a great impact on the treatment efficacy and survival of patients at high risk for cancer. Potential host, environmental, and virus-related risk factors have been introduced. Hepatitis B virus (HBV) is a major cause of end-stage liver diseases such as liver cirrhosis or HCC in endemic areas, and its serologic or virologic status is considered an important risk factor. HCC risk prediction derived from the identification of major risk factors is necessary for providing adequate screening/surveillance strategies to high-risk individuals. Several risk prediction models for HBV-related HCC have been presented recently with simple, efficient, and readily available to use parameters applicable to average- or unknown-risk populations as well as high-risk individuals. Predictive scoring systems of risk estimation to assess HCC development can provide the way to an evidence-based clinical approach for cost- and effort-effective outcomes, capable of inducing a personalized surveillance program according to risk stratification. In this review, the concepts and perspectives of the risk prediction of HCC are discussed through the analysis of several risk prediction models of HBV-related HCC.

Key words: Hepatocellular carcinoma; Hepatitis B virus; Chronic hepatitis B; Risk prediction; Risk factors

Core tip: This review shows the concepts and perspectives of the risk prediction of hepatitis B virus-related hepatocellular carcinoma. Accurate risk scoring systems to predict hepatocellular carcinoma (HCC) development, derived from independent risk factors integrated in aspects of host, environment, and virus, are necessary for performing the strategic processes such as screening/surveillance, diagnosis, and treatment in high-risk individuals of HCC. Globally standardized consensus for HCC risk prediction models should be established on the basis of simplicity, assessability, and reproducibility of the model characteristics available in real clinical setting.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most aggressive malignant neoplasms and a leading cause of cancer-related morbidity and mortality[1]. During the last

few decades, the incidence rate of HCC has increased in most developed countries, but its mortality rate has decreased[2]. Tumor diagnosis at an advanced stage and accompanying chronic liver diseases, including liver cirrhosis, are major limitations of curative management in many cases. The accurate selection of high-risk groups and adequate screening/surveillance programs for HCC detection at an early stage may provide clinical strategies capable of overcoming "tumor diagnosis at an advanced stage"[3]. The early detection of HCC in populations and individuals at high risk is critical in providing curative treatments and in consequently acquiring a survival benefit, which has been validated through a randomized controlled trial of screening for HCC[4].

The hepatitis B virus (HBV) genome consists of partially double-stranded DNA of approximately 3200 base pairs with four overlapping open reading frames encoding the envelope (S), core (C), polymerase (P), and X proteins (Figure 1).

Chronic HBV infection is usually characterized by the presence of hepatitis B surface antigen (HBsAg) in the serum for at least 6 mo after exposure to the virus. Patients with chronic HBV infection have a more than 100-fold increased risk of HCC occurrence compared with uninfected individuals[5]. Therefore, HBV-infected patients have been considered a high-risk group of HCC and regarded as candidates for a precise application of screening/surveillance strategies scheduled by using risk weight-based stratification. In addition to the possession of HBsAg itself, the following HBV-associated biomarkers affecting liver disease progression to cirrhosis and HCC have been suggested: serum titer of HBsAg, hepatitis B e antigen (HBeAg), serum level of HBV DNA, HBV genotype, and HBV mutations[6]. In recent years, the evolution of antiviral therapeutics for chronic HBV infection is a result of the clinical efforts to reduce the development of HCC.

In this article, we discuss the host, environmental, and virus-related risk factors associated with the development of HBV-related HCC and present the risk prediction systems for the development of HCC based on stratification of scoring estimation derived from independent risk factors.

RISK FACTORS

Host factors

The following potential host factors for HCC occurrence in HBV-infected individuals have been suggested based on demographic, clinical, and epidemiologic investigations: male gender, increasing age, genetic susceptibility and family history of HCC, obesity, diabetes, coexistent alcohol consumption or smoking, high serum alanine aminotransferase (ALT) activity, low serum albumin, low platelet counts, high serum alpha-fetoprotein level, and accompanying liver cirrhosis[6]. In relation to these risk factors, several study groups have strongly recommended HCC surveillance strategies in men > 40 years old and women > 50 years old with chronic hepatitis B who have a family history of HCC and accompanying cirrhosis, considering different ethnicities[3,7-10]. Liver cirrhosis, irrespective of etiology, is the most important and independent risk factor for the development of HCC, accounting for 73% to 85% of patients with HCC in HBV-endemic areas[2]. Among the biochemical risk factors, ALT is the most readily available in clinical fields, and its serum level above the upper limit of normal (ULN) is considered an independent risk factor for HCC even in average-risk populations without HBsAg, to say nothing of high-risk subjects seropositive for HBsAg. Subjects in the upper range (0.5-1 × ULN or approximately 25-40 IU/L) of the normal limit of serum ALT levels were reported to be at an increased risk of HCC compared with subjects in the lower range (< 0.5 × ULN or < 25 IU/L)[11,12]. The risk factors mentioned previously are simple to measure, easy to administer, and convenient to apply clinical parameters useful for constructing risk prediction models of HCC.

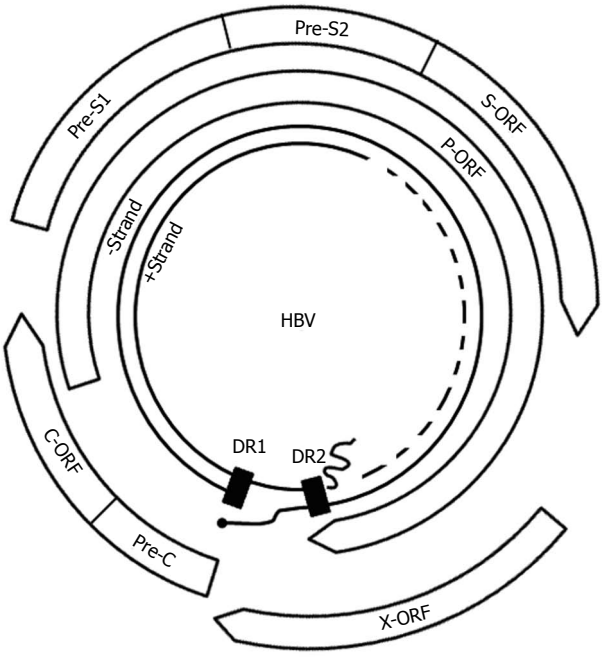

Figure 1 Representative scheme of the hepatitis B virus genome. Hepatitis B virus (HBV) genome consists of partially double-stranded DNA with four overlapping open reading frames. ORF: Open reading frame; DR: Direct repeat.

Environmental factors

Environmental risk factors are difficult to define clearly in clinical settings. Ethnic susceptibility, alcohol consumption, cigarette smoking, co-infection with other viruses, and chemical carcinogens including aflatoxin were representative of environmental factors. Ethnicity is considered a relative risk factor for HCC. Africans, African Americans, and Asians are included in populations for HCC surveillance in HBV-endemic regions[3,7-9]. In these regions, virus infection mainly occurs through perinatal transmission vertically or horizontally[13], resulting in sus-

ceptibility to disease chronicity and relative intractability to antiviral therapy because of long-standing periods of infection. Simultaneous co-infections by other viruses such as hepatitis C virus, hepatitis D virus, and human immunodeficiency virus may be additional risk factors, but they have not been established definitely. Aflatoxin is well known to be a carcinogen capable of developing HCC. Aflatoxin B1 is a representative genotoxic hepatocarcinogen that induces the transversion of guanine (G) to thymine (T) in codon 249 of exon 7 of the *p53* tumor suppressor gene in human hepatocytes (the so-called stop-codon mutation), resulting in the substitution of arginine (A) to serine (S). Mutations of *ras* oncogenes are also found in aflatoxin B1-induced HCC, but are less frequent than the *p53* mutation[14]. These environmental factors are not usually involved in constructing risk prediction models of HCC because of the lack of quantitative assessment as independent risk factors.

Virologic factors

Virologic risk factors have been considerably investigated in cases with hepatitis virus-associated HCC. The clinical implications of the serum HBV DNA level for liver disease progression are recognized in HBV-infected patients. A stepwise increase of the serum HBV DNA level is associated with a corresponding linear increase in the cumulative incidence of HCC as well as the progression of HBV-related liver disease to liver cirrhosis or hepatic decompensation regardless of the serum ALT activity, HBeAg status, and presence of cirrhosis[15,16]. Therefore, the serum HBV DNA level is a major independent virologic risk factor. Furthermore, inactive carriers with chronic HBV infection, who are seronegative for HBeAg have serum levels of HBV DNA less than 4 log copies/mL and serum ALT activity within the normal limit and do not have chronic hepatitis, cirrhosis, or HCC either histologically or clinically, are at risk for HCC and liver-related death compared with individuals not infected with HBV[17]. Hepatitis B viral load has been reported to be a risk factor for post-treatment recurrence of HCC[18]. In these backgrounds, antiviral therapy with nucleoside/nucleotide analogs in patients with HBV-associated liver disease is a main pivot to control HCC development and recurrence. In fact, lamivudine therapy has reduced the incidence of HCC in patients with compensated cirrhosis when viral suppression was sustained[19]. Recently, the quantitative assessment of serum HBsAg has been suggested as a new tool for determining HCC development and for predicting the response to antiviral therapy[20-22]. However, circulating HBsAg in blood, a component of the HBV envelope proteins, is originated from non-infectious viral particles as well as intact Dane particles with viral infectivity; the clinical impact of the serum HBsAg level on HCC development and the antiviral response in patients with chronic HBV infection should be ascertained prospectively. On the other hand, the serum level of HBsAg, like the HBV DNA level, may fluctuate in the natural course of chronic HBV infection[23,24], and changing patterns of the serum HBsAg level through long-term regular monitoring might determine whether the changes could affect the disease progression in HBV-infected patients. Besides these virologic factors, HBeAg/anti-HBe status, HBV genotype, basal core promoter mutations/precore mutations or mutations relevant to deletions within pre-S region, and co-infection with other viruses can be considered risk factors for HCC[25-28]. Among these virologic risk factors, the serum HBV DNA level and HBeAg status are the most valuable and available parameters capable of constructing risk prediction models of HCC. However, the serum HBsAg level, HBV genotype, and HBV mutations are not readily available in clinical settings. The measurement of these factors tends to be required for specific situations such as academic approaches to antiviral therapy, epidemiologic investigations, or scientific interest. Therefore, the application of virologic factors for building risk prediction models of HCC should be granted as evidence-based as a matter of prudence even if most virologic factors provide important information for HCC risk stratification.

RISK PREDICTION SYSTEMS

Risk prediction systems capable of estimating the strength of HCC development are clinically important for identifying patients at high risk who should participate in a scheduled surveillance program. To construct readily available prediction systems of HCC, the risk factors for HCC mentioned previously should be independently established through statistical verification. Statistical techniques adopted in the process should be reliable and reasonable to identify an objective recognition. Next, selected risk factors should be integrated and organized under the consideration of demographic and epidemiologic differences of developing HCC, inducing a systematic stratification of scoring estimation derived from independent risk factors for HCC. Finally, constructed risk prediction systems should be validated internally or externally, which makes individualized surveillance strategies possible. Cancer risk weighed-oriented scoring estimation could provide the advantage in aspects of cost- or effort-effectiveness through a tailored approach to cancer surveillance.

Several predictive scoring systems for the development of HBV-related HCC have been introduced recently (Table 1). Yuen *et al*[11] for the first time deduced and validated the risk score (*i.e.*, the GAG-HCC score) with sensitivity > 84% and specificity > 76% to predict the 5- and 10-year risks for the development of HCC based on age, gender, HBV DNA levels, core promoter mutations, and cirrhosis; they concluded that the risk score could be used to identify high-risk patients with chronic hepatitis B (CHB) for screening and treating HCC. They emphasized the significance of this study with a valuable approach excluding the patients who received any type of established management for CHB capable of affecting the occurrence of HCC. Wong *et al*[29] included two prospective

Table 1 Risk prediction models of hepatocellular carcinoma in patients with chronic hepatitis B virus infection

Ref.	No. of participants/ validation	Parameters of HCC prediction	Risk weights for parameters	Range of weights	Year of risk prediction
Lee *et al*[32], 2013	2227/1113	Age	[0-6]	0-19	5, 10 and 15
		Sex	[0-2]		
		ALT	[0-2]		
		Family Hx of HCC	[0-2]		
		HBeAg/HBV DNA/ HBsAg/Genotype	[0-7]		
Wen *et al*[12], 2012	[1]298051	Age	M1, 2, 3, 4: [0-6]	M1: -1-12	5 and 10
		Sex	M1, 2: [0-2], M3, 4: [0-1]		
		Smoking	M1, 3, 4: [0-1]	M2: 0-23	
		Alcohol	M1, 3, 4: [0-1]		
		Physical activity	M1, 3, 4: [-1-0]	M3: -1-23	
		DM	M1: [0-2], M3, 4: [0-1]		
		ALT	M2: [0-2], M3, 4: [0-1]	M4: -1-30	
		AST	M2: [0-13], M3: [0-12], M4: [0-7]		
		HBV	M4: [0-4]		
		AFP	M4: [0-8]		
Yang *et al*[30], 2011	3584/1505	Age	[0-6]	0-17	3, 5 and 10
		Sex	[0-2]		
		ALT	[0-2]		
		HBeAg	[0-2]		
		HBV DNA	[0-5]		
Yang *et al*[31], 2010	2435/1218	Age	M1, 2, 3: [0-6]	M1: 0-17	5 and 10
		Sex	M1, 2, 3: [0-2]		
		Alcohol	M1: [0-1], M2, 3: [0-2]	M2: 0-20	
		ALT	M1: [0-3], M2: [0-2], M3: [0-1]		
		Family Hx of HCC	M1, 2, 3: [0-2]	M3: 0-20	
		HBeAg	M1: [0-3]		
		HBeAg/HBV DNA	M2: [0-6]		
		HBeAg/HBV DNA/ Genotype	M3: [0-7]		
Wong *et al*[29], 2010	1005/424	Age	[0-3]	0-43.5	5 and 10
		Alb	[0-20]		
		Bil	[0-1.5]		
		HBV DNA	[0-4]		
		Cirrhosis	[0-15]		
Yuen *et al*[11], 2009	[2]820	Age Sex HBV DNA Core promoter mutations Cirrhosis	With core promoter mutations Age (in years) + 16 sex (male = 1; female = 0) + 3 HBV DNA levels (Log copies/mL) + 19 core promoter mutations (mutant = 1; wild-type = 0) + 30 cirrhosis (presence = 1; absence = 0) Without core promoter mutations Age (in years) + 14 sex (male = 1; female = 0) + 3 HBV DNA levels (Log copies/mL) + 33 cirrhosis (presence = 1; absence = 0)	-	5 and 10

[1]The number of participants in a subcohort without hepatitis C virus test results was 298051, with being randomly and equally split into a training set and a validation set. [2]The risk score was assessed by the leave-one-out cross-validation. HCC: Hepatocellular carcinoma; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; DM: Diabetes mellitus; AFP: Alfa fetoprotein; Bil: Bilirubin; Alb: Albumin; M: Model.

cohorts in their study: a training cohort (1005 patients) and a validation cohort (424 patients). A predictive scoring system ranging from 0 to 43.5 was constructed by using five independent risk factors: age, albumin, bilirubin, HBV DNA, and cirrhosis. They concluded that the classification of HCC risk to low-, medium-, and high-risk groups based on this scoring system was accurate in predicting HCC development. They insisted that the score was derived from clinical parameters routinely measurable in large prospective cohorts for a long-term period, and the validation was established with high accuracy in another sizable cohort. Yang *et al*[30] enrolled 3584 patients from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study cohort as a development cohort of risk estimation. Male gender, older age, elevated serum ALT activity, HBeAg positive, and higher serum HBV DNA titer were identified as independent risk factors for HCC; a 17-point risk score from these risk factors was developed. They interpreted that this simple-to-use risk score based on noninvasive clinical variables could accurately predict the risk of HCC in patients with chronic hepatitis B. They also depicted easy-to-use nomograms to accurately predict the risk of HCC in CHB patients,

facilitating risk communication between clinicians and patients[31]. This Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B study suggested that clinicians could make evidence-based decisions about clinical management. Wen *et al*[12] developed five simple risk prediction models with one-by-one escalating manner based on clinically available data from a prospective cohort of 428 584 general subjects. Age, sex, health history, HBV and hepatitis C virus (HCV) status, and serum ALT, aspartate aminotransferase, and alpha-fetoprotein levels were determined to be statistically significant independent predictors of HCC risk. They concluded that prediction models using transaminase data were best able to predict HCC risk even among subjects with unknown or HBV- or HCV-negative infection status. The significance of this study is that setting up a simple, easy-to-administer risk prediction model applicable even in low-risk, average-risk, or unknown-risk subjects as well as a high-risk population was attained. Lee *et al*[32] most recently developed risk prediction models of HCC by integrating host and HBV profiles after identifying independent risk factors such as older age, male, HBeAg, HBV genotype C, and increasing levels of ALT, HBV DNA, and HBsAg associated with an increased risk of HCC. They concluded that the categorization into low, medium, and high HCC risk could enable physicians to estimate the 5-, 10-, and 15-year risk of HCC with excellent accuracy and discriminatory ability. Two points are noteworthy in this study. One was the introduction of the quantitative serum HBsAg level in the analytic process to derive HCC risk models. The serum HBsAg level was determined to be an independent risk factor of HCC development as well as a response assessment to antiviral therapy. The other was the construction of a prediction model of cirrhosis risk, which was not developed before in patients with chronic HBV infection. Because cirrhosis is a precancerous lesion, the development of a cirrhosis risk prediction model has a valuable impact on the selection of candidates for a scheduled surveillance program according to the risk stratification of HCC.

In summary, accurate prediction models of HCC development constructed from readily available clinical and laboratory variables are necessary for performing strategic processes such as screening/surveillance, diagnosis, and treatment in high-risk patients of HCC. A globally standardized consensus for cancer risk prediction models should be established based on simplicity, assessability, and reproducibility of the model characteristics available in real clinical settings. Hereafter, generalized authorization of risk prediction models needs to be confirmed by using internal and external validation with a prospective manner in different populations of regions with epidemiologic versatility of HCC.

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