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Risk stratification for hepatitis B virus related hepatocellular carcinoma

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Key words

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Abstract

Hepatitis B virus (HBV) infection is the major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) worldwide, especially in the Asia–Pacific region. Several hepatitis B viral factors predictive of clinical outcomes in HBV carriers have been identified. The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV (REVEAL-HBV) study from Taiwan illustrated the strong association between HBV-DNA level at study entry and risk of HCC over time. In this community-based cohort study, male gender, older age, high serum alanine aminotransferase level, positive hepatitis B e antigen, higher HBV-DNA level, HBV genotype C infection, and core promoter mutation are independently associated with a higher risk of HCC. Another large hospital-based Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers cohort of Taiwanese patients further validated the findings of REVEAL-HBV. The risk of HCC started to increase when HBV-DNA level was higher than 2000 IU/mL. Both HBV-DNA and HBsAg levels were shown to be associated with HCC development. While HBV-DNA level had better predictive accuracy than HBsAg level, when investigating the overall cohort in patients with HBV-DNA level < 2000 IU/mL, HBsAg level ≥ 1000 IU/mL was identified as a new independent risk factor for HCC. With the results from REVEAL-HBV, a risk calculation for predicting HCC in non-cirrhotic patients has been developed and validated by independent cohorts (Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B).Taken together, ample evidence indicates that HBsAg level can complement HBV-DNA level in predicting HCC development, especially in HBV carriers with low viral load. In conclusion, HBV treatment guidelines should include the risk stratification of HCC to individualize the management of HBV carriers with different levels of HCC risk.

Introduction

Hepatitis B virus (HBV) infection is one of the most common viral infections in humans. It is prevalent in Asia, Africa, Southern Europe, and Latin America, where the prevalence of hepatitis B surface antigen (HBsAg) in the general population ranges from 2% to 20%.[1] The long-term outcomes of chronic HBV infection vary widely; however, a significant proportion of HBV carriers may develop hepatic decompensation, cirrhosis, and even hepatocellular carcinoma (HCC) in their lifetime. It is generally believed that 15–40% of HBV carriers will die of end-stage liver disease.[2]

On the basis of virus–host interactions, the natural history of HBV carriers who are infected in early life can thus be divided into four dynamic phases.[3] During the *immune tolerance phase*, serum HBV-DNA levels are high and hepatitis B e antigen (HBeAg) is present. In the *immune clearance phase*, the majority of carriers seroconvert from HBeAg to anti-HBe. The clinical outcomes of patients with chronic HBV infection depend on the severity and frequency of *hepatitis flares* or so-called acute exacerbations during the immune clearance phase. After HBeAg seroconversion, patients are usually in the *low replication phase or inactive carrier state*, with low HBV-DNA level and normal serum alanine aminotransferase (ALT) level. However, a small proportion of patients continue to have fluctuating HBV-DNA level and intermittent hepatitis flare designated *reactivation phase or HBeAg-negative chronic hepatitis B* (*CHB*). These patients usually have precore or core promoter mutations in the HBV genome that abolish or decrease the production of HBeAg.

The more frequent and severe the hepatitis flare is in the immune clearance phase and/or reactivation phase, the higher is the chance to develop cirrhosis and HCC over time. In general, early HBeAg seroconversion typically confers a favorable outcome, whereas late or absent HBeAg seroconversion after multiple hepatitis flares may accelerate the progression of chronic

Table 1 Qualitative and quantitative hepatitis B viral factors and the level of each risk factor associated with hepatitis B virus-related hepatocellular carcinoma

	Hepatitis B viral factors associated with HCC	
	Qualitative factors	Quanitative factors
Low risk	HBV genotype A/B	Low serum level of HBV-DNA Low serum level of HBsAg
High risk	HBV genotype C/D BCP A1762T/G1764A mutation Pre-S deletion	High serum level of HBV-DNA High serum level of HBsAg

BCP, basal core promoter; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

hepatitis to cirrhosis, and therefore, has an adverse clinical outcome.

The lifetime risk of HBV carriers to develop cirrhosis, liver failure, or HCC may be as high as 15% to 40%.[1–3] The identification of risk factors for the development of advanced liver disease, including cirrhosis and HCC, in HBV carriers is important for implementing effective treatment. Recently, several qualitative and quantitative hepatitis B viral factors affecting the prognosis of HBV carriers have been identified.[3,4] Among these viral factors, baseline serum HBV-DNA level is the main driving force for cirrhosis and HCC development in adult HBV carriers.[5,6] Recently, quantitative HBsAg (qHBsAg) has been increasingly recognized to be a promising biomarker to predict both favorable and adverse outcomes of HBV carriers. Based on the weight of each risk factor associated with HBV-related HCC and through a stratification process, it is possible to identify HBV carriers who are at an increased risk of disease progression and HCC development (Table 1). In this article, hepatitis B viral factors leading to disease progression and the risk stratification for HBV-related HCC will be reviewed and discussed.

Qualitative hepatitis B viral factors for HCC

HBV genotype. According to the divergence in the entire HBV genomic sequences, at least 10 HBV genotypes (A to J) have been defined.[7–9] Several studies suggested that HBV genotype can influence the long-term outcomes of HBV infection. For example, HBV genotype C and D patients, compared with genotype A and B patients, have late or absent HBeAg seroconversion after multiple hepatitis flares that accelerate the progression of chronic hepatitis.[10–12] Most case–control studies and community-based prospective cohort study indicated that patients with genotype C HBV infection have a higher risk of cirrhosis and HCC than those with genotype B infection.[13–17] In addition, several reports have also shown that HBV genotype B was associated with HCC development in young non-cirrhotic patients. Whereas genotype C was associated with HCC development in old cirrhotic patients.[13,18,19]

HBV mutants. Due to the spontaneous error of viral reverse transcription, HBV mutant strains occur during the natural course of infection as well as with antiviral therapy. Mutations in precore, core promoter, and deletion mutation in pre-S/S genes have been reported to be associated with the progression of liver disease, including cirrhosis and HCC. Previous studies revealed that dual mutations in basal core promoter (BCP) A1762T/G1764A were strongly associated with the risk of HCC development.[13,14,20–23]

In a case–control study, we first reported the prevalence of BCP A1762T/G1764A mutation in 250 genotype B- or C-infected HBV carriers with different stages of liver disease. The likelihood of BCP A1762T/G1764A mutation parallels the progression of liver disease, from 3% in inactive carriers to 64% in HCC patients. BCP A1762T/G1764A mutations were significantly associated with the development of HCC compared with those without (odds ratio [OR]: 10.60; 95% confidence interval [CI]: 4.92–22.86; $P < 0.001$), and the risk was observed for both HBV genotypes B and C.[14]

These findings were in line with a longitudinal cohort study. In Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV (REVEAL-HBV) cohort study, HBV BCP mutations were detedrmined in 1526 HBV carriers with serum HBV-DNA level > 2000 IU/mL. Carriers with BCP A1762T/G1764A mutations had a higher hazard ratio (HR) of developing HCC than those without mutations (HR: 1.73; 95% CI: 1.13–2.67; $P = 0.013$).[19] These results were further confirmed by a meta-analysis on 43 studies, showing a summary OR of HCC was 3.79 (95% CI: 2.71–5.29) for BCP A1762T/G1764A mutations.[24] Taking these data together, BCP A1762T/G1764A mutations may play an important role in HBV-related hepatocarcinogenesis.

Deletion mutations in the pre-S gene of HBV genome frequently occur in chronic HBV infection.[25,26] The deletion over pre-S gene may cause accumulation of large surface protein in the endoplasmic reticulum (ER), resulting in ER stress.[27–29] Oxidative DNA damage through ER stress may induce mutagenesis in the host genome and contribute to hepatocarcinogenesis.[30] In our case–control study, the presence of pre-S deletion mutations was an independent risk factor associated with hepatitis activity (OR: 3.91; 95% CI: 1.57–9.76; $P = 0.003$), as well as development of HCC (OR: 3.72; 95% CI: 1.44–9.65; $P = 0.007$).[31,32] Similarly, a longitudinal study from southern Taiwan also showed that pre-S deletion mutations were significantly associated with the development of cirrhosis and HCC over time.[33] In addition, a matched nested case–control study from China further showed that pre-S deletion mutations constituted an independent risk factor for HCC, and their emergence and effect on HCC were independent of BCP mutations.[34] A meta-analysis further indicated that the OR of HCC for pre-S deletion mutations was 3.77 (95% CI: 2.57–5.52).[24]

Because pre-S region contains several functional domains and immune epitopes,[35,36] specific deletions of pre-S region may be associated with the development of HCC. Our previous mapping study of pre-S region suggested that all the deletion regions encompassed T- and B-cell epitopes. Of particular note, the B-cell epitope at amino acid 1–6 of pre-S2 was significantly deleted in HCC patients.[37,38] Regarding the functional domains, there were losses at one or more functional sites in most cases, including the polymerized human serum albumin binding site and nucleocapsid binding site. The deletion of site for viral secretion (amino acid 1–5 of pre-S2 domain) was also significantly associated with the development of HCC.[37,38] Therefore, HBV pre-S deletion mutations may lead to defective host immunity against HBV infection and contribute to more progressive liver cell damage and finally hepatocarcinogenesis.

Quantitative hepatitis B viral factors for HCC

HBV is the smallest human DNA virus with a partially double-stranded circular DNA.[39] The partially double-stranded DNA will transform into covalently closed circular DNA (cccDNA) in the nucleus of hepatocytes after HBV infection. Such HBV cccDNA is responsible for persistent infection of hepatocytes. During HBV replication, pregenomic RNA can be transcribed from cccDNA to serve as the template of negative-strand DNA through reverse transcription, and then fully double-stranded DNA through DNA polymerase within the nucleocapsid, finally with the assembly of envelope protein to form mature HBV virions.[40] Several messenger RNAs (mRNAs) can also be transcribed from cccDNA and then translate to viral proteins.

HBsAg is presumably responsible for receptor binding. It is comprised of large, middle, and major (or small) proteins. Intracellular hepatitis B core antigen (HBcAg) is an inner nucleocapsid surrounding the viral DNA. HBcAg is the major target of cytotoxic T cell. HBeAg is a circulating peptide derived (by peptide cleavage) from the core gene, then modified and secreted from liver cells. HBeAg usually serves as a marker of active viral replication. In addition, small HBsAg and truncated pre-S proteins can be generated from integrated HBV-DNA.[41–44] Therefore, several quantifiable viral factors can be used clinically, including HBV-DNA from the infectious particles and circulating viral proteins such as HBsAg and HBeAg.

Hepatitis B viral load. HBV-DNA quantification assays are available and have been used in clinical practice for more than a decade. Several commercial assays based on molecular biology techniques have been developed to detect and quantify HBV-DNA.[45] More recently, real-time polymerase chain reaction assays to detect and quantify HBV-DNA were recommended by the American Association for the Study of Liver Disease, the European Association for the Study of Liver, and Asian Pacific Association for the Study of the Liver (APASL) to diagnose HBV infection, establish the indication for therapy, and to monitor antiviral treatment responses and emergence of drug resistance.[46–48]

HBV-DNA quantification also provides valuable prognostic information. Recently, the impact of viral load on the risk of HCC was assessed in a population-based prospective cohort of untreated CHB Taiwanese patients (REVEAL-HBV study). Among them, 85% were HBeAg negative and were followed for a mean duration of 11 years. The cumulative incidence of HCC increased with serum HBV-DNA level. It ranged from 1.3% to 14.9% for patients with an HBV-DNA level of less than 300 copies/mL (~60 IU/mL) and10^6 copies/mL (~200 000 IU/mL) or more, respectively ($P < 0.001$). After adjustment for HBeAg status and serum ALT level among other variables, hepatitis B viral load was the strongest predictor of HCC development. The relative risk started to increase at an entry HBV-DNA level of 2000 IU/mL (HR: 2.3; 95% CI: 1.1–4.9; $P = 0.02$). Those with HBV-DNA levels of 200 000 IU/mL or more had the greatest risk (HR: 6.1; 95% CI: 2.9–12.1; $P < 0.001$). Of particular note, the dose–response relationship was most prominent for participants who were seronegative for HBeAg, with normal serum ALT levels, and no cirrhosis at study entry.[6,49]

Similarly, another prospective cohort study in adult HBV carriers with 11 years of follow-up from Haimen City in China also showed that the relative risk for HCC mortality in carriers with low viral load (< 20 000 IU/mL) was 1.7 (95% CI: 0.5–5.7) and 11.2 (95% CI: 3.6–35.0) in those with high viral load (≥ 20 000 IU/mL) compared with the HBV carriers with undetectable viremia.[50]

In our recent study on 390 CHB patients with spontaneous HBeAg seroconversion, those with HBV-DNA levels > 2000 IU/mL at 1 year post HBeAg seroconversion had higher HR of HBeAg-negative chronic hepatitis, a precursor of cirrhosis and HCC, than patients with HBV-DNA levels < 200 IU/mL (HR: 2.4; 95% CI: 1.3–4.4; $P = 0.004$). More importantly, the risk increased in a dose–response relationship.[51] Ample evidence from all these studies indicates that hepatitis B viral load is what induces hepatitis activity and is the strongest factor associated with HCC development in patients with chronic HBV infection.

Although a lower viral load is associated with favorable clinical outcomes such as inactive carrier state, our previous case–control study, including 183 HBV-related HCC patients and 202 HBV carriers, showed that young (≤ 40 years old) HCC patients had lower serum HBV-DNA level than old HCC patients ($\log_{10}$ copies/mL: 4.2 *vs* 4.8, $P = 0.056$). In addition, high serum HBV-DNA level was associated with the development of HCC in old patients (OR: 1.584; 95% CI: 1.075–2.333; $P = 0.02$), rather than in young patients (OR: 0.848; 95% CI: 0.645–1.116; $P = 0.239$).[52] Thus, the host–virus interactions in association with the development of HCC in younger and older patients may be different, and this aspect needs further investigation.

HBsAg quantification. In addition to known hepatitis B viral factors associated with disease progression, the clinical significance of qHBsAg has become increasingly recognized. It is known for a long time that HBsAg is the hallmark of HBV infection and is qualitatively used for the diagnosis of HBV infection in clinical practice. However, this old biomarker has a new role in current management of chronic HBV infection. Serum HBsAg can be produced by three pathways: (i) the translation of transcriptionally active cccDNA molecules to form the envelope of HBV virion; (ii) subviral sepherical or filamentous form of noninfectious particles; and (iii) small HBsAg and truncated pre-S protein can also be generated from HBV-DNA integrated to host genome.[44,53] In the natural course of CHB, HBV-DNA is only from infectious particles, and levels reflect viral replication. Accordingly, a decline of HBV-DNA means reduction of HBV replication. In contrast, HBsAg can be derived from both mature virions and defective particles. Thus serum HBsAg level not only reflects the cccDNA transcription or mRNA translation, but also host immune control over HBV infection.[54,55]

The relationships between qHBsAg, intrahepatic HBV-DNA, and serum HBV-DNA concentration have been analyzed recently. In HBeAg-positive CHB, qHBsAg positively correlated with intrahepatic HBV-DNA and serum HBV-DNA concentration.[56,57] On the contrary, qHBsAg correlated poorly with serum HBV-DNA and did not correlate with intrahepatic HBV-DNA in HBeAg-negative CHB.[57] With regard to clinical phenotypes, qHBsAg was much higher in HBeAg-positive patients with immune tolerance and immune clearance phases than HBeAg-negative patients.[58,59]

An Italian study showed that the combination of qHBsAg < 1000 IU/mL and serum HBV-DNA level < 2000 IU/mL can predict inactive HBV carrier state with a positive predictive value of 88% and negative predictive value of 97% in HBV genotype D patients.[60] Our recent study also showed that low serum levels of HBsAg (< 100 IU/mL), alone or in combination with HBV-DNA levels, at 1 year after HBeAg seroconversion could predict HBsAg loss in patients with HBV genotype B or C infection.[61] In addition, qHBsAg was better than serum HBV-DNA level for the prediction of spontaneous HBsAg loss in HBeAg-negative carriers with a low viral load (< 2000 IU/mL). HBsAg level < 10 IU/mL was the strongest predictor of HBsAg loss in patients with a low viral load.[62]

The earlier lines of evidence indicate that there exists a correlation between qHBsAg and liver disease progression. In the recent update of REVEAL-HBV study, qHBsAg was analyzed in 3411 HBV carriers. The results showed that both HBsAg and HBV-DNA levels are independent predictors of HCC development. The multivariate-adjusted HR of developing HCC increased significantly from 1.0 (reference) for serum levels of HBV-DNA (IU/mL)/HBsAg (IU/mL) of < 2000/< 100 to 9.22 (95% CI: 4.34–19.58) for serum levels of HBV-DNA (IU/mL)/HBsAg (IU/mL) of ≥ 2000/≥ 100.[63] Our hospital-based Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers (ERADICATE-B) study (Fig. 1) also showed similar findings. A total of 2688 non-cirrhotic Taiwanese CHB patients were followed for a mean of 14.7 years. HCC risk increased when patients had increased HBV-DNA level (HR: 4.7; 95% CI: 2.2–10.0), increased qHBsAg (HR: 7.2; 95% CI: 1.8–28.6), and elevated ALT level (HR: 6.6; 95% CI: 2.2–19.8).[64]

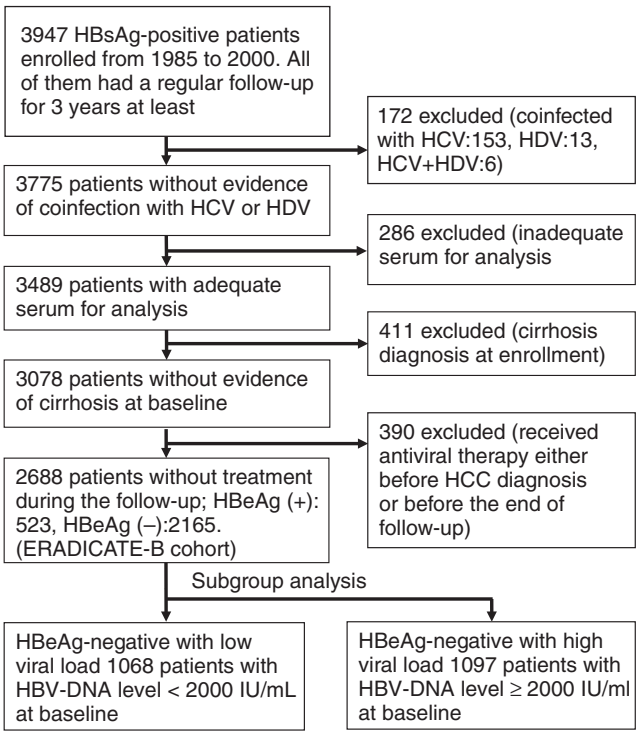

Figure 1 The flow of patients in a hospital-based Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers (ERADICATE-B) study to assess the impact of baseline hepatitis B virus (HBV)-DNA and hepatitis B surface antigen (HBsAg) levels on the risk of HCC development. Adapted from Tseng *et al.*[64]. HCC, hepatocellular carcinoma. HBeAg, hepatitis B e antigen; HCV, hepatitis C virus; HDV, hepatitis D virus.

Factors affecting HCC risk in inactive or low-risk HBV carriers

Although the incidence of HCC is significantly associated with baseline serum HBV-DNA levels in a dose–response relationship,[6,49,64] inactive or low-risk HBV carriers (serum HBV-DNA levels < 2000 IU/mL) still have significantly higher HR for HCC compared with individuals without HBV infection (HR: 4.6; 95% CI: 2.5–8.3).[65] Therefore, it is important to identify factors predictive of HCC other than HBV viral load in these inactive or low-risk HBV carriers.

In the ERADICATE-B study, we evaluated 1068 HBeAg-negative patients with low levels of serum HBV-DNA (< 2000 IU/mL). Risk factors for HBeAg-negative hepatitis as well as HCC development included advanced age (> 50 years old), male gender, elevated levels of ALT, and high qHBsAg (≥ 1000 IU/mL), but not levels of HBV-DNA.[64,66] The 17-year risk of HCC for patients with HBV-DNA < 2000 IU/mL and HBsAg ≥ 1000 IU/mL was significantly higher than that of those with HBV-DNA < 2000 IU/mL and HBsAg < 1000 IU/mL. Multivariate analysis revealed that qHBsAg ≥ 1000 IU/mL was an independent risk factor for HCC development (HR: 13.7; 95% CI: 4.8–39.3).[64] Data from REVEAL-HBV study and ERADICATE-B study all showed that serum HBsAg and HBV-DNA levels were complementary markers in predicting HCC. Therefore, serum HBsAg level should be integrated into the known HCC predictors for future management of patients with chronic HBV infection, particularly in those with low and intermediate viral loads (Fig. 2).

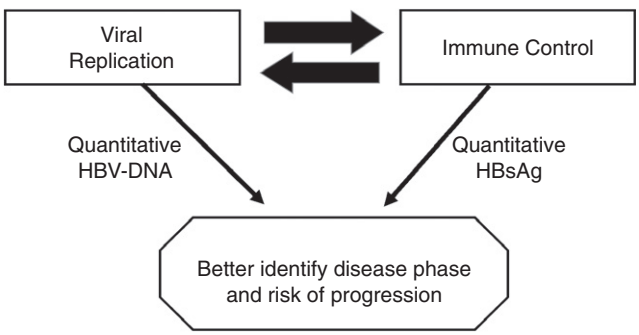

Figure 2 Quantitative hepatitis B virus (HBV)-DNA and hepatitis B surface antigen (HBsAg) are complementary biomarkers.

Risk calculator for HBV-related HCC

Because it is the commonest cause of death from chronic HBV infection, assessment and counseling on risk of HCC in management of CHB patients are urgently needed. Several risk factors predictive of HCC have been identified, including host and viral factors. However, an easy-to-use risk calculator with different weights to different risk factors to predict the risk of HBV-related HCC in a few years has not yet been well established and remains to be validated.[67–70]

Table 2 Cumulative risk score and projected 3-year, 5-year, and 10-year risk of developing hepatocellular carcinoma in patients with chronic hepatitis B

Risk predictor	Risk store	Cumulative risk score	HCC risk (%)		
			At 3rd year	At 5th year	At 10th year
Gender					
Female	0	0	0.0	0.0	0.0
Male	2	1	0.0	0.0	0.1
Age		2	0.0	0.0	0.1
30–34	0	3	0.0	0.1	0.2
35–39	1	4	0.0	0.1	0.3
40–44	2	5	0.1	0.2	0.5
45–49	3	6	0.1	0.3	0.7
50–54	4	7	0.2	0.5	1.2
55–59	5	8	0.3	0.8	2.0
60–65	6	9	0.5	1.2	3.2
ALT, U/L		10	0.9	2.0	5.2
< 15	0	11	1.4	3.3	8.4
15–44	1	12	2.3	5.3	13.4
≥ 45	2	13	3.7	8.5	21.0
HBeAg		14	6.0	13.6	32.0
Negative	0	15	9.6	21.3	46.8
Positive	2	16	15.2	32.4	64.4
HBV-DNA level, copies/mL		17	23.6	47.4	81.6
< 300 (undetectable)	0				
300–9999	0				
10 000–99 999	3				
100 000–999 999	5				
≥ 10^6	4				

Modified from Yang *et al.*[71]
ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Recently, the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B study developed and validated a predictive score for the risk of development of HCC in patients with CHB.[71] This study included risk score development cohort with 3584 non-cirrhotic CHB Taiwanese and a validation cohort with 1050 patients from three independent hospitals of Hong Kong and South Korea. The 17-point risk score is composed of five predictors of HCC, including sex, age, serum ALT level, HBeAg status, and serum HBV-DNA level. The risk score could precisely estimate the risk of HCC development at 3, 5, and 10 years of follow-up. Further receiver operating characteristic curves and calibration chart also confirmed the predictive value of this risk score in non-cirrhotic patients. For example, if a patient has the cumulative risk score of 12, the 3, 5, and 10-year HCC risk is 2%, 5%, and 13%, respectively (Table 2).

Although this risk calculator of HCC in non-cirrhotic CHB patients was externally validated, it is not ready to use in clinical practice. *First*, this risk scoring system of HCC may underestimate risk for patients with very low viral load at baseline. In ERADICATE-B study, the risk of HCC for carriers with HBV-DNA < 2000 IU/mL and HBsAg ≥ 1000 IU/mL was much higher than those with HBV-DNA < 2000 IU/mL and HBsAg < 1000 IU/mL (HR: 13.7; 95% CI: 4.8–39.3).[64] This finding indicated that high HBsAg level itself may reflect inadequate host immune control against HBV infection, leading to an increased HCC risk over time in patients with low viral load.

Second, the potential interactive effects of known hepatitis B viral factors on the development of HCC are not incorporated into this model. In a prospective study, Yu *et al*. provide strong evidence that male patients with both HBV genotype C and very high HBV viral loads had a 26-fold higher risk of HCC than those with other genotypes and low or undetectable viral loads.[72] Our case–control studies also revealed that BCP A1762T/G1764A mutation combined with high viral load was independently associated with the risk of HCC, irrespective of the presence of cirrhosis.[22,23] In addition, combination of mutations of pre-S, precore, and BCP regions, rather than single mutation, was significantly associated with the development of progressive liver diseases and HCC.[33,37,73] Furthermore, the relationships between HCC risk and dynamic changes of serum HBV-DNA, HBsAg, and ALT levels were determined in the ERADICATE-B study. Compared with patients with persistently low levels of HBV-DNA, HBsAg, or ALT, those with persistently high levels of these three factors were at a higher risk of HCC.[64] Therefore, it is essential to incorporate qualitative and quantitative hepatitis B viral factors in risk calculation model to make it more comprehensive and to be clinically useful in various forms of chronic liver disease, including inactive carrier state, chronic hepatitis, and cirrhosis (Fig. 3).

Conclusions

Over the past decade, extensive research on HBV has identified several hepatitis B viral factors such as serum HBsAg level, viral load, genotype, and mutants as powerful contributors to disease progression of CHB patients. According to several population and hospital-based cohort studies, risk stratification for HCC in patients with chronic HBV infection has been established in a preliminary manner. Low risk factors for HBV-related HCC include female gender, younger age (≦ 50 years old), HBV genotype A/B, and low serum levels of ALT, HBV-DNA, and HBsAg. In contrast, high risk factors for HBV-related HCC include male gender, advanced age (> 50 years old), HBV genotype C/D, BCP A1762T/G1764A mutations, pre-S deletion mutations, and high serum levels of ALT, HBV-DNA, and HBsAg. Among them, the modifiable risk factors are serum levels of ALT, HBV-DNA, and HBsAg.

In the future, multivariate risk assessment profiles for HCC should be integrated with current HBV treatment guidelines to enable practicing physicians to have better management of HBV carriers with different HCC risks. Finally, risk modification through antiviral therapy may lead to the prevention of disease progression and eventually reduce the risk of HCC development even among those who start treatment with substantial risk (Fig. 4).

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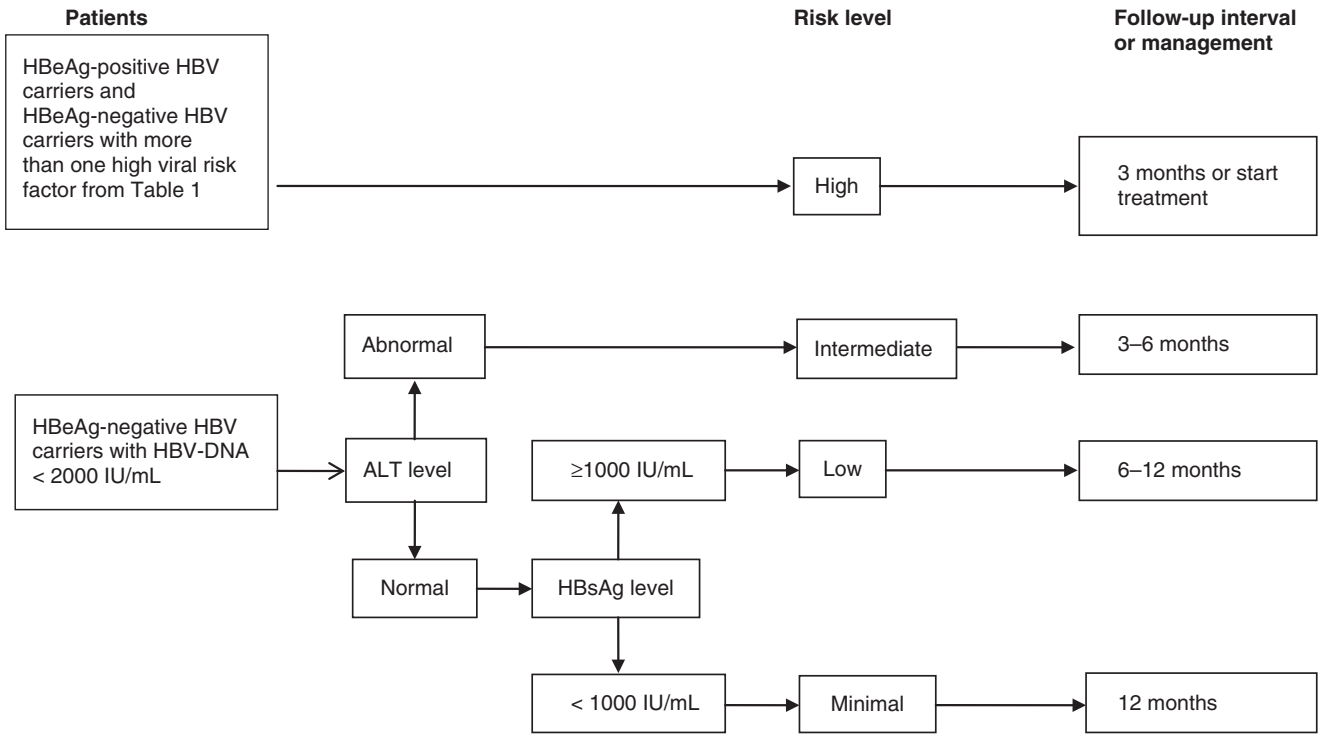

Figure 3 A hypothetical algorithm to categorize risk levels of hepatocellular carcinoma and corresponding management in Asian hepatitis B virus (HBV) carriers. Modified from Tseng *et al.*[66]. ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen.

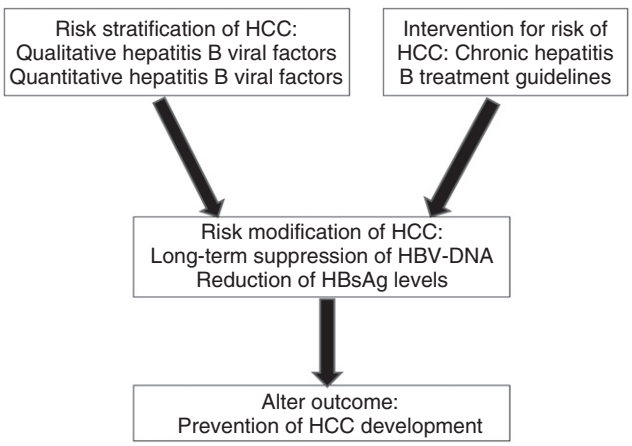

Figure 4 Assessment and modification of risk factors for hepatocellular carcinoma in chronic hepatitis B patients. HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.

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