Review

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Can we use HCC risk scores to individualize surveillance in chronic hepatitis B infection?

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Summary

Chronic hepatitis B is one of the leading causes of hepatocellular carcinoma (HCC) worldwide. Accurate prediction of HCC risk is important for decisions on antiviral therapy and HCC surveillance. In the last few years, a number of Asian groups have derived and validated several HCC risk scores based on well-known risk factors such as cirrhosis, age, male sex and high viral load. Overall, these scores have high negative predictive values of over 95% in excluding HCC development in 3 to 10 years. The REACH-B score was derived from a community cohort of non-cirrhotic patients and is better applied in the primary care setting. In contrast, the GAG-HCC and CU-HCC scores were derived from hospital cohorts and include cirrhosis as a major integral component. While the latter scores may be more applicable to patients at specialist clinics, the diagnosis of cirrhosis based on routine imaging and clinical parameters can be inaccurate. To this end, recent developments in non-invasive tests of liver fibrosis may further refine the risk prediction. The application of HCC risk scores in patients on antiviral therapy and in other ethnic groups should be evaluated in future studies.

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Abbreviations: AFP, alpha-fetoprotein; AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; AST, aspartate aminotransferase; AUROC, area under the receiver-operating characteristics curve; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement.

Introduction

Chronic hepatitis B virus (HBV) infection affects over 350 million people worldwide and remains one of the leading causes of cirrhosis, liver failure and hepatocellular carcinoma (HCC) [1]. In the past three decades, we have witnessed major improvements in the prevention and management of HBV-related HCC. Universal immunization against HBV, now reaching 30 years in some countries, effectively prevents new HBV infection and HBV-related HCC [2]. A landmark randomized controlled trial and multiple observational studies confirmed that antiviral therapy can profoundly reduce HCC risk in cirrhotic patients [3–5]. In patients who have developed HCC, improvements in surgical, locoregional and systemic therapies further contribute to better survival [6]. In addition, antiviral therapy after liver resection may reduce HCC recurrence and mortality [7–9].

At present, immunization has not covered people aged above 30 years, while the majority of HCC occur in middle-aged patients. The full impact of universal immunization will take 2 to 3 more decades to manifest. Besides, antiviral therapy reduces but cannot eliminate the risk of HCC. Therefore, HCC surveillance is still indicated in at risk individuals.

HCC surveillance requires facilities and manpower resources and may not be cost-effective in patients at low risk of HCC [10]. With this background, several Asian groups have derived and validated HCC risk scores based on well-known risk factors to predict future HCC development in patients with chronic hepatitis B. Potential clinical applications of these risk scores include prognostication and selection of patients for antiviral therapy and HCC surveillance. The impact of antiviral therapy on HCC and an introduction to the HCC risk scores have recently been reviewed by the *Journal* [11]. This review further discusses the development of HCC risk scores and the application in real-life clinical practice, and highlights their roles and limitations in different populations.

Key points

- Potent antiviral therapy reduces but does not eliminate the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B. Accurate HCC prediction is important to guide monitoring and surveillance for at-risk patients.
- Risk factors of HCC can be divided into patient factors and viral factors. Cirrhosis is the single most important risk factor of HCC. Based on the risk factors, a number of risk scores have been developed and validated. The most studied scores include the GAG-HCC, CU-HCC and REACH-B scores. Overall, the scores have excellent negative predictive values of over 95% in excluding HCC development in the next 3 to 10 years.
- Since antiviral therapy is an important disease modifier, the application of HCC risk scores in patients on antiviral therapy would overestimate the incidence of HCC. An updated score for treated patients is needed.
- The performance of the HCC risk scores appears to be inferior in Caucasian patients. It is unclear if it is because of geographical differences in the natural history of chronic hepatitis B or the effect of antiviral therapy.
- One potential pitfall of the HCC risk scores is the inclusion of cirrhosis as a major integral component while the diagnosis of cirrhosis is inaccurate. The recent development of non-invasive tests of fibrosis may potentially improve risk prediction further.

Risk factors of HCC in HBV infection

Patient factors

Similar to other chronic liver diseases, cirrhosis is the single most important risk factor for HCC in patients with chronic hepatitis B (Table 1). In East Asian countries, the incidence of HCC ranges from 0.2 per 100 person-years among inactive carriers, 0.6 in patients with non-cirrhotic chronic hepatitis B and 3.7 in those with compensated cirrhosis [12–14]. The corresponding figures in Europe and the United States are 0.02, 0.3, and 2.2 per 100 person-years, respectively [12]. However, since HBV is directly carcinogenic, HCC may arise in a non-cirrhotic liver. This highlights the importance of considering other HCC risk factors in the management of chronic hepatitis B.

As HCC usually develops in the background of liver injury and cirrhosis which takes decades to develop, the incidence of HCC increases with age. Moreover, studies have consistently shown that men have higher rates of HCC than women, with male: female ratios ranging from 2:1 to 4:1 [15]. This may be because men are more likely to smoke, drink alcohol, and have more active hepatitis and higher iron stores. Besides, both estrogen and androgen receptors have been implicated in hepatocarcinogenesis through the upregulation of interleukin-6 and cell cycle-related kinase [16,17].

It has long been observed that HCC runs in families. On average, first-degree relatives of patients with HCC have a 2-fold increase in HCC incidence [18,19]. The effect of family history appears to be synergistic to HBV carriage [20]. Although the observation can be partly explained by HBV infection and similar lifestyles among family members, recent genomic studies have begun to unravel genetic and epigenetic changes conducive to HCC development [21–23].

On another note, chronic hepatitis B patients with obesity and diabetes also have higher risk of HCC [24,25]. This is partly explained by the increased fibrosis progression in patients with metabolic syndrome [26]. In fact, among cirrhotic patients who used tenofovir for 5 years, regression of cirrhosis was less likely in those with diabetes or high body mass index [27]. It remains unclear whether the effect of metabolic syndrome on fibrosis progression and hepatocarcinogenesis is mediated through concomitant non-alcoholic steatohepatitis. In population studies, fatty liver is less common in patients with chronic hepatitis B [28].

Viral factors

Patients with positive hepatitis B e antigen (HBeAg) and high HBV DNA levels have increased risk of HCC. In a population study of 11,893 men in Taiwan, the relative risk of HCC was 60.2 for those with positive hepatitis B surface antigen (HBsAg) and HBeAg and 9.6 for those with positive HBsAg alone, as compared with those with negative HBsAg and HBeAg [29]. Furthermore, baseline HBV DNA is associated with future HCC risk. In the REVEAL-HBV Study, 3653 community non-cirrhotic patients with positive HBsAg were followed up for a mean of 11.4 years [30]. The incidence of HCC was 108 per 100,000 person-years for patients with HBV DNA below 300 copies/ml, 962 for those with HBV DNA 100,000–999,999 copies/ml, and 1152 for those with HBV DNA $\geqslant$1 million copies/ml. It should be noted that the study included only Asian patients aged 30 to 65 years at baseline. The findings cannot be extrapolated to younger patients, in whom positive HBeAg and high HBV DNA are the hallmark of the immune tolerance phase and are not associated with histological activity and HCC development [31].

HBV is divided into different genotypes (A–H) based on a $\geqslant$8% nucleotide sequence difference in the viral genome. Genotypes A and D are originally prevalent in Europe, while genotypes B and C are prevalent in Asia [32]. Due to the large influx of immigrants in North America and Europe, HBV genotypes vary widely within these continents. Among different genotypes, genotype C is associated with delayed HBeAg seroconversion [33]. Because of longer immune clearance phase and prolonged liver injury, patients with HBV genotype C infection are more likely to develop cirrhosis [34] and have a 2- to 5-fold increase in the risk of HCC [35–38]. Furthermore, the T1762/A1764 basal core promoter mutant is more common in genotype C [39]. The mutations are again associated with cirrhosis and HCC [37,39–41].

In recent years, there has been resurgence of interest in HBsAg quantification because the level probably reflects the level and activity of intrahepatic covalently closed circular DNA [42]. A study from Taiwan showed that on the whole HBV DNA is a better predictor of HCC than HBsAg level [43]. However, among patients with HBeAg-negative disease and low HBV DNA <2000 IU/ml, an HBsAg level of $\geqslant$1000 IU/ml had a hazard ratio of 13.7 for HCC as compared with lower HBsAg levels.