Review Article

Title: Disease modifiers and novel markers in HBV-related HCC
Running Title: optimizing prognosis in HBV-related HCC

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Abstract
Chronic hepatitis B (CHB) infection is responsible for 40% of the global burden of hepatocellular carcinoma (HCC) with a high case fatality rate. The risk of HCC differs among CHB subjects owing to differences in host and viral factors. Modifiable risk factors include viral load, use of antiviral therapy, co-infection with other hepatotropic viruses, concomitant metabolic dysfunction-associated steatotic liver disease or diabetes mellitus, environmental exposure, and medication use. Detecting HCC at early stage improves survival, and current practice recommends HCC surveillance among individuals with cirrhosis, family history of HCC, or above an age cut-off. Ultrasonography with or without serum alpha fetoprotein every 6 months is widely accepted strategy for HCC surveillance. Novel tumor-specific markers, when combined with AFP, improve diagnostic accuracy than AFP alone to detect HCC at an early stage. To predict the risk of HCC, a number of clinical risk scores have been developed but none of them are clinically implemented nor endorsed by clinical practice guidelines. Biomarkers that reflect viral transcriptional activity and degree of liver fibrosis can potentially stratify the risk of HCC, especially among subjects who are already on antiviral therapy. Ongoing exploration of these novel biomarkers is required to confirm their performance characteristics, replicability and practicability.

Keywords
Hepatic steatosis, risk prediction, liver fibrosis, viral biomarkers
Background

According to the Global Burden of Disease data estimation, chronic hepatitis B (CHB) infection affects 4.1% of the global population as of year 2019.\textsuperscript{1} CHB is responsible for at least 40% of hepatocellular carcinoma (HCC)\textsuperscript{2} - constitute >80% of primary liver cancer – and led to 905,700 incident cases and 830,200 mortality cases as of year 2020.\textsuperscript{3} Liver cancer was among the top 3 causes of cancer deaths in many countries.\textsuperscript{3} The mortality to incidence ratio, or more commonly known as the case fatality rate, for primary liver cancer is generally high although it varies between different regions in the world, ranged from 0.77 in North America to 0.98 in Africa.\textsuperscript{4} HCC carries a poor prognosis especially if diagnosed at an advanced stage, with 5-year survival <20%.\textsuperscript{5, 6} The universal implementation of vaccination for primary prevention i.e., mother-to-child transmission of hepatitis B virus (HBV) has been extremely effective to bring down the prevalence of CHB among children <5 years old to below 1% in many regions.\textsuperscript{7} As such, the main bulk of disease lies in the existing pool of adult patients who live with CHB. One of the most important goals in the management of CHB patients is to reduce the risk of HCC via secondary prevention measures including antiviral therapy and HCC surveillance for early detection. As the natural history of CHB is heterogeneous, together with differences in host factors, patients are affected with different magnitude of HCC risk. In this review, the risk factors and novel markers for HCC will be discussed.

Disease modifiers for HCC
In CHB infection, a number of risk factors have been reported to contribute to HCC development. They can broadly be classified as modifiable or non-modifiable factors (Figure 1). Most non-modifiable risk factors are related to the host characteristics. Age, sex, family history of HCC and cirrhosis are well known non-modifiable host factors associated with increased risk of HCC. Ethnicity, in particular Sub-Saharan African ethnicity, has been associated with higher risk of, or earlier onset of HCC. Genetic susceptibility plays a role in contributing to hepatocarcinogenesis in HBV. For instance, the intronic SNP (rs17401966) in kinesin family member 1B (KIF1B) (involved in transport of organelles and vesicles), SNPs near HLA-DQ (involved in antigen presentation, thereby antiviral functions and immune surveillance) and STAT (transcription factor for Th1 cell development and production of antiviral cytokines) have been identified in genome-wide association studies to be involved in HBV-HCC susceptibility. However, these studies were performed primarily in East Asians and most have not been replicated. Viral parameters including HBV genotype C and core promotor mutations have been identified as non-modifiable risk factors for HCC. Apart from these factors, it is crucial to understand the modifiable factors, so that appropriate measures can be taken to minimize the risk of HCC in CHB.

**Viral factors**

High viral load is a well-known risk factor for HCC, with a dose-response relationship above a level of 2000 IU/mL, according to the REVEAL-HBV study. In contrast, HBsAg seroclearance is associated with favorable clinical outcomes, with reduced risk of HCC.
especially if age of achieving such endpoint is below 50 years old. Treatment with antiviral therapy can effectively suppress HBV DNA and thereby reduce the risk of HCC. Of note, nucleoside analogues (NUC) cannot increase the rate of HBsAg seroclearance, which happens in ~1% patients every year. A number of novel compounds are being developed to enhance the probability of achieving HBsAg seroclearance, but it remains to be explored whether the benefits from natural HBsAg seroclearance can be extrapolated to novel compound-induced HBsAg seroclearance.

Apart from bringing down the viral load, NUC demonstrates extra effect through reduction of HBV integration to reduce hepatocarcinogenesis. In a randomized controlled trial that compared 3 years of tenofovir disoproxil fumarate (TDF) against placebo in a group of patients not meeting treatment criteria, TDF led to 3.28 fold reduction of HBV integration, compared to 1.81 fold reduction in the placebo group (p=0.0037). With these data, and other evidence supporting the more liberal use of NUC, the threshold to start antiviral therapy has been lowered as reflected by the recently updated World Health Organization guideline that recommends treatment in patients with alanine aminotransferase (ALT) 1 time above upper limit of normal (ULN) and HBV DNA >2,000 IU/mL, regardless of HBeAg status. Similar direction of recommendations is also observed in the recently published Chinese guidelines that suggests antiviral treatment in anyone with detectable HBV DNA with ALT >1 times ULN; or patients with family history of HCC; or aged >30 years old; or presence of significant fibrosis or inflammation.
Compared to HBV mono-infection, co-infection with human immunodeficiency virus (HIV) accelerates liver disease progression, have higher levels of HBV DNA, and higher risk of cirrhosis and HCC. Among HBV-HIV coinfected subjects, HBV DNA >200 IU/mL is associated with hazard ratio of 2.22, antiretroviral therapy with regimens that are also active against HBV is associated with reduced risk of HCC (hazard ratio 0.42). Coinfection with hepatitis C virus (HCV) and hepatitis delta virus (HDV) is similarly associated with at least 2-fold increase risk of HCC compared to HBV mono-infection.

It is therefore recommended to routinely screen for these co-infections among patients with CHB and manage accordingly to minimize the risk of disease complications.

Host factors

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease. At least one-third patients with CHB also suffers from concomitant MASLD. The effect of concomitant hepatic steatosis on risk of HCC in CHB is inconclusive. While some studies reported a protective effect, others report a heightened risk in those with concomitant MASLD and CHB. It is generally believed that MASLD per se is a risk factor for HCC, and concomitant MASLD + CHB should lead to additive if not synergistic risks of HCC. This has been confirmed in biopsy-proven cohorts with MASLD/MASH. However, more recently, an opposite effect has been reported, where imaging-identified hepatic steatosis was observed to be associated with reduced risk of HCC. The discrepancy is likely related to the population characteristics, in which the modality
to diagnose hepatic steatosis contributed to the heterogeneity of clinical course. Study populations that utilized liver biopsy (likely with a clinical indication for biopsy, such as raised ALT or significant fibrosis) to diagnose MASLD had a more unfavorable risk profile than populations that utilized non-invasive means or diagnosis coding to identify hepatic steatosis (more likely incidental finding). The effect of metabolic dysfunction is distinct from the effect of hepatic steatosis - the driver for HCC was predominantly metabolic dysfunction, while pure hepatic steatosis was associated with reduced risk of HCC. How MASLD interacts with CHB in HCC risk remains to be elucidated.

Type 2 diabetes mellitus (T2DM) is increasingly common among CHB patients. Owing to the aging population in many regions, the prevalence of T2DM has almost doubled from 10.6% to 20.1% in the last two decades. T2DM is a known risk factor for HCC even in non-HBV infected population, and has synergistic effect for HCC in CHB patients. The significance of T2DM is highlighted by the incorporation of this factor in the HCC risk prediction scoring system CAMD (cirrhosis, age, male sex, T2DM) which has been externally validated. Among those with CHB + T2DM, poor glycemic control as reflected by higher glycated hemoglobin (HbA1c), longer duration of T2DM and lower time reaching target HbA1c is shown to further increase the risk of HCC. The drug used for treatment of T2DM has also been implicated in HCC risk among patients with CHB. Compared to non-users, use of sodium glucose co-transporter 2 inhibitor (SGLT2i) is shown to reduce HCC risk (HR 0.54, 95%CI 0.33-0.88) among patients with co-existing T2DM and CHB even after matching for age, gender, metabolic factors, cirrhosis and duration of antiviral therapy. Another class of drug commonly used in patients with T2DM or MASLD is
statins – a lipid-lowering agent – which is associated with reduced risk of HCC with a dose-dependent manner.\textsuperscript{39} These observations prompt further evaluation, especially mechanistic studies, to prove a genuine causal relationship.

Cigarette smoking is common among patients with chronic liver disease (\textasciitilde40\%), and negatively impacts incidence and severity of liver fibrosis progression and HCC risk.\textsuperscript{40} It is associated with at least 2-fold increase in the risk of HCC among people with T2DM + CHB.\textsuperscript{37} The underlying mechanisms for cigarette smoking in hepato-carcinogenesis are complex, which involve increased pro-inflammatory cytokines, expression of hepatic cancer cells, epithelial to mesenchymal transition and telomere dysfunction.\textsuperscript{40} Similarly, harmful alcohol use increases the annual incidence of HCC among CHB patients with cirrhosis from 4.1\% to 9.9\%.\textsuperscript{41} In contrast, moderate coffee consumption is a protective factor against HCC development in CHB subjects.\textsuperscript{42, 43}

\textbf{Prediction and early detection of HCC}

\textbf{Standard practice of HCC surveillance}

To reduce morbidity and mortality from HCC, one of the key secondary prevention measures is early identification of HCC by surveillance. Current guidelines advocate ultrasound scan with or without serum alpha feto-protein (AFP) measurement every 6 months among CHB patients with cirrhosis or risk factors for HCC.\textsuperscript{5, 44} Risk factors for
HCC vary between regions, but in general refer to cirrhosis, men ≥40 years old or women ≥50 years old, or family history of HCC. However, AFP is not a perfect tumor-specific marker, as up to 30% HCC are non-AFP secretors.\textsuperscript{45} Also, AFP is not specific for HCC but could be elevated in other conditions such as hepatitis and germ cell tumor.

**Novel tumor-specific biomarkers for early detection of HCC**

A number of alternative tumor-specific markers has been reported to aid early diagnosis of HCC (Figure 2). Protein-induced by vitamin K absence or antagonist-II (PIVKA-II), also known as des-γ-carboxy prothrombin, is a prothrombin precursor that would normally be converted to native prothrombin via the action of a carboxylase that is vitamin-K dependent. In malignant hepatocytes, this carboxylase is lacking, resulting in accumulation of PIVKA-II.\textsuperscript{46} PIVKA-II is much more sensitive than AFP,\textsuperscript{47} and a combination of both PIVKA-II and AFP is superior to AFP or PIVKA-II alone, with pooled sensitivity and specificity of 82% and 85%, respectively with values of the area under the curve (AUC) for DCP, AFP, DCP + AFP, respectively, being 0.88, 0.75, and 0.90.\textsuperscript{48} In the Asia-Pacific expert panel consensus in HCC surveillance and monitoring, 88.2% agreed the approach to combine PIVKA-II and AFP for detection of HCC.\textsuperscript{49} Important considerations should be given among patients who are on vitamin K antagonists or with cholestasis, as these factors might influence PIVKA-II levels.\textsuperscript{47, 50} The glycoform of AFP, the *Lens culinaris* agglutinin-reactive AFP (AFP-L3), is produced by malignant hepatocytes. AFP-L3 combined with AFP and PIVKA-II is more sensitive and specific to
detect early HCC than AFP alone.\textsuperscript{51} However, criticisms arise for the lack of additional benefit to add AFP-L3 to AFP + PIVKA-II in the scoring systems developed to predict HCC (GALAD – gender, age, AFP-L3, AFP, DCP and GAAD – gender, age, AFP, DCP had similar performance characteristics).\textsuperscript{52} Nevertheless, a substantial proportion of HCC express AFP-L3 alone but not AFP nor PIVKA-II.\textsuperscript{53}

Tumor-specific protein 70 (SP70) is an antigen with relative molecular mass of 70 kDa. It is a tumor-derived protein that is involved in gene regulation for promoting cancer cell proliferation and metastasis. SP70 was initially found to be raised in patients with non-small cell lung cancer, and thus is not specific for HCC.\textsuperscript{54} In patients with HCC, combination of SP70 with AFP improved the diagnostic accuracy of HCC (AUC 0.909). Elevated SP70 is also associated with worse recurrence-free survival after curative treatment for HCC.\textsuperscript{55} Like many other tumors, HCC is associated with DNA methylation abnormalities. Certain methylation changes are involved in carcinogenesis, such as promotor-region methylation in CpG islands. With advancement in technology, the methylated DNA markers could be enriched and detected in plasma isolated from cell-free DNA.\textsuperscript{56} A recent study identified a multi-target HCC panel consisting of AFP, AFP-L3, 3 methylated DNA markers and B3GALT6 (a galactosyltransferase) as a novel blood-based biomarker panel to detect early HCC.\textsuperscript{57} Tumor cells are known to release nanometer-sized extracellular vesicles (EV) that are membrane-derived and function by transferring donor cell-derived bioactive molecules. It is recently reported that circulating EVs enriched with polymeric immunoglobulin receptor, known to be aberrantly expressed
in cancer tissue, were elevated in plasma of patients with late-stage HCC and contributed to cancer stemness and tumorigenesis.\textsuperscript{58}

Apart from PIVKA-II and AFP-L3 with commercialized assays available, other tumor-specific markers are currently used as research tool only owing to limited accessibility, need of sophisticated sample processing and lack of procedure/ assay standardization.

**Radiological diagnosis of HCC**

In cirrhotic livers, imaging diagnosis of HCC can be achieved by typical arterial hyperenhancement and portovenous washout among lesions >10mm. Such criteria has been endorsed by EASL clinical practice guidelines\textsuperscript{5} and forms the backbone of the Liver Imaging Reporting And Data System (LI-RADS) endorsed by AASLD guidelines to stratify the probability of a lesion being an HCC, where LR-5 refers to definite HCC.\textsuperscript{59} The sensitivity and specificity for HCC was found to be similarly at \textasciitilde60\% and \textasciitilde90\%, respectively, for imaging-based diagnosis using the EASL criteria or LR-5.\textsuperscript{60} The role of artificial intelligence in enhancing the accuracy of radiological diagnosis and characterization of HCC has been explored, such as the use of convoluted neural network to assist in assigning LI-RADS grades\textsuperscript{61}, histological grades,\textsuperscript{62} or radiomics approach via quantifying radiological characteristics with machine learning models such as texture analysis and topological data.\textsuperscript{63} These approaches are considered exploratory at this juncture pending extensive evaluation and validation. The bottom line is the careful use of contrast-enhanced cross-sectional imaging for sizable lesions in the background of
cirrhotic liver. Histological diagnosis is still necessary for lesions arising from non-cirrhotic livers, indeterminate radiological features, and for the practice of precision medicine.\textsuperscript{64}

**Prediction of HCC**

To identify high-risk individuals for HCC even before its onset, i.e., HCC prediction, many scores have been developed for HCC risk stratification in patients with CHB. These scores comprise of mainly clinical parameters. For instance, REACH-B (sex, age, serum levels of ALT, HBeAg status, HBV DNA level)\textsuperscript{65}, GAG-HCC (age, gender, core promotor mutation, HBV DNA level and cirrhosis)\textsuperscript{8}, CU-HCC (age, albumin, bilirubin, HBV DNA level, cirrhosis)\textsuperscript{10}, LSM-HCC (liver stiffness, age, serum albumin, HBV DNA level)\textsuperscript{66}, CAMD score (discussed above),\textsuperscript{36} PAGE-B (age, gender, platelet count)\textsuperscript{67} and modified REACH-B (age, sex, serum levels of ALT, HBeAg status, liver stiffness).\textsuperscript{68} Age, gender and platelet are commonly incorporated in these scores (Figure 2). Table 1 summarizes the risk scores reported so far for prediction of HCC in CHB patients. Although with acceptable discriminating power,\textsuperscript{69} none of these scores are currently recommended by clinical guidelines for routine use for a few reasons. Firstly, not all scores have been externally validated and since the majority of scores were developed in Asian patients, the performance among Caucasian patients is suboptimal, let alone some ethnicities such as African patients (Table 1). Secondly, most scores reported a high negative predictive value (NPV) of 95-99\% but a low positive predictive value (PPV) \textasciitilde10-40\% (Table 1). Thirdly, certain parameters are prone to subjective interpretation (e.g., presence of cirrhosis on ultrasound) or suffer from limited availability (e.g., HBV mutations, HBV
genotypes), with complicated mathematical formula to calculate a final score. Lastly, the implications of dynamic change in predictive scores with time and treatment on the risk of HCC have been unclear.

Apart from these scores that focus on the clinical parameters, other variables predictive of HCC might also play a role. These include viral biomarkers and liver fibrosis markers (Figure 2).

**Viral biomarkers**

The vast majority of detectable serum circulating HBV DNA is in the form of enveloped/encapsidated rcDNA.\(^7^0\) Although high viral load is a well-known risk factor for HCC,\(^1^5\) this marker will readily become undetectable in virtually all subjects put on NUC and could no longer reflect the HCC risk. In comparison, serum qHBsAg declines slowly with NUC therapy\(^7^1\) and has been shown to associated with HCC risk. The hazard ratio for developing HCC was 13.7 for low viremic (HBV DNA <2000 IU/mL) HBeAg-negative patients with serum qHBsAg ≥3 log compared to those with serum qHBsAg <3 log.\(^7^2\) Similarly serum HBV RNA in the form of encapsidated pgRNA in virus-like particles\(^7^3\) is still detectable in NUC-suppressed patients even after prolonged treatment.\(^7^4\) On-treatment detectable serum pgRNA is associated with 3.5-fold higher risk of HCC in 2 years' time.\(^7^5\) Another biomarker is hepatitis B core-related antigen (HBcrAg), which is a composite of 3 related proteins that share an identical 149 amino acid sequence: HBcAg, HBeAg and a truncated 22 kDa precore protein. While serum HBcrAg is reduced in all
NUC-treated CHB patients, a high post-treatment HBcrAg was associated with >2-fold increase in risk of HCC. Apart from HBV RNA, commercialized assays are available for these viral biomarkers.

Liver fibrosis markers

Liver stiffness measurement (LSM), measured via vibration-controlled transient elastography, allows accurate estimation of the amount of liver fibrosis. The LSM-HCC score (discussed above) and the liver stiffness-spleen diameter to platelet ratio score was associated with higher risk of HCC development, with hazard ratio of 1.541 after adjusting for age, serum albumin level and histological fibrosis stage. The Enhanced Liver Fibrosis (ELF) test is comprised of 3 markers originating in the extracellular matrix of liver that are involved in fibrogenesis: hyaluronic acid, tissue inhibitor of matrix metalloproteinases-1, and amino-terminal pro-peptide of type III procollagen. ELF can predict liver-related morbidity and mortality among patients with chronic liver disease. High ELF score independently predicts HCC development in patients with chronic liver disease from various etiologies, including those with chronic hepatitis B infection and even after HBsAg seroclearance. Mac-2 binding protein glycosylation isomer (M2BPGi) is a glycoprotein that correlates with amount of liver fibrosis. Serum M2BPGi levels were predictive of subsequent HCC development in patients with CHB, regardless of whether they are on NUC therapy. However, M2BPGi is not specific for liver fibrosis but also elevated in other extra-hepatic conditions such as pancreatic adenocarcinoma and idiopathic pulmonary fibrosis. While LSM and ELF are widely available in many clinical
settings, and endorsed in clinical practice guidelines for other liver diseases,\textsuperscript{89, 90} M2BPGi remains to be a research tool.

Conclusion

CHB infection remains to be a major contributor to liver-related morbidity and mortality. To minimize the risk of HCC in patients with CHB, the threshold to start NUC is lowered. The metabolic comorbidities and co-infection with other hepatotropic viruses should be optimized, and modification of lifestyle risk factors carries beneficial effects on prognosis. HCC surveillance with imaging and blood test is recommended for CHB subjects at risk of HCC. Novel biomarkers reflecting viral burden, liver fibrosis, and hepatocarcinogenesis might potentially aid prediction of and early detection of HCC. More studies are needed for these novel markers to be standardized and validated before they can be applied to clinical use.

Conflicts of Interest
Lung-Yi Mak served in the advisory board for Gilead Sciences, Roche Diagnostics, and received speaker fees from Abbvie and Pfizer.

Ethics Statement
This review article is fully based on articles which have already been published and did not involve additional patient participants. Therefore, IRB approval is not necessary.
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Author Contribution
Conceptualization, Writing - original draft, Writing - review & editing: LYM
Reference


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AFP: alpha feto-protein, ALT: alanine aminotransferase, HBeAg: hepatitis B e antigen, NPV: negative predictive value, PPV: positive predictive value

*External validation in non-Asian patients including Caucasian patients or mixed population
Figure 1. Risk factors associated with development of hepatocellular carcinoma among subjects with chronic hepatitis B infection. They can be broadly classified into modifiable factors and non-modifiable factors, and further stratified into viral factors or host factors.
Figure 2. Parameters to predict risk of HCC (clinical parameters, viral biomarkers or liver fibrosis markers) or diagnose HCC (tumor specific markers). Clinical parameters are commonly incorporated in risk scores. Some of them remain to be research tool only.