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HEPATIC CANCER (N PARIKH, SECTION EDITOR)

Risk of HCC in Patients with HBV, Role of Antiviral Treatment

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Abstract

Purpose of Review Risk prediction and reduction of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B virus (HBV) infection has been a hot topic over the last decade. This review summarizes the latest evidence of HCC risk prediction and reduction.

Recent Findings Risk prediction models have been moving from traditional regression analysis on clinical parameters as well as HBV and liver fibrosis biomarkers to novel machine-learning models which maximize data use while minimizing bias. Different studies and meta-analyses have been performed to compare the risk of HCC in chronic HBV patients treated by entecavir versus tenofovir disoproxil fumarate, yet suggested inconsistent results. HCC risk is much reduced by antiviral therapy through sustained viral suppression, while aspirin, metformin, and statin were also found useful as chemoprevention for HCC.

Summary Novel machine-learning models for HCC prediction are going to guide HCC surveillance and the need of chemoprevention for HCC with medications on top of antiviral therapy.

Keywords Aspirin · Hepatitis B virus · Hepatocellular carcinoma · Machine learning · Metformin · Statin

Abbreviations

CHB	Chronic hepatitis B
CI	Confidence intervals
ETV	Entecavir
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
IQR	Interquartile range
LSM	Liver stiffness measurement
NA	Nucleos(t)ide analogues
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate

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Introduction

Primary liver cancer, which is mainly hepatocellular carcinoma (HCC), is currently the sixth most common cancer and the third leading cause of cancer mortality globally; it led to 906,000 incident cases and 830,000 deaths worldwide in 2020 [1]. The risk of HCC varies across geographical regions due to the prevalence of different risk factors. In most of the high-risk HCC areas such as China, the Republic of Korea, and sub-Saharan Africa, chronic hepatitis B virus (HBV) infection is the major contributing factor [1]. Globally, chronic hepatitis B (CHB) infection affects around 296 million people [2]. CHB infection increases the risk of developing advanced liver fibrosis, liver cirrhosis, hepatic decompensation, and HCC, which contributed to 820,000 deaths in 2019 [2]. While liver cirrhosis is one of the most important risk factors for HCC, patients with CHB can develop HCC without cirrhosis (Fig. 1). HBV can integrate into the host genome early in chronic infection, which induces insertional mutagenesis and generates mutated or truncated viral proteins, leading to hepatocarcinogenesis [3, 4]. Both host and viral factors affect the risk of HCC in CHB patients (Fig. 1). Age is an important host risk factor. The risk of HCC starts to increase in CHB patients after 50 years old [5, 6]. Also, HBV-related HCC is male predominant with a two- to

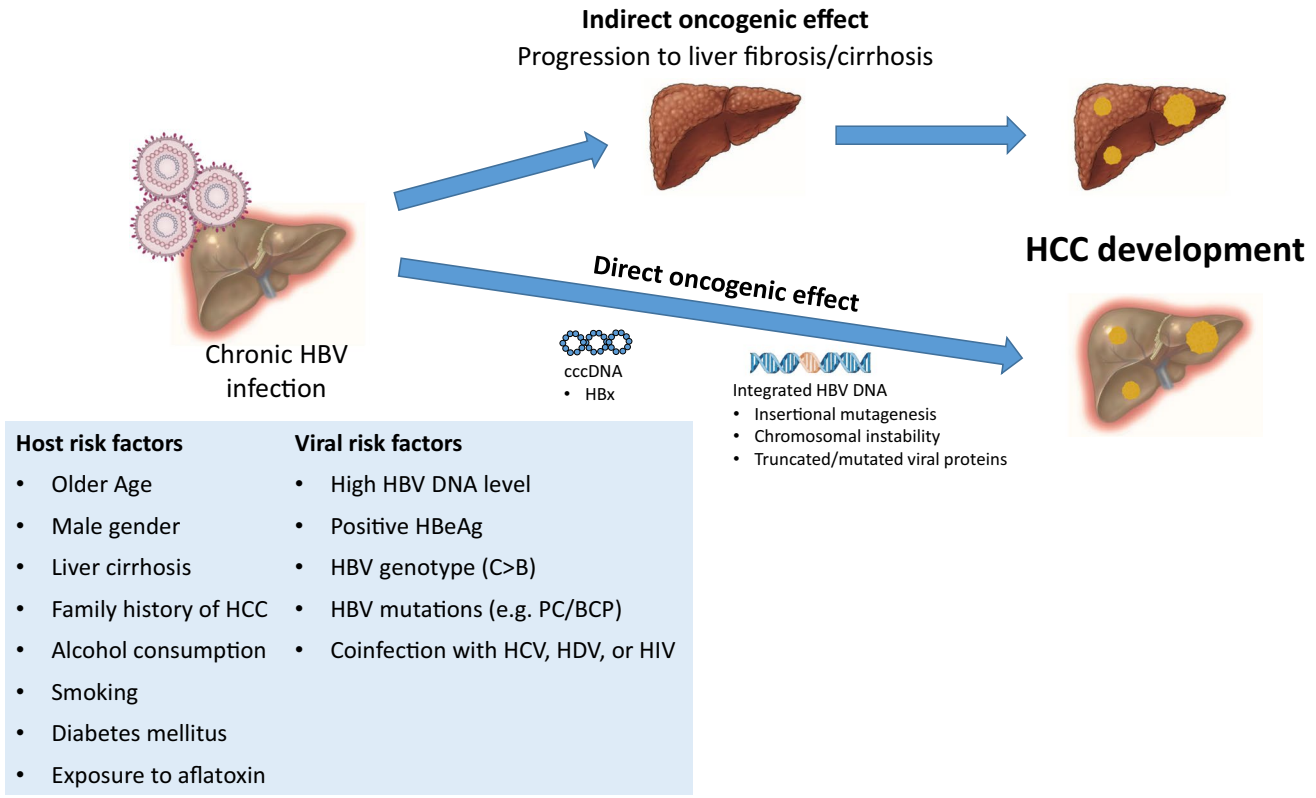

Fig. 1 Risk factors of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B. *BCP* basal core promoter, *HBeAg* hepatitis B e antigen, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HDV* hepatitis D virus, *HIV* human immunodeficiency virus, *PC* precore

three-fold higher incidence in males than females [1]. Some other host risk factors include alcohol consumption, family history of HCC, and the presence of diabetes mellitus [7, 8]. The prevalence of diabetes in CHB patients has been rising due to the aging population [9].

High-serum HBV DNA level is a well-known risk factor for liver cirrhosis and HCC in CHB patients (Fig. 1) [10]. Current first-line antiviral treatment including interferon-alfa and mainly nucleos(t)ide analogues (NAs) effectively suppresses viral replication and reduces the risk of disease progression to liver cirrhosis and HCC [11]. Complete viral suppression is an important treatment goal as it is associated with a low on-treatment risk of HCC [12•], while patients with low-level viremia on treatment still have an elevated risk of HCC [13]. Complete viral suppression also results in histological improvement over time and reversal of liver fibrosis and cirrhosis [14, 15].

HCC Risk Prediction

Several HCC prediction scores were developed for untreated CHB patients. The risk estimation for HCC in CHB (REACH-B) score derived from Taiwanese REVEAL-HBV study was constructed from gender, age, alanine aminotransferase (ALT), hepatitis B e antigen (HBeAg) status, and HBV DNA level and ranges from 0 to 17. The area under the receiver operating characteristic curves (AUROCs) were 0.811, 0.796, and 0.769 at 3, 5, and 10 years, respectively, to predict HCC risk [16]. The Chinese University HCC (CU-HCC) score derived from Hong Kong was composed of age, serum albumin, total bilirubin, HBV DNA, and cirrhosis and ranges from 0 to 44.5. The sensitivity and negative predictive value (NPV) were 82.2% and 97.3%, respectively, by the cutoff value of 5 [17]. Liver stiffness measurement (LSM)-HCC score was refined from CU-HCC score by using LSM, age, serum albumin, and HBV DNA and ranges from 0 to 30 with an AUROC of 0.83 at 5 years [18]. The Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis-HCC (GAG-HCC) score was composed of gender, age, HBV DNA, core promoter mutations, and cirrhosis with AUROCs higher than 0.87 at 5- and 10-year prediction [19]. For antiviral-treated patients, PAGE-B score derived from entecavir (ETV) or tenofovir-treated Caucasians was constructed from age, gender, and platelet counts and ranges from 0 to 25 with AUROCs of 0.76 and 0.77 at 3- and 5-year prediction, respectively [20].

Advanced fibrosis and cirrhosis are important risk factors for HCC development and they can regress by long-term viral suppression in NA-treated CHB patients [15]. Non-invasive assessments for liver fibrosis and cirrhosis are more acceptable to predict the risk of HCC. LSM is a non-invasive tool to assess fibrosis stage and is also used to predict HCC. However, there is a grey zone where advanced fibrosis cannot be diagnosed accurately. Enhanced liver fibrosis (ELF) score based on tissue inhibitor of matrix metalloproteinase type 1, hyaluronic acid, and aminoterminal propeptide of type III procollagen is a widely used combination biomarker for liver fibrosis [21]. It could predict fibrosis and cirrhosis accurately by the cutoff values of 9.8 and 11.3, which achieved a sensitivity of 69% and 83% and a specificity of 98% and 97%, respectively [22]. Combining ELF and LSM had better prediction performance on advanced liver fibrosis than using ELF or LSM alone [21]. The two-step algorithm combining ELF and LSM-HCC score derived from NA-treated CHB patients could improve the accuracy of HCC prediction with a sensitivity of 86.7% and NPV of 95.3% [23].

A number of serum biomarkers have been evaluated and used to monitor disease progression in CHB patients. Hepatitis B surface antigen (HBsAg) is a hallmark of CHB infection and was found positively correlated with intrahepatic covalently closed circular DNA (cccDNA) levels. The correlation between serum HBsAg levels and intrahepatic cccDNA levels is strong in CHB patients with positive HBeAg, but poor in patients with negative HBeAg [24]. HBsAg was found associated with the development of HCC in HBeAg-negative patients with low viral loads [25]. For NA-treated patients with complete viral suppression, HBsAg seroclearance could further reduce the risk of HCC [12•]. Hepatitis B core-related antigen (HBcrAg) including hepatitis B core antigen, HBeAg, and a truncated 22-kDa precore protein is a novel serum viral marker of CHB. HBcrAg levels have a positive correlation with intrahepatic cccDNA levels regardless of the HBeAg status [26]. Several studies found that HBcrAg could predict the risk of HCC accurately in both untreated and NA-treated CHB patients. NA-treated CHB patients with persistently high HBcrAg levels were more likely to develop HCC than those with low HBcrAg levels [27, 28]; the association is stronger among HBeAg-negative patients [29].

Novel HCC Risk Prediction

Most of the current HCC risk prediction models were developed using traditional regression analysis [30], whereas machine-learning approach is fast becoming a competitive alternative [31]. Machine learning, a subtype of artificial intelligence with computer programs enabled to "learn" from data and improve with experience, has arisen in recent years for model development, which allows direct selection of predicting parameters among all available parameters without subjective preselection, and maximizes data use while minimizing bias (Fig. 2). Machine-learning models that incorporate multiple serial parameters measured during follow-up will likely refine our prediction [32].

Our team has recently developed and validated several models built from clinical parameters with popular machine-learning approaches, namely, logistic regression, ridge regression, AdaBoost, decision tree, and random forest. They accurately predict HCC in a territory-wide cohort of 124,006 patients with chronic viral hepatitis in Hong Kong

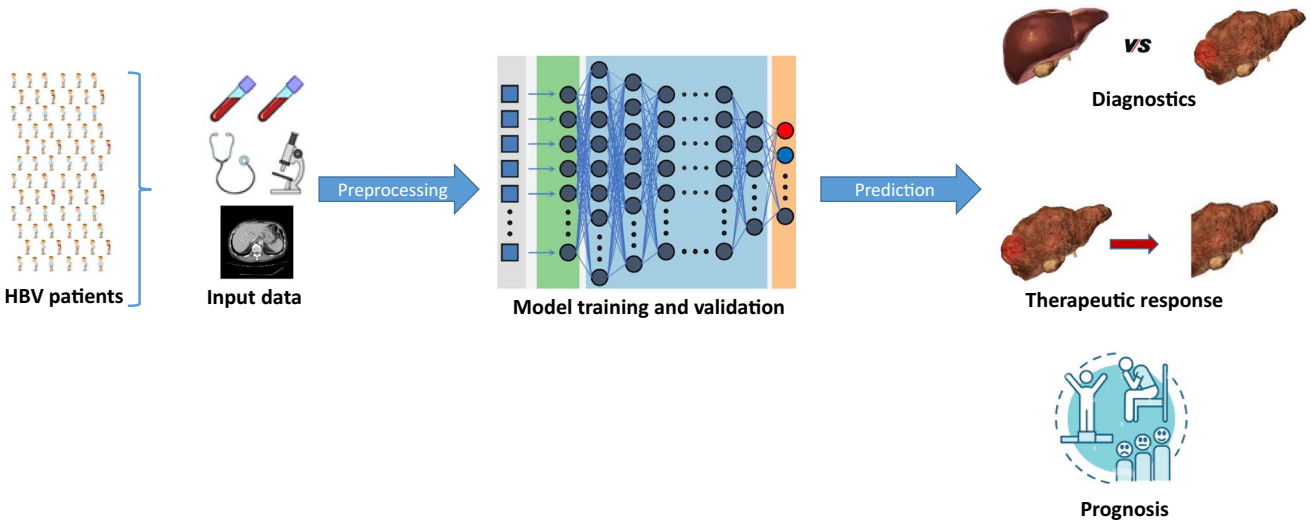

Fig. 2 Hepatocellular carcinoma risk prediction by artificial intelligence and machine learning. *HBV* hepatitis B virus

[33•]. HCC-RS, a novel machine-learning model built from ridge regression, has consistently good performance in both training and validation cohorts, as ridge regression is a technique for analyzing multiple regression data that suffer from multicollinearity. Radiomics signatures based on computed tomography imaging classifiers and digital pathology images were used as machine-learning signatures and found useful to improve the accuracy in diagnosing HCC or predicting HCC recurrence [34]. All these machine-learning models may be deployed as built-in functional keys or calculators in electronic health systems to facilitate early HCC diagnosis and hence reduce HCC mortality. Prospective studies and randomized trials comparing machine-learning model-guided HCC surveillance with routine clinical practice for the early diagnosis of HCC will further define their clinical benefits.

Current Antiviral Treatment

HBV antiviral treatment is pivotal for the risk reduction of hepatic decompensation and HCC in CHB patients [35–38]. Three widely adopted international guidelines, namely, the American Association for the Study of Liver Diseases, European Association for the Study of the Liver (EASL), and Asian Pacific Association for the Study of the Liver guidelines, similarly recommended certain parameters as indications for antiviral treatment [11, 39, 40]. For instance, all CHB patients with cirrhosis and/or HCC with detectable HBV DNA should receive antiviral treatment. Whereas for non-cirrhotic patients, serum ALT level, serum HBV DNA, and degree of liver fibrosis determine the need for antiviral treatment. Generally, those with high HBV viral load (i.e., HBV DNA > 20,000 IU/mL with positive HBeAg or > 2000 IU/mL with negative HBeAg) together with serum ALT > two times of upper limit of normal or evidence of moderate necroinflammation or fibrosis, as evidenced by liver biopsy or transient elastography, are indicated for antiviral treatment. An expanded indication also applies to CHB patients with family history of HCC, as suggested by the EASL guideline [40].

There are two main types of antiviral treatment in use: interferon-alfa and NAs. Interferon-alfa, in form of pegylated interferon, has the advantage of finite treatment duration with higher rates of functional cure of CHB [41–43], probably owing to its direct antiviral and immunomodulatory effect. Yet its use is offset by the side effect profile, need of subcutaneous injection, and contraindication in hepatic decompensation or pregnancy. On the other hand, oral NAs with high-resistance barrier, namely, ETV and tenofovir (either in form of tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]), have favorable safety profiles with a high rate of sustained viral suppression, a cornerstone for reduction in HCC risk [12•, 44]. ETV and TDF have been used invariably as the first line of oral antiviral treatment. TAF, a prodrug of tenofovir, offers greater plasma stability than TDF to deliver active drugs to hepatocytes at the same time reducing systemic tenofovir exposure, hence diminishing its risk of kidney dysfunction and bone loss compared to TDF [45, 46]. TAF is thus encouraged over TDF in older patients with established or at risk of renal or bone diseases [40].

Despite its importance in halting the disease progression, antiviral treatment uptake has been suboptimal worldwide to meet the World Health Organization 2030 viral hepatitis elimination goal [47–49]. In a recent territory-wide registry cohort study conducted by our team in Hong Kong where chronic HBV infection is endemic, 68% of newly diagnosed CHB patients fulfilling treatment indication received antiviral treatment in recent years, while advanced liver fibrosis was the area easily overlooked [50]. In spite of an observed improving rate in antiviral treatment uptake over the past decade, there is still a significant gap to reach HBV elimination. Alongside the CHB management international guidelines for physicians to follow, socioeconomic factors including ways to boost social awareness of the disease as well as policy-based measures such as higher screening rate for chronic HBV infection and loosing of antiviral treatment reimbursement would be vital to improve the current status, which ultimately leads to a reduction in liver-related morbidity and mortality [51].

HCC Risk Reduction with Different Antiviral Treatment

TDF Versus ETV

Both ETV and TDF are potent antiviral therapies that are equally recommended for patients with CHB [11, 39, 40]. They both effectively suppress HBV replications and prevent disease progression and HCC development. Nevertheless, this equal recommendation was first challenged by an observational study from South Korea in 2019 [52•]. Based on a nationwide insurance database and a large hospital cohort, the authors demonstrated a lower risk of HCC in patients receiving TDF than those receiving ETV [52•]. However, a similar Korean multicenter study published a few months later demonstrated a different result that there was no statistically significant difference between the risk of HCC in ETV- and TDF-treated patients. Since then, whether there exists a difference in chemoprevention of TDF and ETV treatment in CHB patients remains an unsettled debate. New studies and meta-analyses have emerged yet suggested inconsistent results (Table 1).

Different studies have compared the treatment responses of ETV and TDF in CHB patients. A meta-analysis of randomized controlled trials with reported treatment responses at 48 weeks suggested that TDF-treated patients achieved a higher rate of undetectable HBV DNA than ETV-treated patients in both HBeAg-positive (88% vs. 61%) and HBeAg-negative patients (94% vs. 88%) [53]. The rate of ALT normalization was similar in ETV-treated patients and TDF-treated patients in HBeAg-positive (70% vs. 66%) and HBeAg-negative patients (76% vs. 73%) [53]. The rate of HBsAg seroconversion in 12 months was comparable between ETV and TDF treatment (19% vs. 20%) [53]. These results were confirmed by a latter network meta-analysis in HBeAg-positive patients which showed an odds ratio (OR) of 0.46 (95% credible interval [CrI] 0.25–0.86) of achieving complete viral suppression, ALT normalization (OR 1.29, 95% CrI 0.75–2.29), and HBeAg seroconversion (OR 0.67, 95% CrI 0.38–1.14) in ETV-treated patients as compared

Table 1 List of meta-analyses from December 2019 to June 2022 that compared entecavir and tenofovir disoproxil fumarate treatment on the risk of hepatocellular carcinoma in patients with chronic hepatitis B (adopted and modified from Choi et al. [93] and Yip et al. [91])

Meta-analyses	Number of included studies	Unadjusted HR (95% CI) *P* value[c]	Adjusted HR[d] (95% CI) *P* value[c]	I^2 in unadjusted HR (%)[e] *P* value[c]	I^2 in adjusted HR (%)[e] *P* value[c]
Zhang et al. (2019) [94][a]	7	N.A.[a, b]	N.A	0% $P=0.78$	N.A
Li et al. (2020) [95]	32	0.87 (0.73–1.04) $P=0.13$	N.A	59.0% $P<0.01$	N.A
Gu et al. (2020) [96]	11	0.75 (0.65–0.87) $P<0.001$	0.77 (0.60–0.99) $P=0.04$	47.0% $P=0.07$	40.0% $P=0.12$
Wang et al. (2020) [97][a]	13	N.A.[a]	N.A	40.0% $P=0.11$	N.A
Dave et al. (2020) [98]	14	N.A	0.79 (0.63–0.99)[b] $P=0.04$	N.A	58.0% N.A
Choi et al. (2020) [99]	15	0.80 (0.69–0.93) $P=0.003$	0.75 (0.58–0.97) $P=0.028$	13.0% $P=0.31$	46.0% $P=0.09$
Liu et al. (2020) [100]	7	N.A	0.75 (0.56–0.96) N.A	N.A	47.5% $P=0.076$
Tseng et al. (2020) [101]	15	0.75 (0.54–1.03) 0.080	0.88 (0.73–1.07) $P=0.20$	76.7% $P<0.0001$	56.4% $P=0.0038$
Cheung et al. (2020) [102]	13	N.A	0.81 (0.67–0.99) $P=0.041$	N.A	43.4% $P=0.066$
Teng et al. (2020) [103]	10	N.A.[a]	N.A.[a]	N.A	N.A
Yuan et al. (2021) [104]	13	0.75 (0.60–0.95) N.A	0.83 (0.66–1.03) N.A	80.9% $P<0.01$	63.0% $P=0.003$
Jeong et al. (2021) [105]	17	N.A.[a]	N.A.[a]	80% $P<0.01$	64% $P=0.01$
Yuan et al. (2022) [106]	24	0.76 (0.67–0.86) N.A	0.78 (0.58–1.04) N.A	52% $P<0.001$	48% $P=0.06$
Huang et al. (2022) [107]	9	N.A	0.84 (0.65–1.08) $P=0.18$	N.A	66% $P<0.01$
Oh et al. (2022) [108]	19	0.72 (0.58–0.90) N.A	0.83 (0.65–1.06) N.A	66.3% $P<0.01$	52.3% $P=0.03$

HRs are reported using ETV as the reference; a HR < 1 associates TDF with reduced risk of developing HCC compared to ETV

CI confidence interval, *HR* hazard ratio, *N.A.* not available

[a]These meta-analyses did not calculate HRs. Zhang et al. (2019) reported an unadjusted rate ratio of 0.66 (0.49–0.89), Wang et al. (2020) reported an unadjusted risk ratio of 0.66 (0.41–1.05), Teng et al. (2020) reported an unadjusted risk ratio of 0.49 (0.38–0.64) and an adjusted risk ratio of 0.53 (0.38–0.73), and Jeong et al. (2021) reported an unadjusted risk ratio of 0.59 (0.35–0.98) and an adjusted risk ratio of 0.67 (0.45–1.02)

[b]Values for Zhang et al. (2019) and Dave et al. (2020) were transformed in order to use ETV as a reference, in line with the other studies

[c]Per convention, the meta-analyses have used a significance level of 0.05

[d]Adjusted HRs are those calculated using covariate adjustment or propensity score matching

[e]I^2 indicates the percentage of the variability in effect estimates that is due to heterogeneity instead of sampling error

to TDF-treated patients [54]. Data were less consistent in HBeAg-negative patients [54]. In addition, TDF as a nucleotide analogue and ETV as a nucleoside analogue may differ in immunological response. Murata et al. demonstrated an increase in serum interferon-lambda3 levels during additional use of nucleotide analogues, but not nucleoside analogues [55]. The rise in interferon-lambda3 can induce interferon-stimulated genes and inhibit HBsAg production [55, 56]. Previous studies also reported a potent antitumor activity of interferon-lambda in murine models of hepatoma [57, 58]. Nevertheless, how the difference in treatment responses of ETV and TDF affects their chemoprevention ability remains unclear.

TDF Versus TAF

TDF and TAF are both prodrugs of tenofovir. In the two Phase III registration trials, TAF shows a similar rate of viral suppression but a higher rate of ALT normalization than TDF [59]. The same is also observed among CHB patients who switched from TDF to TAF treatment [60]. This phenomenon has been confirmed by multiple real-world studies since then [61–64]. Previous studies showed that ALT normalization on treatment was associated with a lower risk of HCC in CHB patients [65, 66]. As TAF is a relatively new drug approved by the U.S. Food and Drug Administration in November 2016 and HCC takes time to develop, data on the risk of HCC of TDF versus TAF treatment in CHB patients remain limited. From the 4-year follow-up data of the two registration trials, TAF was associated with a lower but statistically non-significant risk of HCC than TDF treatment [67]. When compared to the predicted cumulative incidence of HCC by REACH-B score, TAF but not TDF treatment was associated with a significantly reduced HCC cumulative incidence [67]. Regarding real-world data, two Korean propensity score-matched studies showed a comparable cumulative incidence of HCC up to 4 to 5 years in TDF- and TAF-treated patients, with a hazard ratio (95% confidence interval) of 1.04 (0.49–2.18) and 1.18 (0.51–2.73), respectively [68, 69]. The society is actively anticipating more long-term follow-up data on TAF use to see if TDF and TAF exert a different chemopreventive effect on HCC.

HCC Risk Reduction with Other Medications

Although NA therapy effectively inhibits the replication of HBV, the risk of HCC cannot be eliminated [11, 39, 40]. Using NA alone may not suffice to prevent HCC and hence necessitate other effective strategies. Multiple studies have suggested that aspirin, statin, and metformin are associated with a significant reduction in HCC incidence in a dose-dependent or duration-dependent manner [70–73].

Experimental and epidemiological studies have shown that aspirin reduces the occurrence of HCC by exerting its antiinflammatory effects through inhibition of cyclooxygenase-2 (COX-2) [74–76]. A recent meta-analysis suggested that the use of aspirin significantly reduces the risk of HCC by 46% [77]. The prolonged latency effect of aspirin was demonstrated in various studies, in which long-term aspirin users (i.e., ≥ 5 years) experienced at least a 43% lower risk of HCC than aspirin non-users [72, 74, 77, 78]. More studies have also verified that the higher the dose of aspirin use, the better the effect of preventing HCC [73, 77]. In order to achieve the most apparent benefit of aspirin, a nationwide Swedish research study recommended the use of aspirin for 5 years or more at a dose of 1.5 or more standard tablets per week [73]. Although COX-2 inhibition contributes to gastrointestinal bleeding, patients who took aspirin for over 2 years had no significant increase in the risk of gastrointestinal adverse effects [72].

Type 2 diabetes mellitus (DM) is a common risk factor for HCC, while the risk is attenuated by the use of metformin [70]. To date, more evidence indicates that metformin, a first-line antidiabetic drug, is independently associated with a decreased risk of HCC [79, 80]. The mechanism of metformin to prevent HCC is not well understood [81]. Some postulated mechanisms include the regulation of microRNA expression to down-regulate target messenger RNAs, or inhibition of the cell cycle of various gastrointestinal tumors including HCC [82]. A Chinese meta-analysis has shown that treatment with metformin was associated with a 76% reduction in HCC risk among patients with DM [83]. Chen et al. discovered the dose-dependent relationship between metformin use and reduction in HCC risk.

Past studies have reported the beneficial inhibitory effect of statins on HCC incidence [71, 84]. A greater synergistic effect was seen among high-risk NA users in whom concurrent use of statin provided a 59% risk reduction in HCC [71]. Dose–response relationship between statin use and HCC risk was also observed. The higher the cumulative dose of statins used, the greater the risk of HCC reduced [84]. The use of fluvastatin, lovastatin, and rosuvastatin was associated with a 53 to 59% reduction in HCC risk, with a greater effect than the use of other statins such as cerivastatin and pravastatin [84].

Conclusion and Future Perspective

Since the publication of the Cirrhosis Asian Lamivudine Multicenter Study in 2004 [85], multiple observational studies have confirmed the role of antiviral therapy in the prevention of HCC and cirrhotic complications [37, 86]. During the same period, HCC risk scores have evolved from predicting HCC in untreated to treated patients [87].

Currently, the PAGE-B and modified PAGE-B scores have been validated in multiple treatment cohorts and can reasonably be applied in routine clinical practice [20, 88]. Treated patients with low HCC risk scores can be spared from 6-monthly HCC surveillance [89]. However, as the current risk scores are imperfect and often based on clinical and laboratory parameters at a single time point, machine-learning models that incorporate multiple parameters during serial follow-up will likely refine our prediction [33•]. To move the field forward, such prediction models have to be combined with electronic health records without the need for manual data entry. The inclusion of new virologic biomarkers such as HBsAg and HBcrAg will depend on their adoption in clinical care [90].

The relative effect of TDF and ETV on HCC prevention remains a matter of debate [91]. It is unlikely that a randomized controlled trial with an adequate sample size and follow-up duration will ever be conducted to compare these two active treatments, and further observational data will unlikely resolve the issue either. Looking ahead, as TAF has a better side effect profile than TDF, the next interesting question would be to compare the HCC incidence in patients receiving TAF versus other agents. Finally, a number of agents have entered phase 2 development with the goal of achieving functional cure of HBV in a significant proportion of patients [92]. Since patients achieving HBsAg seroclearance have an even lower HCC risk than those with HBV DNA suppression alone [12•], the development of new treatments may one day allow better prevention of this deadly cancer.

Author Contribution All authors were responsible for the interpretation of data and critical revision of the manuscript.

Declarations

Conflict of Interest Terry Yip has served as an advisory committee member and a speaker for Gilead Sciences.
Vincent Wong has served as a consultant or advisory committee member for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Merck, Novo Nordisk, Pfizer, ProSciento, Sagimet Biosciences, and TARGET PharmaSolutions and a speaker for Abbott, AbbVie, Echosens, Gilead Sciences, and Novo Nordisk. He has received a research grant from Gilead Sciences and is a cofounder of Illuminatio Medical Technology Limited.
Grace Wong has served as an advisory committee member for Gilead Sciences and Janssen and as a speaker for Abbott, Abbvie, Ascletis, Bristol-Myers Squibb, Echosens, Gilead Sciences, Janssen, and Roche. She has also received a research grant from Gilead Sciences.
Other authors declared that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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