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Review Article

Hepatitis B Virus-related Hepatocellular Carcinoma – An Update on Epidemiology, Risk Factors and Surveillance

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Introduction

Hepatitis B virus (HBV) infection is a major cause of cirrhosis and hepatocellular carcinoma (HCC), a cancer notorious for its high mortality. The carcinogenesis is related to viral and patient factors as well as gut dysbiosis. Evidence of the protective effects of commonly prescribed drugs, such as aspirin, statins, and metformin, for the development of HCC in high risk patients have recently emerged. Two levels of strategies to prevent HBV-related HCCs exist: primary prevention of HBV infection through nation-wide childhood HBV vaccination, and secondary prevention through first line antivirals (entecavir and tenofovir) in chronic hepatitis B (CHB) patients. Current HCC surveillance is achieved by abdominal ultrasonography at a 6-monthly interval. As population screening for HCC is not cost-effective, risk scores are developed to select surveillance targets.

Epidemiology

Globally, primary liver cancer is the sixth most common cancer, and the fourth in cancer-related mortality [1]. In 2018, the estimated global incidence of liver cancer was 9.3 per 100,000 person-years while the corresponding mortality rate was 8.5 [1]. Asia and Africa lead in incidence, with more than half of the newly diagnosed cases and deaths occurring in China [2]. HCC accounts for 75% of liver cancer cases [3]. The prognosis of HCC is dismal

with a 5-year survival of 18% [4], due to its late presentation, low rate of resectability, high chance of recurrence after resection and poor response to non-surgical management [5].

The majority of HCCs occur in patients with underlying liver disease, chronic infection by hepatitis B virus (HBV) being the leading cause by far, the rest resulting from hepatitis C virus (HCV) infection and alcohol abuse. The global prevalence of HBV infection was still 3.2% in 2017 despite widespread HBV vaccination since the late 1990s [6]. Among the 780,000 HBV-related deaths per year, around 80% has concomitant cirrhosis, an important risk factor for HCC development [7]. Endemic areas have a higher rate of CHB infections due to vertical and perinatal transmission, with a chronicity rate of >90%. In areas with low prevalence, horizontal transmission (sexual and parenteral routes) is more common, with > 95% of acute infections resolving spontaneously.

Between 1990 and 2015, HBV-related HCC incidence significantly decreased by 18.9% against a background of increase in total liver cancer incidence by 75% [8]. This decline is expected to continue in East Asia and Italy [3], which is largely attributed to vaccination against HBV first introduced in 1982. The WHO has launched the Global Health Sector Strategy (GHSS) on viral hepatitis 2016–2021, which calls for the elimination of viral hepatitis B and C as a public health threat by 2030 with an aim to reduce new infections and deaths by 90% and 65%, respectively. The strategies include HBV immunisation, prevention of transmission, and tests and treatment [6].

Apart from HCC [9-11], chronic hepatitis B (CHB) infection can lead to hepatitis flare [12], cirrhosis [13] and hepatic decompensation. Even in its quiescent phase, HBV reactivation triggered by immunosuppressive use could result in life-threatening liver failure [14,15].

Oncogenic factors of HBV-associated HCC

The development of HBV-associated HCC is a complex process which involves viral, patient factors and gut dysbiosis.

Viral factors

HBV infection has direct oncogenic effect, regardless of the degree of underlying liver fibrosis [16]. HBV is a small, non-cytopathic DNA virus and the prototype member of the hepadnaviridae family. The HBV virion or "Dane" particle contains a nucleocapsid with circular, partially double-stranded DNA, an approximately 3,200 base-pair genome surrounded by a lipid envelope [17]. The compact genome encodes four overlapping open reading frames that encode seven proteins: three surface proteins— large, middle, and small—forming HBsAg, the nucleocapsid core or C protein carrying HBV core antigen specificity, the secretory HBeAg, the viral reverse transcriptase or polymerase, and the X protein. Several viral factors initiate or promote hepatic carcinogenesis, which include (1) HBV genotype, (2) HBV integration, (3) specific HBV mutations, and (4) HBx protein.

HBV genotype: There are ten HBV genotypes (A-J). In Southeast Asia, genotypes B and C are the most prevalent, whereas genotypes A and D are common in North America and Europe [18]. In Asian studies, HBV genotype C (Ce and Cs) is associated with more severe liver disease, cirrhosis and the development of HCC compared with genotype B, with subgenotype Ce having a hazard ratio (HR) of 2.75 (95% CI, 1.66-4.56) and subgenotype Cs 1.70 (95% CI, 1.09-2.64). In Western Europe and North America, the rate of sustained remission after seroconversion was higher in genotype A than D, both in patients who seroconverted to anti-HBe during follow-up and in patients with positive anti-HBe at baseline [19,20].

HBV integration: HBV DNA integration in host chromosomes plays a substantial role in oncogenesis, and has been found in the majority (85–90%) of HBV-associated HCC [21]. This process may induce chromosomal instability or alter the expression of host genes through cis-acting mechanisms, and allow the continuous expression of viral oncoproteins such as HBx and truncated preS2/S proteins.

HBV mutations: Because HBV reverse transcription lacks proofreading activity, mutations accumulate and are selected by host immunity and antiviral drugs. Identified HBV mutations that are associated with HCC are in the preC and the preS region. Most commonly associated with HCC development in preC is T1762/A1764 double mutation [22]. Other mutations include C1653T and T1753V [23]. Since the preC region contains essential HBV regulatory elements, these mutations may alter HBV gene expres-

sion and replication. Also, because the HBx open reading frame overlaps the preC region, HBx expression or activity may be affected by preC mutations. PreS mutations are frequently point mutations, deletions or insertions. They may alter the expression and secretion of HBV envelope proteins, resulting in their accumulation and endoplasmic reticulum stress, leading to cell transformation [24].

HBx Protein: HBx is a notorious requisite for initiating and sustaining HBV replication [25]. It transactivates multiple cellular proteins to either directly or indirectly regulate cellular and HBV gene expression, promoting carcinogenesis [26].

Chronic inflammation: Recurrent liver inflammation caused by host immune responses during chronic HBV infection can lead to liver fibrosis and cirrhosis, accelerating hepatocyte turnover rate and promoting the accumulation of mutations [27].

Indicators for hepatitis viral activity

HBsAg &HBeAg: Positivity for hepatitis B surface antigen (HBsAg) has long been associated with the development of HCC. Nevertheless, patients with HBsAg seroclearance can still develop HCC, especially those who have HBsAg seroclearance after age 50 [28].

Positivity for hepatitis B e-antigen (HBeAg) indicates active and sustained HBV replication, a process which leads to malignant transformation through inflicting repeated cycles of hepatocyte necrosis and regeneration. Whether HBeAg seroconversion halts disease progression depends on the stage of life of the patient at the time of HBV infection. Patients infected in adolescence or adulthood are likely to benefit from seroconversion following treatment, while the disease in patients infected in early life still likely progress despite HBeAg seroconversion [29].

HBV DNA: HBV DNA level represents the strongest predictive biomarker associated with disease progression and long-term outcome [30]. In subjects with untreated HBV infection, the incidence of HCC increases with serum HBV DNA in a dose-dependent fashion, and serum HBV DNA level >1million copies/mL was associated with a hazard ratio (HR) of 6.1 compared with those with undetectable serum HBV DNA [31]. In another prospective study, the odds ratio (OR) of HCC development was 3.9 (95% CI: 1.6-9.2) for men who had detectable serum HBV DNA, compared with those who had undetectable level, in a dose-dependent manner [32].

Patient factors

Patient factors that are associated with a higher HCC risk include older age, male sex, cirrhosis, diabetes mellitus (DM), exposure to environmental carcinogens (aflatoxin B1, heavy alcohol and tobacco consumption), HIV coinfection, and HDV superinfection [27]. In all geographical regions, males have a higher incidence of both HBV infections and HCC, and the male: female ratio is more skewed in regions where HCC is more prevalent [33]. Dietary exposure to aflatoxin B1 amplifies HCC risk in CHB patients, through a specific mutation in TP53 at position 249 (R→S) [16].

Cirrhosis and the degree of fibrosis are major determinants of HCC risk. The majority (70%-90%) of HBV-related HCC develops in cirrhotic livers. The cumulative lifetime risk of developing HBV-associated cirrhosis is 41.5% for CHB patients, and that of developing HCC is 21.7% [34]. The annual incidence of HCC in CHB patients with compensated cirrhosis is 2.97% compared to 0.42% in chronic carriers without cirrhosis [35]. The progression to cirrhosis and HCC is affected by the host immune response and is therefore variable. An estimation of HCC risk in CHB patients can be achieved by liver stiffness measurement (LSM) with transient elastography. In patients with cirrhosis, each kilopascal increase in baseline LSM results in a 4% increase in HCC risk, and stiffness regression is a predictor of the HCC risk following antiviral therapy [30].

Host genomics may also influence the risk of HCC development. Single-nucleotide polymorphisms at different human genomic loci (e.g., chromosome 1p36.22, chromosome 6 of human leukocyte antigen [HLA]-DP and HLA-DQ loci, and chromosome 8p12) are associated with higher HCC risks in CHB patients by genome-wide association studies (GWAS) [36,37]. But HCC is among the solid cancers with the fewest somatic mutations that can be targeted with molecular therapies, and to date, no mutations have been used in clinical practice to predict a therapeutic response.

Gut dysbiosis

Literature on the role of the gut microbiota in CHB is lacking. However, as most HBV-related HCC occurred in cirrhotic liver, it should be noted that a leaky gut and dysbiosis are prominent features of liver cirrhosis, as reflected by increased occurrence of gut-derived bacterial infections such as spontaneous bacterial peritonitis, and they may contribute to the development of HCC in cirrhotic patients [38].

Protective factors

Aspirin: Low-dose aspirin use is associated with lower risk of HCC and liver-related mortality in patients with chronic hepatitis. A recent study using large Swedish database (71.5% and 28.5% having CHB and chronic hepatitis C (CHC) infection respectively) showed an inverse-relationship between aspirin use and HCC incidence that was duration dependent, with adjusted subhazard ratio (aSHR) of 0.66 (95% CI: 0.56-0.78) upon 3-5 years use and 0.57 (95% CI: 0.42-0.70) with use of aspirin for >5 years. There was an absolute risk difference of -6.9% (95% CI: −8.1 to 5.7) in terms of 10-year liver-related mortality between aspirin users and non-users [39]. On the other hand, there was no significant increase in gastrointestinal bleeding.

Aspirin may prevent hepatocarcinogenesis through diverse mechanisms including preventing platelet degranulation, modulating bioactive lipids, and inhibiting the proinflammatory cyclooxygenase-2 (COX-2) enzyme [39]. Experimental evidence shows that enhanced hepatocyte COX-2 is sufficient to induce HCC through inducing promoter hypermethylation by reducing TET1, silencing tumor-suppressive genes and activating key oncogenic pathways [40]. Moreover, the observation that indomethacin, one type of nonselective anti-inflammatory drugs (NSAIDs), is able to induce more apoptosis than the selective COX-2 inhibitors in the HCC cells suggests that COX-1 also influences the carcinogensis [41].

Statins: It has also been found that lipophilic statins, but not hydrophilic statins, were associated with reduced risk of HCC in patients with HBV or HCV infection. The 10-year HCC risk was significantly lower among lipophilic statin users with an aSHR of 0.56 (95%CI, 0.41 to 0.79) but not hydrophilic statin users (aSHR, 95%CI, 0.86-1.08). The inverse association between lipophilic statins and HCC risk seemed to be dose-dependent [42]. This is confirmed by recent large-scale meta-analyses [43,44].

As previously reported, HBV genome integration determines several DNA modifications and microdeletions that target HCC-relevant genes and confer hepatocytes growth advantage. Statins inhibit the mevalonate pathway and hence limit the downstream detrimental effects of these growth signalling proteins. Statins are also pro-apoptotic, by activating caspases and decreasing Bcl-2. Moreover, statins inhibit the activation of the proteasome pathway that breaks down molecules with growth-inhibitory effects, such as p21 and p27. The greater chemoprotective effect of lipophobic statins is likely due to greater lipid solubility and membrane permeability which enhance their pharmacological effects, especially in the milieu of hepatoceullar inflammation [44].

Metformin: This insulin-sensitising drug reduces hyperinsulinemia, inhibits hepatic gluconeogenesis, and reduces glycogenolysis. It is independently associated with decreasing HCC occurrence and liver-related mortality [45]. In particular, the reduction in plasma insulin level represents a direct mechanism against carcinogenesis. Indirect mechanisms include the induction of cellular apoptosis, the stimulation of the immune system, and the activation of adenosine monophosphate protein kinase (AMPK). AMPK is a key mediator of the tumour suppressor liver kinase B1 (LKB1), and is suppressed in cancer associated with metabolic syndrome [46]. Via AMPK activiation, metformin reinforces metabolic checkpoints by acting on mTORC1, p53, fatty acid synthase and other molecules for regulating cell growth and metabolism.

A recent meta-analysis reveals that DM is a risk factor for HCC development in CHB patients (HR 1.77, 95% CI 1.28–2.47) and a poor prognostic factor for overall mortality in the same cohort (RR 2.33, 95% CI 1.64–3.31) [47]. Because of the significant joint associations of HbA1c ≥ 9% and chronic liver diseases (including CHB and cirrhosis) with HCC risk, metformin probably lowers this risk by controlling HbA1c levels [48].

Since the current findings are based on observational studies, the clinical utility of these drugs as chemoprevention agents in CHB patients still awaits validation by large-scale randomised controlled trials.

Non-selective beta-blockers: For three decades, non-selective beta-blockers (NSBBs) have been the backbone of treatment for portal hypertension in cirrhosis. Its dual mechanism of action involve s (1) beta-1 blockade, which decreases cardiac output and (2) beta-2 blockade, which leads to unopposed alpha 1 activity in the splanchnic circulation, hence splanchnic vasoconstriction and reduced portal inflow and pressure [49]. Meta-analysis of randomised trials showed that NSBBs may prevent HCC in patients with cirrhosis (risk difference -0.026; 95% CI -0.052 to -0.001; number needed to treat 38 patients) [50].

Coffee consumption: Prospective cohort studies have demonstrated a linear dose-response relationship between coffee consumption and liver cancer risk. In a recent meta-analysis, the pooled RR for the highest consumption group compared with non-/occasional coffee drinkers was0.50 (95% CI: 0.38–0.66) [51]. This protective effect may not be attributable to caffeine as non-coffee caffeine-containing beverages (like green tea) do not reduce HCC risk [52]. As to which chemical in coffee exerts anti-carcinogenic activity still awaits further investigation.

The HCC preventive effect of coffee in CHB patients is less well established. Most studies were conducted in Europe and Japan where the predominant chronic viral hepatitis is HCV. Although CHB patients who were coffee-drinkers had significantly lower baseline serum AST, APRI and FIB-4 index values than non-coffee drinkers, the change in these values, fibrosis progression and HCC risk did differ from non-drinkers after 5 years, unlike that observed in patients with HCV and fatty liver disease [53]. A Korean study performed on patients with chronic liver disease in a HBV-endemic population also confirmed the negative association of coffee consumption with HCC development. However, this association was lost when the subjects were stratified by their HBV status [54].

Prevention of HBV-Related HCC

The prevention of HCC development can be achieved via primary prevention with vaccination and secondary prevention with antivirals (by suppressing viral replication and prevention/regression of fibrosis/cirrhosis).

Primary prevention of hepatitis B infection

Primary prevention of HBV infection is most effectively achieved through vaccination and public education [55]. HBV vaccines were available since the 1980s, using purified preparations of HBsAg generated from yeast (*Saccharomyces cerevisiae*) and recombinant techniques [56]. The WHO recommends HBV vaccination for all children worldwide, with a standard of at least 3 doses in all national immunization programmes, while emphasising timely coverage of the birth dose the prevention of perinatal transmission. For infants born of HBV carrier mothers, an additional injection of hepatitis B immune globulin (HBIG) should be given within 24 hours of birth [57]. However, recent studies show that vaccine failure can occur if the mothers' HBV DNA levels are higher than 200,000 IU/mL. Prescription of tenofovir disoproxil fumarate (TDF) to mothers before the last trimester can reduce the transmission rate from 7% to 0% [58].

In addition, the Immunization Practices Advisory Committee (ACIP) advices persons who are at high risk for HBV infection to receive the vaccine (Table 1) [59]. Compared with the pre-vaccine era from the 1980s to the early 2000s, the proportion of children younger than 5 years of age who became chronically infected fell from 4.7% to 1.3% in 2015, with the remaining infections mostly a result of perinatal transmission from the mother or from other young children [6].

Secondary prevention with antiviral therapy in CHB patients

Strong evidence supports the prevention of HBV-induced HCC in chronic carriers through antiviral therapy [60,61]. EASL guidelines recommend that the endpoints of treatment be, in the order of priorities: (1) the induction of long-term suppression of HBV DNA levels, (2) the induction of HBeAg loss in HBeAg-positive CHB patients, (3) alanine transaminase (ALT) normalization, and (4) HBsAg seroclearance. The two main treatment options for CHB patients are nucleos(t)ide analogues (NAs) and immune modulation by pegylated IFN.

NAs reduce HCC risk by suppressing viral replication [62]; and in patients having undergone curative HCC therapies, it also reduces recurrence risk. The NAs that have been approved for HBV treatment include lamivudine (LAM), adefovir dipivoxil (ADV),

Table 1: Groups for Whom Hepatitis B Vaccine Is Recommended (adapted from ACIP recommendations 1991)

- All infants
- All persons 18 years of age and younger
- Persons at occupational risk, including health care workers and public-safety workers who are exposed to blood
- Clients and staff of institutions for the developmentally disabled
- Patients on haemodialysis
- Recipients of certain blood products, such as clotting factor concentrates
- Household members and sexual partners of HBV carriers
- Adoptees from countries where HBV infection is endemic
- Travelers who plan to spend more than six months in areas with high rates of HBV infection and who will have close contact with the local population
- Short-term travellers who are likely to have contact with blood (e.g., in a medical setting) or sexual contact with residents of areas with high or intermediate levels of endemic disease
- People who have more than one sexual partner in six months
- Men who have sex with other men
- People who illicitly inject drugs
- Inmates of long-term correctional facilities

entecavir (ETV), telbivudine (LDT), TDF and tenofovir alafenamide (TAF), These can be classified into those associated with a low barrier against HBV resistance (LAM, ADV, LDT) and those with a high genetic barrier to HBV resistance (ETV, TDF, TAF). The three current first-line NAs are ETV, TDF and TAF. While ETV has no major side effects, TDF can lead to renal tubular dysfunction (hypophosphatemia and Fanconi syndrome in its severe form), osteopenia and osteoporosis. These side effects of TDF are reduced markedly with the newer preparation of TAF.

An earlier form of therapy, IFN-α has shown inconsistent effects on the risk of HCC occurrence, due to moderate suppression of HBV replication [63]. Its benefit may also be limited to cirrhotic patients. LAM and ADV were effective in reducing HCC risk in CHB patients in different stages of the disease, including asymptomatic, those without cirrhosis and those with cirrhosis. Yet their optimal effects on the long-term outcome may be blunted due to the emergence of drug-resistant HBV [63]. Treatment with a potent NA with high barrier to resistance (i.e., ETV, TDF, TAF) is more effective in the long term, achieving undetectable HBV DNA levels in the vast majority of compliant recipients, while having a favourable safety profile [64]. A nationwide propensity score matched cohort study showed a 63% lower HCC risk, with beneficial effect existing in all subgroups according to age, sex, cirrhosis and DM [62]. A recent meta-analysis shows that TDF may be associated with lower risk of HCC than ETV [65]. There are several explanations. First, nucleotide but not nucleoside analogues induce higher serum interferon lamda-3 level [66], which has potent antitumor activity in murine models of cancer and inhibits HBsAg production [67]. Second, TDF led to a higher rate of serum HBV DNA undetectability at 1 year of treatment compared with ETV [68]. Third, although both NAs have a high genetic barrier to resistance, the 5-year resistance rate of ETV was 1.2% [69], while no drug resistance was documented after 8 years of TDF therapy.

However, whether TDF is superior to ETV in terms of HCC prevention remains controversial. Besides the residual/unmeasured confounding factors inherent to observational studies, studies vary in terms of their sample size, patient characteristics, ethnicity, and study design. The discrepancy in study design is a major hurdle – most of those favouring TDF were retrospective cohort studies, not prospective studies; and they utilized electronic datasets, not clinical records. The accuracy of administrative/claim-based datasets is in doubt, while some important variables may be left

out, such as smoking, alcoholism, HBV DNA level, and drug compliance [70]. Furthermore, the ETV group had longer follow-up than the TDF group by up to 33 months, which may spuriously favor a better preventive effect of TDF over ETV, as HCC takes years to develop.

Whom to treat with NA therapy

The indications for treatment do not discriminate HBeAg status. The EASL guidelines recommend the following groups of patients receive long term NA treatment based on the combination of three criteria: serum HBV DNA levels, ALT, and the severity of liver disease.

These patients include those with (1) HBV DNA of 2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, (2) compensated or decompensated cirrhosis with any detectable HBV DNA level, regardless of ALT levels, and (3) HBV DNA >20,000 IU/ml and ALT >2xULN. For patients with HBeAg-positive chronic HBV infection (defined by persistently normal ALT and high HBV DNA levels), treatment may be started if they are older than 30 years or there is a family history of HCC. In addition, CHB patients with extrahepatic manifestations should also be treated.

Risk Scores & Surveillance

Risk scores

The annual incidence of HCC is 0.2% in CHB patients who are

Table 2: Risk scores for the prediction of HCC in untreated CHB patients.

Risk score	Cohort no. (derivation / validation cohort)	Country	Variables included in risk scores											
			Host factor			Liver disease/ viral activity				Cirrhosis/ fibrosis				
			Age	Sex	Other	HBV DNA	HBeAg	ALT	Other	Cirrhosis	PLT	LSM	Albumin	Other
GAG-HCC [85]	820/ 0	Hong Kong, China	X	X		X				X				
CU-HCC [86]	1055/ 428	Hong Kong, China	X			X				X			X	Bilirubin
REACH-B [87]	3584/ 1505	Taiwan, China/ Hong Kong, China / Korea	X	X		X	X	X						
REACH-B II [88]	2227/ 1113	Taiwan, China	X	X	Family history	X	X	X	HBsAg, genotype					
LS Model [89]	1250/ 0	Korea	X	X		X						X		
LSM-HCC [90]	1035/ 520	Hong Kong, China	X			X						X	X	
LSPS [91]	227/ 0	Korea									X	X		Spleen size
RWS-HCC [92]	583/ 3353	Singapore	X	X					AFP	X				
AGED [93]	628/ 1663	China	X	X		X	X							
D^2AS [94]	971/507	Korea	X	X		X								
APRI/ FIB4 [95]	1006/ 0	Korea	X					X	AST		X			
HCC-ESC [96]	723/ 0	Hong Kong, China	X	X		X		X		X			X	

Abbreviations: HCC: Hepatocellular Carcinoma; NA: Nucleos(t)ide Analogue; CHB: Chronic Hepatitis B; ALT: Alanine Transaminase; PLT: Platelet; LSM: Liver Stiffness Measure; AFP: Alpha Fetoprotein; AST: Aspartate Transaminase

Table 3: Risk scores for the prediction of HCC in untreated CHB patients - Predictability

Risk score	Cohort no. (derivation / validation cohort)	Country	Predictability at 5 years		
			AUROC	NPV in low-risk group (derivation/validation cohort)	PPV in high-risk group (derivation /validation cohort)
GAG-HCC [85]	820/ 0	Hong Kong, China	0.88/ -	98%/ -	14%/ -
CU-HCC [86]	1055/ 428	Hong Kong, China	-/ 0.76	98%/ 98%	29%/ 27%
REACH-B [87]	3584/ 1505	Taiwan, China/ Hong Kong, China / Korea	0.8/ 0.78	99.2%/ -	21%/ -
REACH-B II [88]	2227/ 1113	Taiwan, China	0.89/ 0.84	-	-
LS Model [89]	1250/ 0	Korea	0.80/ - (3-year)	-	-
LSM-HCC [90]	1035/ 520	Hong Kong, China	0.83/ 0.83	99.4%/ 99.7%	8.8%/ 7.6%
LSPS [91]	227/ 0	Korea	0.83/ -	97.5%/ -	36%/ -
RWS-HCC [92]	583/ 3353	Singapore	0.92/ 0.77/ 0.83/ 0.90	98.9%/ 97%/ 97%/ 93%	-
AGED [93]	628/ 1663	China	0.76/ 0.73	-	-
D^2AS [94]	971/507	Korea	0.89/ 0.88	99.4%/ 99.6%	22%/ 14%
APRI/ FIB4 [95]	1006/ 0	Korea	0.78/ -	99.3%/ -	11%/ -
HCC-ESC [96]	723/ 0	Hong Kong, China	0.95/ -	100%/ -	13%/ -

Abbreviations: HCC: Hepatocellular Carcinoma; CHB: Chronic Hepatitis B; AUROC: Area Under the Receiver Operating Characteristic Curve; NPV: Negative Predictive Value; PPV: Positive Predictive Value

Table 4: Risk scores for the prediction of HCC in NA-treated CHB patients.

Risk score	Cohort no. (derivation / validation cohort)	Country	Variables included in risk scores								
			Host factor			Liver disease/ viral activity		Cirrhosis/ fibrosis			
			Age	Sex	Other	AFP	Cirrhosis	PLT	LSM	Albumin	Other
REACH-Bm [97]	192/0	Korea	X	X			X			X	
PAGE-B [98]	1325/ 490	Europe	X	X				X			
HCC-RESCUE [99]	990/ 1071	Korea	X	X			X				
APA-B [100]	883/ 442	Taiwan, China	X			X		X			
CAMD [101]	23851/ 19321	Taiwan, China/ Hong Kong, China	X	X	DM		X				
mPAGE-B [102]	2001/ 1000	Korea	X	X				X		X	
AASL [103]	944/ 298	Korea	X	X					X	X	

Abbreviations: HCC: Hepatocellular Carcinoma; NA: Nucleos(t)ide Analogue; CHB: Chronic Hepatitis B; ALT: Alanine Transaminase; PLT: Platelet; LSM: Liver Stiffness Measure; AFP: Alpha Fetoprotein; AST: Aspartate Transaminase

exceed 40 years old and 3-8% in cirrhotic carriers [71], which can be reduced by NAs [72]. The accurate identification of high-risk CHB patients permits cost-effective prevention against HCC in this group, such as through streamlining treatment initiation, clinic follow-up and HCC surveillance interval. A systematic selection of candidates for such intervention can be achieved by calculating HCC risk scores in CHB patients. Twelve risk scores for CHB patients who are treatment-naïve (Table 2 and 3) and seven for NA-treated (Table 4 and 5) have been developed. Variables included in these risk scores can be categorized into host factors, hepatitis activity, and liver fibrosis or cirrhosis. In both subgroups, the most frequent variables included are age (18 out of 19) and sex (14 out of 19). Risk scores for the NA-treated group do not include variables denoting hepatitis activity, such as HBV DNA, HBeAg and ALT. These indices are modifiable risk factors [73].

The accuracy of prediction of these scores are expressed by the area under the receiver operating characteristic curve (AUROC), for HCC development over 5-10 years. A high negative predictive value (NPV) helps rule out HCC development. For treatment-naïve CHB patients, REACH-B, LSM-HCC, D2AS, APRI/FIB4, HCC-ESC have the highest NPV (>99%) (Table 3), while most risk scores for NA-treated patients have NPV >99% cut-off for the low-risk group (Table 5). It is worth noting, however, that there is no evidence in favour of frequent score reassessments in untreated HBV infections with a fluctuating course, and in untreated patients with indications for treatment [74].

Surveillance

HCC surveillance aims to detect tumours at an early stage to increase the likelihood of curative treatments and to improve survival. The choice of surveillance modality requires consideration of the cost, sensitivity and specificity for the disease, and an improvement in outcome quantified by quality-adjusted life year [75,76]. However, it is difficult to conduct a randomised controlled trial, as patients will not assume the risk of being assigned non-surveillance [77]. Existing trials demonstrated survival benefits of surveillance despite methodologic limitations [78,79]. The current EASL guidelines recommend surveillance for all cirrhotic patients

Table 5: Risks scores for the prediction of HCC in NA-treated CHB patients - Predictability

Risk score	Cohort no. (derivation / validation cohort)	Country	Predictability at 5 years		
			AUROC	NPV in low-risk group (derivation / validation cohort)	PPV in high-risk group (derivation / validation cohort)
REACH-Bm[97]	192/0	Korea	0.81 (3 year)	-	-
PAGE-B[98]	1325/ 490	Europe	0.82/ 0.82	100%/ 100%	17%/ 16%
HCC-RESCUE[99]	990/ 1071	Korea	0.77/ 0.81	99.5%/ 98%	37%/ 41%
APA-B[100]	883/ 442	Taiwan, China	0.83/ 0.86	98.1%/ 99.1%	46%/ 45%
CAMD[101]	23851/ 19321	Taiwan, China/ Hong Kong, China	0.82/ 0.76	99.7%/ 99.1%	11%/ 14%
mPAGE-B[102]	2001/ 1000	Korea	0.82/ 0.82	99.3%/ 98.1%	18%/ 18%
AASL [103]	944/ 298	Korea	0.80/ 0.81	100%/ 100%	18%/ 31%

Abbreviations: HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogue; CHB, chronic hepatitis B; AUROC, area under the receiver operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value

(strong recommendation) and non-cirrhotic HBV patients at intermediate or high risk of HCC according to PAGE-B risk score for Caucasian subjects [71]. The threshold for HCC surveillance to be cost-effective is a population an annual incidence of 1.5% [80]. Abdominal ultrasonography every 6 months is the recommended method for surveillance, with or without measuring serum AFP levels. However, ultrasound results are operator-dependent, with a sensitivity of 47-84% and a specificity >90% [81]. Recent studies also established factors correlated with surveillance inadequacy, which include male sex, obesity and morbid obesity, alcohol or non-alcoholic steatohepatitis with and without cirrhosis, advanced liver disease (Child–Pugh class B cirrhosis), inpatient status, and elevated ALT [82].

With regard to serological test, AFP is the most widely tested biomarker in HCC. When combined with ultrasonography, AFP measurement provided an additional 6-8% dectection' replaces AFP levels provided additional detection of 6–8% of cases not previously identified by ultrasound alone [83]. This was deemed inadequate to counterbalance the false-positive results of AFP. Therefore, the EASL guidelines recommend ultrasonography alone as the most appropriate test to perform surveillance.

Does the reversal of cirrhosis abolish the need for surveillance?: HCC risk increases as fibrosis progresses along the spectrum to cirrhosis. A multicentre study showed that the HCC risk in NA-treated non-cirrhotic patients did not change change over 5 years, but that in cirrhotic patients decreased significantly during this time. Indeed, the reversal of cirrhosis lowers HCC risk, but even so the annual HCC incidence is still not low enough (>1.5%) to abolish the need for surveillance [84].

Conclusion

Despite declining incidence of HBV-related HCC worldwide, it still accounts for substantial cancer-related mortality. Various viral and patient factors contribute to its development, and there has been progress mapping the molecular pathways underlying these processes. HCC prevention can be achieved by primary prevention (vaccination) and secondary prevention (antivirals including ETV, TDF, and TAF). Whether TDF has a greater effect than ETV in terms of HCC prevention remains controversial. Potential chemopreventive agents like aspirin, statins, metformin, and NSBBs deserve further investigations by randomized controlled trials. For HCC surveillance, several risk scores with very high negative predictive value can be utilized for biannual assessment with ultrasonography.

Specific Author Contributions

Ms. Kit Lam Chung was involved with literature search; and writing of the manuscript; and approval of the final version of the manuscript. Dr. Ka Shing Cheung was involved in critical revision of the manuscript for important intellectual content; supervision; and approval of the final version of the manuscript. Professors Ching Lung Lai was involved in critical revision of the manuscript for important intellectual content; supervision; and approval of the final version of the manuscript.

Potential Competing Interests

LCL has given sponsored lectures for Bristol Myers Squibb and Gilead. There are no competing interests for the other authors.

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