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Review

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Viral hepatitis as a risk factor for the development of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the fourth leading global cause of tumor-related mortality. HCC has a high prevalence in patients with chronic liver diseases, and it mostly results from cirrhosis caused by infection with blood-borne viruses. Despite the implementation of various diagnostic and prevention strategies, the rates of new HCC cases and mortality are increasing globally due to the aging and growth of the world population as well as their increased exposure to dominant risk factors like alcohol, hepatitis B and C, and clinical correlates of metabolic syndrome. Modeling studies indicate that sanitation practices, implementation of vaccination programs against hepatitis B, and expanded recognition and treatment of patients with chronic hepatitis B and C could greatly contribute to the eradication of viral hepatitis B and C. While the availability of generic antiviral drugs could partially overcome the bottleneck represented by the lack of resources in low and middle-income countries, where viral hepatitis is the leading cause of liver cancer, the enthusiasm for the prevention of liver cancer through antiviral therapy is mitigated by the risk of cancer in many patients who are treated late in the hepatitis course. The present work aimed to review in detail the various types, epidemiology, and carcinogenesis mechanisms of viral infections that are associated with a significantly increased risk for the development of HCC.

Keywords: Antiviral agents, hepatitis viruses, hepatocellular carcinoma, blood-borne hepatitis, cirrhosis, hepatitis B vaccine

INTRODUCTION

Chronic infections with blood-borne hepatitis B (HBV), hepatitis C (HCV), and hepatitis D (HDV) viruses are the dominant causes of hepatocellular carcinoma (HCC) worldwide. In 2018, the death toll of HCC was 810,000 persons, and the attributable fractions of HCC due to HBV and HCV were 33% and 21%, respectively[1,2]. In selected regions of Eurasia, the Far East, and Africa, HDV stands as a significant risk factor for HCC and liver-related mortality[3]. While this cancer is on the rise globally, reflecting the continuing growth of the world population, the threat is not annulled by the lifestyle changes of people at risk, and many hopes are posed on the delivery of effective sanitation interventions. Mirroring the frequency and geographical distribution of blood-borne viral hepatitis, the prevalence of HCC has long been lower in developed regions than in developing regions. Yet, more recently, some peculiar changes in disease trends have emerged. Based on the 2012 data of the World Health Organization (WHO), HCC mortality was on the rise in northern Europe, North America, and some parts of Asia (China, India, and Korea), mainly as a consequence of epidemics of blood-borne viral hepatitis due to such parenteral risk behaviors, such as drug injections, tattoos, and unsafe sex. Conversely, HCC is declining in traditionally high-risk countries, including the Mediterranean European nations, Japan, and Hong Kong, as a consequence of improved sanitation, screening of blood donors, and mass vaccination of newborns against HBV. Of note, the latter also prevents the spread of HDV, another important player in the arena of HCC known to enhance cancer risk in HBV carriers[4-6]. While projections have predicted a decline of HCC mortality following massive access of infected patients to antiviral therapy against HBV and HCV, currently, only a minority of individuals with chronic hepatitis B (CHB) or C have been diagnosed, and an even smaller percentage of them has received effective antiviral therapy. The global goal of eliminating viral hepatitis as a public health threat by 2030 is expected to prevent HCC-related mortality by 65%. It would require a 7% annual decline of the global burden of viral hepatitis, a goal that has been reached by only a dozen countries to date[7].

HEPATITIS B

HBV is a small, partially double-stranded DNA virus and a major contributor to chronic liver disease. The virus has a specific predilection for the liver, where it persists in hepatocyte nuclei in the form of chromosomal insertions of HBV DNA sequences and episomal covalently-closed circular DNA (cccDNA)[8]. Approximately 15%-40% of HBV carriers develop CHB[9]. The 5-year cumulative incidence of cirrhosis in untreated CHB is 8%-20%, with an annual risk of HCC in cirrhotic patients of 2%-5%[10]. At the beginning of the 1980s, a highly effective HBV vaccine was developed, and it proved to be very successful in reducing the disease burden. Nevertheless, the global number of HBV infections remains to be high, in part due to ineffective vaccination implementation programs in many less-developed countries and a high rate of perinatal transmission in certain parts of the world[11].

HBV is generally considered to be the strongest epidemiologic factor associated with HCC. Worldwide, CHB is responsible for almost half of all HCC cases, but the importance of this risk factor varies significantly between regions (e.g., critical in East Asia, but less so in Europe)[12]. Many studies have revealed that HBV-infected patients have a 15- to 20-fold increased risk for the development of HCC compared to non-infected individuals[13,14]. However, several effective antiviral therapies (e.g., nucleoside/nucleotide analogs (NAs) have been developed for patients with HBV over the last decade, and these agents were shown to reduce the rate of HCC occurrence in cirrhotic HBV patients[15].

Risk factors for HCC in HBV patients

A long list of risk factors for disease progression to HCC in CHB patients have been described. Firstly, several host-related factors have been shown to influence the HCC risk, with a higher risk in older patients and HBV carriers of African American origin[16-19]. Additionally, HCC is known to have a male

preponderance, and several single-nucleotide polymorphisms have been identified to be associated with a higher genetic susceptibility for HCC[16,18-22]. Also, the lifestyle of HBV carriers can have a profound influence on HCC risk. For instance, heavy alcohol use was found to accelerate the development of cirrhosis in HBV patients, ultimately resulting in a 1.3- to 8.4-fold increase in HCC risk[23]. Similarly, tobacco smoking in HBV carriers was described to be directly correlated with the development of liver cancer. In this respect, a meta-analysis from 2010 reported a synergistic effect in HCC risk for individuals who smoke and have HBV infection. Compared to HBV-negative nonsmokers, the risk of HCC was 1.87 times greater for HBV-negative smokers, 15.8 for HBV-positive nonsmokers, and 21.6 for HBV-positive smokers[24]. More recently, this finding was confirmed in a large Chinese population-based case-control study[25]. There is an increasing body of evidence indicating an important role of metabolic risk factors in the disease process of CHB. For example, a high body mass index (BMI) has been shown to worsen the disease outcomes of HBV carriers. In a large Korean population-based cohort study, a strong association was revealed between high BMI and a higher risk for HCC among patients with CHB infection[26]. Also, diabetes mellitus (DM) was shown to have a synergistic impact on the HBV disease course, as amply illustrated by a large meta-analysis, including almost 22,000 patients with CHB[27]. In this analysis, HBV patients with type 2 DM were found to have a significantly increased risk of HCC (pooled HR = 1.77, 95%CI: 1.28-2.47) and worse overall mortality (pooled RR = 1.93, 95%CI: 1.64-2.27) compared to CHB patients without DM[27]. That being said, the relationship between nonalcoholic fatty liver disease (NAFLD) and hepatitis is complex and requires further clarification. Interestingly, HBV infection seems to protect patients from the development of steatosis, metabolic syndrome, and insulin resistance[28], whereas the presence of NAFLD-related steatosis impacts on the replication of HBV. The results of a large case-control study revealed that treatment-naïve CHB patients with NAFLD had significantly lower levels of serum HBV DNA compared to CHB without steatosis[29]. This, however, does not protect against liver damage, as the presence of steatosis was found to be associated with a higher rate of liver fibrosis and subsequent progression to HCC in HBV-infected patients, independent of antiviral therapy[30,31].

Also, specific virus-related features have been shown to impact the HCC risk, including HBV DNA levels, viral genotype, hepatitis B e-antigen/surface antigen (HBeAg/HBsAg) levels, mutations in the HBV genome, and coinfections with other hepatitis viruses or human immunodeficiency virus (HIV)[19,20,32-34]. With respect to viral factors, a high viral load has proved to be a strong predictor of the HCC risk, independent of whether or not the patient has cirrhosis, or displays high levels of serum HBsAg levels[18,20,32]. In relation to the HBV genotype, a large meta-analysis, which included more than 14,500 patients, demonstrated that genotype C was associated with a higher risk of HCC compared to the other major genotypes[35]. In the past, several large-scale studies have established baseline HBV DNA levels as a prognostic indicator in CHB patients. However, given the fact that the new effective antiviral therapies can induce a complete viral response in the majority of patients, the prognostic significance of serum HBV DNA levels has substantially diminished[36]. Finally, studies have also identified double mutations in the basal core promoter of the HBV genome as an independent predictor for an increased risk of HCC[37].

Accumulating evidence indicates that an occult hepatitis B infection (OBI) may be a risk factor for HCC. OBI refers to a condition in which HBV DNA persists in the liver tissue (and the serum in some cases) in the absence of circulating HBsAg[38]. A long list of studies has demonstrated the persistence of HBV infection in a large proportion of HBsAg-negative HCC patients[39]. While the exact relationship between OBI and HCC remains to be elucidated[40], the available data suggest that OBI is not carcinogenic *per se*, but that the minimal lesions produced by the presence of the occult virus might induce a worse liver disease course in the presence of co-existing causative agents of liver injury (e.g., HCV and alcohol abuse)[39]. This hypothesis is supported by studies indicating a higher prevalence of OBI in HCV-infected patients with HCC compared to HCV carriers who do not develop HCC[41-43]. Other studies, however, failed to show a correlation between serum anti-HBV detectability and HCC risk in HCV-infected patients[44,45].

Table 1. HCC prediction models for HBV-infected patients

	CU-HCC[18]	GAG-HCC[49]	REACH-B[16]	mREACH-B[52]	LSM-HCC[50]	PAGE-B[51]
Components	Age Albumin Bilirubin Cirrhosis HBV DNA	Age Gender BCP mutation Cirrhosis HBV DNA	Age Gender ALT level HBeAG status HBV DNA	Age Gender ALT level HBeAG status LS value	Age Albumin HBV DNA Liver stiffness	Age Gender Platelet level
Risk score	Low: < 5	Low: < 100	Low: ≤ 5	Low: < 10	Low: < 11	Low: ≤ 9
	Medium: 5-20		Medium: 6-11			Medium: 10-17
	High: > 20	High: ≥ 100	High: ≥ 12	High ≥ 10	High: ≥ 11	High: ≥ 18
Negative predictive value	97% at 10 years	99% at 10 years	98% at 10 years	96.8% at 5 years	99.4% at 10 years	100% at 5 years

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; BCP: basal core promoter; CU: Chinese University; GAG: Guide with age, gender, HBV DNA, core promoter mutations and cirrhosis; LSM: liver stiffness measurement; PAGE-B: score based on age, gender, and platelets count for HCC in CHB; REACH-B: risk estimation for HCC in CHB; mREACH-B: modified REACH-B

Therefore, the most recent report of the Taormina occult HBV expert panel concluded that further studies on molecular epidemiology and carcinogenesis are required to confirm the role of OBI in HCC development[40].

As such, both viral- and host-related features were shown to profoundly impact HCC development in patients with HBV. However, the most important variables with respect to the HCC risk relate to the stage of liver disease. Historically, assessing the fibrosis status of the liver required a liver biopsy. However, due to the invasive nature of liver biopsy and its potential complications, this cannot be performed routinely in all CHB patients. To address this, several noninvasive methods have been validated to assess fibrosis in patients with chronic liver disease, of which transient elastography using the FibroScan® device is the most popular[46-48].

In order to help clinicians predict the risk of HCC in patients with CHB, several risk scores have been designed that incorporate host, viral, and liver characteristics. An overview of the most frequently used HCC risk prediction models is depicted in Table 1[16,18,49-51]. Of note, most of these scoring systems were validated before the availability of effective direct-acting antiviral (DAA) therapies. To assess the performance of the different risk scores in a contemporary setting, these conventional HCC prediction models were compared to the "modified risk estimation for HCC in CHB" (mREACH-B) score[52]. After a median follow-up of 75.3 months, 125 of the 1,308 subjects (9.6%) enrolled in this study developed HCC. Interestingly, the mREACH-B score proved to be associated with a significantly higher area under the receiver operating characteristic curve (AUROC) for the prediction of HCC development at 3 and 5 years (AUROC: 0.828 and 0.806, respectively), compared to the "liver stiffness measurement-HCC" (LSM-HCC) (AUROC: 0.777 and 0.759, respectively), "guide with age, gender, HBV DNA, core promoter mutations and cirrhosis-HCC" (GAG-HCC) (AUROC: 0.751 and 0.757, respectively), REACH-B (AUROC: 0.717 and 0.699, respectively), and "Chinese university-HCC" (CU-HCC) (AUROC: 0.698 and 0.700, respectively) scores ($P < 0.05$)[52]. As such, the prognostic performance of the mREACH-B score seems to be superior to that of the more conventional risk models.

Carcinogenic mechanisms

A potential carcinogenic mechanism that is mediated through HBV consists of HBV genome integration. In the vast majority of HCC cases (80%-90%), HBV DNA was found to be integrated into the host hepatocyte genome[53]. Cancer-related DNA integrations do not occur randomly; interestingly, they seem to be an early event that occurs before the development of HCC. Large-scale sequencing studies revealed recurrent HBV DNA integration sites at genetic loci that encode for proteins with a potential role in the initiation of hepatocellular carcinogenesis (e.g., *CCNE1, TERT,* and *MLL4*)[53,54]. Immune-mediated processes ultimately

play a dominant role in the development of HCC in HBV-infected patients. In this light, elevated serum levels of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β are typical hallmarks of HBV-infected patients[55]. The long-lasting hepatic inflammation caused by the host's immune defense in response to CHB infection accelerates hepatocyte turnover, leading to increased mutations. As such, the proinflammatory environment in the liver of HBV patients indirectly contributes to the development of liver fibrosis, cirrhosis, and HCC progression[56].

In recent years, several studies have revealed an important role for micro-RNAs (miRNAs) in the HBV-related tumorigenesis. The miRNAs are small noncoding RNAs of 20-25 nucleotides in length that regulate the expression of certain target genes. For instance, HBeAg induces the expression of macrophage miRNA-155, which leads to an accelerated liver injury through the increased production of inflammatory cytokines (mediated by the targeting of *BCL-6, SHIP-1,* and *SOCS-1*)[57]. A deregulated miRNA expression (e.g., downregulation of miRNA-145 and upregulation of miRNA-224) occurs early and accumulates overtime in the stages of HBV-associated multistep hepatocarcinogenesis[58]. Apart from the deregulated miRNA expression, HBV was also shown to cause other epigenetic changes and regulate the expression of cellular oncogenes and tumor suppressor genes through a process of promotor hypo- or hypermethylation[59].

HBV-encoded proteins also play a role in the inflammation processes that lead to the development of HCC. In this respect, the HBV core protein and its splice variant HBeAg stimulate an immune response in the host, resulting in an increased production of proinflammatory cytokines[60]. A special role in hepatocarcinogenesis has also been described for the HBx protein, per the model of transgenic mice expressing HBx protein published in 1991[61]. Further research into the role of HBx revealed that this protein transactivates binding sites for the transcription factors AP-1 and NF-κB, and it activates the p53 and β-catenin signaling pathways involved in chromatin remodeling. All these signaling cascades were shown to be involved in the development of HCC (recently reviewed by Kanda *et al.*[62]). As such, HBx seems to play an essential role in the transcriptional modulation that contributes to hepatocarcinogenesis[62].

Prevention of HBV-related HCC

In 2016, the WHO, along with other health authorities, launched a campaign for expanding the recognition and treatment of HBV with the goal of eliminating viral hepatitis by 2030[63]. A package of high impact interventions of high impact was designed, following modeling studies of hepatitis epidemiology, with the anticipation of benefits conferred by articulated interventions like sanitation and even mass vaccination against HBV of newborns. Indeed, early-in-life infection with HBV is the major risk factor fueling the global reservoir of CHB, and it predisposes those individuals to HCC development. In WHO's vision, vaccination of all newborns is linked with the implementation of screening of blood donors and harm reduction policies for people who inject drugs (i.e., exchange of sterile syringes and needles coupled with opioid substitution therapies)[63]. Strategies to interrupt vertical transmission of HBV through vaccination are in place in almost all WHO member countries, yet only 39% of newborns received the HBV vaccine globally[64]. By 2015, however, 84% of all infants globally received the vaccine (WHO target for 2020 was set at 90%). Over the last few years, the accumulated evidence showed that vaccination had substantially contributed to shrinking the burden of HBV by over 30%. In China, campaigns of mass vaccination led to a decline of HBsAg carrier state from approximately 90% in the eighties to 1% nowadays. In turn, this averted 2.8-3.5 million future HBV-related deaths, of which the majority is associated with HCC[64]. The immune prophylaxis against HBV is long-lasting, although multiple long-term studies have demonstrated a decline of protective serum anti-HBs levels (10 IU/mL) over time. While 60% of vaccinated people are anti-HBs serum positive at year 20, more than 95% retain the ability to mount an anamnestic response after a challenge dose at that time point[65]. However, to achieve optimal rates of immunization (95%), all neonates need to receive their first dose of the HBV vaccine as soon as possible after birth, preferably within 24 h.

In contrast, neonates born to HBV-infected mothers should receive the vaccine along with hepatitis B immunoglobulins within 12 h[66]. Suboptimal immunoprophylaxis in neonates can occur and is related to mothers with positive serum HBeAg or high viral load. Suboptimal immunoprophylaxis can also be due to the delivery of less than the recommended three doses of vaccine, an event which occurs in 60% of HBV vaccine recipients. In adulthood, failure to achieve 95% immunization rates is mostly seen in persons older than 60 years of age and patients with morbidities like cancer, immunosuppression, renal failure, HIV, and organ transplantation. Mammalian cell-derived recombinant vaccines incorporating preS1 and preS2 antigens have shown enhanced immunogenicity and might be used to overcome non-response to second-generation recombinant vaccines.

While HBV vaccination stands as the only pragmatic approach to prevent mortality from the HDV, a recent report from WHO sheds a dark light on the other pillar of the WHO campaign of viral hepatitis elimination, being the prolonged treatment of the HBV infected population with NAs. Currently, less than 10% of all patients chronically infected with HBV have been identified and successfully linked to care with anti-HBV antivirals. This constraint might have important consequences as chemoprevention of HCC is more likely to be successful when antiviral therapy is started before the development of cirrhosis[67]. The advent of a safe, effective, and user-friendly third-generation NAs, such as tenofovir disoproxil fumarate and entecavir, overrode the constraints represented by first- and second-generation anti-HBV NAs that caused studies to be flawed by referral biases, high rates of treatment failures, and ultimately by suboptimal percent suppression of HBV. Collectively, both population and cohort studies that have been carried out in both hemispheres of the globe showed that the incidence and mortality of HCC could have been prevented in a majority of patients if they received NAs for more than five years[68,69]. Given the differences in patient access (entecavir is contraindicated in lamivudine-experienced patients), market distribution, and genetic sequences of HBV polymerase targeted by the two NAs, non-randomized studies comparing the HCC risk reduction following HBV suppression were unable to conclusively demonstrate the superiority of one regimen over the other[70]. Both NAs fail to clear the nuclei of infected hepatocytes from HBV DNA sequences integrated into chromosomes and from free viral cccDNA, two events that are known to play a role in the neoplastic transformation of the liver in HBV carriers[67]. More recently, both cohort and population studies provided some evidence that statins and aspirin may confer protection against HCC in HBV carriers. This effect was described to result in their ability to interfere with liver cell metabolism and inflammatory processes engaged in cell carcinogenesis. In a cohort of more than 7000 patients with CHB, statins were associated with a cumulative dose-response reduction of HCC risk of 74% over an observation period of 7 years, after adjustment for important confounders like age, sex, cirrhosis, antiviral therapy, and correlates of metabolic syndrome[71]. These observations confirm previous observations and aligned with other studies of statins showing potential anticancer activity in other cancer types (i.e., breast, colon, and prostate cancer) through inhibition of the downstream products of the mevalonate pathway, which are crucial for malignant cell proliferation while inhibiting hepatic fibrogenesis, another significant risk factor of HCC[72-74]. Last but not least, statins may also counteract HBV by slowing down cholesterol synthesis and HBV replication[75]. In Taiwan, a nationwide cohort study of more than 10,000 patients with CHB showed a statistically significant risk reduction of HCC in patients who received daily aspirin compared with 1:4 matched controls[76]. Prevention of HCC by aspirin is biologically plausible, considering that this drug may prevent the progression of liver disease and liver carcinogenesis through different mechanisms involving blockade of platelets, modulation of bioactive lipids, and inhibition of the proinflammatory cyclooxygenase-2 enzyme[77-79].

HEPATITIS C

While HBV is the most common underlying HCC etiology worldwide, HCV is responsible for most cases in Western countries[1]. In patients with a chronic HCV infection, the risk of HCC gradually increases as liver fibrosis progresses. Once cirrhosis is established, the annual incidence of HCC is high, at 1% to 7%

per year[17]. Overall, it has been established that HCV infected patients have a 15-20 fold increased risk of developing HCC compared with HCV negative patients[14,80,81].

Risk factors for HCC in HCV patients

The rate of HCC progression varies greatly among patients with chronic HCV infection, and this is due to the existence of a complex interplay between host, viral, and environmental factors. Similar to what was described for HBV, the most important risk factor for the development of HCC in patients with a chronic HCV infection is the underlying liver disease[82]. Apart from that, several other concurrent risk factors that impact the HCC risk in patients with HCV have been identified. To begin, male sex and older age have universally been described as independent risk factors for the development of HCC in patients with a chronic HCV infection[82-84]. Also, a coinfection with HBV or HIV seems to influence the course of an HCV infection. Several studies have demonstrated that coinfection with HIV promotes the progression of fibrosis and cirrhosis in patients with HCV, resulting in a significantly increased risk for severe liver disease[85-88]. As a result, it is widely accepted that an HIV coinfection in HCV patients also increases the risk of HCC compared to HCV mono-infected patients[89]. However, recent data from two prospective French cohorts demonstrate that this is no longer the case in the current context of more effective combination antiretroviral therapies and increased access to HCV therapy. In this analysis, the 5-year cumulative incidence of HCC and liver decompensation did not differ significantly between HIV/HCV coinfected and HCV mono-infected patients (8.5% *vs.* 13.2%, $P = 0.12$ and 12.8% *vs.* 15.6%, $P = 0.40$, respectively)[90]. Also, patients with a dual HBV/HCV infection have a higher risk of progression to cirrhosis and decompensated liver disease compared to patients with an HCV mono-infection[91,92]. Already in 1998, a meta-analysis of more than 30 case-control studies demonstrated a synergistic effect of HCV and HBV on the incidence of HCC[14]. This observation was later confirmed by a second, Chinese meta-analysis indicating that a dual infection by HBV and HCV was associated with a higher risk of HCC than each infection alone [odds ratio (OR) for the development of HCC for coinfected patients: 35.7][13]. Similarly, an Italian study reported a yearly HCC incidence of 6.4% in HBV/HCV coinfected patients as compared to 2.0% and 3.7% in HBV and HCV mono-infected patients, respectively. At 10-years, this translated into a cumulative HCC rate of 45%, 16%, and 28%, respectively[93]. For HBV/HCV dual infection, the research data suggest that the HBV replication status is the crucial factor affecting the risk for HCC. HCV patients with active HBV replication have twice the risk of HCC compared to those with latent HBV and HCV, while the risk in coinfected patients with undetectable HBV DNA levels is similar to that of mono-infected HCV patients[83]. As discussed in the section on HBV, more research is needed to shed light on the potential effect of OBI on the risk for HCC in HCV-infected patients[40]. Intriguingly, certain HCV genotypes seem to be associated with a higher risk of HCC, particularly genotype 3 which is associated with an 80% higher risk of HCC compared to genotype 1[94], contradicting a previous meta-analysis that associated genotype 1 with a 78% increased risk of HCC relative to all other genotypes and a 60% increased risk among patients with cirrhosis[95].

Similar to what was described for HBV, there are significant associations between lifestyle factors and the HCC risk in HCV patients. A meta-analysis has shown a significant increase in the relative risk of HCC in smokers (relative risk 23) compared to non-smokers (relative risk 7.9) with HCV[24]. Also, alcohol consumption was shown to accelerate liver fibrosis in HCV-infected patients, resulting in an increased risk for progression to cirrhosis and HCC. In a study evaluating the natural history of liver fibrosis progression in 2,235 HCV patients, daily alcohol consumption of at least 50 g resulted in a 34% increase in the rate of fibrosis progression[96]. In line with this, a meta-analysis involving more than 15,000 HCV patients demonstrated that heavy alcohol intake (210-560 g per week) was associated with a 3.54 relative risk for the development of decompensated cirrhosis[97]. A study that specifically looked into the effect of alcohol on the development of HCC in HCV patients revealed a 2-fold increase in HCC risk for drinkers of more than 60 g per day[98]. Similarly, a case-control study revealed an OR for HCC development of 26.1 in HCV-carriers with an alcohol intake of 0-40 g/day, rising to 62.6 and 126 among patients drinking a daily dose of

41-80 g and more than 80 g per day, respectively[99]. Interestingly, studies have indicated that the synergistic effect of alcohol on the HCC risk in HCV patients is not restricted to heavy drinkers and that even light to modest alcohol use can promote the development of cirrhosis (and subsequent HCC) in HCV patients[100]. In line with this, a study including 192 HCV patients with compensated cirrhosis, reported a 5-year cumulative HCC rate of 10.6% among abstainers as compared to 23.8% among HCV patients with a light to moderate alcohol consumption (median intake: 15 g/day)[101].

HCV also comes with an increased risk of HCC in patients with DM. A meta-analysis evaluating the association between DM and HCC in chronic HCV patients indicated a 2- to 3-fold increased risk[102]. Similarly, a population-based cohort study from Taiwan indicated that DM increases the risk of HCC in HCV-infected patients (HR = 1.36, 95%CI: 1.16-1.68;)[103]. Finally, NAFLD is a prominent characteristic of a chronic HCV infection. In patients with genotype 3 HCV, the presence of NAFLD is directly linked to the viral load, and in this setting, the NAFLD is considered to be of viral origin[104]. In contrast, in patients with other HCV genotypes, the NAFLD is linked to host factors such as obesity. Studies have consistently identified (NAFLD-related) steatosis as an independent factor associated with fibrosis progression in HCV patients[105-108]. As such, it is not surprising to see that several studies (both retrospective and prospective) have demonstrated that steatosis in HCV patients is also strictly associated with the development of HCC[109-113]. An interesting study in this respect demonstrated that American chronic HCV patients were found to progress more rapidly to HCC than their counterparts in China, with underlying fatty liver disease as the prominent factor fueling this difference[114].

Several prediction models for HCC have been developed for patients with an HCV infection (e.g., HALT-C, REVEAL-HCV, and $SCORE_{HCC}$), but the performances of these scores are suboptimal, and their use and validity in clinical practice are limited[115-117].

Carcinogenic mechanisms

In contrast to HBV, HCV is a single-stranded RNA virus with little potential to integrate its genetic material into the host. Therefore, HCV must exhibit its tumorigenic potential less directly. The mechanisms involved in this process mainly involve two parts: induction of chronic inflammation and the expression of viral proteins. HCV-induced HCC development is a multistep process that involves the establishment of chronic HCV infection, persistent chronic hepatic inflammation, progressive liver fibrogenesis, initiation of neoplastic clones accompanied by irreversible somatic genetic/epigenetic alterations, and progression of the malignant clones in a carcinogenic tissue microenvironment[118].

Several proinflammatory cytokines, including TNF-α, IL-1, IL-23, IL-6, and lymphotoxins α and β have been implicated in chronic liver inflammation and the development of HCC[119]. Specifically, for HCV-mediated hepatocarcinogenesis, a high ratio of TNF-α/IL-10 levels has been observed in the sera of patients with severe liver damage and HCC[120]. Apart from immunological disturbances, epigenetic processes were found to be involved in the development of HCV-related HCC. Like HBV-related HCC, HCV also seems to profoundly impact the expression of certain miRNAs[121]. Similar to HBV, miRNA-155 also plays a role in the development of HCC in HCV-infected patients. miRNA-155 levels are markedly increased in patients infected with HCV, and this overexpression was found to stimulate hepatocyte proliferation and tumorigenesis by activating Wnt signaling[122]. Other epigenetic studies have suggested a prominent role for noncoding RNAs in the development of HCV-related HCC[123,124].

With respect to the role of HCV-related proteins in the development of liver cancer, the HCV core protein and NS5A seem to be of interest[62]. In 1996, the HCV core protein was found to induce a carcinogenic phenotype in primary rat embryo through a RAS-mediated mechanism[125]. The HCV core protein was also shown to activate the MAPK signaling pathway, upregulate Wnt/β-catenin signaling, suppress apoptosis

pathways, and activate TGF-β, PI3K/Akt/mTOR, NF-κB, p53, IL-6/Stat3, and the androgen receptor pathways. Through these pathways, the HCV core protein could regulate cell growth, differentiation, apoptosis, transcription, and angiogenesis[62,126]. Similarly, NS5A interacts with multiple pro-oncogenic pathways, including β-catenin, PI3K/Akt/mTOR, NF-κB, and p53[62,126].

Finally, insulin resistance, commonly observed in patients with HCV, plays a crucial role in the development of HCC in HCV patients. Intensive research identified that cross-talk between the HCV core protein and molecules regulating insulin signaling might affect HCV-related hepatocarcinogenesis[62].

Prevention of HCV-related HCC

Every year, *de novo* HCV affects 1.75 million persons, and more than 350,000 people die of HCV-related cirrhosis or liver cancer[66,127]. Since new HCV infections outnumber the sum of people who die of end-stage hepatitis C and those pharmacologically cured, HCV elimination is also a priority of the WHO[63]. This goal is achievable because the virus lacks a non-human reservoir, cannot amplify in the environment and can be identified with simple and accurate diagnostic tests. At the same time, practical interventions can be delivered to interrupt transmission and cure both acute and chronic infections[128]. With an articulated package of interventions similar to the one in place for HBV elimination, except for vaccine prophylaxis, which is not available, the strategy designed by WHO is expected to provide treatment to 90% of all infected individuals by 2030 worldwide[63]. The clinical benefits of HCV elimination are undisputed and are already well-established since the ages of interferon therapy for HCV. The treatment strategy is also well acknowledged by all international liver societies, which strongly recommend antiviral treatment of all HCV infected patients, independent of the severity of the underlying liver disease[129,130]. A sustained virologic response (SVR) heralds improvement of portal hypertension and fibrosis progression in patients with chronic hepatitis and may reduce HCC incidence and all-cause mortality[130]. Significant HCC chemoprevention already surfaced in the interferon studies, where an SVR was found to be associated with a relative risk reduction of 74% compared to non-responders[131]. This HCC chemoprevention by SVR was further amplified by the advent of safe and effective DAA against HCV. These agents extended the range and clinical benefits of antiviral therapy. Also, DAAs can be indicated in patients with decompensated liver disease who were either ineligible for treatment with interferon or did not respond to the therapy. HCC chemoprevention by DAA was firmly established through the retrospective scrutiny of large cohorts of patients in the US, Europe, and Asia. Moreover, this finding was further confirmed by prospective population studies. In a Veterans Health Administration cohort, which included more than 20,000 patients with advanced liver disease and multiple comorbidities, DAAs reduced the risk of developing HCC by 72% compared to non-responders[132]. More recently, an analysis of the Veterans Affair cohorts including more than 15,000 HCV patients demonstrated that patients who achieved an SVR after DAA treatment had a significantly lower all-cause mortality (78.9% reduction) and a lower HCC incidence (83.5% reduction) than those who did not achieve an SVR [Figure 1][133,134].

In a prospective population study in Sicily, Italy, the incidence rate of HCC at one year was 2.6% in SVR patients compared to 8% in non-responders with a clear cut association between HCC risk and liver disease severity[134]. Importantly, these studies had the additional merit of wiping out any doubt about the safety of DAA therapy in patients with advanced hepatitis C as they counteracted the initial observations of high rates of clinically aggressive *de novo* HCC after an SVR to DAA that were identified in small groups of cirrhotic patients in Spain and Italy[135-137]. Nowadays, it is clear that early occurrence of *de novo* HCC is confined to patients who harbor magnetic resonance imaging (MRI)-undefined liver nodules at the onset of DAA therapy and is promoted by the imbalance of field immunity caused by the swift eradication of HCV[136]. Early, aggressive recurrence was also a complication of HCV eradication with DAAs in patients with a history of HCC[137,138], where antiviral therapy aims to halt the progression of hepatitis C towards liver failure and prevent the onset of second primary tumors which result from both direct and indirect

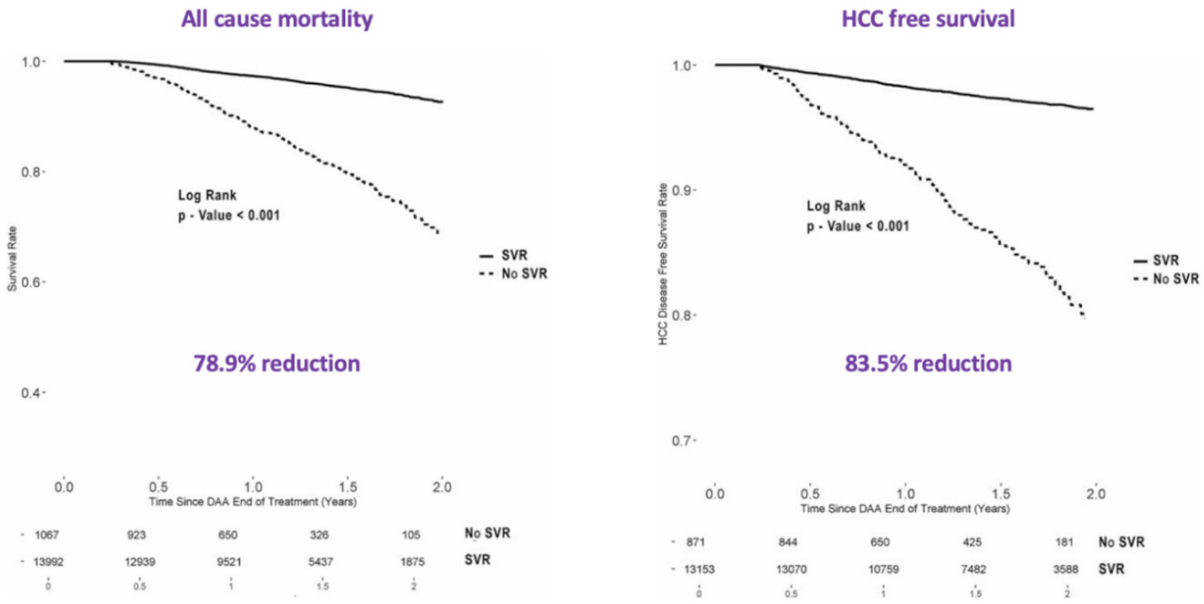

Figure 1. Reduction in HCC incidence and all-cause mortality in patients with advanced hepatitis C who achieve an SVR to DAA. Data from the Veteran Health Administration cohort[133]. HCC: Hepatocellular carcinoma; SVR: sustained virologic response; DAA: direct-acting antiviral

carcinogenic damage of hepatocellular DNA fueled by unrested HCV replication[139]. The latter usually takes place 1 to 2 years after the cure of a primary HCC (late recurrence), at variance with earlier recurrence that is caused by the proliferation of pre-existing cancer cells surviving the removal of the primary tumor, for which no effective adjuvant therapy exists. The early recurrence depends on tumor size and cell grading, reflecting the cancer cells that invade the tumor vessels and/or to tumor satellites emerging far from parental HCC[140], the evidence is mounting that early recurrence of HCC in DAA-treated patients is often bound to pre-existing liver nodules with undefined vascular patterns at MRI[138].

In a final note on anti-HCV therapy, it is important to underscore that achieving an SVR to antiviral therapy does not tell the whole story. In fact, data from Lens *et al.*[141] reported in 2017 indicate that obtaining an SVR to all-oral anti-HCV therapy in patients with HCV-associated cirrhosis indeed leads to decrease in a hepatic venous pressure gradient, but that clinically significant hypertension did persist in 78% of patients. These patients have a continued risk for liver decompensation, and subsequently, maintain a higher risk of HCC[141].

A recent study based on Swedish nationwide registries has demonstrated a significant reduction of HCC risk in a population including more than 50,000 HCV infected and 10,000 HBV infected adults. The latter had been chronically exposed to low doses of aspirin (HR = 0.69, 95%CI: 0.62-0.76). After adjusting for relevant confounding morbidities, chemoprevention of liver cancer was confirmed and found to be associated with a similar risk reduction of liver-related mortality[142]. These findings align with studies done in HBV patients showing chemoprevention of HBV-related liver cancer following long-term exposure to aspirin.

HEPATITIS D

HDV is a small replication-defective RNA virus that relies on HBV to replicate and propagate. Due to a lack of dedicated studies assessing the prevalence of HDV, the global disease burden of HDV is likely underestimated[143]. In a recently published systematic review and meta-analysis, 650-700 million people

have a chronic HBV infection globally, of whom 60-70 million have an HDV coinfection, which is almost twice as much as the previous estimate[144]. HDV does not integrate into the genome of hepatocytes, making a direct oncogenic mechanism unlikely. However, preliminary data have indicated the potential indirect oncogenic effects of this virus. HDV can modify several key signaling pathways with a known role in cirrhosis and hepatocarcinogenesis, including the activation of the TGF-β, NF-κB, and JAK-STAT signaling pathways[145-147].

Studies comparing HCC incidence between HBV/HDV coinfected and HBV mono-infected patients provide better insights on the oncogenic impact of HDV. A critical Eurohep study demonstrated that HBV/HDV-positive cirrhotic patients followed for a median of 6.6 years had a twofold increase in mortality risk compared to patients with HBV-related cirrhosis[148]. Moreover, the estimated risk for HCC was 13% among cirrhotic HBV/HDV patients compared to 2%-4% for cirrhotic patients with an HBV mono-infection, corresponding to a threefold increase in HCC risk for coinfected patients[148]. Also, a large Swedish retrospective cohort study demonstrated a significantly higher risk of HCC for patients with acute (RR = 6.1, 95%CI: 2.8-11.7) or chronic (RR = 3.9, 95%CI: 1.6-7.2) HDV[149]. Similarly, an American study, including 2,175 HBV patients, found a 2.9-fold increase in the incidence of HCC in individuals with an HBV/HDV coinfection (OR = 2.1, 95%CI: 1.1-3.9)[150].

Cohort studies evaluating the HCC incidence among patients with HDV yielded variable results. Among 299 HDV infected patients who were included in a single-center Italian study (diagnosed between 1987 and 2006), 46 HCC cases were reported, accounting for an annual rate of 2.8%[151]. Interestingly, the authors of this analysis later identified high serum levels of HDV RNA as a predictor of cirrhosis and liver cancer in HDV patients[152]. In a large cohort study which included 1,576 HDV patients, the annual HCC incidence was slightly lower at 1.9%[153]. The results obtained in other cohort studies with a fewer patients were inconsistent and reported an annual HCC incidence among HDV patients of 3%-13%[154-156]. Finally, a recent study addressed the HDV-associated mortality in HIV/HBV coinfected patients. HDV infection appeared to be strongly associated with overall death (HR = 2.33, 95%CI: 1.41-3.84), liver-related death (HR = 7.71, 95%CI: 3.13-18.97), and HCC occurrence (HR = 9.3, 95%CI: 3.03-28.61)[157].

Very recently, a meta-analysis pooling data from 93 studies compared the HCC risk in patients with HBV/HDV and HBV alone (68 case-control studies with 22,862 patients and 25 cohort studies with 75,427 patients) was published[5]. Patients with HBV/HDV had a significantly higher HCC risk than patients with an HBV mono-infection (pooled OR = 1.28, 95%CI: 1.05-1.57). Of note, this association was particularly pronounced in studies with HIV-infected patients (pooled OR = 7.13, 95%CI: 2.83-17.92)[5].

In summary, though most studies evaluating the incidence of HCC in HDV-infected patients have provided low-level evidence, data support an association between HDV and the development of HCC. Similar to what was described for HBV and HCV, the objective of antiviral treatment in patients with a chronic HDV infection is to eliminate HDV and HBV and, as such, prevent the long-term detrimental effects of hepatitis D on the liver. Unfortunately, the treatment options for patients with HDV are limited, and HDV elimination is not commonly achieved. In fact, 1-year of interferon-α (IFN-α) only induces a sustained HDV clearance in 10%-20% of patients[158]. More recently, several studies have evaluated the use of pegylated IFN-α in HDV patients. While response rates in these trials were higher than what was seen with classical IFN-α, sustained clearance of HDV RNA proved feasible in only about a quarter of patients[159-161]. Data on the impact of IFN-α treatment on the natural history of hepatitis D are scarce. In an extended follow-up of 36 chronic HDV patients treated with one year of IFN-α found that some patients experienced regression of their advanced stage fibrosis, indicating a positive effect on the natural HDV disease course[162]. Less favorable data come from the HIDIT trial in which pegylated IFN-α was used to treat chronic HDV. In this trial, 58% of patients who were shown to be HDV RNA negative 6 months

after therapy experienced a late HDV relapse[163]. Interestingly, these late relapses were not associated with clinical complications. This might indicate that a prolonged virologic response to pegylated IFN-α, even if not sustained, can be clinically relevant in patients with chronic hepatitis D[163].

CONCLUSION

Blood-borne viral hepatitis is a dominant cause of HCC worldwide, and the positive effect of their eradication on the risk of developing HCC has been extensively demonstrated even in patients carrying significant metabolic comorbidities that predispose them to the neoplastic transformation of the liver. Along this line, intriguing data have emerged, suggesting a significant chemoprophylactic activity of liver metabolism modifiers such as statins and aspirin. All in all, the implementation of articulated interventions of sanitation make reaching the WHO goal of viral elimination more realistic in some small countries like Georgia or Iceland, where elimination programs can easily be run, than in large countries where it is difficult even to identify hepatitis carriers. Further mitigating our belief of being on the right track for global elimination of viral hepatitis was the increasing hesitance against hepatitis B vaccination. In recent years, it has amounted to the level of reaching an alarming proportion of 30% in many high-income countries. While this could be counteracted by the recent pandemic of 2019 coronavirus disease (shortly, COVID-19) that has restored confidence in public health policies based on vaccination, another critical point in the fight against viral HCC is the existence of awareness campaigns and screening programs, since the first essential step in the viral hepatitis cure pathway is to be aware of the infection. Identification of defined risk cohorts, including baby-boomers, people who inject drugs, prisoners, and men who have sex with men, improves the cost-effectiveness of screening programs aimed to target infected populations; however, determining the infectious status is irrelevant if effective linkage-to-care programs are not in place. The availability of generic antivirals can partially overcome the bottleneck represented by the lack of resources in low and middle-income countries where HBV and HCV prevail as risk factors for HCC.

DECLARATIONS

Authors' contributions

Equally made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Alqahtani SA, Colombo M

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Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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