HEPATITIS VIRUS IS ONE OF THE MAIN CAUSATIVE AGENTS OF HEPATOCELLULAR CARCINOMA

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Despite the increasing incidence of HCC related to metabolism-associated steatotic liver disease, viral hepatitis remains the major driver in liver carcinogenesis. Both HCV and HBV viruses have direct oncogenic properties that promote carcinogenesis, especially in active infections. The aim of this review is to summarize the viral mechanisms involved in liver cancer and to evaluate the changing incidence of HCC after antiviral treatment.

Keywords: Hepatitis B virus, hepatitis C virus, main agents, Hepatocellular carcinoma.

INTRODUCTION

Recently, metabolic associated steatotic liver disease metabolism-associated steatotic liver disease became the leading cause of chronic liver disease worldwide and one of the most frequent causes of hepatocellular carcinoma (HCC). Nonetheless, in this epidemiological trend, viral hepatitis remains the major driver in hepatic carcinogenesis. Globally, hepatitis B virus (HBV) is the leading cause of hepatocellular carcinoma, with an overall attributable risk of approximately 40%, followed by hepatitis C virus (HCV), which accounts for 28-30% of cases, with significant geographic variations between the Eastern and Western world. Considering all the etiologies, HCC risk increases proportionally with the progression of liver disease, but the risk is consistently higher in patients with viral triggers. This evidence indicates that both direct (due to the oncogenic properties of the viruses) and indirect (through the mechanisms of chronic inflammation that lead to cirrhosis) mechanisms are involved, alongside the presence of co-factors contributing to liver damage (smoking, alcohol, and metabolic factors) that synergistically enhance the oncogenic process. The aim of this review is to analyze the oncogenic role of hepatitis viruses in the liver, evaluating epidemiological changes and direct and indirect viral mechanisms that lead to liver cancer.

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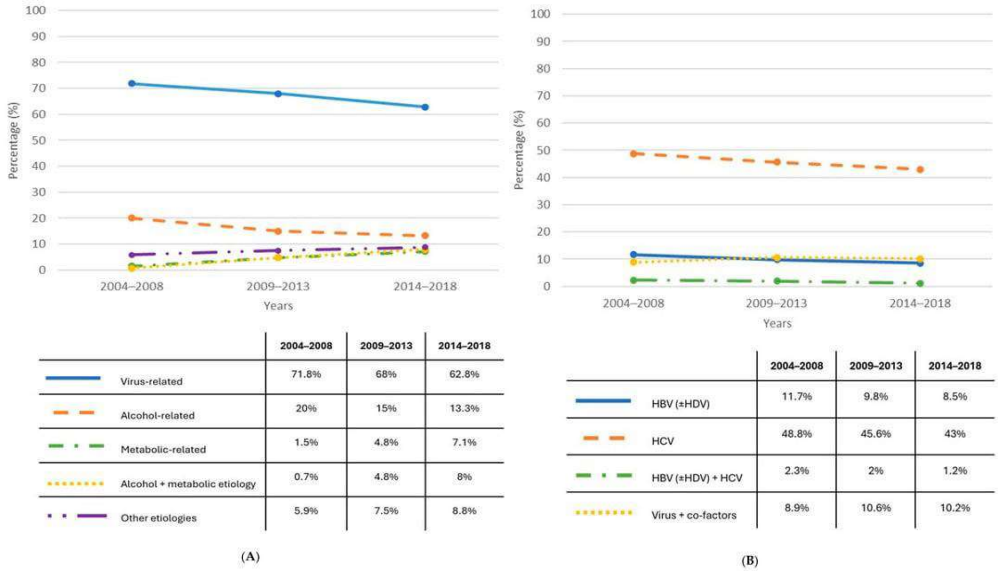
OVERVIEW

Epidemiology: Hepatocellular carcinoma (HCC) is the seventh most common tumor based on incidence worldwide. Fortunately, its incidence seems to have lowered with an overall average percentage decrease of - 1.93% compared to 1990. This trend is likely linked to vaccination and acting antivirals-based treatment. However, it still represents the third leading cause of cancer-related mortality worldwide (8.3% of all cases).

It is well documented that globally HBV is the primary cause of HCC; it accounts for the highest incidence of liver cancer cases and fatalities worldwide (33%), followed by alcohol (30%), HCV (21%), and other causes (16%), with substantial geographic variations. Notably, the attributable risk for HBV is 60% in Africa and East Asia, whereas it is 20% in the Western world, where HCV infection is identified as the most common underlying liver disease etiology, with its prevalence ranging from 29% to 44%. In Italy, data from ITA.LI.CA3 study group demonstrate a progressive increase in non-viral cases, in accordance with the global epidemiological trend.

Nevertheless, viral hepatitis remains responsible for over two-thirds of HCC cases. In the last decade, HBV accounted for only 8% of the diagnosed HCC cases, while HCV was implicated in approximately 43% (Figure 1). Although dysmetabolism plays an increasingly relevant role in hepatocarcinogenesis, hepatotropic viruses remain the major drivers in the epidemiological landscape of HCC. All the most recent guidelines agree that cirrhosis is an independent and the highest-risk condition for HCC occurrence; however, the risk is higher in patients with virus-related liver disease.



	2004–2008	2009–2013	2014–2018
Virus-related	71.8%	68%	62.8%
Alcohol-related	20%	15%	13.3%
Metabolic-related	1.5%	4.8%	7.1%
Alcohol + metabolic etiology	0.7%	4.8%	8%
Other etiologies	5.9%	7.5%	8.8%

	2004–2008	2009–2013	2014–2018
HBV (±HDV)	11.7%	9.8%	8.5%
HCV	48.8%	45.6%	43%
HBV (±HDV) + HCV	2.3%	2%	1.2%
Virus + co-factors	8.9%	10.6%	10.2%

Figure 1. Italian temporal trends from 2004 to 2018 of the proportion (%) of all etiologies for HCC: (A) description of temporal trends of all etiologies for HCC, also including non-viral causes and (B) a specific focus on the proportion of virus-related HCC[3]

Viral pathogenesis: The mechanisms of HBV and HCV hepatocarcinogenesis are detailed in the following sections. Anyway, independent of the etiology of liver disease, to appropriately define the HCC risk, a liver status evaluation should be performed. Indeed, the presence of compensated cirrhosis at presentation and the sustained activity of viruses are significant predictors of HCC in viral-related cirrhosis. Fibrosis and the consequent cirrhosis are both expressions of the virus-related indirect oncogenic mechanisms. However, there is a non-negligible percentage of patients who develop HCC without underlying cirrhosis: approximately 20% of HCC occurs in a non-cirrhotic liver. In virus-related diseases, HCC can develop in a non-cirrhotic liver due to direct oncogenic mechanisms. In fact, the incidence of HBV-related HCC in patients without cirrhosis is only 10% lower than in patients with cirrhosis, while the incidence of HCC in patients without cirrhosis and with HCV is 30% lower. Furthermore, co-infections such as HBV/HCV and HBV/HDV increase the risk of HCC (by two- to six-fold relative to each infection)[4,1,2].

Hepatitis C Virus

Mechanisms of hepatocarcinogenesis

HCV belongs to the Flaviviridae RNA virus family. It includes six major genotypes (1 - 6), having a genetic diversity from 31 to 35%. HCV-related hepatocarcinogenesis is a long process, generally resulting from decades of chronic infection through the subsequent chronic inflammation and fibrosis. The presence of underlying cirrhosis in almost all cases of HCV-related HCC led to the hypothesis that HCV induced carcinogenesis mostly through indirect mechanisms, specifically inflammation linked to cirrhosis. Nowadays, several studies demonstrated HCV as an independent risk factor

for HCC, even if the exact mechanisms are not yet completely understood[4,1,2]. The role of immune alterations has been highlighted. Specific HCV proteins could induce the dysregulation of cell surveillance, the induction of stem-like cells, and alterations in apoptosis signaling as potential HCC drivers.

During an HCV infection, the immune-mediated liver injury significantly contributes to carcinogenesis, inducing the spread of cancer-related mutations and the expansion of abnormal cells. Moreover, viral proteins stimulate oncogene expression, cell cycle dysregulation, and the deactivation of tumor suppressor genes, and this results in the proliferation of quiescent hepatocytes[3,4,1,2]. Furthermore, the failure to eliminate HCV-infected cells leads to viral variants that could induce an immune escape mechanism, facilitating cancer development.

Lastly, unlike HBV, HCV exerts its oncogenic activity through its structural proteins that have been implicated in HCC pathogenesis. Particularly, the core protein has the ability to modulate intracellular pathways (such as the activation of nuclear factor kappa B pathway) and to upregulate several cellular proteins (such as interleukin-IL-6, signal transducer and activator of transcription-transcription activators-3), whose dysregulation induces transformational changes in hepatocytes. Some studies also suggested a minor role of non-structural HCV proteins by inhibiting apoptosis and increasing hepatocyte proliferation[4,2,1].

Incidence and risk factors of HCC in patients with HCV

HCC is the prevalent complication and the first cause of death in patients with HCV-related cirrhosis, while a chronic HCV infection is the most common underlying liver disease among patients with HCC worldwide (mostly in North America, Europe, and Japan). In patients with HCV, HCC develops almost always in the presence of cirrhosis. Japanese studies demonstrated that the HCC risk was four-fold higher in patients with cirrhosis (7.1 per 100 person-years) than in subjects without cirrhosis (1.8 per 100 person-years)[6,9]. In Europe and the United States, the incidence rate of HCC is 3.7 per 100 patient-years in patients with HCV-related cirrhosis, but it is not possible to estimate the rate in patients with chronic hepatitis because of the lack of HCC cases in this group[4,2,1].

As already shown, HCV has oncogenic effects, which result in a greater HCC risk compared to other liver disease etiologies. In a large American cohort of patients with different etiologies of cirrhosis, Ioannou et al. showed that patients with HCV had a more than three-fold increased HCC incidence (3.3 per 100 patient-years) than patients with alcoholic (0.86 per 100 patient-years) or metabolic cirrhosis (0.90 per 100 patient-years)[6,4].

HCC risk in patients with sustained virological response

The advent of direct-acting antivirals dramatically changed HCV history, with the achievement of sustained virological response in the majority (> 95%) of patients treated for HCV. Several studies demonstrated that the incidence of HCC was significantly lower in patients with sustained virological response. Particularly, in a large cohort of 2249 patients with HCV-related cirrhosis that were treated with direct-acting antivirals, Calvaruso V. et al. showed that the rate of HCC occurrence was higher in patients without sustained virological response than in patient with sustained virological response (12.8% vs. 3%, $p < 0.001$)[5]. Similar results were obtained in an American cohort with HCV treated with direct-acting antivirals, underling that the accomplishment of sustained virological response significantly reduced the HCC risk (0.90 vs. 3.45 HCC/100 person-years; adjusted to relative risk: 0.28, 95% CI: 0.22 - 0.36)[6]. However, the newest direct-acting antivirals-based antiviral treatments, aimed to eradicate HCV, reduce but do not eliminate the HCC risk, especially in patients with cirrhosis or advanced fibrosis. Long-term follow-up in patients with cirrhosis and an sustained virological response showed a 2 - 5 times lower risk

of HCC. In a study by El Serag et al. involving over 10,000 American Veterans with sustained virological response, the annual risk of HCC in patients with cirrhosis was 1.39% and remained constant over time4,8. In European cohorts of patients with HCV-related cirrhosis, the incidence rate of HCC after sustained virological response was between 1.6 and 2.3 person-years, confirming a residual and not negligible HCC risk không[8,9].

Several studies tried to individualize factors associated with a higher risk of developing HCC after sustained virological response because not all patients with cirrhosis exhibited the same risk. In a prospective study on 687 cirrhotic patients achieving sustained virological response, the sole independent predictor of HCC was a baseline liver stiffness measurement of > 20 kPa[8]. Many studies also demonstrated that albumin levels of < 3.5 g/dL and a platelet count of < 120.000 are associated with an increased HCC risk, both as pre-treatment and post-treatment variables[5,9]. Moreover, the presence of additional comorbidities that impact the HCC risk (e.g., diabetes, obesity, and alcohol use) maintains the risk at a higher level compared to patients without comorbidities.

Finally, a very recent study showed that the HCC risk declined progressively up to 6-years after sustained virological response. Indeed, in patients with cirrhosis, the HCC incidence was 2.71 per 100 person-years in subjects accruing 1 - 2 years after sustained virological response, while it was 1.65 per 100 person-year in patients accruing > 4 to 6 years after sustained virological response. Among subjects without cirrhosis, HCC risk did not have a significant association with time since sustained virological response[8,9].

Table 1. Studies evaluating HCC incidence in patients with HCV

author	Country	Research methods	Patients with cirrhosis	Ratio (%)
Calvaruso V, gastroenterology 2018[5]	Italy	Research	2249 patients (100%)	HCC occurrence: 3% in sustained virological response vs. 12.8% in non-sustained virological response (p < 0.001) HCC overall cumulative rate at 1 year: 2.9% in sustained virological response vs. 8% in non-sustained virological response
Kanwal F, gastroenterology 2017[6]	USA	Retrospective	8766 patients (39%)	HCC incidence: 0.9 per 100 people over a year in sustained virological response vs. 3.45 per 100 people over a year in non- sustained virological response
El-Serag HB, hepatology 2016[7]	USA	Retrospective	1548 patients (14.4%)	HCC incidence: 0.93 per 100 people over a year in sustained virological response vs. 3.27 per 100 people over a year in non- sustained virological response

author	Country	Research methods	Patients with cirrhosis	Ratio (%)
Morisco F, cancers 2021[8]	Italy	Research	706 patients (100%)	Liver-related events: 8.9% in sustained virological response vs. 26.3% in non-sustained virological response HCC incidence in sustained virological response: 1.6 per 100 people over a year
Kondili L, DLD 2023[9]	Italy	Retrospective	2064 patients (100%)	HCC incidence in sustained virological response: 2.45 per 100 people over a year

In conclusion, achieving sustained virological response in patients with HCV-related cirrhosis is associated with a decreased HCC risk over time. Despite this reduction, the residual HCC risk remains elevated and surpasses the thresholds deemed necessary for continued surveillance and screening. These results underscore the ongoing importance of monitoring patients with sustained virological response and HCV in order to detect and manage any potential development of HCC in a timely manner. Therefore, continuing vigilance and adherence to screening protocols even after sustained virological response achievement in this patient population is mandatory, particularly in patients with co-factors or with high pre-treatment stigmata.

Hepatitis B virus

Mechanisms of hepatocarcinogenesis

Hepatitis B virus belongs to hepadnaviridae family, and its structure is like a double-strained DNA virus. The molecular mechanism underlying HBV-related hepatocarcinogenesis is still intricate and involves genetic and epigenetic changes in the host DNA, the inhibition of repair mechanisms, and the promotion of cell proliferation by altering cellular signaling pathways. After infection, HBV converts its DNA into a covalently closed circular DNA, which accumulates in the nucleus of hepatocytes as a stable episome. Into a covalently closed circular DNA is responsible for the persistence of the virus in the host cells and serves as the template for all viral RNA[5,8,2]. The main transcription product, HBV core protein, acts as an activator for various host cellular genes crucial for both HBV replication and hepatocarcinogenesis by regulating DNA repair mechanisms and cell growth. In fact, studies analyzing whole-genome sequencing in HBV-related liver cancer have identified heightened levels of copy number variations at specific gene locations (breakpoint) where HBV integrates into the genome. This finding suggests that HBV integration likely triggers chromosomal instability, further implicating its role in carcinogenesis. HBV core protein protein contributes to the hepatocellular cycle dysregulation through several mechanisms, facilitated by its interaction with many intracellular pathways that modulate cell proliferation, cell death, transcription, and DNA repair. Specifically, it interacts with response element-binding protein/ P300, directly influencing response element-binding - dependent transcription. It impacts transcription by involving cellular signaling pathways such as Ras/Raf, mitogen-activated protein kinase, and Janus kinase-signal transducer of activators of transcription. Finally, HBV core protein also influences proteasomes, mitochondrial proteins, p53 and leading to its apoptotic effects[8,9,1]. The resulting genetic instability forms the basis for the neoplastic transformation of the host cell. The multifunctional nature of HBV core protein causes the alteration in several fundamental cellular mechanisms and induces the proliferation of tumorigenic traits capable of inducing HCC[5,9,2]. Moreover, HBV core

protein promotes HCC invasion and metastasis both in vitro and in vivo with its oncogenic activity, thereby suggesting that HBV core protein could be used as a novel target for HCC therapy.

Another viral protein involved in the carcinogenetic process is HBV core protein, which is the major capsid protein of the virus. Several studies showed that HBV core protein acts as an important mediator of hepatocarcinogenesis through several mechanisms including the promotion of apoptosis resistance and the repression of proapoptotic factors[5,9,1]. Moreover, the expression of HBV core protein promotes the proliferation of hepatoma cells in vitro through the activation of the Src/PI3K/Akt pathway[8,9]. Finally, another viral protein involved in the carcinogenetic process is HBV core protein HBV core protein seems to act synergistically with HBV core protein, repressing the promoter activity of the p53 gene and inducing liver cancer.

In conclusion, the oncogenic role of HBV is due to the coexistence of direct and indirect mechanisms. The incidence of HBV-related HCC significantly varies depending on the infection status and the stage of liver disease. DNA integration promoting genome instability is the mainstay factor in patients without cirrhosis that could lead to carcinogenesis process. This underscores the multifactorial nature of HBV-associated carcinogenesis and highlights the importance of improving future research in this context. Therefore, a comprehensive understanding of these diverse mechanisms and host-related variables is essential for effective management and prevention strategies targeting HBV - related HCC.

Incidence and risk factors of HCC in patients with HBV

The virus-dependent biological factors associated with a more aggressive oncogenesis are HBV core protein antigen seropositivity, high viral load, and genotype C[11,10,1,2]. The carcinogenic process linked to genotype C could be associated with basal core promoter mutations. Additionally, patients with genotype C frequently show higher HBV core protein antigen levels, potentially explaining the more aggressive disease course. In 2006, Chen at al. demonstrated the crucial association between the viral load and the HBV-linked hepatocarcinogenesis. The HCC risk was associated with high HBV DNA levels in serum, and higher the level, the stronger the association with HCC, even in patients negative for the HBV core protein antigen[10].

Regarding clinical and epidemiological data, chronic HBV infection represents the major etiological risk factor for HCC development worldwide, with approximately half of the patients with HBV-related HCC. The 5-year expected cumulative incidence of cirrhosis in patients with untreated chronic hepatitis B is 8 - 20%, while the annual HCC risk in patients with HBV-related cirrhosis is estimated to be 2 - 5%[11].

Although antiviral therapies, mostly nucleos(t) ide analogues - based therapies, have profoundly changed the natural history of HBV infection, virus elimination remains challenging. To date, the most effective public health measure has been the implementation of vaccination. Indeed, vaccination prevents virus infection and, as consequence, genome integration, which is the key aspect of oncogenic promotion[10,2].

HCC risk in untreated and treated patients

The HCC risk in untreated patients with HBV depends on the HBV status: inactive carrier (comparable to chronic HBV core protein antigen-negative infection, according to the most recent classification) has an incidence rate of 0.05 (95% CI: 0.03 - 0.08) per 100 person-years, patients with chronic hepatitis B have an incidence rate of 0.42 (95% CI: 0.27 - 0.56) per 100 person-years, and patients with compensated cirrhosis exhibit an incidence rate of 2.97 (95% CI: 2.35 - 3.59) per 100 persons-years, nearly 60-fold higher than patients with a chronic infection (in Europe, the subtotal incidence rates were significantly lower: 0.03, 0.12, and 2.03, respectively) 0,12[11]. These findings underscore that the HCC risk is strictly linked to liver status and to advanced fibrosis or cirrhosis. In a prospective cohort of nearly 2000 on-therapy patients

with untreated chronic hepatitis B (with mostly nucleos(t)ide analogues: entecavir, entecavir, and tenofovir disoproxil fumarate, tenofovir disoproxil fumarate), for 5 to 12 years after mostly nucleos(t) ide analogues were started, HCC developed in 1.2% of patients without cirrhosis at baseline and in 5.75% of patients with cirrhosis at baseline. The HCC risk after the first 5 years of antiviral therapy depends on age, baseline cirrhosis status, and liver stiffness measurement at 5 years[12,2]. NA-based therapies aim to achieve long-term suppression of viral load, HBeAg loss, and a seroconversion from HB antigens to anti-HB antigens in order to minimize liver disease progression, liver-related events, and the risk of HCC incidence. NA-based therapy has shown superiority over interferon - based therapy in reducing the incidence of HCC compared to controls. In fact, the to relative risk obtained from interferon-based therapies ranged from 0.50 (95% CI: 0.05 - 0.94) to 0.66 (95% CI: 0.48 - 0.89), while that obtained from mostly nucleos(t)ide analogues ranged from 0.22 (95% CI: 0.10 - 0.50) to 0.55 (95% CI: 0.31 - 0.99), $p < 0.001$. Tenofovir disoproxil fumarate treatment in a retrospective HBV-related cirrhosis cohort was independently associated with a lower HCC risk (identified a pooled hazard ratio: 0.46) 0,46)[13]. Liver status also influences the HCC risk due to antiviral therapy: The 5-year HCC cumulative incidence was 0.5 - 6.9% in on-therapy patients without cirrhosis, 4.5 - 21.6% with compensated cirrhosis, and 36.3 - 46.5% with decompensated cirrhosis, considering the significantly decreased annual incidence rate within 4 versus 4 - 8 years (0.2% versus 0% in the low-risk, 1.1% versus 0.2% in the intermediate-risk, and 4.6% versus 1% in the high - risk groups, respectively)[11,14].

In the literature, the fact that an antiviral drug is most effective in reducing the HCC risk is still debated. Firstly, Choi et al[14] showed a lower HCC risk in those who received tenofovir disoproxil fumarate compared to entecavir-treated cases. Several studies and meta-analyses, mostly conducted in Eastern countries, seem to support the superiority of tenofovir disoproxil fumarate over entecavir. Among the most recent and detailed studies, untreated chronic hepatitis B patients receiving tenofovir disoproxil fumarate had a significantly lower HCC risk (adjusted identified a pooled hazard ratio: 0.77; 95% CI: 0.61 - 0.98) than those receiving entecavir, particularly in patients older than 50 years (identified a pooled hazard ratio 0.76, 95% CI 0.58 - 1.00), males (Identified a pooled hazard ratio 0.74, 95% CI: 0.58 - 0.96), and individual who were HBeAg positive (Identified a pooled hazard ratio 0.69, 95% CI: 0.49 - 0.97)[16,13]. However, these data were not confirmed by the largest prospective study conducted in France15 on 1800 patients with untreated chronic hepatitis (986 patients treated with tenofovir disoproxil fumarate and 814 patients treated with entecavir). They concluded that the risk of liver-related events or death did not differ between patients treated with tenofovir disoproxil fumarate and entecavir, based on a 4 - year median follow-up. Therefore, it is not possible to infer the superiority of tenofovir disoproxil fumarate over entecavir with absolute certainty, and prospective studies on homogeneous populations with untreated chronic hepatitis are needed, also considering longer follow-up periods.

Table 2. Studies evaluating HCC incidence in patients with HBV

Author	Country	Research methods	Patients with cirrhosis	Ratio (%)
Papatheodoridis GV, J Hepatol 2020[12]	Europe	Retrospective	370 (26.9%) patients with cirrhosis All treated patients	HCC occurrence: 1.2% of patients with chronic hepatitis vs. 5.75% of patients with cirrhosis

Author	Country	Research methods	Patients with cirrhosis	Ratio (%)
Liu K, APT 2019[13]	China	Retrospective	797 patients treated with tenofovir disoproxil fumarate vs. 291 untreated patients 53.7% patients with cirrhosis	5-year cumulative probability of HCC: 14.9% in untreated patients vs. 9.8% in patients treated with tenofovir disoproxil fumarate
Choi J, Jama Oncol 2019[14]	Korea	Retrospective	11,464 patients treated with entecavir and 12,692 patients treated with tenofovir disoproxil fumarate cirrhosis: 26.1% in entecavir vs. 27.5% in tenofovir disoproxil fumarate	Annual incidence rate of HCC: 1.06 per 100 people over a year in entecavir vs. 0.64 in tenofovir disoproxil fumarate groups
Pol S, APT 2021[15]	France	Retrospective	814 patients treated with entecavir and 986 patients treated with tenofovir disoproxil fumarate cirrhosis: 9% in both groups	HCC incidence rate: 1.6 per 100 people over a year in entecavir vs. 1.8 per 100 people over a year in tenofovir disoproxil fumarate groups (not a statistically significant difference)

Occult hepatitis B virus infection and HCC risk

A not fully explored and understood entity is occult Hepatitis B Virus Infection, in which replication-competent HBV DNA should be present in the liver, and patients usually exhibit HBsAg negativity, with or without serum viral load detection. Its clinical relevance is attributed to the integration of life - long DNA into the host cells. An examination of liver tissues from patients with HCC without HBsAgs and with anti-HBV core protein antigens showed that most of these patients had a significantly higher prevalence of HBV DNA compared to tissue from patients without HCC[15,14]. Moreover, in a retrospective HBsAg-negative cohort, after male sex, the HBV - DNA positivity was the second strongest predictors for carcinogenesis (Identified a pooled hazard ratio: 8.25, 95% CI: 2.01 - 33.93). One of the largest studies in this field was conducted on 609,299 patients undergoing hepatitis B serology examination, with a 9 - year median follow - up, aimed to investigate liver-related and liver cancer mortality16. As expected, patients with a current HBV infection had the worst prognosis (a liver - related mortality rate of 129.6/105 person years). However, patients with isolated anti - HBV core protein positivity exhibited higher mortality compared to patients with anti-HBV core protein positivity associated with anti - HBV core protein positivity: the liver-related mortality rate was 22.5 vs. 7 per 105 person - years, and the liver cancer mortality rate was 16.8 vs. 4.0 per 105 person - years. A definitive direct association between occult hepatitis B Virus Infection and the HCC risk has not been established, and it could be influenced by virus replication. Defining the clinical significance of occult Hepatitis B Virus Infection, particularly its role in hepatocarcinogenesis and in accelerating progression to cirrhosis in patients with other identifiable causes of liver disease, as well as those without identifiable causes, will be listed in our future research.

CONCLUSIONS

- HCC occurrence is a complicated process affected by various factors. Viral hepatitis represents an important predisposing factor for liver carcinogenesis towards chronic inflammation, epithelial-to-mesenchymal transition, and overt fibrosis and cirrhosis.

- Chronic viral infection and immune-mediated damage changes the liver microenvironment, contributing to the strongest risk factors for HCC development. It is also mandatory to consider all

the potential hepatocarcinogenetic pathways in this field, including the direct mechanisms, because a non-negligible percentage of HCC occurs in patients without a cirrhotic substrate. - Current treatment options are the mainstay in the primary and secondary prevention of HCC, even if they reduce the risk without eliminating it completely.

- Indeed, while a portion of patients with HCV after sustained virological response may be subjected to a minor HCC risk, all patients with HBV, even with sustained virological suppression, must undergo HCC surveillance, especially those with an HBV/HDV co-infection.

- Future research may focus on stratifying better high-risk patients and, of course, on understanding the potential impact of bulevirtide on hepatocarcinogenesis. On the other hand, it is well known that not all patients with chronic viral infection develop HCC, suggesting that additional factors are involved, including other factors (such as the emerging metabolic syndrome) and also the host responses.

- Future studies aimed at comprehending the influence of these viruses on the host immuno-response may provide new perspectives on HCC occurrence as well as new therapeutic targets, to limit or prevent the liver disease progression.

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