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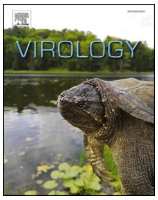

Epidemiological, diagnostic, therapeutic and prognostic impact of hepatitis B and D virus infection on hepatocellular carcinoma: A review of the literature

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) accounts for >90% of primary liver cancer cases, and chronic infections with hepatitis B virus (HBV) and hepatitis D virus (HDV) are major contributors.

Methods: A comprehensive literature review was conducted using the MEDLINE (PubMed) database, focusing on studies related to HBV, HDV, and HCC.

Results: HBV contributes to HCC through mechanisms like viral integration into the host genome, chronic inflammation, and immune modulation, leading to genomic instability and altered cell signaling. HDV exacerbates HBV-induced liver damage, accelerating fibrosis and cirrhosis, and significantly increasing HCC risk. Antiviral therapies and vaccinations have majorly reduced the burden of HBV-related HCC, but HDV remains challenging to treat due to limited therapeutic options. Emerging treatments like Bulevirtide showed promising results.

Conclusion: This review highlights the critical impact of HBV and HDV co-infections on HCC development, emphasizing the need for more effective therapeutic strategies. While advances in antiviral therapies have reduced the incidence of HBV-related HCC, the high burden of HDV-related complications persists. Future research should focus on improving treatments for HDV and understanding its unique contribution to HCC pathogenesis.

1. Introduction

Hepatocellular carcinoma (HCC) stands as the most prevalent primary liver cancer (75–90%), and it is a leading cause of liver-related morbidity and mortality. Its incidence is projected to exceed 1 000 000 cases annually by 2025, with Asia and Africa bearing the greatest burden (Park et al., 2010). However, mortality rates are on the rise also in North America and Europe, notably among individuals with compensated cirrhosis (Bray et al., 2018).

Chronic liver inflammation, often triggered by viral infections like hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis delta virus (HDV), significantly contributes to the development of HCC (Venook et al., 2010). These infections induce chronic hepatitis, oxidative stress, and disrupted cell signaling, driving the malignant transformation of hepatocytes (Fig. 1). While HBV integrates into the host genome and HCV induces metabolic reprogramming, exacerbating liver fibrosis and cirrhosis, HDV exacerbates liver disease progression when coinfecting with HBV, synergically increasing the risk of HCC (Ni and Chen, 2010) (Fig. 2).

Viral transmission of hepatitis B primarily occurs through sexual contact or exposure to infected blood or biological fluids, with vertical transmission from mother to child during birth or early infancy being

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common. Fortunately, the implementation of universal childhood HBV vaccination since 1992 has significantly reduced chronic hepatitis B (CHB) prevalence, particularly in Asian countries. This decline in CHB cases has corresponded with a decrease in HCC among younger individuals (Llovet et al., 2021a), (Galle et al., 2018). Beyond viral causes, independent risk factors like alcohol abuse, diabetes, obesity, aflatoxin exposure and metabolic dysfunction-associated fatty liver disease (MAFLD) also contribute to HCC (Wild and Montesano, 2009). Although immunization and antiviral therapies have mitigated viral hepatitis-associated HCC, MAFLD is emerging as a primary cause (Hernaez and Peck-Radosavljevic, 2023), (Valery et al., 2018). Despite advancements, the prognosis for patients remains grim, with a 5-year survival rate of 30%–50%. (Brar et al., 2020), (Vitale et al., 1985). Recent studies shed light on unique molecular mechanisms underlying HBV-HDV related HCC, emphasizing viral-induced gene mutations and epigenetic regulation (Trung et al., 2020a). Advanced technologies like next-generation sequencing offer comprehensive insights into the genomic, epigenomic and transcriptomic landscapes of HCC, facilitating the development of targeted therapies and personalized treatment strategies(Jiang et al., 2021).

The study aimed to investigate the impact of HBV and HDV on HCC by conducting a comprehensive review of existing literature. Both, experimental and clinical studies, were included, with a systematic search conducted on the MEDLINE (PubMed) database using keywords such as "HBV", "HCC " and "HDV". Additionally, references cited within retrieved papers were reviewed to ensure a comprehensive collection of relevant literature. This approach facilitated an in-depth analysis of the clinical implications of HBV and HDV coinfection in HCC.

2. Epidemiology

HBV infection is public health menace and approximately 254 million people are chronic HBV surface antigen (HBsAg) carriers. (Lampertico et al., 2017), (Hepatitis B) The global prevalence of HBsAg positive subjects is 3.6–4.1%, but it has a large temporal and geographical variety with different estimations and disease-related burden between low (<2%) and high (>8%) endemicity levels. (Sheena et al., 2022), (Schweitzer et al., 2015) There are nine known genotypes of HBV (A-I) with >40 genetic subtypes that have been recently reviewed elsewhere (Chen et al., 2023); a tenth putative genotype (J) has been proposed, but whether it represents a separate genotype is controversial. (Locarnini et al., 2013), (Velkov et al., 2018) Briefly, genotypes A-E determine 96% of the global CHB infections, with the most common being genotype C (26%) and D (22%) (Velkov et al., 2018). According to the geographical area, genotype C is the most common in Eastern and South-Eastern Asia, genotype A and D in Europe and North Africa, genotype A and E in Sub-Saharan Africa, while genotypes F-H were common in Latin America.(Chen et al., 2023), (Velkov et al., 2018), (Tong and Revill, 2016) In clinical practice, genotyping is not routinely performed as modern high-genetic barrier antivirals achieve high rates of virological remission independently of the genotype, but a different response to interferon treatment has been previously reported (Lampertico et al., 2017). Of note, genotype C has been associated with an increased risk of progression to fibrosis/cirrhosis and HCC as compared to genotype B in Asian cohort studies; (Yang et al., 2008), (Kao et al., 2000), (Su et al., 2006) however genotype B has been more frequently described in young and non-cirrhotic patients. (Kao et al., 2000), (Liu and Kao, 2013) Data on HCC risk and HBV genotype in other geographical areas are limited and controversial. (Sukowati et al., 2024), (Fernandes da Silva et al., 2023)

Regarding HDV, accurately evaluating its epidemiology presents numerous hurdles due to methodological disparities and evolving epidemic dynamics. This is particularly challenging in regions with low HBV prevalence, where obtaining representative samples for HDV testing necessitates large population sizes. Selection criteria for HBsAg and subsequent HDV testing can result in non-representative sampling, further complicating estimations (Stockdale et al., 2020a), (Razavi-Shearer et al., 2018).

Globally, the estimated prevalence of anti-HDV in the general population ranges from 0.11% to 0.98%, but it escalates to 4.5%–13.02% among HBsAg-positive individuals. Regional variations abound, with a 3% prevalence among HBsAg-positive individuals in Europe and 6% in Africa, collectively representing approximately 12–72 million HDV seropositive individuals worldwide. While Northern Europe is traditionally considered a low endemicity area, HDV infection is hyperendemic in certain geographic hotspots and populations within Europe,

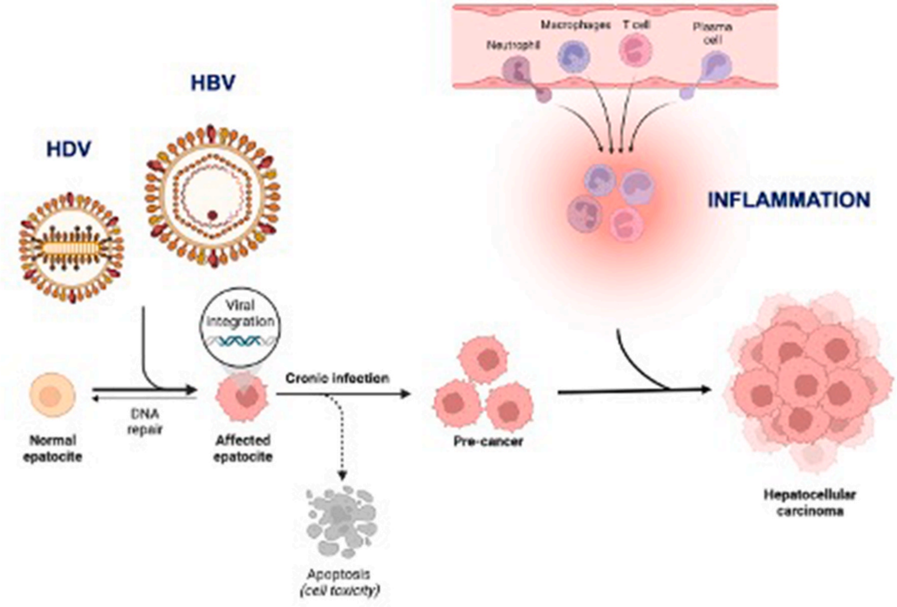

Fig. 1. Viral carcinogenesis.
The figure illustrates how chronic HBV and HDV infections lead to hepatocellular carcinoma (HCC) through viral integration, chronic inflammation, and apoptosis. HDV amplifies HBV-induced liver damage and HCC development.

particularly in endemic pockets such as Moldova and Eastern Europe, where the highest reported prevalence in HBsAg-positive individuals is observed(Stockdale et al., 2020b).

From a recent study emerges a lower HDV prevalence than previously described if data are adjusted for geographical distribution, disease stage and special populations. This study also found out that the highest prevalence of HDV was in Mongolia as China has the highest absolute number of HDV infected patients (Razavi-Shearer et al., 2024).

Genotype disparities add complexity to HDV epidemiological studies; eight genotypes have been identified, but genotype 1 is predominant on a global scale. Other genotypes exhibit more localized distribution, such as genotype 2 in Asia, genotype 3 in Latin America, genotype 4 in Japan and China, genotype 5 in West Africa, and genotypes 6–8 in Central Africa (Brunetto et al., 2023). European countries have reported HDV genotypes 5–7 as the most common, underscoring the dynamic nature of HDV epidemiology influenced by migration and globalization trends. In an Asian cohort study, genotype 1 was associated with a higher risk of HCC as compared to genotype 2 (Su et al., 2006). An association between genotype 1 and higher rate of progression and complications related to cirrhosis was found also in European study, but it is likely that place of birth, genotype, and persistent viremia all contribute to carcinogenesis in CHD (Roulot et al., 2020a).

3. Pathogenesis of HBV and HDV infection and HCC development

3.1. HBV and hepatocellular carcinoma

The hepatitis B virion consists of an inner nucleocapsid core that contains the viral DNA and an outside lipoprotein envelope. Viral genome encodes seven proteins: envelope antigens (Small-protein or S or HBsAg, Middle-protein or M, Large-protein or L), a non-structural antigen (HBeAg), the core antigen (HBcAg), HBV polymerase and X protein (HBx). When the host fails to resolve acute HBV infection, it becomes chronic, and up to 40% of untreated patients progresses to cirrhosis (Pollicino and Caminiti, 2021). HBV conventionally doesn't exhibit cytopathic activity (Wei et al., 2017). Instead, liver tissue damage results from the immune response against viral antigens, leading to chronic inflammation and immune depression, promoting hepatocarcinogenesis. Immunological alterations in the tumor microenvironment involve dysregulation of key signaling pathways, cytokine production, and impaired T cell and innate immune cell function (Zhang et al., 2018). Inflammation activates nuclear factor (NF)-κB and STAT3, promoting tumor immune escape, angiogenesis, and invasiveness, in this way IL-6 and IL-22 play significant roles in STAT3 activation (Williams et al., 2012a), (Nishimura, 2021). Additionally, tumor-associated macrophages, particularly the M2-phenotype, release TGF-β, inducing $CD8^+$ T-cell exhaustion and promoting HCC development. TGF-β also inhibits anti-oncogenic M1-macrophages and suppresses NK and dendritic cell activity(Liu et al., 2020). Moreover, TGF-β and IL-10 activate regulatory T cells (T-reg), which antagonize $CD8^+$ T-cell function, contributing to immune escape in HBV-related HCC (Papatheodoridi and Papatheodoridis, 2023), (Mesri et al., 2014).

Viral factors significantly contribute to tumorigenesis in CHB-related HCC. HBV-DNA integration in the host genome provokes genomic instability, deletions, and translocations, including alterations in long non-coding RNAs (lncRNAs) and microRNAs increasing the DNA recombination rate (Gao et al., 2019). In 2021, Chen and colleagues discovered that microRNA-30B-5P downregulates MINPP1 expression, promoting tumor proliferation and migration in HBV-positive HCC patients (Chen, 2021). The most common site of HBV-mediated insertional mutations is within the TERT promoter (15–25%), resulting in the overexpression of telomerase, which is responsible for the maintenance of telomere length, inhibition of cellular senescence, and promotion of cancer cell growth (Trung et al., 2020b), (D'souza et al., 2020), (Trung et al., 2020c), (Yuan et al., 2019). In a study of 95 HCC patients, researchers analyzed the distribution of common HBV-DNA integration sites using targeted sequencing and found frequent HBV integration in TERT, along with increased TERT mRNA expression, which was associated with more aggressive tumor behavior (Jia et al., 2020), (Rizzo et al., 2022). HBx exerts its effects by modulating various pathways (Zhang et al., 2017). For instance, it inhibits cancer cell apoptosis by enhancing the expression of hepatoma upregulated protein (HURP) and

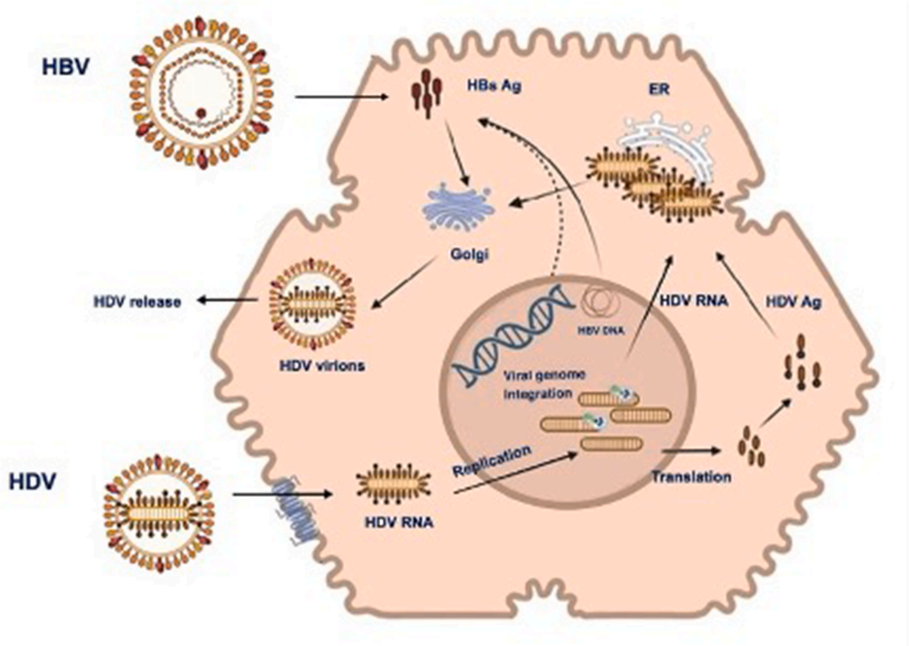

Fig. 2. HBV and HDV life cycle.
The image illustrates the interaction between HBV and HDV within a hepatocyte, where HBV integrates its DNA into the host genome and produces viral proteins. HDV relies on HBV's proteins for its replication and assembly, leading to the release of both viruses from the cell.

special AT-rich binding protein 1 (SATB1) genes, leading to increased production of the anti-apoptotic protein Survivin (BIRC5) (Gao et al., 2019). Moreover, HBx can disrupt the transcriptional regulation and DNA-binding of p53, a key regulator of apoptosis, cell cycle arrest, and DNA repair processes. Furthermore, it can impair mitochondrial function by altering their membrane potential and increasing calcium content, resulting in excessive generation of reactive oxygen species (ROS) and oxidative stress (Rizzo et al., 2022), (Zhang et al., 2021). HBx also upregulates the Wnt/β-catenin signaling pathway and modulates matrix metallo proteinases (MMP), which digest fibrous capsules in tumors and result in increasing the epithelial–mesenchymal transition (EMT) and metastasis (An et al., 2018), (Lim et al., 2019).

Envelope proteins and preS/S gene mutant variants also contribute to the production of abnormal proteins, result in the accumulation of ROS in endoplasmic reticulum and, consequently, exacerbating genomic instability (Rizzo et al., 2022), (Pollicino et al., 2014)

Another mechanism can play a role in HCC development and it can be explained by the clonal expansion theory. As is well known, to maintain liver homeostasis all hepatocytes undergo turnover. The random death of hepatocytes leads to a proliferation of surviving hepatocytes with a consequent loss of complexity of the hepatocyte population. Hepatocyte death during HBV infection is sustained by a host immune response. It has been shown that during chronic HBV infection, the population of hepatocytes that survives is larger than in normal conditions.Furthermore, with a greater severity of the infection, there will be a greater number of deaths of hepatocytes and consequently a greater clonal expansion mainly of hepatocytes that have a growth advantage or are able to evade the immune response (e.g. because they are deficient in HBV-presenting antigens), thus resulting in an advantage for survival. This can facilitate the emergence of preneoplastic lines and therefore represent a risk factor for the development of HCC (Mason et al., 2021).

3.2. HDV and hepatocellular carcinoma

HDV is a circular single-strand negative-sense RNA-deficient virus characterized by encoding only one protein or δ antigen (HDAg). HDV infection occurs exclusively in individuals infected with HBV due to its dependence on HBsAg for de novo infection, progeny virion assembly, and release (Hughes et al., 2011), thus is considered as satellite virus (Pearlman, 2023), (Lucifora and Delphin, 2020).

HDV viral entry is mediated by HBV-envelope, then HDV RNA is released into the cytoplasm and further transported to the nucleus where RNA replication occurs; however, intracellular HDV RNA replication is autonomous (D'souza et al., 2020). HDV encodes only for the antigenic protein HDAg, synthesized in two forms: the Small HDAg (S-HDAg) and the Large HDAg (L-HDAg), which are structurally identical, but L-HDAg has an extra 19 amino acid chain in the C-term (Papatheodoridi and Papatheodoridis, 2021).

HDV appears to exacerbate fibrosis, cirrhosis and HCC development in chronic viral hepatitis, compared to patients with HBV only (Benegiamo et al., 2013), (Romeo et al., 2018). As an RNA virus unable to integrate viral genes into the host genome, HDV does not require HBV to access the hepatocyte nucleus, as HDV RNA can initiate its replication independently, based on in vitro models of HDV mono-infection (Puigvehí et al., 2019).Thus, HDV seems to have a role in carcinogenesis of HCC, but it is difficult to estimate since, HBV has an oncogenic role itself in developing of HCC (Pearlman, 2023).

An answer to this question comes from a study of Choi et colleagues that examined the effects of HDV-encoded-only protein, in particular the large hepatitis delta antigen (L-HDAg), on TGF-beta. They demonstrated that L-HDAg may induce liver fibrosis through the upregulation of TGF-beta-induced signal transduction, thus increasing the transcription of c-Jun (Hess et al., 2004a). TGF-beta is linked to the modulation of cell growth, proliferation and apoptosis and is also a fibrogenic factor. L-HDAg also is able to activate hepatitis B virus X protein-mediated TGF-beta and AP-1 signalling cascades; this synergistic molecular mechanism could explain why HDV infection may contribute to hepatocyte transformation by promoting inflammation and is associated with a higher risk of developing HCC compared to HBV monoinfection (Choi et al., 2007a)

Additionally, HDV-induced epigenetic changes, such as long non-coding RNAs (lncRNAs), could also play a role in hepatocyte transformation (Costante et al., 2023). Specifically, Williams et al. showed, in 2012, that L-HDAg induced the expression of the NADPH oxidase 4 (NOX4) gene, resulting in the generation of ROS in vitro (Williams et al., 2012b). This led to the activation of NF-κB and signal transducer and activator of transcription 3 (STAT3) in a dose-dependent manner (Majumdar et al., 2012), (Williams et al., 2012a). Therefore, research suggests that L-HDAg may upregulate transforming growth factor-beta (TGF-β) -mediated transcriptional activity of c-Jun, contributing to cell growth, proliferation, and apoptosis modulation (Choi et al., 2007b). Moreover, L-HDAg can synergistically enhance pathways involved in HCC development in conjunction with HBV proteins, such as HBx (Chang et al., 2022).

In 2021, Yu et al. conducted an advanced study using microarray dataset analysis, comparing cancerous and para-cancerous specimens from individuals with CHB or CHD-related HCC. They identified seven genes closely associated with mitotic cell cycle and DNA replication (CDC6, CDC45, CDCA5, CDCA8, CENPH, MCM4, MCM7) that were differently expressed, predominantly upregulated, only in the CHD-driven HCC subgroup. Therefore, the alteration of pathways involving these genes appears to be selectively mediated by HDV (Yu et al., 2021). These findings collectively demonstrate that the molecular profile of CHD-related HCC is characterized by an overexpression of genes involved in cell cycle regulation.

HDV infection has been associated also with premature aging of immune cells, impaired T-cell functionality, and elevated levels of the senescence marker like CD57 in CD8 T cells. In this way, Schirdewahn et al., suggests a potential link between HDV infection and immune cell senescence, ultimately contributing to hepatocarcinogenesis (Schirdewahn et al., 2016).

Additionally, intrahepatic expression of Chitinase 3-like 1, a marker indicating increased susceptibility of aging livers to fibrosis progression, was found to be higher in liver tissues of patients with HDV/HBV compared to those with HCV-, HBV-, or alcohol-related cirrhosis (Nishimura, 2021).

4. Diagnosis and clinical implications in HBV/HDV infected patients

HDV can be transmitted in coinfection with HBV, simultaneously, or in superinfection in patient already affected by HBV. Coinfection in most cases (90–95%) resolve spontaneously, as a consequence of HBV clearance by host immune system (Pearlman, 2023). By contrast, superinfection (80% of cases), brings to a relapse of hepatitis and progression to chronic HDV infection, resulting in rapid deterioration of the pre-existing HBV-related liver damage and high morbidity and mortality rates (Buti et al., 2011), (Negro, 2014). In rare cases, coinfection may lead to a severe acute to fulminant hepatitis. (Negro, 2014), (Rizzetto, 2016).

Biochemical test can distinguish coinfection by superinfection; in fact, serologic pattern of coinfection is characterized by the presence of anti-HDV IgM, high levels of HDV RNA and detection of anti-HBc IgM antibodies, while superinfection by the detection of anti-HDV IgM antibodies and anti-HBc IgG antibodies (Rizzetto, 2016), (Sakugawa et al., 2004).

It is imperative to enforce, standardize, and desirably automatize HDV screening among patients with HBV, as the rates of universal screening are still very low according to a recent survey (Rao et al., 2024). In all HBsAg-positive patients, HDV should be tested at least once and yearly in subjects at high risk of infection and re-testing is indicated in case of acute decompensation or aminotransferase flare (Brunetto et al., 2023).

It is therefore of utmost importance to stratify for the risk of HCC and diagnose patients with advanced/cirrhosis, as screening with ultrasound every 6 months together with blood exams and viraemic status is recommended even in patients in therapy for HDV (Brunetto et al., 2023).

The risk of HCC correlates with the severity of liver fibrosis, as in other etiologies. In patients with HBV, the annual incidence of HCC is approximately 2–8% in those with cirrhosis and 0.2–0.6% in those without cirrhosis. For patients co-infected with HBV and HDV, there is a 2 to 3-fold increase in the risk of cirrhosis and 3 to 5-fold increase in the risk of HCC as compared to patients affected by HBV monoinfection, and time to progression is shorter (Alfaiate et al., 2020), (Da et al., 2019). It is estimate that HDV infection is to be attributed to 18% of cirrhosis and 20% of HCC among patient with HBV monoinfection (Stockdale et al., 2020c). HCC cumulative incidence reaches from 2.3% at 1 year to 7.5% at 5-year in non-cirrhotic patients, rising to 5.4% at 1 year and 23.1% at 5 years in those with advanced liver fibrosis (Jang et al., 2021).

In such patients, other risk factors seem to contribute to progression of liver disease; they include male gender, older age, low albumin, high gamma-glutamyl transferase or transaminase, and low cholinesterase (Lutterkort et al., 2017). Persistent HDV viremia, HBV active replication, coinfection with HIV or HCV, diabetes, obesity and alcohol abuse identify patients with high risk of disease progression (Brunetto et al., 2023), (D'Arminio Monforte, 2023), (Gish et al., 2024). Moreover genotype 1 of HDV is associated with a significantly higher incidence of cirrhosis and mortality (Roulot et al., 2020b).

To stratify the risk of HCC in patients with chronic HBV, several predictive models have been developed, including REACH-B, PAGE-B, mPAGE-B, CU-HCC, HCC-RESCUE, CAMD, APA-B, REAL-B, AASL-HCC, and RWS-HCC (seok Kim et al., 2022). Except for PAGE-B, these models were primarily developed and tested in Asian patients with HBV, which may limit their applicability in clinical practice in the Europe due to differences in transmission factors, HBV genotype, and distribution of other risk factors between Asian and non-Asian populations (Voulgaris et al., 2020). Additionally, these models were developed in cohorts with varying proportions of patients undergoing antiviral treatment and those with cirrhosis, complicating their application in routine clinical practice. Meanwhile, there are no studies that have examined the performance of these HCC risk models in patients with HBV and HDV coinfection. Similarly, the aMAP risk score, which predicts hepatocellular carcinoma development in patients with chronic hepatitis, has not been validated in coinfected patients (Fan et al., 2020). In this context, non-invasive tests (NITs) such as APRI, FIB-4, algorithm including values of LSM (liver stiffness measurement) and SSM (spleen stiffness measurement) could be useful to assess the degree of fibrosis and stratify the risk of developing HCC (Dajti et al., 2021).

LSM can non-invasively diagnose significant and advanced fibrosis and therefore stratify also for the risk of HCC. Data on non-invasive diagnosis of cirrhosis in CHD are limited, but very promising, so they support the use of NTIs to diagnose cirrhosis and portal hypertension. In a preliminary study from 77 patients (30% with cirrhosis), LSM showed an accuracy of 0.90, which further improved after combining it with serological parameters such as gamma-glutamyl transferase (GGT), platelet count, and alanine aminotransferase (ALT) into the Delta-4 Fibrosis Score (D4FS) score (Da et al., 2020). Another multicentre and larger study (144 patients, 15% with cirrhosis) confirmed the accuracy of LSM (AUC = 0.89) and proposed the cut-offs of >12.5 kPa and >15.1 to respectively suspect and confirm the diagnosis of cirrhosis among patients with CHD; values lower than these cut-offs had an excellent negative predictive value of 98–99% and these findings were validated in an external cohort of 132 patients (Duarte-Rojo et al., 2024), (Sandmann et al., 2024). Moreover, Baveno VII consensus recommends the use of NITs to stratify also for the severity of portal hypertension (de Franchis et al., 2022). A multicenter study of 143 patients with HBV/HDV-related cirrhosis undergoing hepatic venous pressure gradient (HVPG) confirmed that LSM and platelet count can accurately diagnose clinically significant portal hypertension with similar cut-offs to those proposed for other etiologies (Jachs et al., 2024).

All the available evidence supports the role of NITs as reliable tool to identify patients with cirrhosis. Nevertheless, liver biopsy remains the gold standard, particularly when there is a discrepancy between imaging results and blood tests or when other liver diseases, such as autoimmune overlap syndromes, need to be investigated (Brunetto et al., 2023), (Sandmann et al., 2024).

5. Antiviral treatments and HCC prevention

Current treatment strategies for HBV and HDV can reduce HCC risk, but do not eliminate it. The lack of an HBV therapy aimed to eradicate the viand limited treatment options for HDV bring us to enforce the research for searching more effective therapies. Treatment of HCC linked to chronic viral hepatitis is aimed to prevent it, improving liver histology and improving survival rate (Hess et al., 2004b). Early prophylaxis and treatment are the strategies of choice to reduce the incidence of HBV/HDV-induced HCC (Alfaiate et al., 2020).

Vaccination against HBV is the primary strategy for HCC prevention. A 30-year report from Taiwan shows that the incidence of HCC decreased by more than 80%, and mortality declined by over 90% in cohorts of patients born after the initiation of the vaccination program (Chiang et al., 2013). Another study confirms that the vaccination program against HBV results in a decrease of HBV related morbidity and mortality, included incidence of HCC (Goldstein et al., 2005)The HBV vaccine prevents HDV infection by stopping HBV infection in the first place, but there are no vaccines available to protect individuals with established HBV infection from HDV.

Interferon is an off label recommended therapy as treatment of HDV. 2018 Guideline from the American Association for the Study of Liver Disease (AASLD) recommended one year of peginterferon alfa (PegIFN-2a) administration for elevated HDV RNA and transaminase levels (Terrault et al., 2018). Interferon alfa inhibits HDV replication decreasing viral loads, however, adverse effects are frequent and relapse often occurs (Zhang and Urban, 2020).

IFNλ, which targets a single site on hepatocytes, is expected to be better tolerated than PegIFNα. In a phase II study, the 180 μg dose administered for 48 weeks resulted in a 2-log reduction in HDV RNA in 50% of patients by the end of treatment, with 36% maintaining this reduction six months later. At both the end of treatment and six months post-discontinuation, 36% of patients had undetectable HDV RNA. Combined virologic response and ALT normalization were observed in 14% of patients at the end of treatment and in 29% six months later. An open-label phase II study investigated the combination of LFN (50 mg twice daily) and ritonavir with IFNλ (180 μg/week) for 24 weeks in 26 patients with chronic delta hepatitis. The study found that 77% of patients had a >2 log reduction in HDV RNA, with 50% achieving undetectable HDV RNA at the end of treatment, and 23% maintaining undetectable levels 24 weeks into follow-up (Etzion et al., 2019a). However, the phase 3 LIMT-2 trial was prematurely stopped due to hepatobiliary toxicity causing liver decompensation in some patients.

The use of effective antiviral therapies, such as **nucleoside and nucleotide analogues (NAs)** including entecavir (ETV), tenofovir alafenamide fumarate (TAF), and tenofovir disoproxil fumarate (TDF), has improved the prognosis for patients with chronic HBV infection by preventing progression to HCC and enhancing survival rates(Llovet et al., 2021b). Many studies have aimed to evaluated HCC incidence in HBV patient treated with nucleoside and nucleotide analogues. A systematic review showed that HCC developed in 2.8% of threated patients, significantly lower (p value 0.003) than in untreated patients (6.4%) and that achievement of virological remission is crucial to the reduction of HCC incidence (Papatheodoridis et al., 2010). Another cohort study confirms this results showing a significantly lower incidence of HCC at 7 years in threated patients than controls (7.32% vs 22.7%; p value <

0.001) (Wu et al., 2014). Moreover, a study on Caucasian patients affected by HBV demonstrated a decrease of HCC incidence after 5 years of Tenofovir disoproxil fumarate or entecavir treatment (Papatheodoridis et al., 2017). However, these antiviral therapy does not achieve a complete elimination of HBV DNA in liver cells (Chiang et al., 2013). A study evaluated that in HBV-cirrhotic patients, beside the use of antiviral therapy, other independent risk factor for HCC were male gender, age <55 years, presence of comorbidity such as diabetes mellitus and grade of hepatic dysfunction (Hsu et al., 2014). Moreover, HBV nucleoside and nucleotide analogues are ineffective against HDV (Jang et al., 2021), (Marrero et al., 2018).

Bulevirtide (BLV), a first-in-class entry inhibitor, is a linear, 47-amino-acid lipopeptide that binds to the sodium taurocholate cotransporting polypeptide (NTCP) on hepatocyte membranes, blocking HBV and HDV entry. In the phase 2 MYR202 study, BLV (2, 5, or 10 mg) combined with TDF was well tolerated and significantly reduced HDV RNA and ALT levels over 24 weeks in CHD patients compared to TDF alone (Wedemeyer et al., 2023a). Phase 3 MYR301 study data at 48 weeks showed BLV monotherapy (2 or 10 mg) was superior to no anti-HDV treatment based on combined virologic and biochemical responses, with similar efficacy between doses and good tolerance (Gane et al., 2020), (Wedemeyer et al., 2023b).

In 2020, BLV at 2 mg/day was conditionally approved in the EU for treating CHD in adults with compensated liver disease, with full approval granted in July 2023. It is now recommended by the European Association for the Study of the Liver (EASL) clinical guidelines for HDV (Brunetto et al., 2023).

In Wedemeyer et al. trial, it was demonstrated that BLV monotherapy for 96 weeks in patients with CHD led to sustained improvements in combined virologic and biochemical responses, as well as liver stiffness, from week 48 onward at both the 2-mg and 10-mg doses. Additionally, patients with suboptimal virologic responses at week 24 benefited from continued therapy, with the majority achieving virologic response or biochemical improvement by week 96 (Wedemeyer et al., 2024). This data is supported by Killer et al., who reported a significant decrease in liver stiffness during BLV treatment, with a baseline median of 10.6 kPa dropping to 7.6 kPa at month 12 (Killer et al., 2024).

Real-world data from over 500 patients in Europe support the findings from clinical trials, showing improvements in liver function and reductions in HDV RNA (Zöllner et al., 2022), (Dietz-Fricke et al., 2023), (Degasperi et al., 2022). Despite the promising results, there is a high relapse rate, which necessitates prolonged treatment. In another study, Anolli et al. described a case where a patient with compensated cirrhosis and HDV infection was treated with BLV monotherapy for three years. The patient showed a sustained off-BLV cure of HDV infection, maintaining undetectable HDV RNA levels both in serum and liver tissue during a 72-week follow-up after discontinuation of the therapy (Anolli et al., 2023).

Stopping BLV therapy after achieving long-term HDV-RNA suppression appears to be safe, with effective virologic response upon retreatment in cases of relapse, as described in the study by Jachs et al. However, these findings are based on a small patient sample, necessitating further studies to establish precise discontinuation guidelines and thoroughly assess the safety of stopping BLV (Jachs et al., 2023).

In the recent study by Allweiss et al., it emerged that in patients treated with BLV, intrahepatic HDV RNA loads strongly correlated with peripheral virological HDV RNA measurements and that the decline induced by BLV in the plasma reflected the decrease of HDV RNA in the liver (Allweiss et al., 2024).

In the 2024 study by Dietz-Fricke et al., off-label administration of BLV in patients with decompensated HDV cirrhosis was evaluated, showing virologic and biochemical response rates like those observed in patients with compensated liver disease. Significant improvements were also noted in surrogates of hepatic function and portal hypertension (Dietz-Fricke et al., 2024).

The analysis of these trials suggests that BLV therapy can effectively reduce liver stiffness levels, as well as decrease the viral load and replication within hepatocytes. This may potentially lead to a lower incidence of HCC even in decompensated patients. However, these findings are preliminary and require further validation through additional clinical trials.

Novel therapeutics under clinical evaluation include:

Lonafarnib, a farnesyltransferase inhibitor that blocks the assembly and release of HDV particles. Clinical trials have demonstrated significant virus level reduction with Lonafarnib, though it is associated with adverse events affecting normal cellular function (Etzion et al., 2019b). Ongoing trials are evaluating HBsAg secretion inhibitors for HDV treatment, showing promising results with high rates of HBV and HDV suppression during and after treatment when combined with PegIFNα or Ritonavir (Etzion et al., 2023).

Nucleic acid polymers target the host HSP40 chaperone DNA JB12 to block HBV and HDV replication. In a phase II study with 12 patients, 15 weeks of REP 2139-Ca followed by REP 2139 and PegIFN, then PegIFN alone for 33 weeks, led to 6 patients becoming HBsAg negative with HBs seroconversion (Stern et al., 2023). After 3.5 years, 4 out of 11 maintained an HBV functional cure, 7 had undetectable HDV RNA, and 6 had normalized ALT levels. A subcutaneous form of REP 2139 was tested in France, showing positive results in patients who failed BLV treatment (Bazinet et al., 2017a), (Bazinet et al., 2020). In another study, 12 patients with compensated cirrhosis received REP 2139 and PegIFN alfa-2a weekly for 48 weeks, with five showing a virological response and three achieving undetectable HDV RNA (Bazinet et al., 2017b).

Future potential therapies include **Small interfering RNA** (siRNA) agents that can prevent synthesis of viral antigens (Lok et al., 2021). A recent study, carried out on murine model with humanized liver, aimed to evaluate the use of a Human monoclonal anti-HBs. A-specific antibody on chronic HBV/HDV infection (Burm et al., 2023). The human monoclonal anti-HBsAg-specific antibody, produced using classical hybridoma technology, target the entry step of virus and diminishing circulating HBsAg blocking viral spread (Wedemeyer et al., 2023c). Decreasing the viral loads in patients with chronic HBV/HDV superinfection may provide a window for other antiviral therapies. It could have implication also in HBV/HDV coinfection. However, the exact mechanism of HDV involvement in HCC has not been clarified yet, so more research investment is imperative (Shen et al., 2023).

Moreover, due to the almost recent introduction of HDV therapies, literature is lacking data regarding the incidence of HCC In patients treated with these medications.

Finally, orthotopic liver transplantation (OLT) is a common treatment for end-stage liver disease and HCC, and HBV and HBV/HDV coinfection remain a non-negligible cause for requiring OLT. In Europe, as an example, liver transplants for cirrhosis caused by HDV infection account for approximately 3–5% of all liver transplants, with higher rates observed in regions like the Mediterranean and Eastern Europe (European Liver Transplant Registry, ELTR) (Cortesi et al., 2023).

6. Conclusion and future perspectives

Due to the essential interdependency of HDV on HBV, the precise mechanism underlying HCC development remains unclear. It remains uncertain whether HCC arises due to the combined effects of both HBV and HDV, is a consequence of underlying cirrhosis, or is directly induced by HDV's oncogenic properties (Anolli et al., 2023; Jachs et al., 2023). Studies have indicated that HCC associated with HDV infection is characterized by the upregulation of genes responsible for regulating cell cycle progression, DNA replication, and DNA damage repair. This suggests that genome instability plays a significant role in hepatocarcinogenesis induced by HDV.

To obtain a deeper understanding of HDV's role in carcinogenesis, further research at the molecular level, accounting for genotype variations, is imperative. Additionally, due to the elevated biological risk of HCC occurrence in CHD patients, they should be considered a very high-risk subgroup. This suggests that personalized screening schedules should be adopted to detect HCC at its earliest stages and in particular that tailored screening program are necessary to detect patients with HDV. It will be important in the coming years to perform studies to assess the risk of HCC incidence among patients treated with HDV drugs such as BLV or lonafarnib and controls. Well conducted observational studies are needed to understand deeply the exact role of HDV in hepatocarcinogenesis, both at the molecular level and with the clinical implications.

CRediT authorship contribution statement

Angelo Bruni: Investigation, Data curation. **Chiara Castellana:** Validation, Supervision, Methodology. **Elton Dajti:** Data curation. **Giovanni Barbara:** Writing – review & editing, Supervision. **Giovanni Marasco:** Writing – original draft. **Marcello Maida:** Writing – original draft. **Gaetano Serviddio:** Supervision. **Antonio Facciorusso:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Declaration of competing interest

References

Alfaiate, D., Clément, S., Gomes, D., Goossens, N., Negro, F., 2020. Chronic hepatitis D and hepatocellular carcinoma: a systematic review and meta-analysis of observational studies. J. Hepatol. 73 (3), 533–539. https://doi.org/10.1016/J.JHEP.2020.02.030.

Allweiss, L., et al., 2024. Blocking viral entry with bulevirtide reduces the number of HDV-infected hepatocytes in human liver biopsies. J. Hepatol. 80 (6), 882–891. https://doi.org/10.1016/j.jhep.2024.01.035.

An, P., Xu, J., Yu, Y., Winkler, C.A., 2018. Host and viral genetic variation in HBV-related hepatocellular carcinoma. Front. Genet. 9 (JUL). https://doi.org/10.3389/FGENE.2018.00261.

Anolli, M.P., et al., 2023. A 3-year course of bulevirtide monotherapy may cure HDV infection in patients with cirrhosis. J. Hepatol. 78 (4), 876–880. https://doi.org/10.1016/J.JHEP.2022.12.023.

Bazinet, M., et al., 2017a. Safety and efficacy of REP 2139 and pegylated interferon alfa-2a for treatment-naive patients with chronic hepatitis B virus and hepatitis D virus co-infection (REP 301 and REP 301-LTF): a non-randomised, open-label, phase 2 trial. Lancet. Gastroenterol. Hepatol. 2 (12), 877–889. https://doi.org/10.1016/S2468-1253(17)30288-1.

Bazinet, C.M., et al., 2017b. Safety and efficacy of REP 2139 and pegylated interferon alfa-2a for treatment-naive patients with chronic hepatitis B virus and hepatitis D virus co-infection (REP 301 and REP 301-LTF): a non-randomised, open-label, phase 2 trial. Artic. Lancet. Gastroenterol. Hepatol. 2, 877–889. https://doi.org/10.1016/S2468-1253(17)30288-1.

Bazinet, M., et al., 2020. Safety and efficacy of 48 Weeks REP 2139 or REP 2165, tenofovir disoproxil, and pegylated interferon alfa-2a in patients with chronic HBV infection naïve to nucleos(t)ide therapy. Gastroenterology 158 (8), 2180–2194. https://doi.org/10.1053/J.GASTRO.2020.02.058.

Benegiamo, G., Vinciguerra, M., Guarnieri, V., Niro, G., Andriulli, A., Pazienza, V., 2013. Hepatitis delta virus induces specific DNA methylation processes in Huh-7 liver cancer cells. FEBS Lett. 587 (9), 1424–1428. https://doi.org/10.1016/J.FEBSLET.2013.03.021.

Brar, G., et al., 2020. Hepatocellular carcinoma survival by etiology: a SEER-medicare database analysis. Hepatol. Commun. 4 (10), 1541–1551. https://doi.org/10.1002/HEP4.1564.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca - Cancer J. Clin. 68 (6), 394–424. https://doi.org/10.3322/CAAC.21492.

Brunetto, M.R., et al., 2023. EASL Clinical Practice Guidelines on hepatitis delta virus. J. Hepatol. 79 (2), 433–460. https://doi.org/10.1016/J.JHEP.2023.05.001.

Burm, R., et al., 2023. A human monoclonal antibody against HBsAg for the prevention and treatment of chronic HBV and HDV infection. JHEP Rep. 5 (3), 100646. https://doi.org/10.1016/j.jhepr.2022.100646.

Buti, M., et al., 2011. Clinical outcome of acute and chronic hepatitis delta over time: a long-term follow-up study. J. Viral Hepat. 18 (6), 434–442. https://doi.org/10.1111/J.1365-2893.2010.01324.X.

Chang, T.E., Su, C.W., Huang, Y.S., Huang, Y.H., Hou, M.C., Wu, J.C., 2022. Hepatitis D virus dual infection increased the risk of hepatocellular carcinoma compared with hepatitis B virus mono infection: a meta-analysis. J. Chin. Med. Assoc. 85 (1), 30–41. https://doi.org/10.1097/JCMA.0000000000000606.

Chen, W., et al., 2021. “Hepatitis B Virus P Protein Initiates Glycolytic Bypass in HBV-Related Hepatocellular Carcinoma via a FOXO3/miRNA-30b-5p/MINPP1 axis” https://doi.org/10.1186/s13046-020-01803-8.

Chen, J., Li, L., Yin, Q., Shen, T., 2023. A review of epidemiology and clinical relevance of Hepatitis B virus genotypes and subgenotypes. Clin. Res. Hepatol. Gastroenterol. 47 (7). https://doi.org/10.1016/J.CLINRE.2023.102180.

Chiang, C.J., Yang, Y.W., You, S.L., Lai, M.S., Chen, C.J., 2013. Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. JAMA 310 (9), 974–976. https://doi.org/10.1001/JAMA.2013.276701.

Choi, S.H., Jeong, S.H., Hwang, S.B., 2007a. Large hepatitis delta antigen modulates transforming growth factor-beta signaling cascades: implication of hepatitis delta virus-induced liver fibrosis. Gastroenterology 132 (1), 343–357. https://doi.org/10.1053/J.GASTRO.2006.10.038.

Choi, S.H., Jeong, S.H., Hwang, S.B., 2007b. Large hepatitis delta antigen modulates transforming growth factor-β signaling cascades: implication of hepatitis delta virus-induced liver fibrosis. Gastroenterology 132 (1), 343–357. https://doi.org/10.1053/J.GASTRO.2006.10.038.

Cortesi, P.A., et al., 2023. Economic impact of European liver and intestine transplantation association (ELITA) recommendations for hepatitis B prophylaxis after liver transplantation. Transpl. Int. 36 (Jan). https://doi.org/10.3389/TI.2023.10954.

Costante, F., et al., 2023. Molecular and clinical features of hepatocellular carcinoma in patients with HBV-HDV infection. J. Hepatocell. Carcinoma 10, 713–724. https://doi.org/10.2147/JHC.S384751.

Da, B.L., Heller, T., Koh, C., 2019. Hepatitis D infection: from initial discovery to current investigational therapies. Gastroenterol Rep (Oxf) 7 (4), 231. https://doi.org/10.1093/GASTRO/GOZ023.

Da, B.L., Surana, P., Kleiner, D.E., Heller, T., Koh, C., 2020. The Delta-4 fibrosis score (D4FS): a novel fibrosis score in chronic hepatitis D. Antivir. Res. 174, 104691. https://doi.org/10.1016/J.ANTIVIRAL.2019.104691.

Dajti, E., et al., 2021. “Risk of Hepatocellular Carcinoma after HCV Eradication: Determining the Role of Portal Hypertension by Measuring Spleen Stiffness,” https://doi.org/10.1016/j.jhepr.2021.100289.

de Franchis, R., et al., 2022. Baveno VII – renewing consensus in portal hypertension. J. Hepatol. 76 (4), 959–974. https://doi.org/10.1016/j.jhep.2021.12.022.

Degasperi, E., et al., 2022. Bulevirtide monotherapy for 48 weeks in patients with HDV-related compensated cirrhosis and clinically significant portal hypertension. J. Hepatol. 77 (6), 1525–1531. https://doi.org/10.1016/J.JHEP.2022.07.016.

Dietz-Fricke, C., et al., 2023. Treating hepatitis D with bulevirtide – real-world experience from 114 patients. JHEP Rep. 5 (4), 100686. https://doi.org/10.1016/J.JHEPR.2023.100686.

Dietz-Fricke, C., et al., 2024. Safety and efficacy of off-label bulevirtide monotherapy in patients with HDV with decompensated Child-B cirrhosis-A real-world case series. Hepatology. https://doi.org/10.1097/HEP.0000000000000847.

Duarte-Rojo, A., Patel, K., Rockey, D.C., 2024. Noninvasive assessment of liver fibrosis and portal hypertension. Curr. Opin. Gastroenterol. 40 (3), 148–155. https://doi.org/10.1097/MOG.0000000000001019.

D’Arminio Monforte, D., et al., 2023. Determinants of worse liver-related outcome according to HDV infection among HBsAg positive persons living with HIV: data from the ICONA cohort. Liver Int. 00, 1–11. https://doi.org/10.1111/liv.15804.

D’souza, S., Lau, K.C.K., Coffin, C.S., Patel, T.R., 2020. Molecular mechanisms of viral hepatitis induced hepatocellular carcinoma. World J. Gastroenterol. 26 (38), 5759–5783. https://doi.org/10.3748/WJG.V26.I38.5759.

Etzion, O., et al., 2019a. PS-052-End of study results from LIMT HDV study: 36% durable virologic response at 24 weeks post-treatment with pegylated interferon lambda monotherapy in patients with chronic hepatitis delta virus infection. J. Hepatol. 70 (1), e32. https://doi.org/10.1016/S0618-8278(19)30058-1.

Etzion, O., et al., 2019b. PS-052-End of study results from LIMT HDV study: 36% durable virologic response at 24 weeks post-treatment with pegylated interferon lambda monotherapy in patients with chronic hepatitis delta virus infection. J. Hepatol. 70 (1), e32. https://doi.org/10.1016/S0618-8278(19)30058-1.

Etzion, O., et al., 2023. Week 48 results of the phase 3 D-LIVR study, a randomized double-blind, placebo-controlled trial evaluating the safety and efficacy of Lonafarnib-boosted with Ritonavir with or without Peginterferon Alfa in patients with chronic hepatitis delta. J. Hepatol. 78, S10. https://doi.org/10.1016/S0168-8278(23)00451-8.

Fan, R., et al., 2020. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J. Hepatol. 73 (6), 1368–1378. https://doi.org/10.1016/j.jhep.2020.07.025.

Fernandes da Silva, C., Keeshan, A., Cooper, C., 2023. Hepatitis B virus genotypes influence clinical outcomes. https://doi.org/10.3138/canlivj-2023-0003. , vol. 6, no. 3, pp. 347–352, Oct. 2023, doi: 10.3138/CANLIVJ-2023-0003.

Galle, P.R., et al., 2018. EASL clinical practice guidelines: management of hepatocellular carcinoma. J. Hepatol. 69 (1), 182–236. https://doi.org/10.1016/J.JHEP.2018.03.019.

Gane, E., et al., 2020. “48 Weeks of High Dose (10 Mg) Bulevirtide as Monotherapy or with Peginterferon Alfa-2a in Patients with Chronic HBV/HDV Co-infection,” https://doi.org/10.1016/S0168-8278(20)30651-6.

Gao, Q., et al., 2019. Integrated proteogenomic characterization of HBV-related hepatocellular carcinoma. Cell 179 (2), 561–577.e22. https://doi.org/10.1016/J.CELL.2019.08.052.

Gish, R.G., et al., 2024. Association of hepatitis delta virus with liver morbidity and mortality: a systematic literature review and meta-analysis. Hepatology 79 (5), 1129–1140. https://doi.org/10.1097/HEP.0000000000000642.

Goldstein, S.T., Zhou, F., Hadler, S.C., Bell, B.P., Mast, E.E., Margolis, H.S., 2005. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int. J. Epidemiol. 34 (6), 1329–1339. https://doi.org/10.1093/IJE/DYI206.

Hernaez, R., Peck-Radosavljevic, M., 2023. MAFLD, HCC and the dilemma of (changing) terminology in liver diseases. Gut 72 (1), 9–11. https://doi.org/10.1136/GUTJNL-2022-326992.

Hess, J., Angel, P., Schorpp-Kistner, M., 2004a. AP-1 subunits: quarrel and harmony among siblings. J. Cell Sci. 117 (Pt 25), 5965–5973. https://doi.org/10.1242/JCS.01589.

Hess, J., Angel, P., Schorpp-Kistner, M., 2004b. AP-1 subunits: quarrel and harmony among siblings. J. Cell Sci. 117 (Pt 25), 5965–5973. https://doi.org/10.1242/JCS.01589.

Hsu, Y.C., et al., 2014. Determinants of hepatocellular carcinoma in cirrhotic patients treated with nucleos(t)ide analogues for chronic hepatitis B. J. Antimicrob. Chemother. 69 (7), 1920–1927. https://doi.org/10.1093/JAC/DKU041.

Hughes, S.A., Wedemeyer, H., Harrison, P.M., 2011. Hepatitis delta virus. Lancet 378 (9785), 73–85. https://doi.org/10.1016/S0140-6736(10)61931-9.

Jachs, M., et al., 2023. Long-term follow-up of patients discontinuing bulevirtide treatment upon long-term HDV-RNA suppression. JHEP Rep 5 (8). https://doi.org/10.1016/J.JHEPR.2023.100751.

Jachs, M., et al., 2024. Validation of Baveno VII criteria and other non-invasive diagnostic algorithms for clinically significant portal hypertension in hepatitis delta. J. Hepatol. 0 (0). https://doi.org/10.1016/j.jhep.2024.03.005.

Jang, T.Y., et al., 2021. Role of hepatitis D virus infection in development of hepatocellular carcinoma among chronic hepatitis B patients treated with nucleotide/nucleoside analogues. Sci. Rep. 11 (1). https://doi.org/10.1038/S41598-021-87679-W.

Jia, L., Gao, Y., He, Y., Hooper, J.D., Yang, P., 2020. HBV induced hepatocellular carcinoma and related potential immunotherapy. Pharmacol. Res. 159 (Sep). https://doi.org/10.1016/J.PHRS.2020.104992.

Jiang, Y., Han, Q., Zhao, H., Zhang, J., 2021. The mechanisms of HBV-induced hepatocellular carcinoma. J. Hepatocell. Carcinoma 8, 435. https://doi.org/10.2147/JHC.S307962.

Kao, J.H., Chen, P.J., Lai, M.Y., Chen, D.S., 2000. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology 118 (3), 554–559. https://doi.org/10.1016/S0016-5085(00)70261-7.

Killer, A., et al., 2024. Dynamics of virological and clinical response parameters of bulevirtide treatment for hepatitis D: real-world data. Gastro Hep Advances 3 (3), 353–360. https://doi.org/10.1016/J.GASTHA.2024.01.001.

Lampertico, P., et al., 2017. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J. Hepatol. 67 (2), 370–398. https://doi.org/10.1016/J.JHEP.2017.03.021.

Lim, C.J., et al., 2019. Multidimensional analyses reveal distinct immune microenvironment in hepatitis B virus-related hepatocellular carcinoma. Gut 68 (5), 916–927. https://doi.org/10.1136/GUTJNL-2018-316510.

Liu, C.J., Kao, J.H., 2013. Global perspective on the natural history of chronic hepatitis B: role of hepatitis B virus genotypes A to J. Semin. Liver Dis. 33 (2), 97–102. https://doi.org/10.1055/S-0033-1345716.

Liu, Y., et al., 2020. TRIM25 promotes the cell survival and growth of hepatocellular carcinoma through targeting Keap1-Nrf2 pathway. Nat. Commun. 11 (1). https://doi.org/10.1038/S41467-019-14190-2.

Llovet, J.M., et al., 2021a. Hepatocellular carcinoma. Nat. Rev. Dis. Prim. 7 (1). https://doi.org/10.1038/s41572-020-00240-3.

Llovet, J.M., et al., 2021b. Hepatocellular carcinoma. Nat. Rev. Dis. Prim. 7 (1). https://doi.org/10.1038/S41572-020-00240-3.

Locarnini, S., Littlejohn, M., Aziz, M.N., Yuen, L., 2013. Possible origins and evolution of the hepatitis B virus (HBV). Semin. Cancer Biol. 23 (6 Pt B), 561–575. https://doi.org/10.1016/J.SEMCANCER.2013.08.006.

Lok, A.S., Negro, F., Asselah, T., Farci, P., Rizzetto, M., 2021. Endpoints and new options for treatment of chronic hepatitis D. Hepatology 74 (6), 3479–3485. https://doi.org/10.1002/HEP.32082.

Lucifora, J., Delphin, M., 2020. Current knowledge on hepatitis delta virus replication. Antivir. Res. 179. https://doi.org/10.1016/J.ANTIVIRAL.2020.104812.

Lutterkort, G.L., et al., 2017. Non-invasive fibrosis score for hepatitis delta. Liver Int. 37 (2), 196–204. https://doi.org/10.1111/LIV.13205.

Majumdar, A., et al., 2012. Hepatic stem cells and transforming growth factor β in hepatocellular carcinoma. Nat. Rev. Gastroenterol. Hepatol. 9 (9), 530–538. https://doi.org/10.1038/nrgastro.2012.114, 2012 9:9.

Marrero, J.A., et al., 2018. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. Hepatology 68 (2), 723–750. https://doi.org/10.1002/HEP.29913.

Mason, W.S., Jilbert, A.R., Litwin, S., 2021. Hepatitis B virus DNA integration and clonal expansion of hepatocytes in the chronically infected liver. Viruses 13 (2). https://doi.org/10.3390/V13020210.

Mesri, E.A., Feitelson, M.A., Munger, K., 2014. Human viral oncogenesis: a cancer hallmarks analysis. Cell Host Microbe 15 (3), 266–282. https://doi.org/10.1016/J.CHOM.2014.02.011.

Negro, F., 2014. Hepatitis D virus coinfection and superinfection. Cold Spring Harb Perspect Med 4 (11). https://doi.org/10.1101/CSHPERSPECT.A021550.

Ni, Y.H., Chen, D.S., 2010. Vaccination des enfants contre l'hépatite B: l'expérience taïwanaise. Pathol. Biol. 58 (4), 296–300. https://doi.org/10.1016/J.PATBIO.2009.11.002.

Nishimura, N., et al., 2021. "Chitinase 3-like 1 Is a Profibrogenic Factor Overexpressed in the Aging Liver and in Patients with Liver Cirrhosis" https://doi.org/10.1073/pnas.2019633118/-/DCSupplemental.

Papatheodoridi, M., Papatheodoridis, G.V., 2021. Is hepatitis delta underestimated? Liver Int. 41 (S1), 38–44. https://doi.org/10.1111/LIV.14833.

Papatheodoridi, A., Papatheodoridis, G., 2023. Hepatocellular carcinoma: the virus or the liver? Liver Int. 43 (S1), 22–30. https://doi.org/10.1111/LIV.15253.

Papatheodoridis, G.V., Lampertico, P., Manolakopoulos, S., Lok, A., 2010. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J. Hepatol. 53 (2), 348–356. https://doi.org/10.1016/J.JHEP.2010.02.035.

Papatheodoridis, G.V., et al., 2017. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 66 (5), 1444–1453. https://doi.org/10.1002/HEP.29320.

Park, N.H., Chung, Y.H., Lee, H.S., 2010. Impacts of vaccination on hepatitis B viral infections in korea over a 25-year period. Intervirology 53 (1), 20–28. https://doi.org/10.1159/000252780.

Pearlman, B., 2023. Hepatitis delta infection: a clinical review. Semin. Liver Dis. 43 (3), 293–304. https://doi.org/10.1055/A-2133-8614.

Pollicino, T., Caminiti, G., 2021. HBV-integration studies in the clinic: role in the natural history of infection. Viruses 13 (3). https://doi.org/10.3390/V13030368.

Pollicino, T., Cacciola, I., Saffioti, F., Raimondo, G., 2014. Hepatitis B virus PreS/S gene variants: pathobiology and clinical implications. J. Hepatol. 61 (2), 408–417. https://doi.org/10.1016/J.JHEP.2014.04.041.

Puigvehí, M., Moctezuma-Velázquez, C., Villanueva, A., Llovet, J.M., 2019. The oncogenic role of hepatitis delta virus in hepatocellular carcinoma. JHEP Rep. 1 (2), 120. https://doi.org/10.1016/J.JHEPR.2019.05.001.

Rao, S., Qazi, S., Lee, D., Molliner, C., Martin, P., Jones, P.D., 2024. Multiple barriers impede screening for hepatitis delta: an internet-based survey of healthcare providers. Am. J. Gastroenterol. https://doi.org/10.14309/AJG.0000000000002810.

Razavi-Shearer, D., et al., 2018. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet. Gastroenterol. Hepatol. 3 (6), 383–403. https://doi.org/10.1016/S2468-1253(18)30056-6.

Razavi-Shearer, D., et al., 2024. Adjusted estimate of the prevalence of hepatitis delta virus in 25 countries and territories. J. Hepatol. 80 (2), 232–242. https://doi.org/10.1016/J.JHEP.2023.10.043.

Rizzetto, M., 2016. The adventure of delta. Liver Int. 36, 135–140. https://doi.org/10.1111/liv.13018.

Rizzo, G.E.M., Cabibbo, G., Craxì, A., 2022. Hepatitis B virus-associated hepatocellular carcinoma. Viruses 14 (5), 986. https://doi.org/10.3390/V14050986, 2022, Vol. 14, Page 986.

Romeo, R., et al., 2018. Hepatitis delta virus and hepatocellular carcinoma: an update. Epidemiol. Infect. 146 (13), 1612–1618. https://doi.org/10.1017/S0950268818001942.

Roulot, D., et al., 2020a. Origin, HDV genotype and persistent viremia determine outcome and treatment response in patients with chronic hepatitis delta. J. Hepatol. 73 (5), 1046–1062. https://doi.org/10.1016/J.JHEP.2020.06.038.

Roulot, D., et al., 2020b. Origin, HDV genotype and persistent viremia determine outcome and treatment response in patients with chronic hepatitis delta. J. Hepatol. 73 (5), 1046–1062. https://doi.org/10.1016/J.JHEP.2020.06.038.

Sakugawa, H., Yamashiro, T., Maeshiro, T., 2004. Hepatitis D and hepatitis E. Nihon Naika Gakkai Zasshi 93 (11), 2351–2356. https://doi.org/10.2169/naika.93.2351.

Sandmann, L., et al., 2024. Liver stiffness measurement as a noninvasive method for the diagnosis of liver cirrhosis in patients with chronic hepatitis D virus infection. Aliment. Pharmacol. Ther. 59 (6), 752–761. https://doi.org/10.1111/APT.17878.

Schirdewahn, T., et al., 2016. "The Journal of Infectious Diseases the Third Signal Cytokine Interleukin 12 rather than Immune Checkpoint Inhibitors Contributes to the Functional Restoration of Hepatitis D Virus-specific T Cells," https://doi.org/10.1093/infdis/jiw514.

Schweitzer, A., Horn, J., Mikolajczyk, R.T., Krause, G., Ott, J.J., 2015. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 386 (10003), 1546–1555. https://doi.org/10.1016/S0140-6736(15)61412-X.

seok Kim, H., et al., 2022. Comparative performance of risk prediction models for hepatitis B-related hepatocellular carcinoma in the United States. J. Hepatol. 76 (2), 294–301. https://doi.org/10.1016/J.JHEP.2021.09.009.

Sheena, B.S., et al., 2022. Global, regional, and national burden of hepatitis B, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. Gastroenterol. Hepatol. 7 (9), 796–829. https://doi.org/10.1016/S2468-1253(22)00124-8.

Shen, C., Jiang, X., Li, M., Luo, Y., 2023. Hepatitis virus and hepatocellular carcinoma: recent advances. Cancers 15 (2). https://doi.org/10.3390/CANCERS15020533.

Stern, C., et al., 2023. Safety and efficacy of REP 2139-Mg in association with TDF in chronic hepatitis delta patients with decompensated cirrhosis. J. Hepatol. 78, S1160. https://doi.org/10.1016/S0168-8278(23)03298-1.

Stockdale, A.J., et al., 2020a. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. J. Hepatol. 73 (3), 523–532. https://doi.org/10.1016/J.JHEP.2020.04.008.

Stockdale, A.J., et al., 2020b. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. J. Hepatol. 73 (3), 523–532. https://doi.org/10.1016/j.jhep.2020.04.008.

Stockdale, A.J., et al., 2020c. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. J. Hepatol. 73 (3), 523–532. https://doi.org/10.1016/J.JHEP.2020.04.008.

Su, C.W., et al., 2006. Genotypes and viremia of hepatitis B and D viruses are associated with outcomes of chronic hepatitis D patients. Gastroenterology 130 (6), 1625–1635. https://doi.org/10.1053/J.GASTRO.2006.01.035.

Sukowati, C.H.C., Jayanti, S., Turyadi, T., Muljono, D.H., Tiribelli, C., 2024. Hepatitis B virus genotypes in precision medicine of hepatitis B-related hepatocellular carcinoma: where we are now. World J. Gastrointest. Oncol. 16 (4), 1097–1103. https://doi.org/10.4251/WJGO.V16.I4.1097.

Terrault, N.A., et al., 2018. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67 (4), 1560–1599. https://doi.org/10.1002/HEP.29800.

Tong, S., Revill, P., 2016. Overview of hepatitis B viral replication and genetic variability. J. Hepatol. 64 (1 Suppl. l), S4–S16. https://doi.org/10.1016/J.JHEP.2016.01.027.

Trung, N.T., et al., 2020a. Clinical significance of combined circulating TERT promoter mutations and miR-122 expression for screening HBV-related hepatocellular carcinoma. Sci. Rep. 10 (1). https://doi.org/10.1038/S41598-020-65213-8.

Trung, N.T., et al., 2020b. Clinical significance of combined circulating TERT promoter mutations and miR-122 expression for screening HBV-related hepatocellular carcinoma. Sci. Rep. 10 (1). https://doi.org/10.1038/S41598-020-65213-8.

Trung, N.T., et al., 2020c. Clinical significance of combined circulating TERT promoter mutations and miR-122 expression for screening HBV-related hepatocellular carcinoma. Sci. Rep. 10 (1). https://doi.org/10.1038/S41598-020-65213-8.

Valery, P.C., Laversanne, M., Clark, P.J., Petrick, J.L., McGlynn, K.A., Bray, F., 2018. Projections of primary liver cancer to 2030 in 30 countries worldwide. Hepatology 67 (2), 600–611. https://doi.org/10.1002/HEP.29498.

Velkov, S., Ott, J.J., Protzer, U., Michler, T., 2018. The global hepatitis B virus genotype distribution approximated from available genotyping data. Genes 9 (10), 495. https://doi.org/10.3390/GENES9100495, 2018, Vol. 9, Page 495.

Venook, A.P., Papandreou, C., Furuse, J., Ladrón de Guevara, L., 2010. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. Oncol. 15 (S4), 5–13. https://doi.org/10.1634/THEONCOLOGIST.2010-S4-05.

Vitale, A., et al., 1985. Epidemiological Trends and Trajectories of MAFLD-Associated Hepatocellular Carcinoma 2002-2033: the ITA.LI.CA Database. https://doi.org/10.1136/gutjnl-2021-324915.

Voulgaris, T., Papatheodoridi, M., Lampertico, P., Papatheodoridis, G.V., 2020. Clinical utility of hepatocellular carcinoma risk scores in chronic hepatitis B. Liver Int. 40 (3), 484–495. https://doi.org/10.1111/LIV.14334.

Wedemeyer, H., et al., 2023a. Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial. Lancet Infect. Dis. 23 (1), 117–129. https://doi.org/10.1016/S1473-3099(22)00318-8.

Wedemeyer, H., et al., 2023b. A phase 3, randomized trial of bulevirtide in chronic hepatitis D. N. Engl. J. Med. 389 (1), 22–32. https://doi.org/10.1056/NEJMOA2213429.

Wedemeyer, H., et al., 2023c. Treatment with siRNA JNJ-73763989 plus nucleos (t)ide analogue (NA) decreases HBsAg and HDV RNA levels in patients with chronic hepatitis D (CHD): part 1 of the REEF-D study. J. Hepatol. 78, S34. https://doi.org/10.1016/S0168-8278(23)00487-7.

Wedemeyer, H., et al., 2024. Bulevirtide monotherapy in patients with chronic HDV: efficacy and safety results through week 96 from a phase 3 randomized trial. J. Hepatol. 0 (0). https://doi.org/10.1016/j.jhep.2024.05.001.

Wei, F., Zheng, Q., Li, M., Wu, M., 2017. The association between hepatitis B mutants and hepatocellular carcinoma. Medicine (United States) 96 (19). https://doi.org/10.1097/MD.0000000000006835.

Wild, C.P., Montesano, R., 2009. A model of interaction: aflatoxins and hepatitis viruses in liver cancer aetiology and prevention. Cancer Lett. 286 (1), 22–28. https://doi.org/10.1016/J.CANLET.2009.02.053.

Williams, V., et al., 2012a. Large hepatitis delta antigen activates STAT-3 and NF-κB via oxidative stress. J. Viral Hepat. 19 (10), 744–753. https://doi.org/10.1111/J.1365-2893.2012.01597.X.

Williams, V., et al., 2012b. Large hepatitis delta antigen activates STAT-3 and NF-κB via oxidative stress. J. Viral Hepat. 19 (10), 744–753. https://doi.org/10.1111/J.1365-2893.2012.01597.X.

Wu, C.Y., et al., 2014. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. Gastroenterology 147 (1). https://doi.org/10.1053/J.GASTRO.2014.03.048.

Yang, H.I., et al., 2008. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. J. Natl. Cancer Inst. 100 (16), 1134–1143. https://doi.org/10.1093/JNCI/DJN243.

Yu, Z., et al., 2021. “Microarray Data Mining and Preliminary Bioinformatics Analysis of Hepatitis D Virus-Associated Hepatocellular Carcinoma,” https://doi.org/10.1155/2021/1093702.

Yuan, X., Larsson, C., Xu, D., 2019. Mechanisms underlying the activation of TERT transcription and telomerase activity in human cancer: old actors and new players. Oncogene 38 (34), 6172–6183. https://doi.org/10.1038/S41388-019-0872-9.

Zhang, Z., Urban, S., 2020. Interplay between hepatitis D virus and the interferon response. Viruses 12 (11). https://doi.org/10.3390/V12111334.

Zhang, B., Han, S., Feng, B., Chu, X., Chen, L., Wang, R., 2017. Hepatitis B virus X protein-mediated non-coding RNA aberrations in the development of human hepatocellular carcinoma. Exp. Mol. Med. 49 (2). https://doi.org/10.1038/EMM.2016.177.

Zhang, Y., et al., 2018. “ CD8 + T-cell response-associated evolution of hepatitis B virus core protein and disease progress ,”. J. Virol. 92 (17). https://doi.org/10.1128/JVI.02120-17.

Zhang, Y., et al., 2021. C-terminal truncated HBx initiates hepatocarcinogenesis by downregulating TXNIP and reprogramming glucose metabolism. Oncogene 40 (6), 1147–1161. https://doi.org/10.1038/S41388-020-01593-5.

Zöllner, C., Hofmann, J., Lutz, K., Tacke, F., Demir, M., 2022. Real-life experiences with bulevirtide for the treatment of hepatitis delta—48 weeks data from a German centre. Liver Int. 42 (11), 2403–2407. https://doi.org/10.1111/LIV.15408.

Hepatitis B.” Accessed: September. 1, 2024. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.