HBV Integration and Its Implications for Chronic Hepatitis B: A Survey

Abstract

The integration of hepatitis B virus (HBV) DNA into the host genome is a critical factor in the pathogenesis of chronic hepatitis B (CHB) and its progression to hepatocellular carcinoma (HCC). This survey paper explores the multifaceted role of HBV integration, highlighting its contribution to genomic instability, immune evasion, and oncogenesis. The persistence of integrated HBV DNA complicates therapeutic strategies, as current antiviral therapies are insufficient in eradicating it, limiting the efficacy of achieving a functional cure. The survey emphasizes the need for innovative therapeutic approaches, including targeted antiviral therapies and immune modulation, to mitigate the impact of HBV integration. Advances in machine learning and genomic profiling offer promising avenues for early detection and personalized treatment strategies. The paper underscores the importance of comprehensive surveillance and targeted interventions, particularly in high-prevalence regions, to reduce the global burden of HBV-related liver diseases. Continued research into the mechanisms of HBV integration and its clinical implications is essential for improving patient outcomes and developing effective therapeutic interventions. The integration of artificial intelligence and novel biomarkers into clinical practice holds potential for enhancing the precision of diagnosis and treatment, addressing the challenges posed by HBV-related liver diseases.

1 Introduction

1.1 Significance of HBV Integration

The integration of hepatitis B virus (HBV) DNA into the host genome is crucial in the pathogenesis of chronic hepatitis B (CHB), influencing disease progression and therapeutic strategies. This integration is not incidental; it plays a fundamental role in the early stages of CHB, occurring almost immediately post-infection [1]. It is linked to continuous production of hepatitis B surface antigen (HBsAg), which is vital for viral persistence and serves as a key marker for treatment endpoints aimed at enhancing clinical outcomes [2].

Furthermore, HBV integration significantly contributes to hepatocarcinogenesis by inducing genetic alterations that promote oncogenic processes [3]. The integrated viral DNA can induce chromosomal instability and activate oncogenes, increasing the risk of hepatocellular carcinoma (HCC) [4]. CHB itself is an independent risk factor for HCC initiation, even in the absence of cirrhosis, underscoring the oncogenic potential of HBV integration [5]. Given the global health threat posed by liver cancer, particularly in high-incidence regions such as China, understanding the mechanisms by which HBV integration influences cancer development is imperative [6].

The global burden of liver cancer, especially in areas with high chronic hepatitis B prevalence, necessitates region-specific prevention and control strategies [7]. By elucidating the role of HBV integration in CHB pathogenesis and its implications for liver cancer, research can inform clinical practices and therapeutic approaches aimed at mitigating the impact of this persistent viral infection.

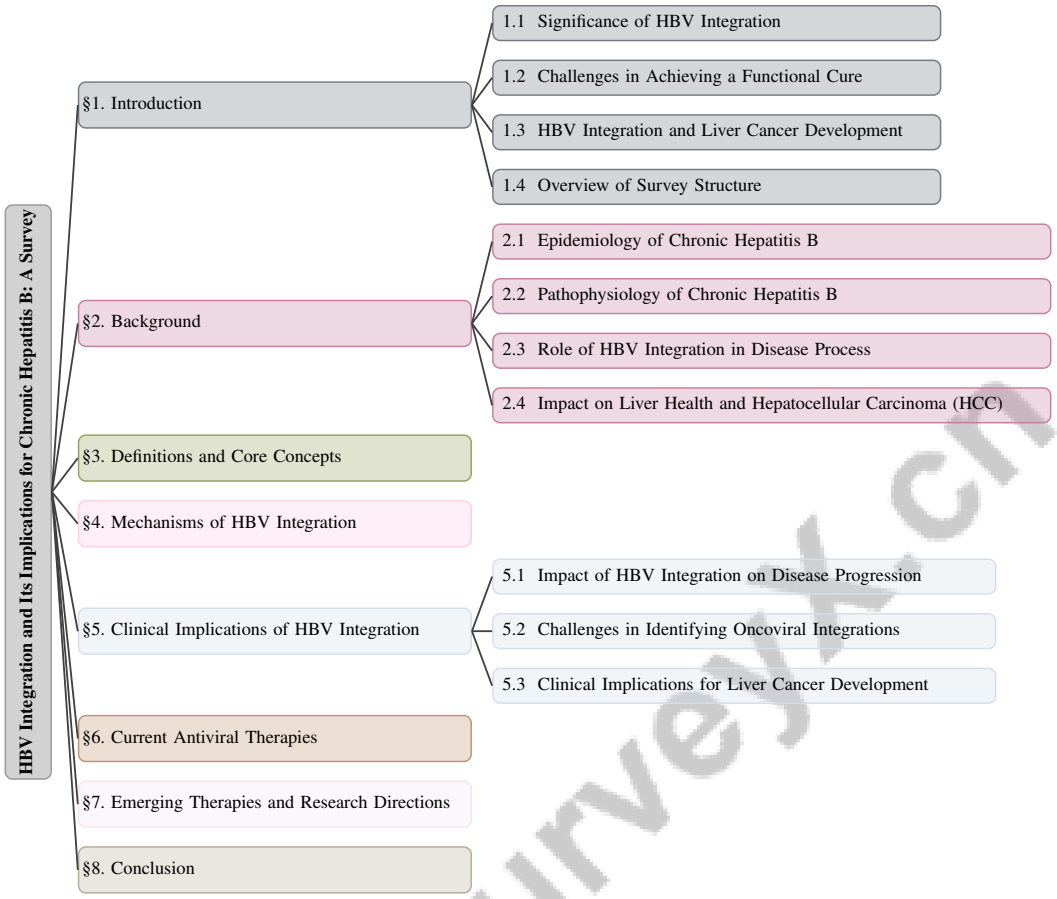

Figure 1: chapter structure

Thus, HBV integration serves as both a marker of disease severity and a target for future therapeutic interventions aimed at reducing HCC incidence and improving patient outcomes.

1.2 Challenges in Achieving a Functional Cure

Achieving a functional cure for chronic hepatitis B (CHB) is hindered by multiple complex challenges, primarily due to the persistence of integrated HBV DNA and its significant impact on the host immune response. This integration acts as a template for ongoing viral replication and contributes to oncogenesis, limiting the efficacy of existing antiviral therapies, which fail to eradicate integrated viral DNA. The low rate of spontaneous HBsAg loss, with current antiviral therapies achieving less than 1% annual HBsAg loss in patients, highlights the limited effectiveness of these treatments [2].

The interplay between immune cells during HBV infection is intricate, often resulting in immune tolerance and subsequent liver damage, complicating therapeutic strategies [4]. Dysfunction and hyperactivation of HBsAg-specific B cells, which do not mature into antibody-secreting cells due to the presence of serum HBsAg, represent significant challenges in overcoming immune tolerance [8]. This immune evasion mechanism is a critical barrier to achieving a functional cure.

Moreover, the initial integration sites of HBV and their implications for oncogenesis remain inadequately characterized, hindering the development of targeted therapeutic interventions [1]. Current methodologies primarily rely on classical statistical analyses, which inadequately capture the complex interplay of risk factors influencing liver cancer development [6]. This limitation reflects broader challenges in accurately identifying and prioritizing key genes and pathways essential for developing effective therapies for hepatocellular carcinoma (HCC).

The complexities associated with chronic HBV infection, including the significant risk of HBV reactivation and persistent immune tolerance challenges, underscore the urgent need for innovative

therapeutic strategies. These may include advanced immunotherapies and direct-acting antivirals that aim to control viral replication while restoring effective host immune responses, addressing the underlying immune dysfunction contributing to HBV-related HCC progression [4, 9, 10]. Addressing these obstacles is crucial for advancing towards a functional cure for chronic hepatitis B, necessitating a deeper understanding of the underlying mechanisms and the development of more effective therapeutic approaches.

1.3 HBV Integration and Liver Cancer Development

The integration of hepatitis B virus (HBV) DNA into the host genome is a critical event in the pathogenesis of liver cancer, particularly hepatocellular carcinoma (HCC). This process induces structural genomic alterations, such as chromosomal fusions and deletions, contributing to oncogenesis in HCC. Integrated HBV DNA, while characteristic of chronic hepatitis B infection, exacerbates liver damage and accelerates HCC progression [11]. Understanding the initial sites of HBV integration and their kinetic profiles is essential for comprehending viral persistence and HCC onset [1].

Liver cancer is among the most prevalent malignancies globally, with a particularly high burden in China, accounting for over half of the global incidence and mortality rates [12]. The disease is often diagnosed at advanced stages due to the limited sensitivity and specificity of current surveillance methods, highlighting the need for improved early detection strategies [13]. The five-year survival rate for liver cancer remains low, emphasizing the urgency for effective screening and diagnostic approaches [13].

The role of HBV integration in modulating viral replication and promoting HCC development is multifaceted, involving disruption of host genomic integrity and activation of oncogenic pathways [14]. Addressing the challenge of eliminating integrated HBV DNA is vital for preventing viral reactivation and subsequent HCC onset [15]. Machine learning approaches, such as LCPM, have shown promise in predicting liver cancer occurrence by analyzing critical risk factors, offering potential avenues for early intervention and prevention [6]. Understanding the mechanisms and timing of HBV integration is crucial for developing targeted therapeutic interventions aimed at mitigating the oncogenic potential of HBV integration and improving patient outcomes.

1.4 Overview of Survey Structure

This survey meticulously explores the multifaceted role of hepatitis B virus (HBV) integration in chronic hepatitis B (CHB) and its implications for liver health, particularly hepatocellular carcinoma (HCC). The paper is structured to provide a comprehensive understanding of HBV integration, beginning with an introduction that highlights its significance in CHB pathogenesis and the associated challenges in achieving a functional cure. This is followed by an in-depth background section outlining the epidemiology and pathophysiology of CHB, emphasizing the role of HBV integration in disease progression and its impact on liver health, including HCC development.

Subsequent sections define key terminology and elucidate core concepts related to viral integration, alongside identifying biomarkers relevant to hepatitis B and liver cancer. The survey delves into the molecular mechanisms of HBV integration, detailing pathways involved and factors influencing integration frequency and sites, supported by insights from mutational landscape analyses.

The clinical implications of HBV integration are examined, focusing on its effect on disease progression, challenges in identifying oncogenic integrations, and its contribution to liver cancer development. The review provides a comprehensive analysis of contemporary antiviral therapies, evaluating their effectiveness and inherent limitations while emphasizing recent advancements in monitoring therapeutic responses. It discusses the approval of 96 antivirals by the FDA from 1987 to 2019, notably for HIV treatments, highlighting the urgent need for new antiviral agents due to the emergence of resistant viral strains. Additionally, the review explores innovative therapeutic strategies, such as nanotechnologies and monoclonal antibodies, aimed at enhancing treatment efficacy and addressing the challenges posed by viral infections, including the critical need for improved monitoring techniques to optimize patient outcomes [9, 2, 16, 17, 18].

The survey concludes by exploring emerging therapies and research directions, including targeted antiviral therapies, immune modulation, and innovative platforms for studying HBV integration. This structured approach aims to provide a comprehensive analysis of HBV integration's role in chronic

hepatitis B (CHB), elucidating its significance in the progression of liver diseases, including cirrhosis and HCC, while exploring its implications for disease management and guiding future research directions in understanding viral persistence and therapeutic interventions [19, 11, 7, 20, 14].The following sections are organized as shown in Figure 1.

2 Background

2.1 Epidemiology of Chronic Hepatitis B

Chronic hepatitis B (CHB) remains a critical global health issue, with prevalence rates surpassing 8% in regions like sub-Saharan Africa and East Asia. These areas house the majority of the 296 million people living with CHB, significantly influencing hepatocellular carcinoma (HCC) incidence [21, 22]. HBV transmission varies geographically: vertical transmission is common in endemic regions, while in areas like North America and Western Europe, infections are often acquired in adulthood through sexual contact or intravenous drug use [23]. This geographic variation affects age distribution and HCC risk, a major complication of chronic HBV infection. Rising HCC incidence and mortality, especially in developing countries, highlight the urgent need for effective CHB management and prevention [23]. For example, Egypt's increasing HCC incidence reflects global trends and underscores HBV's role as a liver cancer risk factor [24]. Data from China's Ningbo Health Commission show a significant liver cancer burden, with 184 positive cases among 55,891 samples, emphasizing CHB's public health impact in high-prevalence areas [6]. Globally, liver cancer mortality is high, influenced by CHB prevalence and factors like hepatitis C virus (HCV) infection and aflatoxin exposure [22]. These trends necessitate comprehensive surveillance and targeted interventions to alleviate CHB and its complications, including liver cancer. Addressing global CHB disparities and improving access to vaccination, early diagnosis, and antiviral therapy are essential public health strategies.

2.2 Pathophysiology of Chronic Hepatitis B

CHB involves a complex interplay of viral and host factors affecting disease progression and liver health. Persistent HBV infection leads to viral DNA integration into the host genome, resulting in continuous viral replication and antigen production, crucial for immune evasion and establishing a viral reservoir [25]. The presence of hepatitis B surface antigen (HBsAg) in the bloodstream is a key biomarker for disease activity and therapeutic endpoints [6]. Persistent viral antigen expression fosters immune tolerance, where the host immune system fails to eliminate the virus, exacerbated by dysfunctional HBsAg-specific B cells that cannot mature into antibody-secreting cells [25]. Disease progression is also influenced by host genetic predisposition and environmental factors, which can exacerbate liver damage and elevate HCC risk. HBV DNA integration induces chromosomal instability and activates oncogenic pathways, facilitating HCC development [6]. Machine learning approaches, such as the Liver Cancer Prediction Model (LCPM), analyze critical risk factors and enhance biomarker detection for HCC, focusing on risk prediction, diagnosis, staging, and treatment response [6, 25]. Understanding CHB pathophysiology and disease progression mechanisms is vital for developing targeted therapeutic interventions and improving patient outcomes.

2.3 Role of HBV Integration in Disease Process

HBV integration into the host genome is pivotal in CHB progression and its complications. While integration represents a replicative dead-end for the virus, it induces significant structural genomic changes that complicate therapeutic efforts. Persistent infection, characterized by immune tolerance and covalently closed circular DNA (cccDNA) presence in hepatocyte nuclei, serves as a template for continuous viral replication and antigen production [10]. Integration is linked to chromosomal instability and oncogenic pathway activation, crucial in liver disease pathogenesis, particularly HCC [3]. The frequency of integration events increases with disease progression, indicating a direct correlation between HBV integration and disease advancement [1]. This correlation underscores HBV integration's role in promoting viral persistence and immune evasion, as integrated viral DNA continuously produces proteins that modulate the host immune response, affecting both global and HBsAg-specific humoral immunity [8]. HBV integration is associated with host gene deregulation and genetic instability, exacerbating liver damage and fostering a cancer-conducive environment [3]. Integrated viral sequences act as mutagens, disrupting cellular functions and promoting oncogenic

transformation, contributing to high liver cancer incidence in CHB individuals [23]. Studying HBV integration poses challenges, including distinguishing between viral sequences contributing to cancer and accurately detecting low HBsAg levels in occult hepatitis B infection (OBI) [2]. Advanced detection methods and in vitro models are necessary to elucidate HBV integration's complex role in disease pathogenesis [1]. HBV integration is crucial in CHB progression by inducing genetic alterations that promote viral persistence, immune evasion, and oncogenesis. Understanding HBV integration's molecular mechanisms into the host genome is essential for developing targeted therapeutic strategies to mitigate its detrimental effects on liver health, potentially leading to conditions like liver cirrhosis and HCC. Recent studies indicate that HBV integration occurs early in infection, preferentially in regions associated with active gene expression and chromatin accessibility, correlating with disease progression. Elucidating these mechanisms can better address HBV-related liver disease challenges and improve patient outcomes [5, 19, 11, 7, 14].

2.4 Impact on Liver Health and Hepatocellular Carcinoma (HCC)

HBV integration into the host genome significantly impacts liver health and is critical in HCC pathogenesis. The integration process induces genetic alterations that disrupt hepatocyte function and promote oncogenic processes contributing to HCC development [3]. This is particularly concerning in high-prevalence regions like China, where HCC incidence and mortality rates are alarmingly high [21]. The immune responses involved in HBV infection play a vital role in liver health, influencing HCC progression. The immune system's inability to effectively clear HBV results in chronic inflammation and liver damage, precursors to carcinogenesis [4]. The persistent presence of HBV DNA, significantly contributing to HBsAg transcripts, exacerbates this risk by continuously modulating immune responses and promoting oncogenic pathways [3]. Computational pathology, leveraging deep learning techniques, has emerged as a vital tool for improving liver tumor detection and characterization [13]. Despite advancements in imaging and computational methods, late HCC diagnosis remains a significant challenge, contributing to its status as a leading cause of cancer-related mortality worldwide [26]. Innovative approaches, such as Pathways of Distinction Analysis (PoDA), have uncovered critical genomic differences in liver cancer that could inform future therapeutic strategies [27]. Epidemiological data suggest that countries with higher Human Development Index (HDI) and Gross Domestic Product (GDP) per capita exhibit lower liver cancer incidence and mortality rates, highlighting the role of socioeconomic factors in disease prevalence and outcomes [21]. Current prevention and treatment strategies, while somewhat effective, are inadequate to address the global burden of HBV-related liver diseases, underscoring the need for enhanced surveillance and innovative therapeutic interventions [22]. Understanding how HBV integration affects liver health and contributes to HCC development is crucial for advancing therapeutic interventions. Ongoing research into the genetic and immunological mechanisms underlying HBV integration is essential for improving patient outcomes and addressing the global health crisis associated with HBV-related liver diseases, including cirrhosis and HCC. Insights into the patterns and timing of HBV DNA integration into the host genome and its impact on immune response and tumorigenesis will provide valuable information for developing targeted therapies and improving prognostic strategies for affected individuals [11, 19, 7].

In the context of chronic hepatitis B and liver cancer management, it is crucial to understand the interconnectedness of various concepts that underpin the field. Figure 2 illustrates the hierarchical structure of key concepts related to this area, categorizing essential terminology and biomarkers into primary categories and subcategories. This figure not only highlights the immune response and disease management strategies but also emphasizes the role of HBV DNA integration and the significance of both established and emerging biomarkers. Such a comprehensive framework is vital for advancing clinical practice and improving patient outcomes, thereby providing a clearer understanding of the complexities involved in managing these conditions.

3 Definitions and Core Concepts

3.1 Key Terminology in Chronic Hepatitis B

Understanding chronic hepatitis B (CHB) requires familiarity with essential terms related to its pathogenesis and progression. Hepatitis B virus (HBV) integration into the host genome complicates immune responses and disease management. The immune response in CHB is primarily mediated by

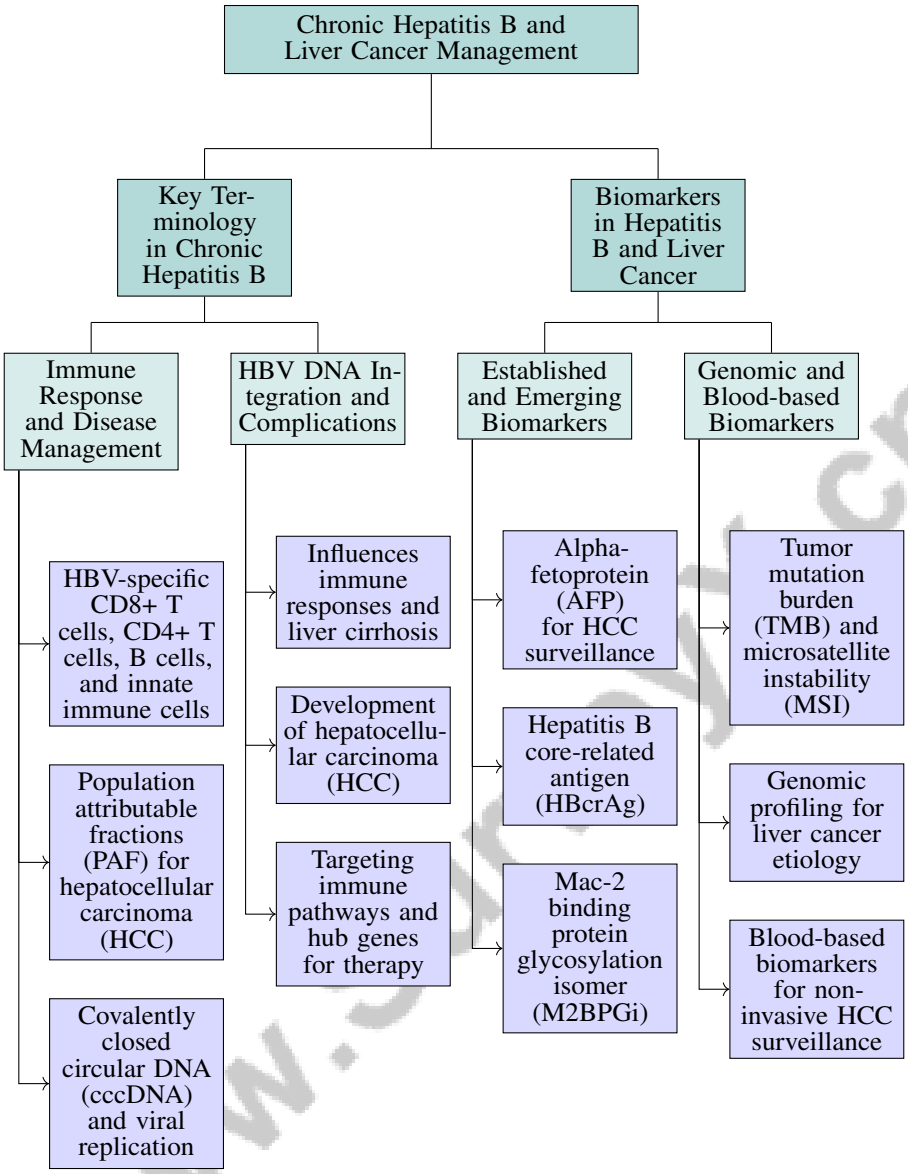

Figure 2: This figure illustrates the hierarchical structure of key concepts related to chronic hepatitis B and liver cancer management, categorizing essential terminology and biomarkers into primary categories and subcategories. It highlights the immune response and disease management strategies, the role of HBV DNA integration, and the significance of established and emerging biomarkers in advancing clinical practice and improving patient outcomes.

HBV-specific CD8+ T cells, CD4+ T cells, B cells, and innate immune cells, crucial for controlling and clearing HBV infection [4]. Population attributable fractions (PAF) estimate the proportion of hepatocellular carcinoma (HCC) cases attributable to major risk factors, including hepatitis B and C infections, alcohol consumption, tobacco use, obesity, and diabetes, providing insights into the global burden of CHB and informing public health strategies [28].

Covalently closed circular DNA (cccDNA) is a stable form of HBV DNA in infected hepatocytes, serving as a template for viral replication and posing a challenge to achieving a functional cure for CHB. The persistence of cccDNA facilitates continuous production of viral antigens, such as hepatitis B surface antigen (HBsAg), contributing to immune tolerance and serving as a significant biomarker for monitoring disease progression and treatment efficacy. Integrated HBV DNA, commonly found

in infected patients' livers, influences immune responses and the development of complications like liver cirrhosis and HCC [11, 10].

The interplay between chronic HBV infection and the host immune system is pivotal in understanding HCC development. Chronic HBV infection triggers a complex immune response characterized by fluctuations in immune tolerance and activation, contributing to liver inflammation and cellular regeneration—key factors in HCC development. HBV DNA integration and resulting immune dysregulation complicate CHB management and HCC prevention. Recent research emphasizes targeting specific immune pathways and hub genes to enhance therapeutic strategies aimed at improving patient outcomes in HBV-related liver diseases [4, 11, 5]. Familiarity with these concepts is essential for researchers and clinicians developing effective therapeutic interventions and public health policies to mitigate CHB's impact.

3.2 Biomarkers in Hepatitis B and Liver Cancer

Biomarkers are crucial for the early diagnosis and management of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) infection [25]. They serve as essential tools in liver cancer surveillance and therapeutic monitoring, providing insights into disease progression and treatment efficacy. Alpha-fetoprotein (AFP) is widely utilized for HCC surveillance, with a sensitivity of 82.6% and specificity of 71.2% in certain populations, such as the Indonesian cohort [29]. However, reliance on AFP alone is insufficient, necessitating novel biomarkers to enhance diagnostic accuracy.

Emerging biomarkers like hepatitis B core-related antigen (HBcrAg) and Mac-2 binding protein glycosylation isomer (M2BPGi) show promise in managing CHB by offering insights into viral replication and liver fibrosis, aiding comprehensive disease assessment [30]. Integrating these biomarkers into clinical practice could improve patient stratification at risk for HCC and guide therapeutic decisions.

Genomic alterations also serve as critical indicators of liver cancer risk. Tumor mutation burden (TMB), microsatellite instability (MSI), and alterations in DNA damage response genes are associated with liver cancer and hepatitis B, presenting potential predictive biomarkers for disease progression and therapeutic response [31]. Recent studies propose distinct mutational signatures, highlighting the importance of genomic profiling in understanding liver cancer etiology and its association with specific risk factors [32].

Blood-based biomarkers are gaining attention for their non-invasive nature and potential utility in HCC surveillance. These emerging biomarkers require rigorous validation to confirm clinical applicability and reliability across diverse populations [33]. Ongoing research into these novel biomarkers underscores the dynamic landscape of liver cancer diagnostics and the continuous effort to improve early detection and patient outcomes.

Integrating diverse biomarkers—encompassing protein, genomic, and blood-based indicators—is essential for advancing hepatitis B and liver cancer management. By enhancing diagnostic and prognostic tool accuracy, these biomarkers can significantly improve clinical practice and patient outcomes for those suffering from chronic hepatitis B and related liver cancers. Recent advancements in artificial intelligence (AI) facilitate the identification and implementation of effective biomarkers crucial for early detection and management of HCC, a leading cause of cancer-related mortality. Biomarkers such as HBcrAg and others are explored for their predictive capabilities regarding HCC occurrence and recurrence, while novel serum markers aim to enhance diagnostic sensitivity and specificity, ultimately providing a more personalized treatment approach to improve survival rates and quality of life for patients at risk of liver malignancies [30, 5, 26, 34, 25].

4 Mechanisms of HBV Integration

4.1 Molecular Pathways of HBV Integration

The integration of hepatitis B virus (HBV) DNA into the host genome is a crucial mechanism contributing to the progression from chronic hepatitis B (CHB) to severe liver diseases, including hepatocellular carcinoma (HCC). This process involves the insertion of HBV DNA into active chromatin regions, resulting in genomic alterations that promote oncogenesis [1, 7]. Such integration leads to chromosomal instability and the activation of oncogenic pathways through structural changes

like non-homologous interchromosomal rearrangements [35]. These disruptions can deregulate host genes, facilitating malignant transformation, as outlined in theoretical frameworks linking HBV integration with hepatitis B surface antigen (HBsAg) expression [3].

Advanced sequencing techniques have revealed preferential HBV integration patterns involving oncogenes and tumor suppressor genes [19]. Tools like VIcaller aid in analyzing viral sequences and integration events, identifying fusion transcripts and genomic alterations [16]. Innovative approaches, including CRISPR-Cas9 technology, are being explored to excise integrated HBV DNA and target the covalently closed circular DNA (cccDNA) reservoir, offering potential therapeutic strategies [15]. Understanding these molecular pathways is vital for developing interventions to prevent CHB progression to severe liver diseases. Techniques like Marker-Controlled Watershed Segmentation (MCWS) enhance liver tumor detection, further elucidating HBV-related oncogenesis [36].

4.2 Factors Influencing Integration Frequency and Sites

The frequency and specific sites of HBV integration into the host genome are influenced by factors critical to understanding CHB pathogenesis and progression to liver diseases like HCC. Early integration events are associated with chromatin characteristics such as accessibility and replication timing, highlighting the non-random nature of HBV integration [7]. These events favor regions of active transcription and chromatin accessibility, enhancing the virus's oncogenic potential [16, 7, 37].

Host genomic landscape impacts the frequency and specific sites of viral integration. Repetitive sequences and fragile sites create environments conducive to HBV integration, leading to genomic instability and potential oncogenic pathway activation [27, 3]. The host's cellular environment, including DNA repair mechanisms and transcriptionally active regions, further modulates the integration process. Advanced computational methods like MCWS improve the detection and segmentation of liver tumors, providing insights into the spatial distribution of HBV integration sites [36]. Understanding these factors is vital for developing targeted therapeutic interventions to mitigate the adverse effects of HBV integration on liver health [11, 19, 7].

4.3 Insights from Mutational Landscape Analysis

Mutational landscape analysis offers critical insights into HBV integration and its role in liver disease pathogenesis, particularly HCC. By examining comprehensive mutational profiles, researchers identify distinct mutational signatures associated with specific risk factors, enhancing the understanding of molecular mechanisms driving oncogenesis [32]. Advanced strategies, including deep learning approaches, facilitate the retention of comprehensive mutational data, enabling thorough exploration of the mutational landscape [38].

The integration of HBV DNA into the host genome correlates with distinct mutational profiles indicative of genomic instability and oncogenic pathway activation. HBV integration preferentially occurs in regions of open chromatin associated with high gene expression and early replication timing [19, 7]. This integration is linked to increased HBV load and enriches cancer-related pathways, contributing to poorer disease-free and overall survival rates [3]. Identifying these profiles through mutational landscape analysis informs the development of targeted therapeutic strategies aimed at mitigating the oncogenic potential of HBV integration. Understanding these landscapes is essential for advancing CHB management and reducing HBV-related liver cancer incidence.

5 Clinical Implications of HBV Integration

The integration of hepatitis B virus (HBV) into the host genome significantly impacts the pathogenesis and progression of liver diseases, especially hepatocellular carcinoma (HCC). This process enhances viral persistence, disrupts cellular functions, and promotes liver cirrhosis and HCC by facilitating replication-independent viral antigen expression, thereby evading the immune system and promoting tumorigenesis [20, 14]. Understanding these implications is crucial for developing effective surveillance and therapeutic strategies, particularly in elucidating the transition from chronic hepatitis B to HCC.

5.1 Impact of HBV Integration on Disease Progression

HBV integration is pivotal in the progression from chronic hepatitis B (CHB) to HCC. It exacerbates genomic instability and disrupts tumor suppressor genes, accelerating oncogenesis through chromosomal rearrangements and deletions [3, 34]. Integrated HBV DNA sustains viral persistence by continuously producing viral antigens, especially hepatitis B surface antigen (HBsAg), which serves as a marker for treatment monitoring and predicts treatment outcomes [34]. This persistent expression modulates the host immune response, inducing immune tolerance and facilitating chronic infection, thus increasing the risk of liver disease progression [3].

Advancements in diagnostic assays and novel biomarkers have improved early HCC detection, enhancing patient outcomes [26]. Models like the Liver Cancer Prediction Model (LCPM) provide insights into risk factor contributions, enabling targeted interventions for liver cancer prevention [6]. Innovative therapeutic approaches, including immunotherapy and novel antiviral agents, show potential in restoring immune responses and addressing HBV integration complexities that contribute to disease progression and liver cancer development [9, 2, 11, 7, 10]. Coupled with adherence to HCC surveillance protocols, these strategies are essential for improving early detection rates and treatment efficacy.

5.2 Challenges in Identifying Oncoviral Integrations

Identifying oncoviral integrations contributing to HCC development is challenging due to CHB complexity and diverse liver conditions. Major obstacles include the lack of reliable blood biomarkers for early HCC detection and the invasive nature of liver biopsies, limiting comprehensive genomic data collection from large CHB cohorts. Variability in HBsAg levels, influenced by genetic differences among HBV strains and host immune responses, complicates result interpretation and oncogenic integration identification [34].

The heterogeneity of HCC and underlying liver conditions complicates patient stratification and targeted therapy development. Variability in immune responses among HCC patients further complicates predictive biomarker identification for immune checkpoint inhibitor responses, necessitating comprehensive genomic profiling and advanced computational approaches [26]. Logistical barriers to surveillance and limited disease awareness hinder effective monitoring and early detection of HBV-related liver malignancies.

Innovative computational methods, such as Marker-Controlled Watershed Segmentation (MCWS), enhance liver tumor detection but face challenges in accurately identifying small tumors and managing poor-quality images, hindering precise classification and understanding of the mutational landscape [26]. The unstructured nature of radiology reports complicates the extraction of necessary information for machine learning algorithms to classify tumor subtypes and identify critical integration events.

Addressing these challenges is crucial for improving oncoviral integration identification and enhancing patient outcomes in chronic HBV management and associated liver cancers. As liver disease epidemiology evolves due to conditions like non-alcoholic fatty liver disease and alcohol-associated liver disease, comprehensive surveillance strategies must address barriers to early detection, including limited disease awareness and the unique characteristics of at-risk populations, such as those without cirrhosis. Enhanced surveillance methods, integrating advanced imaging techniques and biomarkers, along with educational initiatives, are essential for improving early detection rates and reducing liver disease-related mortality [39, 6, 33, 25].

5.3 Clinical Implications for Liver Cancer Development

HBV integration into the host genome is critical in HCC pathogenesis, significantly influencing its onset and progression by inducing genomic instability and activating oncogenic pathways, particularly in early HBV infection stages where integration events occur in transformation-susceptible regions [7]. The specific gene alterations associated with HBV integration highlight its complex role in liver cancer development [14].

Comprehensive surveillance and management strategies are essential for HCC development in CHB contexts. Research advances have elucidated immune mechanisms in HCC, leading to new therapeutic strategies that leverage immune modulation to enhance patient outcomes [40]. Restoring immune balance, especially of HBV-specific T cells, is crucial for preventing HCC in chronic HBV patients

[4], emphasizing the importance of immune-based interventions in managing HBV-related liver malignancies.

Combining biomarkers such as alpha-fetoprotein (AFP), AFP-L3, and PIVKA II significantly enhances early HCC detection rates, indicating promising advancements in diagnostic accuracy [41]. Integrating these biomarkers into clinical practice could improve patient stratification for HCC risk and guide therapeutic decisions. Advanced computational frameworks like LDCSF for classifying histopathological images demonstrate superior performance in liver cancer diagnosis, providing robust tools for enhancing early detection and treatment strategies [13].

Emerging therapeutic approaches, such as CRISPR-Cas9 technology, show potential in eradicating HBV infection by targeting integrated viral DNA, thereby mitigating its oncogenic potential [15]. These innovative strategies underscore the need for personalized treatment approaches that consider individual genetic and metabolic profiles [42]. The decline in liver cancer incidence and mortality rates in regions like China, particularly among younger populations, highlights the effectiveness of targeted prevention strategies [12].

Despite advancements, challenges persist in early detection and management of HBV-related HCC. The weak association between tumor mutation burden and response to PD-1 inhibitors indicates a need for future research into alternative predictive biomarkers [31]. Developing natural language processing pipelines for liver cancer prediction shows promise for clinical text applications and disease prediction tasks, offering avenues for improving surveillance and early intervention [43].

The proposed method significantly enhances liver cancer patient classification into risk groups compared to traditional methods, validating the effectiveness of data expansion and compression techniques [44]. Identifying critical risk factors based on contribution scores in decision-making provides insights beyond classical statistical methods, aiding targeted intervention development [6].

A comprehensive understanding of the clinical implications of HBV integration in liver cancer progression is essential for developing targeted therapeutic strategies, as it reveals mechanisms by which HBV integration contributes to genetic instability, clonal selection, and immune evasion, ultimately enhancing patient outcomes in HBV-related liver diseases [11, 7]. Continued research into the genetic and immunological underpinnings of HBV integration will be critical in addressing the global challenge posed by HBV-related liver diseases.

6 Current Antiviral Therapies

6.1 Overview of Current Antiviral Agents

Chronic hepatitis B (CHB) management predominantly relies on antiviral therapies aimed at suppressing viral replication and slowing disease progression. Nucleos(t)ide analogs (NAs) such as entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide are preferred due to their strong antiviral efficacy and favorable safety profiles, inhibiting the conversion of viral RNA into DNA, thus reducing viral load and liver damage [17]. Emerging strategies, including nanotechnology-based delivery systems, promise enhanced drug bioavailability and targeted tissue delivery, optimizing therapeutic outcomes [17]. Additionally, monoclonal antibodies targeting viral antigens offer innovative therapeutic and prophylactic potential for CHB management [17].

The CRISPR-Cas system represents a groundbreaking advancement in antiviral therapy, enabling precise targeting and removal of integrated HBV DNA from the host genome, addressing a core challenge in CHB treatment by eliminating a persistent replication and antigen source [17]. Combining CRISPR-Cas with existing antiviral agents could potentially achieve a functional cure for hepatitis B. Integrating these novel therapies into clinical practice requires rigorous clinical trials to evaluate safety, efficacy, and long-term outcomes, particularly regarding HBV infection and associated liver diseases. A thorough understanding of HBV DNA integration and immune responses is essential for formulating effective treatment strategies [11, 43, 25, 18]. Continued advancements in antiviral therapy development hold significant promise for improving CHB management and reducing the global burden of this chronic infection.

6.2 Efficacy and Limitations of Current Therapies

Current antiviral therapies for CHB are evaluated based on their ability to suppress viral replication and prevent disease progression. Nucleos(t)ide analogs like tenofovir and entecavir have demonstrated superior viral suppression and safety compared to older treatments, effectively reducing HBV DNA levels and improving liver histology [45, 18]. However, genetic variability and the emergence of drug-resistant HBV strains pose challenges to long-term treatment success [17]. This genetic diversity necessitates personalized therapeutic approaches to optimize patient outcomes, highlighting the need for new drug development to broaden therapeutic options and address resistance issues [17].

Quantitative assessment of treatment efficacy often involves costly or scarce standard substances in calibration procedures [46]. This underscores the need for innovative quantitative methods to accurately evaluate therapeutic effectiveness and guide clinical decision-making. Despite these challenges, ongoing advancements in antiviral therapies and the integration of novel strategies offer hope for improved CHB management. Continued research and clinical trials are crucial to overcoming existing therapy limitations, especially for persistent infections like HBV and HCV. Current treatments often require lifelong administration due to the risk of viral rebound upon cessation, and the emergence of resistant strains emphasizes the urgent need for innovative therapeutic strategies. Exploring new antiviral agents, including small interfering RNA (siRNA) and core assembly modulators (CAMs), alongside immunomodulatory therapies, may significantly enhance patient outcomes by potentially achieving functional cures, as evidenced by the limited rates of hepatitis B surface antigen (HBsAg) loss with current therapies [9, 2, 16, 17, 18].

6.3 Advancements in Antiviral Therapy Monitoring

Recent advancements in monitoring antiviral therapy for CHB have significantly improved treatment outcome assessments and therapeutic strategy optimization. Traditional methods focus on quantifying HBV DNA levels and HBsAg titers to evaluate antiviral efficacy. However, variability in viral replication and antigen expression presents challenges, necessitating more precise and reliable monitoring techniques. This need is underscored by the complex interplay of viral factors in oncogenesis, as recent studies highlight the diverse roles of oncoviruses in cancer etiology and the importance of accurately quantifying viral antigens to inform treatment strategies and predict disease outcomes [16, 34, 46, 37].

Innovative quantitative methods have emerged, offering enhanced accuracy in assessing antiviral therapy effectiveness without reliance on standard substances. The framework proposed by Gan et al. facilitates practical quantitative analysis validated through experimental studies [46]. This approach enables accurate measurement of treatment efficacy, informing clinical decisions regarding therapeutic adjustments and patient management. Advanced technologies such as next-generation sequencing and digital PCR have revolutionized the monitoring of HBV genetic variability and resistance mutations. These techniques allow comprehensive analysis of viral populations, enhancing our understanding of the mechanisms behind drug-resistant strains and guiding the selection of targeted antiviral therapies. By integrating data from diverse sources, researchers can identify specific viral integrations and mutations contributing to resistance, ultimately facilitating the development of more effective, personalized antiviral regimens [17, 16, 37, 7]. The ability to detect low-frequency variants and monitor changes in viral quasispecies enhances therapy monitoring precision and supports personalized treatment strategies.

Biomarkers such as hepatitis B core-related antigen (HBcrAg) and Mac-2 binding protein glycosylation isomer (M2BPGi) offer additional tools for assessing liver fibrosis and disease progression, complementing traditional virological markers. These serum biomarkers, including tumor-associated proteins, immune mediators, and HBsAg levels, provide critical insights into the host's immune response to antiviral therapy and overall hepatic health, enabling thorough assessment of treatment efficacy and early detection of hepatocellular carcinoma (HCC) in high-risk patients [26, 34, 25].

As antiviral therapy continues to evolve, advancements in monitoring techniques are crucial for optimizing chronic hepatitis B management. By enhancing the precision and reliability of treatment evaluations, these innovative approaches significantly improve patient outcomes and facilitate the development of functional cures for persistent viral infections, which pose substantial public health challenges and contribute to high morbidity and mortality rates globally [16, 17].

7 Emerging Therapies and Research Directions

7.1 Targeted Antiviral Therapies and Genomic Alterations

Targeted antiviral therapies addressing genomic alterations due to hepatitis B virus (HBV) integration are crucial in chronic hepatitis B (CHB) management and hepatocellular carcinoma (HCC) prevention. CRISPR/Cas9 technology exemplifies a cutting-edge approach by excising integrated HBV DNA and disrupting covalently closed circular DNA (cccDNA), thereby reducing the viral reservoir and oncogenic risk [17]. Emerging therapies, such as nanotechnology-based delivery systems, enhance drug bioavailability and target specific tissues, improving therapeutic outcomes [17]. Integrating novel strategies with existing antiviral agents is vital for achieving a functional cure.

Future research should focus on combination therapies that merge antiviral agents with immunotherapeutic strategies to enhance the potential for a functional cure [17]. Investigating novel antiviral agents and immune modulators, especially those targeting HBV integration, is critical [34]. Emphasizing early integration events may significantly impact therapeutic approaches.

Artificial intelligence (AI) and machine learning techniques present new opportunities for liver cancer detection, prediction, and prognostication by improving the precision of identifying genomic alterations and targeted therapies [6]. Future research could optimize parameter selection and apply these methods to other cancer types [27]. Innovative methodologies, such as graphical user interfaces (GUIs) and wavelet transform techniques, are proposed to enhance feature extraction accuracy in liver cancer detection [17]. Validating hub genes in clinical settings and exploring their roles in HCC pathogenesis and treatment are essential for translating research findings into practice.

7.2 Immune Modulation and Combination Therapies

Integrating immune modulation and combination therapies offers significant promise for addressing HBV integration in chronic hepatitis B (CHB) and its progression to HCC. These strategies aim to bolster the host immune response against HBV, mitigating viral integration effects and reducing liver cancer risk. Future therapies should enhance HBV-specific immune responses, representing a novel approach targeting HBV integration [4]. Combination therapies targeting multiple metabolic pathways are crucial for enhancing immune cell function and treatment outcomes [42]. Optimizing dual-staining methods and exploring additional cytokine combinations could further bolster HBsAg-specific B cell function [8].

Targeting HBV integrations in liver cancer has profound therapeutic implications, potentially preventing oncogenic transformation and improving patient outcomes [7]. Focusing on early integration events and their impact on genomic stability allows for targeted interventions addressing HBV-related liver malignancies. Incorporating advanced computational techniques, such as natural language processing, into clinical practice enhances the accuracy of extracting clinical features and managing medical texts [43]. These innovations improve patient stratification precision and guide personalized therapeutic approaches.

7.3 Innovative Platforms and Techniques

Exploring innovative platforms and techniques is essential for advancing HBV integration studies and their implications for CHB and liver cancer. Advanced technologies like ultra-deep sequencing and HBV sequence capture enhance understanding of HBV integration mechanisms and timing, informing targeted therapeutic interventions by elucidating the relationship between HBV integration, chromatin accessibility, and selective pressures contributing to hepatocarcinogenesis [11, 7].

Recent advancements in imaging and computational techniques have improved histopathological image classification and segmentation, crucial for analyzing HBV integration sites and their oncogenic potential. The sliding window approach enhances image classification, offering applications in HBV integration research [47]. Combining this with convolutional neural networks provides a robust framework for accurately identifying integration sites and understanding disease progression.

Integrating local depth convolutional layers with transformers offers a powerful method for leveraging local features while maintaining global contextual understanding [13]. This approach enhances image-based analyses precision, crucial for studying complex genomic landscapes associated with HBV integration. Future research should refine patient selection criteria and explore combination therapies,

particularly immune-based approaches, to enhance treatment efficacy and safety [9]. Establishing a national research network could foster collaboration among institutions, enhancing treatment accessibility and facilitating knowledge and resource sharing [24].

Innovative computational frameworks, such as H-DenseUNet, are being explored to improve segmentation accuracy for small liver tumors, often challenging to detect [48]. Enhancing model parallel training could increase these models' depth and effectiveness, offering new avenues for precise characterization of HBV integration sites. The integration of natural language processing (NLP) into clinical practice enhances the accuracy of extracting clinical features from medical texts, which could improve the precision of HBV integration studies [43]. Expanding the lexicon and dataset size, alongside refining the NLP pipeline, could broaden its clinical applications and improve patient stratification for targeted interventions.

8 Conclusion

The exploration of hepatitis B virus (HBV) integration reveals its critical influence on the pathogenesis of chronic hepatitis B (CHB) and its progression to hepatocellular carcinoma (HCC). The integration into the host genome contributes significantly to genomic instability and oncogenic pathway activation, complicating CHB management and increasing liver cancer risk. This highlights the importance of adopting multidisciplinary approaches in CHB management, emphasizing personalized treatment strategies tailored to individual patient profiles for optimal outcomes.

HBV integration events hold promise as prognostic markers for liver cancer, particularly in understanding the role of HBV-human chimeric transcripts in hepatocarcinogenesis. Additionally, the integration of artificial intelligence (AI) in clinical settings could enhance biomarker detection and application, although rigorous validation of these AI models is necessary for clinical relevance.

Enhanced surveillance and preventive strategies are crucial, especially in high-risk populations, to curb the growing incidence of HCC. Adherence to surveillance protocols for HCC has been shown to improve early detection and survival rates, underscoring the necessity of regular monitoring in CHB management. Furthermore, targeted screening for high-risk groups is essential to address the societal impact of liver cancer, particularly among the elderly.

Future research should aim to investigate the mutational landscape in larger, geographically diverse cohorts to better understand the association with various risk factors. Improving data collection methodologies and examining the influence of emerging risk factors on liver cancer incidence are also imperative. Establishing validated benchmarks across diverse populations and integrating them into routine clinical practice will be critical for advancing the management of HBV-related liver diseases.

The necessity for personalized immunotherapy approaches for HCC is clear, emphasizing the need to understand the tumor microenvironment and immune cell interactions for effective treatment development. Ongoing research in these areas will be vital in enhancing patient outcomes and tackling the global challenge of HBV-related liver diseases. Notably, evidence suggests that patients with normal ALT levels may still face risks of oncogenic transformations due to HBV integrations.

References

[1] Ranjit Chauhan, Norma D Churchill, Patricia M Mulrooney-Cousins, and Tomasz I Michalak. Initial sites of hepadnavirus integration into host genome in human hepatocytes and in the woodchuck model of hepatitis b-associated hepatocellular carcinoma. *Oncogenesis*, 6(4):e317–e317, 2017.

[2] Maryam Moini and Scott Fung. Hbsag loss as a treatment endpoint for chronic hbv infection: Hbv cure. *Viruses*, 14(4):657, 2022.

[3] Ondrej Podlaha, George Wu, Bryan Downie, Raghuraman Ramamurthy, Anuj Gaggar, Mani Subramanian, Zhishen Ye, and Zhaoshi Jiang. Genomic modeling of hepatitis b virus integration frequency in the human genome. *PloS one*, 14(7):e0220376, 2019.

[4] Yongyan Chen and Zhigang Tian. Hbv-induced immune imbalance in the development of hcc. *Frontiers in immunology*, 10:2048, 2019.

[5] Sedigheh Behrouzifar. Identifying downregulated hub genes and key pathways in hbv-related hepatocellular carcinoma using systems biology approach, 2023.

[6] Jinpeng Li, Yaling Tao, and Ting Cai. Investigating critical risk factors in liver cancer prediction, 2021.

[7] Mayuko Furuta, Hiroko Tanaka, Yuichi Shiraishi, Takuro Unida, Michio Imamura, Akihiro Fujimoto, Masahi Fujita, Aya Sasaki-Oku, Kazuhiro Maejima, Kaoru Nakano, et al. Characterization of hbv integration patterns and timing in liver cancer and hbv-infected livers. *Oncotarget*, 9(38):25075, 2018.

[8] Loghman Salimzadeh, Nina Le Bert, Charles-A Dutertre, Upkar S Gill, Evan W Newell, Christian Frey, Magdeleine Hung, Nikolai Novikov, Simon Fletcher, Patrick TF Kennedy, et al. Pd-1 blockade partially recovers dysfunctional virus–specific b cells in chronic hepatitis b infection. *The Journal of clinical investigation*, 128(10):4573–4587, 2018.

[9] Antonio Bertoletti and Nina Le Bert. Immunotherapy for chronic hepatitis b virus infection. *Gut and liver*, 12(5):497, 2018.

[10] Iman Ibrahim Salama, Samia M Sami, Somaia I Salama, Ghada A Abdel-Latif, Fatma A Shaaban, Walaa A Fouad, Aida M Abdelmohsen, and Hala M Raslan. Current and novel modalities for management of chronic hepatitis b infection. *World Journal of Hepatology*, 15(5):585, 2023.

[11] Teresa Pollicino and Giuseppe Caminiti. Hbv-integration studies in the clinic: role in the natural history of infection. *Viruses*, 13(3):368, 2021.

[12] Rongshou Zheng, Chunfeng Qu, Siwei Zhang, Hongmei Zeng, Kexin Sun, Xiuying Gu, Changfa Xia, Zhixun Yang, He Li, Wenqiang Wei, et al. Liver cancer incidence and mortality in china: temporal trends and projections to 2030. *Chinese Journal of Cancer Research*, 30(6):571, 2018.

[13] Liangrui Pan, Yutao Dou, Zhichao Feng, Liwen Xu, and Shaoliang Peng. Ldcsf: Local depth convolution-based swim framework for classifying multi-label histopathology images, 2023.

[14] Thomas Tu, Magdalena A Budzinska, Nicholas A Shackel, and Stephan Urban. Hbv dna integration: molecular mechanisms and clinical implications. *Viruses*, 9(4):75, 2017.

[15] Hao Li, Chunyu Sheng, Shan Wang, Lang Yang, Yuan Liang, Yong Huang, Hongbo Liu, Peng Li, Chaojie Yang, Xiaoxia Yang, et al. Removal of integrated hepatitis b virus dna using crispr-cas9. *Frontiers in cellular and infection microbiology*, 7:91, 2017.

[16] Xun Chen, Jason Kost, Arvis Sulovari, Nathalie Wong, Winnie S Liang, Jian Cao, and Dawei Li. A virome-wide clonal integration analysis platform for discovering cancer viral etiology. *Genome research*, 29(5):819–830, 2019.

[17] Bruna Carolina Gonçalves, Mario Gabriel Lopes Barbosa, Anna Paula Silva Olak, Natalia Belebecha Terezo, Leticia Nishi, Maria Angélica Watanabe, Poliana Marinello, Daniele Zendrini Rechenchoski, Sergio Paulo Dejato Rocha, and Lígia Carla Faccin-Galhardi. Antiviral therapies: advances and perspectives. *Fundamental & Clinical Pharmacology*, 35(2):305–320, 2021.

[18] Korean Association for the Study of the Liver (KASL et al. Kasl clinical practice guidelines for management of chronic hepatitis b. *Clinical and molecular hepatology*, 25(2):93, 2019.

[19] Liu Yang, Song Ye, Xinyi Zhao, Liyan Ji, Yinxin Zhang, Pingyu Zhou, Jun Sun, Yanfang Guan, Yingxin Han, Chao Ni, et al. Molecular characterization of hbv dna integration in patients with hepatitis and hepatocellular carcinoma. *Journal of Cancer*, 9(18):3225, 2018.

[20] Thomas Tu, Henrik Zhang, and Stephan Urban. Hepatitis b virus dna integration: in vitro models for investigating viral pathogenesis and persistence. *Viruses*, 13(2):180, 2021.

[21] Martin CS Wong, Johnny Y Jiang, William B Goggins, Miaoyin Liang, Yuan Fang, Franklin DH Fung, Colette Leung, Harry HX Wang, Grace LH Wong, Vincent WS Wong, et al. International incidence and mortality trends of liver cancer: a global profile. *Scientific reports*, 7(1):45846, 2017.

[22] Joo Hyun Oh and Dae Won Jun. The latest global burden of liver cancer: A past and present threat. *Clinical and molecular hepatology*, 29(2):355, 2023.

[23] Prashanth Rawla, Tagore Sunkara, Pradhyumna Muralidharan, and Jeffrey Pradeep Raj. Update in global trends and aetiology of hepatocellular carcinoma. *Contemporary Oncology/Współczesna Onkologia*, 22(3):141–150, 2018.

[24] Wafaa M Rashed, Mohamed Ahmed Mohamed Kandeil, Mohamed O Mahmoud, and Sameera Ezzat. Hepatocellular carcinoma (hcc) in egypt: A comprehensive overview. *Journal of the Egyptian National Cancer Institute*, 32:1–11, 2020.

[25] Arian Mansur, Andrea Vrionis, Jonathan P Charles, Kayesha Hancel, John C Panagides, Farzad Moloudi, Shams Iqbal, and Dania Daye. The role of artificial intelligence in the detection and implementation of biomarkers for hepatocellular carcinoma: outlook and opportunities. *Cancers*, 15(11):2928, 2023.

[26] José D Debes, Pablo A Romagnoli, Jhon Prieto, Marco Arrese, Angelo Z Mattos, André Boonstra, and Escalon Consortium. Serum biomarkers for the prediction of hepatocellular carcinoma. *Cancers*, 13(7):1681, 2021.

[27] Rosemary Braun and Kenneth Buetow. Pathways of distinction analysis: a new technique for multi-snp analysis of gwas data, 2011.

[28] Aileen Baecker, Xing Liu, Carlo La Vecchia, and Zuo-Feng Zhang. Worldwide incidence of hepatocellular carcinoma cases attributable to major risk factors. *European Journal of Cancer Prevention*, 27(3):205–212, 2018.

[29] Chyntia Olivia Maurine Jasirwan, Alessa Fahira, Lianda Siregar, and Imelda Loho. The alpha-fetoprotein serum is still reliable as a biomarker for the surveillance of hepatocellular carcinoma in indonesia. *BMC gastroenterology*, 20:1–8, 2020.

[30] Takako Inoue and Yasuhito Tanaka. Novel biomarkers for the management of chronic hepatitis b. *Clinical and molecular hepatology*, 26(3):261, 2020.

[31] Celina Ang, Samuel J Klempner, Siraj M Ali, Russell Madison, Jeffrey S Ross, Eric A Severson, David Fabrizio, Aaron Goodman, Razelle Kurzrock, James Suh, et al. Prevalence of established and emerging biomarkers of immune checkpoint inhibitor response in advanced hepatocellular carcinoma. *Oncotarget*, 10(40):4018, 2019.

[32] Eric Letouzé, Jayendra Shinde, Victor Renault, Gabrielle Couchy, Jean-Frédéric Blanc, Emmanuel Tubacher, Quentin Bayard, Delphine Bacq, Vincent Meyer, Jérémy Semhoun, et al. Mutational signatures reveal the dynamic interplay of risk factors and cellular processes during liver tumorigenesis. *Nature communications*, 8(1):1315, 2017.

[33] Daniel Q Huang, Amit G Singal, Fasiha Kanwal, Pietro Lampertico, Maria Buti, Claude B Sirlin, Mindie H Nguyen, and Rohit Loomba. Hepatocellular carcinoma surveillance—utilization, barriers and the impact of changing aetiology. *Nature Reviews Gastroenterology & Hepatology*, 20(12):797–809, 2023.

[34] Markus Cornberg, Vincent Wai-Sun Wong, Stephen Locarnini, Maurizia Brunetto, Harry LA Janssen, and Henry Lik-Yuen Chan. The role of quantitative hepatitis b surface antigen revisited. *Journal of hepatology*, 66(2):398–411, 2017.

[35] Eva G Álvarez, Jonas Demeulemeester, Paula Otero, Clemency Jolly, Daniel García-Souto, Ana Pequeño-Valtierra, Jorge Zamora, Marta Tojo, Javier Temes, Adrian Baez-Ortega, et al. Aberrant integration of hepatitis b virus dna promotes major restructuring of human hepatocellular carcinoma genome architecture. *Nature Communications*, 12(1):6910, 2021.

[36] Mahmoudreza Moghimhanjani and Ali Taghavirashidizadeh. Analysis of liver cancer detection based on image processing, 2022.

[37] Marc Zapatka, Ivan Borozan, Daniel S Brewer, Murat Iskar, Adam Grundhoff, Malik Alawi, Nikita Desai, Holger Sültmann, Holger Moch, et al. The landscape of viral associations in human cancers. *Nature genetics*, 52(3):320–330, 2020.

[38] Fabio Zamio. Dlsom: A deep learning-based strategy for liver cancer subtyping, 2024.

[39] Patrick S Harris, Ross M Hansen, Meagan E Gray, Omar I Massoud, Brendan M McGuire, and Mohamed G Shoreibah. Hepatocellular carcinoma surveillance: an evidence-based approach. *World journal of gastroenterology*, 25(13):1550, 2019.

[40] Romain Donne and Amaia Lujambio. The liver cancer immune microenvironment: Therapeutic implications for hepatocellular carcinoma. *Hepatology*, 77(5):1773–1796, 2023.

[41] Letter.

[42] Flora Yang, Leena Hilakivi-Clarke, Aurpita Shaha, Yuanguo Wang, Xianghu Wang, Yibin Deng, Jinping Lai, and Ningling Kang. Metabolic reprogramming and its clinical implication for liver cancer. *Hepatology*, 78(5):1602–1624, 2023.

[43] Honglei Liu, Yan Xu, Zhiqiang Zhang, Ni Wang, Yanqun Huang, Yanjun Hu, Zhenghan Yang, Rui Jiang, and Hui Chen. A natural language processing pipeline of chinese free-text radiology reports for liver cancer diagnosis, 2020.

[44] Ashkan Zeinalzadeh, Tom Wenska, and Gordon Okimoto. A neural network model to classify liver cancer patients using data expansion and compression, 2016.

[45] Jinlin Hou, Guiqiang Wang, Fusheng Wang, Jun Cheng, Hong Ren, Hui Zhuang, Jian Sun, Lanjuan Li, Jie Li, Qinghua Meng, et al. Guideline of prevention and treatment for chronic hepatitis b (2015 update). *Journal of clinical and translational hepatology*, 5(4):297, 2017.

[46] Feng Gan, Gang Ye, Langxia Liu, and Xiaohui Liu. A general theory for direct quantitative analysis of antigen, 2012.

[47] Aymen Sadraoui, Ségolène Martin, Eliott Barbot, Astrid Laurent-Bellue, Jean-Christophe Pesquet, Catherine Guettier, and Ismail Ben Ayed. A transductive few-shot learning approach for classification of digital histopathological slides from liver cancer, 2024.

[48] Xiaomeng Li, Hao Chen, Xiaojuan Qi, Qi Dou, Chi-Wing Fu, and Pheng Ann Heng. H-denseunet: Hybrid densely connected unet for liver and tumor segmentation from ct volumes, 2018.

Disclaimer:

SurveyX is an AI-powered system designed to automate the generation of surveys. While it aims to produce high-quality, coherent, and comprehensive surveys with accurate citations, the final output is derived from the AI's synthesis of pre-processed materials, which may contain limitations or inaccuracies. As such, the generated content should not be used for academic publication or formal submissions and must be independently reviewed and verified. The developers of SurveyX do not assume responsibility for any errors or consequences arising from the use of the generated surveys.