Check for updates

OPEN ACCESS

DOI: 10.46903/gjms/24.1.2214

REVIEW ARTICLE

TOWARD PRECISION HEPATOLOGY: GENOMIC AND IMMUNOLOGIC DETERMINANTS OF DISEASE PROGRESSION IN CHRONIC HBV AND HCV INFECTION

Shuaibu Abdullahi Hudu[1,2], Abdulgafar Olayiwola Jimoh[3]

[1]Center for Health Research, Northern Border University, Arar 91431, Kingdom of Saudi Arabia. [2]Department of Microbiology, College of Medicine, Northern Border University, Arar 91431, Kingdom of Saudi Arabia, [3]Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto 840232, Sokoto State, Nigeria

ABSTRACT

Hepatitis B and C remain significant causes of cirrhosis and hepatocellular carcinoma, especially in the Middle East, where HBV genotype D and HCV genotype 4 are predominant. Despite the expansion of vaccination programs and new direct-acting antivirals, many patients still progress to advanced liver disease due to complex host–virus interactions involving genetic, epigenetic, and immune system balance. This study compiles recent research on viral genotypes, host immunogenetic polymorphisms, and multi-omics advances to capture long-term profiles of liver injury. Key viral factors include the pathogenic roles of DNA integration and immune-escape mutations in HBV, as well as NS5A resistance variants in HCV. Host factors involve HLA allele diversity, interferon-lambda and cytokine gene polymorphisms, and immune checkpoint regulation. Multi-omics technologies, analyzing genomics, transcriptomics, proteomics, metabolomics, and immunomics, are shaping the era of precision hepatology by enabling detailed molecular profiling of tissues and responses to fibrosis stages. To maximize the benefits of precision hepatology in the Middle Eastern population, integrating with national genomic databases and linking to multi-omics data is crucial for identifying population-specific biomarkers. Additionally, translating detection into treatment through local biorepositories and omics collaboration is essential to improve national models, support Saudi Vision 2030, and achieve global hepatitis elimination goals.

KEY WORDS: Chronic hepatitis; Genomics; Hepatocellular carcinoma; Immunogenetics; Multi-omics; Precision hepatology.

Cite as: Hudu SA, Jimoh AO. Toward precision hepatology: genomic and immunologic determinants of disease progression in chronic HBV and HCV infection.[review article]. Gomal J Med Sci 2026 Jan-Mar;24(1):91-9. https://doi.org/1046903/gjms/24.1.2214

1. INTRODUCTION

Infection with the hepatitis B virus (HBV) and the hepatitis C virus HCV) is the most common cause of chronic infection globally. Infections due to HBV resulted in over 250 million people developing the disease worldwide. Approximately one million deaths per year are due to HBV-related liver illness.[1] Like HBV, HCV infects more than 58 million people globally and is accountable for an estimated 290,000 fatalities annually.[2] Despite advances in antiviral therapy and vaccination, progression from chronic infection to liver cirrhosis or HCC has not been fully described. Virology, host genetics, hepatocellular immunology, and liver microarchitecture may still be better understood to influence this process. Both HBV and HCV have distinctive epidemiologic and molecular characteristics in the Middle East, particularly in Saudi Arabia and its surroundings. HBV prevalence in the Middle East has historically ranged from 2 to 8 percent. [3] It has been primarily associated with genotype D. The Middle East's endemicity, along with other regional cofactors such as metabolic syndrome, obesity, and the prevalence of type 2 diabetes, may have an effect by instigating the progression to liver fibrosis and HCC.[4] However, advocacy studies integrating host immunological aspects of viral genomics in Middle Eastern traditions

Corresponding Author:

Dr. Shuaibu Abdullahi Hudu
Center for Medical Research,
Northern Border University,
Arar 91431, Kingdom of Saudi Arabia.
E-mail: abdullahi.Hudu@nbu.edu.sa

Date Submitted: 03-10-2025
Date Revised: 04-03-2026
Date Accepted: 15-03-2026

remain limited.

The clinical continuum from chronic infection to cirrhosis and HCC is a complex and multifactorial phenomenon influenced by viral and host factors. The viral determinants include genotype, viral load, quasispecies diversity, integration of viral DNA into host genomes, and epigenetic modifications. In the context of HBV, viral replication and host immune dynamics determine whether the infection clears or persists, whereas in the latter, immune-mediated inflammation and viral integration events can unleash cascades of carcinogenic pathways. In HCV, despite the revolutionizing direct-acting antiviral treatment, residual immune dysfunction and genetic predilections are the drivers of progression in a small subset of patients. The technological evolution over the past few decades in high-throughput sequencing, single-cell transcriptomics, and systems immunology is reimagining these scenarios. Multi-omics studies highlight intrahepatic immune heterogeneity, epigenetic dysregulation, and dysregulated cytokine signaling that foster fibrogenesis and hepatocarcinogenesis. However, the use of clan informatics in clinical precision hepatology remains limited in resource-poor academic settings. The catchphrase "Precision hepatology" challenges the traditional "one-size-fits-all" approach to antiviral treatments and risk assessment, emphasizing biomarker-guided surveillance and tailored actions based on patients' viral, genomic, and immunologic fingerprints.[5] This is especially significant in Middle Eastern populations, with their unique prevalence patterns, epigenetic influences, and environmental factors. However, the lack of globally representative genomic collections and immunologic profiling creates gaps in this comprehensive view.

There is an urgent unmet need for translational research integrating viral genomics with host immune signatures in the region. Specifically, HLA polymorphisms, interferon-lambda genotypes, cytokine gene variants, and checkpoint-molecule expression have not been studied for their roles in determining progression to cirrhosis or HCC in Saudi Arabia and surrounding Middle Eastern countries. This unavailability hampers biomarker discovery and precludes the deployment of personalized therapeutic strategies. The current narrative review thus considers and integrates the available evidence on genomic and immunologic determinants of chronic HBV and HCV-related disease progression in the regional context. The focus is on Saudi Arabia, but the broader Middle East is also covered, which may guide and inform research strategies in other countries of the region. By integrating knowledge of molecular virology, host immunogenetics, and insights from omics-driven research, the narrative aims to outline a conceptual basis for precision hepatology in these areas. This evidence-based integrated framework can eventually guide screening for key biomarkers, novel therapeutic targets, and therapeutic paths for the personalized management of viral hepatitis.

2. EPIDEMIOLOGIC CONTEXT OF HBV AND HCV IN THE MIDDLE EAST

The Middle East and North Africa present a unique epidemiological landscape for the burden of chronic viral hepatitis. This region features a highly diverse population, high migration rates, and distinct genotype distributions, all of which significantly influence long-term disease progression and clinical outcomes. Despite public health improvements, HBV and HCV infections continue to be significant causes of cirrhosis and hepatocellular carcinoma throughout the region. The World Health Organization estimates that approximately 18 million people are infected with HBV and 15 million with HCV in the Eastern Mediterranean Regional Office, with these infections accounting for nearly 50% of all liver-related deaths in the area. [1]

2.1 Epidemiology of the hepatitis B virus

The epidemiology of hepatitis B virus (HBV) in the Middle East shows substantial inter-country variability, reflecting differences in vaccination coverage, blood safety, and access to healthcare. Prior to the introduction of universal HBV immunization in the late 1980s and early 1990s, several Gulf and Levant countries exhibited high endemicity, with HBsAg prevalence exceeding 6–10%.[6] Following widespread implementation of infant vaccination programs, HBV prevalence has declined markedly across the region. In Saudi Arabia, for example, HBsAg prevalence decreased from approximately 7–8% in the pre-vaccination era to around 1–1.5% in recent population-based estimates, with rates below 0.1% reported among vaccinated younger cohorts. [7] Nevertheless, HBV still causes a clinically relevant proportion of chronic liver diseases among those infected before vaccination. Genotype D is the prevalent strain in the Arabian Peninsula and surrounding areas, while genotypes A and E coexist in some ethnic groups. Molecular epidemiology suggests that genotype D is associated with higher chronicity rates, lower interferon response, and increased frequencies of core and pre-core mutations, leading to immune escape. Hepatitis B virus infection is well-established in the area and remains a challenge, as frequent OBI reporting among donated blood and hemodialysis patients complicates transfusion safety and screening.

2.2 Hepatitis C Virus Epidemiology

The Middle East exhibits HCV epidemiology characterized by variation between countries and a tendency toward specific genotypes. Historically, Egypt has had the highest global prevalence (>10%) due to previous parenteral-based anti-schistosomal campaigns.[8] Nevertheless, active national programs have significantly reduced this

prevalence. Conversely, Recent systematic reviews indicate that Saudi Arabia, Oman, and Kuwait have a low HCV prevalence in the general population (0.3–1.5%), but substantially higher rates persist among high-risk groups, including people who inject drugs, hemodialysis patients, and some expatriate populations. Across the Arab world, HCV genotype 4 remains predominant, representing the majority of infections in Saudi Arabia and accounting for most cases in Egypt, while genotype 1 is the second most common. [9] Genotype 4 infection has been shown to accelerate fibrosis progression, result in suboptimal response to pegylated-interferon-based therapy, and express unique immune-evading NS5A variants, as evidenced by regional studies. While the Direct-Acting Antiviral (DAA)-induced cure rate is optimal for HCV, genotype-related differences in the initiation of inflammation and post-treatment fibrosis regression persist and differ significantly across subpopulations.

2.3 Co-infection and Comorbidities

While HBV/HCV co-infection is rare, it correlates with an increased risk of hepatic decompensation and HCC.[10] In addition, emerging hepatotropic viruses, such as the hepatitis D virus, and novel agents, such as Torque Teno Virus, may influence immune modulation and the disease course and have epidemiological relevance for HCV.[11] Furthermore, type 2 diabetes and lifestyle diseases characterizing Gulf populations accelerate liver disease progression through metabolic inflammation and immunological dysregulation. [12]

2.4 Public Health Response and Deficiencies

Regional governments have built control measures, such as newborn HBV immunization, blood donor screening, and the mainstreaming of hepatitis services in state non-communicable disease plans. Saudi Arabia and Egypt stand out for their progress in elimination initiatives, marked by “substantial” surveillance and depenalized access to therapy centers, which simplify access to DAAs.[9] However, several weaknesses remain, including inadequate molecular surveillance, limited or absent representation of regional genotypes in global databases, and limited immunogenetic research to inform precision medicine. Multicenter genomic consortia do not exist, necessitating the exploration of host-viral interactions across various ethnic and environmental contexts.

3. MOLECULAR DETERMINANTS OF DISEASE PROGRESSION

The wide range of reactions linking chronic Hepatitis B and C infections to more serious conditions, such as cirrhosis and hepatocellular carcinoma, is governed by a complex network of interactions involving variations in viral genomes and diverse host cellular responses. However, these reactions are not limited to the factors mentioned, as many epigenetic changes also occur. In this context, understanding molecular prerequisites is essential to precision medicine because it not only clarifies the pathway but also helps identify prognostic biomarkers and develop new, more effective intervention strategies.[13]

3.1 Viral Genomic Variability

Both HBV and HCV exhibit extensive genomic heterogeneity, which significantly influences their pathobiology. HBV is a partially double-stranded DNA virus that is divided into at least 10 genotypes.[14] Genotype D, the most common in Middle Eastern countries, is more likely to result in chronic infection, produce precore or core mutations that lead to HBeAg negativity, and increase the risk of hepatocellular carcinoma. Mutations at the basal core promoter (A1762T/T/G1764A) and in the pre-S regions alter viral protein composition and immune recognition. [15] Additionally, recombination events between genotypes have been observed in Saudi and Egyptian cohorts, suggesting that the virus has a unique mechanism for adapting to immune pressure. HCV is an RNA virus with an error-prone polymerase that exists as a quasispecies within a single patient. The predominant regional genotype 4, especially subtype 4a, harbors distinct sequence markers in the NS5A and E2 domains that facilitate immune escape and influence treatment outcomes. Specific amino acid changes, such as NS5A L31M and Y93H, increase resistance to DAAs and correlate with fibrosis progression.

3.2. Viral Integrations and Oncogenic Features

Hepatitis B virus (HBV) infection involves the integration of viral DNA into the host hepatocyte genome, a process that drives oncogenesis. Integration causes chromosomal instability, insertional mutagenesis, and the activation of oncogenes *TERT, CCNE1*, and MLL4. [16] Importantly, integration can occur early in infection, before cirrhosis is detectable, and serves as a molecular landmark for the clonal expansion of hepatocytes. The HBV X protein exacerbates this process by disrupting DNA damage response, DNA repair, and interferon pathways, resulting in epigenetic redox reprogramming that sanctions carcinogenesis. [17] For the hepatitis C virus, there is no DNA intermediate, and integration occurs indirectly. However, chronic inflammation and oxidative stress cause somatic mutations and epigenetic dysregulation of tumor-suppressor genes. Among the persistent expression of viral proteins is hepatitis C virus core, NS3, and NS5A, which promote reactive oxygen species production, lipid accumulation, and endoplasmic reticulum ER stress, leading to fibrosis and neoplastic transformation.

3.3. Epigenetics and Transcriptomics

In addition to genetic factors, epigenetic modifications influence the persistence and progression of HBV and HCV infections. Viral proteins directly recruit host chromatin-modulated cells to suppress antiviral responses, and chronic inflammation leads to wide-

spread host methylome programming. [18] Recently, single-cell and spatially resolved transcriptomic studies have examined hepatocytes and immune cells in chronically infected livers. Notable gene expression changes include interferon signaling, markers of mitochondrial dysfunction, and pro-fibrotic mediators, as identified by comparing aggressive-disease groups.[19] Planning patient-specific networks using transcriptomic data combined with viral genomics helps identify molecular informatics systems that predict individual disease progression, thereby aiding diagnosis and therapy.

4. HOST IMMUNOLOGIC DETERMINANTS

The immunologic environment surrounding chronic HBV and HCV infections is a key factor in viral persistence, fibrosis progression, and HCC development. Host genetic responses, involving both innate and adaptive immune components, have dual roles.[20] They are essential for clearing the virus but can cause chronic inflammation and damage if dysregulated. In fact, variations in immune gene expression, cytokine polymorphisms, and pathways are associated with cell exhaustion, contributing to the variability in disease outcomes within individuals and across populations.

4.1 Innate immune response is as follows

The innate immune response is the body's first line of defense against hepatotropic viruses. Pattern-recognition receptors initiate this response by detecting viral nucleic acids and stimulating type I interferon production. However, both HBV and HCV have developed mechanisms to counteract this pathway. HBV polymerase and HBx inhibit RIG-I signaling and MAVS expression, while HCV NS3/4A protease cleaves MAVS and TRIF to block interferon production. [21] Polymorphisms in the TLR3 and TLR9 genes, as well as in the genes for type III interferon (IFNL3/4), affect susceptibility to liver disease and influence treatment outcomes. Furthermore, NK cell function is impaired during chronic infection; their cytotoxic activity is believed to be inversely correlated with the degree of fibrosis.

4.2 Adaptive Immune Landscape

Adaptive immunity is essential for long-term control of infection, but it becomes increasingly ineffective over time. $CD8^+$ T cells specific to HBV and HCV tend to become exhausted, as evidenced by elevated PD-1, CTLA-4, and TIM-3, along with diminished effector functions. [22] These exhausted and ineffective T cells cannot eliminate infected hepatocytes, contributing to ongoing low-grade necroinflammation. $CD4^+$ helper T-cell responses are also impaired, limiting the production of effective antibodies and cytotoxic memory. Additionally, B-cell dysregulation plays a key role; ongoing antigen exposure causes polyclonal B-cell activation, leading to the production of non-neutralizing antibodies and the formation of immune complexes that worsen liver inflammation. The CXCR5-CCL13 axis, which is involved in germinal center formation, is disrupted in chronic infections, leading to abnormal intrahepatic B-cell clustering and increasing the risk of HCC.[23]

4.3 Cytokine and Chemokine Networks

Cytokines are critical in the immunological orchestration of HBV and HCV infection by balancing antiviral resistance and inflammation. Pro-inflammatory mediators such as TNF-α, IL-6, and IL-1β trigger HSC activation, thereby promoting fibrosis. Anti-inflammatory cytokines, such as IL-10, enhance viral resistance by inhibiting Th1 and cytotoxic responses. IL-17 and related Th17 cytokines promote accelerated fibrosis by recruiting neutrophils and modulating MMP activity. [23] Notably, cytokine gene polymorphisms promote disease progression, as the IL-10 promoter variant and TNF-α polymorphisms correlate with HCC susceptibility in Saudi and Egyptian patients. [24] Meanwhile, systems immunology approaches ensure cytokine profile data integration with specificity for unique inflammatory biomarkers that predict cirrhosis or HCC progression.

4.4 Immune Checkpoints and Therapeutic Implications

Markers of exhaustion, such as PD-1, CTLA-4, and LAG-3, are upregulated in chronic hepatitis and could be potential therapeutic targets.[22] While immune checkpoint blockade is established in oncology, reactivating these targets in the context of viral hepatitis should be applied cautiously due to the high risk of hepatotoxic immune reactivation. Novel approaches can explore combining PD-1 blockade with therapeutic HBV vaccines and antiviral therapies to restore T-cell function. These incredibly complex immune networks in Table 1 underscore the need for precision immunologic profiling within regional populations to inform biomarker-driven therapeutic design.

5. HOST GENOMIC AND IMMUNOGENETIC FACTORS

Host genetic diversity plays a crucial role in determining clinical outcomes in both chronic HBV and HCV infections. While virus-specific factors like infectivity and replication dynamics also contribute, host immunogenetic variability primarily influences response strength, infection persistence, and the risk of fibrotic or cancerous transformation. Genome-wide association studies and candidate-gene analyses have identified multiple host loci linked to disease development. These associations vary by region and ethnicity, including in Middle Eastern populations. This review highlights locally relevant immunogenetic features.

5.1 Human Leukocyte Antigen Polymorphisms

The HLA region on chromosome 6 contains crucial

Table 1. Summary of Key Immune Pathways and Their Clinical Correlations in Chronic HBV and HCV

Immune Component	Key Molecules/Genes	Mechanistic Role	Effect on Disease Outcome	Representative References
Innate immune sensors	TLR3, TLR9, RIG-I, cGAS–STING	Detect viral nucleic acids and trigger interferon responses	Genetic polymorphisms influence viral clearance and persistence	[25]
NK cells	NKG2D, IFN-γ, perforin	Cytotoxic elimination of infected hepatocytes	Dysfunction correlates with advanced fibrosis	[26]
B cells	CXCL13–CXCR5 axis	Antibody production and germinal-center organization	Dysregulation linked to HCC development	[23]
Cytokine milieu	IL-10, IL-17, TNF-α, IFNL3/4	Modulate inflammation and fibrosis	Specific polymorphisms associated with progression and HCC risk	[23]

TLR – Toll-like receptor; RIG-I – Retinoic acid-inducible gene I; cGAS – Cyclic GMP-AMP synthase; STING – Stimulator of interferon genes; NK – Natural killer; IFN-γ – Interferon-gamma; PD-1 – Programmed cell death protein 1; CTLA-4 – Cytotoxic T-lymphocyte–associated protein 4; TIM-3 – T-cell immunoglobulin and mucin-domain–containing protein 3; CXCL13 – C-X-C motif chemokine ligand 13; CXCR5 – C-X-C chemokine receptor 5; HCC – Hepatocellular carcinoma; IL – Interleukin; TNF-α – Tumor necrosis factor-alpha; IFNL – Interferon lambda.

loci for antigen presentation. Specific HLA class I and II alleles influence whether the virus resolves or becomes chronic. For HBV, HLA-DPA103:01 and HLA-DPB102:01 are associated with viral resolution, whereas HLA-DPB104:02 is associated with chronic infection. Cytotoxic T-cell responses differ due to specific viral peptide binding, which can suppress immune responses. In HCV, HLA-DQB103:01 and HLA-DRB111:01 are associated with viral resolution. Understanding how different HLA alleles interact with the virus can help redefine epitope pools for existing vaccines and therapies tailored to regional populations. Some alleles have been identified as risk factors for advanced fibrosis in the Middle East. Studies from Saudi Arabia and Egypt report higher frequencies of HLA-DQB1*06 and DRB1*13 in patients with advanced fibrosis, indicating a population-specific genetic pattern.[27]

5.2 Cytokine and Immune-Regulatory Gene Variants

Gene modulation is another key factor in hepatic inflammation and fibrogenesis. IFNL3/4, previously described as IL28B expression, is the strongest genetic determinant of spontaneous and treatment-induced HCV clearance.[23] The allele rs12979860 CC, common in Arabs, is associated with a stronger antiviral response, which improves outcomes with pegylated interferon therapy. Additionally, pro-inflammatory cytokine genes, such as TNF-α, IL-10, and TGF-β1, and their signaling pathways harbor polymorphic variants that either predispose to or protect against disease progression.[24] IL-17A genetic variants and CXCL13 have each been implicated in the CHB disease course and immune responses, but further studies are required to determine whether their alleles, when combined, independently predict inflammation severity.

5.3 Lipid-Metabolic and Oncogenic Susceptibility Genes

In addition to immune-regulatory loci, several metabolic and oncogenic genes contribute to cancer progression. The PNPLA3 I148M polymorphism is a key predictor of hepatic steatosis, fibrosis, and the risk of hepatocellular carcinoma across various liver conditions, including chronic viral hepatitis.[12] The MBOAT7 and TM6SF2 polymorphisms affect lipid balance and inflammation and are more common in Middle Eastern populations. Additionally, genetic variations in oxidative-stress-related loci, such as SOD2 and NQO1, increase hepatocyte susceptibility to injury and tumor development.[12]

5.4 Epigenetic Regulation and Host-Virus Interaction

The host's epigenetic machinery regulates variation in immune responses and viral clearance among individuals. The core protein can influence the DNMT1 DNA methylation system, as well as the EZH2 and HDAC1 histone-modifying enzymes, thereby im-

pacting oncogenic transcriptional programs and tumor suppressor loci.[28] HBx uses similar pathways in the CDKN2A and SOCS1 genes. [29] Methylation profiling of Middle Eastern patients showed distinct methylation patterns associated with fibrosis and viability, indicating that regional environmental and genetic differences significantly affect the epigenetic interaction between the host and the virus.

6. INTEGRATION OF MULTI-OMICS AND PRECISION APPROACHES

High-throughput technologies have transformed hepatology from a descriptive virology into a multidimensional systems biology field. Integrating multi-omics data, including genomic, transcriptomic, proteomic, metabolomic, and immunomic information, provides a comprehensive view of host–virus interactions and helps identify biomarkers and treatment targets that drive precision medicine. [30] In cases of chronic HBV and HCV, these technologies trace molecular continuums that link viral persistence, immune dysregulation, and progression to cirrhosis or HCC.

6.1 Genomics and transcriptomics

Viral and host genome sequencing enable detailed maps of mutational landscapes and transcriptional programs. Whole-genome sequencing of HBV and HCV reveals integration sites, drug-resistance mutations, and intra-host sequence diversity, all of which can predict treatment outcomes; host transcriptomic analysis uncovers ISG signatures, mitochondrial dysfunction biomarkers, and pro-fibrotic gene networks associated with histologic stages. Single-cell RNA sequencing identifies distinct hepatocyte and immune cell clusters linked to chronic inflammation and DAA-resolved regression issues. Viral genomic variability, influenced by host transcriptional reprogramming, produces robust models for predicting viral evolution.[11] Proteomic analysis reveals functional gene expression, including post-translational modifications and signaling cascades involved in hepatocyte injury.[31] Metabolomics enhances these findings by analyzing bile acid metabolism, lipid oxidation, and amino acid fluxes associated with viral activity and fibrogenesis. A metabolic signature, marked by increased lysophosphatidylcholines and acylcarnitines, distinguishes cirrhotics from early fibrotic patients.

6.2 Immunomics and Systems Integration

By comparison, immunomics, or the high-resolution mapping of immune repertoires and cytokine interaction networks, has expanded our understanding of host variation in antiviral responses. High-dimensional flow cytometry and single-cell proteomic approaches have enabled deep phenotyping of T- and B-cell exhaustion and, when integrated with circulating biomarkers, can be linked to transaminase (ALT/AST) dynamics during immune reconstitution after antiviral therapy.[32] Systems biology pipelines integrate multi-omic data using trained machine-learning frameworks to identify hub genes that regulate the balance between self-limited and persistent infections.

6.3 Toward Precision Hepatology

These simulated findings mark the start of precision hepatology, an era driven by multi-omic discoveries combined with clinical phenotyping. Prognostic models that utilize multi-omic data can classify patients by fibrosis risk, treatment options, and susceptibility to hepatocellular carcinoma. For example, combining HBV integration records with host-unaffected transcriptomics can accurately predict HCC development 5 years in advance. [16] However, clinical interpretation faces challenges due to data harmonization issues, limited bioinformatics capacity, and a lack of country-specific data. Therefore, a national multi-omics consortium can address these obstacles and identify clinically relevant biomarkers tailored to regional genomics and environmental factors. Table 2 summarizes the complementary omics methods and their clinical associations.

Table 2. Overview of Multi-Omics Modalities and Their Applications in Precision Hepatology

Omics Layer	Primary Data Type	Representative Insights	Clinical Utility / Biomarker Potential	References
Transcriptomics	mRNA and non-coding RNA expression	ISG activation, fibrotic gene signatures, microRNA dysregulation	Staging fibrosis, predicting DAA outcomes	12
Proteomics	Protein abundance and post-translational modifications	Cytokeratin-18, complement, PD-L1 levels	Non-invasive biomarkers of necroinflammation	33
Metabolomics	Serum and hepatic metabolite profiles	Bile-acid, lipid, and amino-acid perturbations	Early detection of fibrosis and metabolism-linked HCC	34
Immunomics	Immune-cell phenotypes and cytokine networks	Exhaustion markers (PD-1, LAG-3), CXCL13–CXCR5 signaling	Immune profiling, treatment personalization	22

ISG – Interferon-stimulated gene; DAA – Direct-acting antiviral; PD-L1 – Programmed death-ligand 1; PD-1 – Programmed cell-death protein 1; LAG-3 – Lymphocyte activation gene-3; CXCL13 – C-X-C motif chemokine ligand 13; CXCR5 – C-X-C chemokine receptor 5; HCC – Hepatocellular carcinoma

7. TRANSLATIONAL INSIGHTS AND CLINICAL IMPLICATIONS

The convergence of genomic, immunogenic, and multi-omic discoveries in clinical hepatology indicates a revolution that challenges traditional models of precision medicine. Applying these findings in clinical practice is expected to improve patient prognosis, enhance antiviral and immunomodulatory therapies, and advance methods for monitoring cirrhosis and HCC. In Middle Eastern minority populations, where specific HBV genotype D and HCV genotype 4, along with unique host patterns, have led to region-specific variations, integrating preclinical molecular insights is essential to achieving high-quality outcomes. Clinical scores like the APRI and FIB-4 have limited diagnostic and prognostic value due to their narrow molecular scope. Genomic markers such as IFNL3 single-nucleotide polymorphisms, PNPLA3 variants, and HBV integration patterns serve as independent predictors of hepatitis progression and HCC development in patients with fibrosis. [35] Multicenter, integrated molecular signatures that combine viral and tumorigenic markers with metabolomic profiles have been shown to outperform traditional single-marker models, with several metabolomic and multi-omic panels demonstrating diagnostic accuracies (AUCs) well above 80 for early HCC and strong discrimination across fibrosis stages in multicenter validations.[4] These innovative approaches enable dynamic patient evaluation and monitoring, allowing more targeted treatment strategies. Immune support therapies, complementing vaccines that target PD-1, CTLA-4, and other immune checkpoints, have demonstrated effectiveness in overcoming immune resistance. Regarding HCV, metabolic and immunological profiling after sterilizing therapy may identify a small group of patients at risk for fibrosis, guiding additional antifibrotic or metabolic treatments. [22]

8. EXPERT OPINION AND FUTURE DIRECTIONS

The rapidly evolving landscape of viral hepatology offers a remarkable opportunity to shift the field from reactive treatment to proactive, personalized care. As an expert in molecular and clinical microbiology, I believe that the future of hepatitis research in the Middle East will be shaped by the ability to integrate multi-omic data with a nuanced, tailored healthcare approach. The main challenge is not just generating more genetic or immunologic data but analyzing these data within the context of patient complexity, comorbidities, and local healthcare system realities. Although the past decade has seen significant breakthroughs in understanding how host-virus interactions lead to progression from chronic infection to cirrhosis and hepatocellular carcinoma, the overall picture remains unclear—especially for genotype D HBV and genotype 4 HCV infections, which are common in Saudi Arabia and neighboring countries. These types have unique molecular and immunological features that cannot be directly extrapolated from East Asian or Western populations. Moving forward, research will need to focus on intensive regional molecular epidemiology, whole-genome sequencing, and immunoprofiling, combined with translational studies focused on Arab and African-Arab populations. Simultaneously, there must be a fundamental shift from descriptive "association" studies toward mechanistic and predictive research. Instead of merely exploring, integration of multi-omic data should become the primary focus for unraveling host-pathogen interactions. Systems biology approaches supported by artificial intelligence could soon enable real-time threat assessment and personalized treatment guidance at the bedside. Effectively utilizing these tools will require strong interdisciplinary collaboration among clinicians, bioinformaticians, immunologists, and policymakers. Saudi Vision 2030's health-innovation goals and Gulf biobank initiatives provide a promising start for this development, contingent on sustained investment in data and personnel.

Additionally, translating laboratory discoveries into equitable clinical benefits is equally vital. Precision hepatology will only be achieved if lab-based genomics insights help improve survival rates and quality of life in Arar, Riyadh, and Cairo, rather than simply feeding global databases. To bridge this gap, effective consent models tailored to local culture, an affordable sequencing pipeline, and ongoing physician training in molecular interpretation are necessary. Incorporating omics-based risk assessment into national hepatitis elimination programs is a proper way to close the gap and enable earlier diagnosis of fibrosis and malignancy in high-risk groups. The future of this field lies in integrating genomics, immunotherapy, and digital medicine. T-cell rejuvenation programs, neoantigen-targeted vaccines, and personalized checkpoint modulators show promise for achieving functional HBV cures and stable HCV immunoreversion. At the same time, wearables and biosensors, coupled with AI-driven clinical decision support, will enable continuous monitoring of hepatic biomarkers, shifting post-treatment follow-up from reactive to proactive. Finally, regional scientific leadership is crucial. The Middle East should transition from a data-consuming to a data-producing region in global health. Establishing the "Gulf Precision Hepatology Consortium" with coordinated sequencing, governance, and translation pipelines can transform the region's contribution to the virus-liver dataset. If successful, these approaches will not only fill the existing gap but also embody the concept of genuine precision care: delivering the proper treatment to the right patient at the right time and on the proper grounds.

9. CONCLUSION

Chronic hepatitis B and C are increasingly converging toward a shared precision-medicine framework driven by viral genomics, host immunogenetics, and multi-omic profiling. Interactions between viral genotypes and host molecular pathways critically influence disease progression and treatment response, while emerging omics technologies offer opportunities for improved risk stratification, biomarker discovery, and targeted interventions. For Middle Eastern populations, the underrepresentation of HBV genotype D and HCV genotype 4 highlights the need for region-specific genomic reference datasets and longitudinal biobank-based research. Integrating omics-guided diagnostics, digital clinical tools, and emerging immunotherapies into routine hepatology practice will be essential to advancing durable viral control and achieving long-term disease elimination goals.

REFERENCES

1. World Health Organization. Global hepatitis report 2024: action for access in low- and middle-income countries. Geneva: WHO; 2024.
2. Shearer DMR, Cheinquer H, Razavi H, Collaborators PO. Adjusted estimate of the prevalence of hepatitis delta virus in 25 countries and territories. J Hepatol. 2024;80(2):232–42. https://doi.org/10.1016/j.jhep.2023.10.012
3. Al-Faleh FZ. Hepatitis B infection in Saudi Arabia. Ann Saudi Med. 1988;8:474–80.
4. Alqahtani SA, Abaalkhail F, Alghamdi S, Bzeizi K, Al-Hamoudi WK, Paik JM, et al. The burden of metabolic dysfunction-associated steatotic liver disease and viral hepatitis in Saudi Arabia. Saudi J Gastroenterol. 2024;30:310–8. https://doi.org/10.4103/sjg.sjg_123_24
5. Osonoi S, Takebe T. Organoid-guided precision hepatology for metabolic liver disease. J Hepatol. 2024;80:805–21. https://doi.org/10.1016/j.jhep.2023.12.017
6. Alali AA, Abo-Shehada MN. Prevalence of hepatitis B virus infection in the Gulf Cooperation Council: a systematic review and meta-analysis. BMC Infect Dis. 2022;22:819. https://doi.org/10.1186/s12879-022-07757-2
7. Jareebi MA, Awam AA, Otayf DAH, Almraysi SA, Alqamaryat IH, Alghamdi AA, et al. Prevalence and diagnostic determinants of hepatitis B infection among Saudi adults: implications for targeted screening and early detection. Diagnostics. 2025;15:3050. https://doi.org/10.3390/diagnostics15203050
8. Salomon I, Olivier S, Egide N. Advancing hepatitis C elimination in Africa: insights from Egypt. Hepat Med Evid Res. 2024:37–44. https://doi.org/10.2147/HMER.S456789
9. Mahmud S, Chemaitelly H, Alaama A, Hermez J, Abu-Raddad L. Characterizing trends and associations for hepatitis C virus antibody prevalence in the Middle East and North Africa: meta-regression analyses. Sci Rep. 2022;12:20637. https://doi.org/10.1038/s41598-022-24637-7
10. Awadh AA, Alharthi AA, Alghamdi BA, Alghamdi ST, Baqays MK, Binrabaa IS, et al. Coinfection of hepatitis B and C viruses and risk of hepatocellular carcinoma: systematic review and meta-analysis. J Glob Infect Dis. 2024;16:127–34. https://doi.org/10.4103/jgid.jgid_45_24
11. Apol ÁD, Sølund C, Vinten C, Underwood AP, Bukh J, Weis N. Cure of chronic hepatitis C virus infection after DAA treatment only partially restores the functional capacity of exhausted T cell subsets: a systematic review. Front Immunol. 2025;16:1546915. https://doi.org/10.3389/fimmu.2025.1546915
12. Kozlitina J, Sookoian S. Global epidemiological impact of PNPLA3 I148M on liver disease. Liver Int. 2025;45:e16123. https://doi.org/10.1111/liv.16123
13. Ringelhan M, McKeating J, Protzer U. Viral hepatitis and liver cancer. Philos Trans R Soc Lond B Biol Sci. 2017;372:20160274. https://doi.org/10.1098/rstb.2016.0274
14. de Andrade Souza MF, Mergulhã GN, de Andrade SJT, de Lima Procó RE. Comparison of genomes of the Hepadnaviridae family. J Biosci Med. 2024;12:236–45. https://doi.org/10.4236/jbm.2024.124019
15. Kumar R. Review on hepatitis B virus precore/core promoter mutations and their correlation with genotypes and liver disease severity. World J Hepatol. 2022;14:708–18. https://doi.org/10.4254/wjh.v14.i4.708
16. Qian Z, Liang J, Huang R, Song W, Ying J, Bi X, et al. HBV integrations reshaping genomic structures promote hepatocellular carcinoma. Gut. 2024;73:1169–82. https://doi.org/10.1136/gutjnl-2023-329876
17. Xiao Q, Liu Y, Li T, Wang C, He S, Zhai L, et al. Viral oncogenesis in cancer: from mechanisms to therapeutics. Signal Transduct Target Ther. 2025;10:151. https://doi.org/10.1038/s41392-025-0151-9
18. Locatelli M, Faure-Dupuy S. Virus hijacking of host epigenetic machinery to impair immune response. J Virol. 2023;97:e0065823. https://doi.org/10.1128/jvi.00658-23
19. Zou J, Li J, Zhong X, Tang D, Fan X, Chen R. Liver in infections: a single-cell and spatial transcriptomics perspective. J Biomed Sci. 2023;30:53. https://doi.org/10.1186/s12929-023-00853-7
20. He J, Miao R, Chen Y, Wang H, Liu M. The dual role of regulatory T cells in hepatitis B virus infection and related hepatocellular carcinoma. Immunology. 2024;171:445–63. https://doi.org/10.1111/imm.13987
21. Li A, Yi Z, Ma C, Sun B, Zhao L, Cheng X, et al. Innate immune recognition in hepatitis B virus infection. Virulence. 2025;16:2492371. https://doi.org/10.1080/21505594.2025.2492371

22. Lan X, Zebley CC, Youngblood B. Cellular and molecular waypoints along the path of T cell exhaustion. Sci Immunol. 2023;8:eadg3868. https://doi.org/10.1126/sciimmunol.adg3868
23. Wang B, Wang M, Ao D, Wei X. CXCL13-CXCR5 axis: regulation in inflammatory diseases and cancer. Biochim Biophys Acta Rev Cancer. 2022;1877:188799. https://doi.org/10.1016/j.bbcan.2022.188799
24. Vasilev G, Ivanova M, Stanilov I, Miteva L, Stanilova S, Manolova I. Influence of IL10 and TGFB1 promoter polymorphisms on serum cytokine levels in development and severity of RA. Int J Mol Sci. 2022;23:11955. https://doi.org/10.3390/ijms231911955
25. Chen Y, Lin J, Zhao Y, Ma X, Yi H. Toll-like receptor 3 (TLR3) regulation mechanisms and roles in antiviral innate immune responses. J Zhejiang Univ Sci B. 2021;22:609–32. https://doi.org/10.1631/jzus.B2100010
26. Martínez-Chantar M, Delgado T, Beraza N. Revisiting the role of natural killer cells in non-alcoholic fatty liver disease. Front Immunol. 2021;12:640869. https://doi.org/10.3389/fimmu.2021.640869
27. Jawdat D, Uyar FA, Alaskar A, Müller CR, Hajeer A. HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 allele and haplotype frequencies of 28,927 Saudi stem cell donors typed by next-generation sequencing. Front Immunol. 2020;11:544768. https://doi.org/10.3389/fimmu.2020.544768
28. MacLennan SA, Marra MA. Oncogenic viruses and the epigenome: how viruses hijack epigenetic mechanisms to drive cancer. Int J Mol Sci. 2023;24:9543. https://doi.org/10.3390/ijms24049543
29. Schollmeier A, Glitscher M, Hildt E. Relevance of HBx for hepatitis B virus-associated pathogenesis. Int J Mol Sci. 2023;24:4964. https://doi.org/10.3390/ijms24094964
30. Ambikan A, Akusjärvi SS, Sperk M, Neogi U. System-level integrative omics analysis to identify the virus-host immunometabolic footprint during infection. Adv Immunol. 2024;164:73–100. https://doi.org/10.1016/bs.ai.2024.01.004
31. Hardesty JE, Warner JB, Wilkey DW, Phinney BS, Salemi MR, Merchant ML, et al. Hepatic proteomic changes associated with liver injury caused by alcohol consumption in Fpr2−/− mice. Int J Mol Sci. 2024;25:9807. https://doi.org/10.3390/ijms25019807
32. Narmada BC, Khakpoor A, Shirgaonkar N, Narayanan S, Aw PPK, Singh M, et al. Single-cell landscape of functionally cured chronic hepatitis B patients reveals activation of innate and altered CD4-CTL-driven adaptive immunity. J Hepatol. 2024;81:42–61. https://doi.org/10.1016/j.jhep.2024.03.005
33. Ye J, Lai J, Luo L, Zhou T, Sun Y, Zhong B. Cytokeratin 18 fragment in liver inflammation and fibrosis: systematic review and meta-analysis. Clin Chim Acta. 2025;569:120147. https://doi.org/10.1016/j.cca.2025.120147
34. Anh NH, Long NP, Min YJ, Ki Y, Kim SJ, Jung CW, et al. Molecular and metabolic phenotyping of hepatocellular carcinoma for biomarker discovery: a meta-analysis. Metabolites. 2023;13:1112. https://doi.org/10.3390/metabo13111112
35. Amoroso M, Augustin S, Moosmang S, Gashaw I. Non-invasive biomarkers prognostic of decompensation events in NASH cirrhosis: a systematic literature review. J Mol Med. 2024;102:841–58. https://doi.org/10.1007/s00109-024-02456-7

CONFLICT OF INTEREST
Authors declare no conflict of interest.
GRANT SUPPORT AND FINANCIAL DISCLOSURE
None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	SAH, AOJ
Acquisition, Analysis or Interpretation of Data:	SAH, AOJ
Manuscript Writing & Approval:	SAH, AOJ

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.