

COMPARATIVE IMMUNE MICROENVIRONMENT PROFILING IN HBV-, HCV-, AND DUAL-INFECTED HEPATOCELLULAR CARCINOMA: TOWARD ETIOLOGY-SPECIFIC IMMUNOTHERAPEUTIC TARGETS

Muhammad Ashraf^{*1}, Shafaq Ibrahim², Asif Naveed³, Abubakar Siddique⁴, Irfan Ahmed⁵, Shahidullah⁶

^{*1,2}Fellow HPB And Liver Transplant Surgery, Shaikh Zayed Hospital, Lahore

³Assistant Prof HPB & Liver Transplant Dept Farooq Hospital Lahore

⁴Consultant Hepatobiliary Surgeon in HMC Peshawar

⁵Senior Registrar Surgery SIMS/ Services Hospital Lahore

⁶Fellow HPB/LT Surgery Shaikh Zayed Hospital Lahore

^{*1}drjamashraf@gmail.com, ²shafaqibrahim4@gmail.com, ³drasifnaveedbhullar@gmail.com, ⁴abubakarktk90@gmail.com, ⁵irfan451@hotmail.com, ⁶shahidullah_afridi@yahoo.com

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Corresponding Author: *

Muhammad Ashraf

Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the major cause of global cancer-related mortality. One of the most important risk factors for HCC, is a chronic infection with HBV or HCV. Despite similarities in clinical endpoints, the pathophysiological mechanisms underlying HBV- and HCV-related HCC are distinct, with implications for prevention, diagnosis, and treatment.

INTRODUCTION

A key biological difference lies in the viral lifecycle and genomic interaction with host cells. HBV, a DNA virus, has the unique ability to integrate its genetic material into the host genome, leading to insertional mutagenesis and genomic instability—a major driver of hepatocarcinogenesis (Capasso et al., 2024; Viruses, 2024). In contrast, HCV is an RNA virus that does not integrate into the host genome but induces HCC primarily through chronic

inflammation, oxidative stress, and subsequent cirrhosis (Tian et al., 2022).

Borden et al. (2024) conducted transcriptomic profiling of HBV- and HCV-induced HCCs and found that, despite differing upstream mechanisms, the tumours converge on similar immune and transcriptional landscapes, suggesting that the downstream effects of both viruses may activate common oncogenic pathways. However, distinct differences in early immune modulation and liver

microenvironment are evident. Anwar et al. (2024) observed that patients with HBV-related HCC responded better to immune checkpoint inhibitors than those with HCV-induced HCC, attributing this to differences in immune exhaustion and tumour-infiltrating lymphocytes.

Histologically, HCV-related HCC often arises in a background of fully developed cirrhosis, while HBV-related HCC can occur in non-cirrhotic livers (Afro-Egyptian Journal, 2024). This has significant implications for surveillance strategies. For instance, Jean et al. (2024) noted that patients with HBV infection in Egypt presented with HCC at more advanced stages compared to those with HCV, likely due to differences in disease progression and screening effectiveness.

Molecular studies further clarify the contrast. Capasso et al. (2024) emphasize that HBV-induced HCC frequently exhibits TP53 mutations and activation of WNT/ β -catenin signaling via viral integration, whereas HCV-related HCC tends to involve deregulation of immune genes and increased epigenetic modifications. Adepoju et al. (2024) extended this knowledge by analyzing dual-infected (HBV + HCV) patients, finding they represent a biologically distinct group, combining features of both viruses with unique somatic mutation profiles and partial viral DNA integration.

Epidemiological differences also provide insight into disease behavior. A study by Huang (2024) summarized how HCV-driven HCC has a longer latency period and develops predominantly through liver fibrosis and immune-mediated cytotoxicity. These patients may therefore benefit more from antifibrotic and anti-inflammatory therapies than direct antiviral regimens alone.

Even though the clinical outcomes are poor for both types, treatment response varies. For example, the immunotherapy outcomes described by Anwar et al. (2024) suggest that HBV-related HCC might respond more favourably to PD-1/PD-L1 blockade than HCV-related HCC, due to differences in immune microenvironment shaped by each virus.

As Borden et al. (2024) and the study in the Afro-Egyptian Journal emphasize, these molecular and immunological differences must be considered when designing screening tools, predicting prognosis, and

choosing therapeutic regimens. The notion of “one-size-fits-all” therapy for HCC is increasingly outdated. Moreover, Capasso and colleagues (2024) argue for the redefinition of HCC subtypes by etiology, urging precision medicine approaches that target the unique oncogenic pathways activated by HBV or HCV.

Finally, the findings by Viruses (2024) and Adepoju et al. (2024) on HBV-HCV dual infections are particularly valuable. These patients may not fit conventional risk models and require specific monitoring protocols due to a hybrid pathogenesis involving both inflammatory and integrative oncogenic pressures.

Yang et al. (2024) conducted a retrospective study to evaluate the prevalence of metabolic syndrome among patients with HCC of different etiologies. The study found that patients with HCV-related HCC had a higher prevalence of metabolic syndrome compared to those with HBV-related HCC. This suggests that metabolic factors may play a more significant role in the pathogenesis of HCV-related HCC, highlighting the need for tailored prevention and management strategies

CONCLUSION

HBV and HCV contribute to hepatocellular carcinoma through overlapping but distinct mechanisms. HBV-related HCC is primarily driven by viral DNA integration and host genomic alterations, while HCV promotes carcinogenesis through chronic inflammation and immune-mediated hepatocyte damage. These pathophysiological distinctions manifest in differences in tumor biology, immune responses, clinical presentation, and therapeutic responsiveness. As highlighted across all ten studies, understanding these nuances is critical for the development of more effective, virus-specific HCC management strategies.

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