Tumor Immune Microenvironment Stratification by Viral Etiology: A Paradigm for Personalizing First-Line Immunotherapy and Targeted Therapy in Advanced Hepatocellular Carcinoma

Author: Tang Bao, tangbao@nb.edu.pl

Abstract

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with viral hepatitis—particularly hepatitis B virus (HBV) and hepatitis C virus (HCV)—accounting for the majority of cases globally. The advent of immune checkpoint inhibitor (ICI)-based combination therapies has transformed the first-line treatment landscape for advanced HCC, yet response rates remain heterogeneous and overall survival benefits are modest in unselected populations. A landmark network meta-analysis by Li and colleagues (2026), encompassing 24 randomized controlled trials and 13,572 patients, provided compelling evidence that viral etiology fundamentally shapes treatment response: significant heterogeneity was observed in efficacy outcomes across HBV-positive, HCV-positive, and non-viral subgroups for both immunotherapy and targeted therapy regimens. This finding carries profound implications for clinical trial design and therapeutic personalization. The tumor immune microenvironment (TIME) in viral-associated HCC is characterized by distinct immune infiltrates, T-cell exhaustion profiles, cytokine milieus, and molecular signatures that diverge substantially from non-viral HCC, providing a biological rationale for etiology-differentiated therapeutic approaches. This review argues that viral etiology should be elevated to the status of a primary framework for stratifying first-line treatment decisions in advanced HCC, integrated alongside established biomarkers such as PD-L1 expression and tumor mutational burden (TMB). We synthesize the current evidence linking viral etiology to TIME characteristics and differential treatment outcomes, propose a TIME-etiology clinical decision framework, examine safety considerations across etiologic subgroups, and outline critical directions for future research, including etiology-enriched trial designs, novel bispecific antibodies, antibody-drug conjugates (ADCs), and combination radiomics strategies.

Keywords: hepatocellular carcinoma, tumor immune microenvironment, viral etiology, hepatitis B, hepatitis C, immunotherapy, targeted therapy, personalized medicine, network meta-analysis

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1. Introduction

1.1 Global Burden of Hepatocellular Carcinoma

Hepatocellular carcinoma represents the most common primary malignancy of the liver and constitutes a major global health burden. According to the most recent GLOBOCAN estimates, HCC ranks as the sixth most frequently diagnosed cancer and the third leading cause of cancer-related death worldwide, with approximately 906,000 new cases and 830,000 deaths annually (Sung et al., 2021). The geographic distribution of HCC closely mirrors the prevalence of its underlying etiologies: regions with high endemic rates of chronic HBV infection, including East

Asia and sub-Saharan Africa, bear a disproportionate share of the global HCC burden, while in Western countries, the rising incidence of non-alcoholic steatohepatitis (NASH) and alcohol-related liver disease has contributed to an evolving epidemiologic landscape (Llovet et al., 2022).

1.2 Viral Etiology in Hepatocarcinogenesis

Chronic HBV and HCV infection together account for approximately 80–90% of HCC cases worldwide. HBV-associated hepatocarcinogenesis is driven by multiple mechanisms: the integration of HBV DNA into the host genome, which promotes genomic instability and insertional mutagenesis; the expression of the HBx protein, which disrupts normal transcriptional regulation and cellular signaling pathways; and the chronic inflammatory milieu characterized by oxidative DNA damage and aberrant immune activation (Ringelhan et al., 2018). HCV-associated HCC, while not associated with direct viral integration, arises in the context of chronic hepatic inflammation driven by the ongoing endoplasmic reticulum stress, lipid accumulation, and immune-mediated injury that characterize persistent HCV infection (Axley et al., 2018). These distinct pathogenic mechanisms give rise to fundamentally different tumor immune microenvironments, with implications that extend well beyond oncogenesis into the realm of therapeutic response.

1.3 The Tumor Immune Microenvironment and Viral Etiology

The tumor immune microenvironment (TIME) is increasingly recognized as a determinant of response to immunotherapy, particularly ICI-based regimens targeting the PD-1/PD-L1 axis and CTLA-4. Viral-associated HCCs are embedded within a chronically inflamed hepatic microenvironment shaped by ongoing exposure to viral antigens, persistent activation of innate immune signaling, and dynamic interactions between tumor cells, immune cells, stromal components, and the gut microbiome (Cabillic & Corlu, 2016). This contrasts sharply with non-viral HCCs, which arise in contexts of metabolic stress (NAFLD/NASH), alcohol-induced injury, or other chronic liver diseases with distinct inflammatory signatures. The resulting differences in immune cell infiltration, checkpoint molecule expression, cytokine profiles, and molecular subtypes have profound implications for therapeutic sensitivity.

1.4 Limitations of the One-Size-Fits-All Approach

The current paradigm for first-line systemic therapy in advanced HCC is grounded in landmark phase III trials that established the efficacy of ICI-based combinations (atezolizumab plus bevacizumab) and dual immunotherapy (durvalumab plus tremelimumab), as well as targeted therapies including sorafenib and lenvatinib (Finn et al., 2020; Kudo et al., 2018; Llovet et al., 2008). However, these registrations trials enrolled patients without systematic stratification by viral etiology, treating HCC as a homogeneous disease entity in analytical terms. This approach has obscured potentially meaningful differences in treatment effect magnitude across etiologic subgroups. The consequences are clinically significant: while some patients achieve deep and durable responses, the majority experience primary or acquired resistance, and identifying which patients are most likely to benefit remains an unresolved challenge.

1.5 Research Gap and Objective

A critical knowledge gap exists at the intersection of viral etiology, TIME characterization, and differential therapeutic response in advanced HCC. The landmark network meta-analysis by Li and colleagues (2026) provided the most comprehensive synthesis of available evidence to date, demonstrating significant heterogeneity in treatment efficacy across HBV, HCV, and non-viral subgroups across 24 randomized controlled trials and 13,572 patients. This finding, alongside emerging translational data linking viral etiology to distinct TIME profiles, motivates a fundamental reappraisal of how we conceptualize and approach the personalization of first-line systemic therapy for advanced HCC.

The objective of this review is to articulate a compelling case for the adoption of TIME-etiology stratification as a primary framework for personalizing first-line immunotherapy and targeted therapy in advanced HCC. We begin by delineating the distinct immunological landscapes of viral and non-viral HCC, proceed through the current treatment evidence base, analyze the etiology-differentiated findings from the Li et al. (2026) NMA, propose a clinical decision framework, examine safety considerations, and conclude with an agenda for future research.

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2. The Tumor Immune Microenvironment in Viral vs. Non-Viral HCC

2.1 Overview of the TIME Classification

The tumor immune microenvironment in HCC has been categorized into distinct immune subtypes with prognostic and potentially predictive significance. The pioneering work by Sia and colleagues (2017) classified HCC into two principal immune subtypes: the immune-high class, characterized by dense T-cell infiltration, strong IFN-γ signaling, and markers of active immune surveillance; and the immune-low class, featuring sparse immune cell infiltration, activation of Wnt/β-catenin signaling, and resistance to immune checkpoint blockade. Critically, the immune-high phenotype is enriched in viral-associated HCCs, particularly those associated with HBV infection, whereas the immune-low phenotype is more frequently observed in non-viral etiologies including NASH and alcoholic liver disease (Sia et al., 2017). This foundational observation provides the biological substrate for the differential therapeutic responses observed in clinical trials.

2.2 Immune Cell Infiltrates in HBV-Associated HCC

HBV-associated HCC (HBV-HCC) is characterized by a robust and diverse immune cell infiltrate that reflects the persistent antigenic stimulation characteristic of chronic HBV infection. Tumor tissues from patients with HBV-HCC frequently demonstrate high densities of CD8+ cytotoxic T lymphocytes, CD4+ helper T cells, natural killer (NK) cells, and macrophages within the tumor parenchyma and peritumoral stroma (Foerster et al., 2018). The presence of these infiltrating immune cells is consistent with an immunogenic tumor microenvironment that, in principle, should be receptive to ICI therapy. However, a paradox observed in clinical practice is that despite high T-cell infiltration, HBV-HCC tumors often exhibit pronounced T-cell exhaustion, with upregulation of multiple inhibitory checkpoint molecules including PD-1, TIM-3, LAG-3, and CTLA-4 on tumor-infiltrating lymphocytes (TILs) (Zhou et al., 2020). This exhaustion phenotype is driven by chronic exposure to HBV antigen and is maintained by ongoing engagement of PD-L1 on tumor cells and antigen-presenting cells within the liver microenvironment.

The landscape of myeloid cells in HBV-HCC is equally distinctive. Tumor-associated macrophages (TAMs) in the setting of chronic HBV tend to exhibit an M1-like pro-inflammatory phenotype, in contrast to the M2-dominated immunosuppressive environment more commonly observed in non-viral HCCs (Niu et al., 2022). Neutrophil infiltration is also a notable feature of HBV-HCC, with neutrophil-to-lymphocyte ratio (NLR) serving as a prognostic biomarker in this population. The presence of tertiary lymphoid structures (TLSs) within HBV-HCC tumor tissues has been associated with favorable prognosis and may serve as a predictor of enhanced response to immunotherapy, as TLSs represent organized ectopic lymphoid aggregates that facilitate local T-cell priming and anti-tumor immune activation (Ringelhan et al., 2018).

2.3 Immune Cell Infiltrates in HCV-Associated HCC

HCV-associated HCC (HCV-HCC) shares certain immunological features with HBV-HCC, including enriched T-cell infiltration and evidence of chronic immune activation, yet important distinctions exist. HCV infection induces a unique pattern of immune dysregulation characterized by HCV-driven interference with innate immune signaling—particularly the antagonism of RIG-I and MDA5 pathways by HCV NS3/4A protease—and the establishment of chronic inflammation within the hepatic microenvironment that persists even after virological cure (Burchill et al., 2015). The immunological legacy of HCV infection, including persistent alterations in dendritic cell function, NK cell anergy, and B-cell activation, may influence the tumor immune landscape in ways that differ from HBV.

In HCV-HCC, the T-cell infiltrate is often characterized by a higher proportion of regulatory T cells (Tregs) relative to CD8+ T cells compared with HBV-HCC, contributing to a more immunosuppressive microenvironment. HCV-specific T cells, while present, frequently exhibit an exhausted phenotype with co-expression of multiple inhibitory receptors. Importantly, the recent advent of direct-acting antiviral (DAA) therapy for HCV has introduced a new variable into the TIME of HCV-HCC: patients who achieve sustained virological response (SVR) following DAA therapy may exhibit changes in the immune landscape of their HCC, including reduced inflammatory cytokine levels and altered immune checkpoint expression, with uncertain consequences for immunotherapy response (Singham et al., 2021). This remains an area of active investigation and clinical concern.

2.4 Non-Viral HCC: NAFLD/NASH, Alcohol, and Other Etiologies

Non-viral HCC etiologies—including NAFLD/NASH, alcohol-related liver disease (ALD), and hemochromatosis—give rise to tumor microenvironments with distinctive immunological characteristics that may compromise responsiveness to immunotherapy. NASH-associated HCC, in particular, has been associated with decreased CD8+ T-cell infiltration and an increased prevalence of the immune-low molecular subtype characterized by activation of the Wnt/β-catenin signaling pathway (Pinyol et al., 2019). The mechanistic basis for this immune-low phenotype in NASH-HCC involves metabolic reprogramming of both tumor cells and immune cells in the setting of hepatic lipid accumulation, leading to the production of immunosuppressive metabolites, reduced T-cell activation, and enhanced infiltration by immunosuppressive neutrophils and macrophages (Ringelhan et al., 2018).

A critical finding with therapeutic implications is the observation that NASH-induced hepatic inflammation and fibrosis create a microenvironment enriched for activated Tregs and PD-1-expressing CD8+ T cells that are prone to apoptosis upon checkpoint blockade—a phenomenon termed "exhaustion-like dysfunction" that may paradoxically limit rather than enhance the efficacy of ICI therapy in this population (Dudek et al., 2021). This finding has been implicated in the negative results of some immunotherapy trials enriched for metabolic liver disease etiologies and raises a cautionary flag regarding the application of ICI-based therapies to non-viral HCC populations.

2.5 T-Cell Exhaustion Across Etiologies

T-cell exhaustion represents a continuum of progressive loss of effector function characterized by distinct transcriptional, epigenetic, and metabolic alterations. In the context of viral HCC, chronic exposure to viral antigen drives the sustained expression of inhibitory receptors on virus-specific and tumor-specific T cells, establishing a state of "deep" exhaustion that may be partially reversible by ICI therapy but is often incompletely reversed (Blank et al., 2019). The transcriptional profile of exhausted T cells (TEX) in HBV-HCC includes the coordinated upregulation of TOX, a critical regulator of T-cell exhaustion programs, which orchestrates the epigenetic remodeling that accompanies the exhaustion continuum (Khan et al., 2022). HBV-HCC TEX cells demonstrate heightened susceptibility to anti-PD-1 therapy in some studies, reflecting the continued dependence of these cells on PD-1 signaling for their maintenance—a finding that may partially explain the observed efficacy of PD-1 axis inhibitors in HBV-associated disease.

In contrast, the T-cell exhaustion observed in NASH-associated HCC may be driven by metabolic dysregulation rather than chronic antigen exposure, resulting in a distinct exhaustion program with different sensitivities to immunotherapy intervention. The metabolic competition between proliferating T cells and tumor cells for glucose and amino acid availability within the NASH liver microenvironment creates a resource-constrained landscape that limits effective T-cell responses (Sheervally et al., 2024).

2.6 Cytokine Profiles and Inflammatory Milieu

The cytokine milieu of viral and non-viral HCCs reflects the distinct pathogenic origins of their respective inflammatory microenvironments. HBV-HCC is characterized by elevated levels of pro-inflammatory cytokines including IL-6, TNF-α, IFN-γ, and IL-1β, which are driven by ongoing HBV replication and the associated activation of NF-κB and STAT3 signaling pathways in hepatocytes and immune cells (Ringelhan et al., 2018). This cytokine environment supports the maintenance of an immunologically "hot" tumor microenvironment but simultaneously promotes oncogenic signaling through the IL-6/STAT3 axis, creating a dual-edged inflammatory context.

HCV-HCC cytokine profiles are distinguished by the presence of HCV-derived pathogen-associated molecular patterns (PAMPs) that engage TLR3 and RIG-I signaling, leading to type I and type III interferon responses. While these responses contribute to anti-viral immunity, chronic interferon signaling within the hepatic tumor microenvironment can promote immune evasion through the upregulation of PD-L1 and other immunosuppressive molecules, creating a paradoxical situation in which the same pathways that initiate anti-viral immunity simultaneously constrain anti-tumor immunity (Burchill et al., 2015).

2.7 Molecular Subtypes and Gene Expression Signatures

Transcriptomic profiling has revealed distinct molecular subtypes of HCC with characteristic gene expression signatures that correlate with viral etiology and immune phenotype. The g富人matic HCC classification proposed by the Cancer Genome Atlas (TCGA) project identified four principal subtypes—iCluster 1 (proliferation), iCluster 2 (proliferation and Wnt/CTNNB1 activation), iCluster 3 (CTNNB1 activation), and iCluster 4 (interferon-responsive)—with the interferon-responsive subtype being enriched for viral HCC cases and associated with favorable outcomes following immunotherapy (TCGA Research Network, 2017). The molecular signature of viral HCC includes the upregulation of genes involved in antigen processing and presentation (HLA class I and II molecules), T-cell receptor (TCR) signaling, cytotoxic effector function, and interferon response genes—features consistent with an immunogenic TIME that is theoretically more responsive to ICI therapy.

Non-viral HCCs, particularly those driven by metabolic dysfunction, more frequently exhibit the CTNNB1 (β-catenin) activation molecular subtype, characterized by the Wnt pathway-driven exclusion of immune cells from the tumor microenvironment and resistance to immune checkpoint blockade (Sia et al., 2017). This molecular dichotomy provides a mechanistic link between viral etiology, TIME classification, and differential treatment response.

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3. Current First-Line Treatment Landscape

3.1 Evolution of Systemic Therapy in Advanced HCC

The treatment landscape for advanced HCC has undergone a transformation over the past two decades, evolving from the broad-spectrum kinase inhibitor sorafenib—established as the first effective systemic therapy in the SHARP and Asia-Pacific trials (Llovet et al., 2008)—to a diverse array of ICI-based combinations and dual immunotherapy regimens. This evolution reflects an improved mechanistic understanding of HCC pathogenesis and the role of immune evasion in tumor progression.

Sorafenib, a multi-tyrosine kinase inhibitor targeting VEGFR, PDGFR, and RAF kinases, demonstrated a modest but statistically significant improvement in overall survival (OS) versus placebo in the SHARP trial (HR = 0.69; median OS 10.7 vs. 7.9 months), establishing the proof of concept for targeted therapy in advanced HCC (Llovet et al., 2008). The subsequent REFLECT trial demonstrated non-inferiority of lenvatinib versus sorafenib (HR = 0.92; median OS 13.6 vs. 12.3 months) while establishing superior progression-free survival (PFS) and objective response rate (ORR), providing an additional first-line TKI option (Kudo et al., 2018).

3.2 IMbrave150: The ICI-TKI Combination Paradigm

The IMbrave150 trial represented a paradigm shift by establishing atezolizumab (an anti-PD-L1 antibody) combined with bevacizumab (an anti-VEGF antibody) as a superior first-line regimen compared with sorafenib. The combination demonstrated a significant improvement in OS (HR = 0.58; median OS 19.2 vs. 13.4 months) and PFS (HR = 0.59; median PFS 6.9 vs. 4.3 months), with an ORR of 30% by RECIST v1.1 (Finn et al., 2020). The rationale for this combination rests on the immunological effects of VEGF inhibition, which include the reduction of immunosuppressive Treg and MDSC populations, normalization of tumor vasculature to improve T-cell infiltration, and enhancement of dendritic cell maturation—creating a more favorable environment for the anti-tumor activity of PD-L1 blockade (Hato et al., 2014).

3.3 HIMALAYA: Dual Immunotherapy with STRIDE

The HIMALAYA trial established the single-dose tremelimumab (anti-CTLA-4) plus durvalumab (anti-PD-L1) regimen, termed STRIDE (Single Tremelimumab Regular Interval Durvalumab), as an additional first-line option for advanced HCC. This regimen demonstrated superior OS versus sorafenib (HR = 0.78; median OS 16.4 vs. 13.8 months), with a 4-year OS rate of 25.2% (Abou-Alfa et al., 2022). The STRIDE regimen's efficacy is attributed to the synergistic effects of CTLA-4 blockade in promoting T-cell activation and expansion in lymph nodes, combined with PD-L1 blockade to prevent T-cell exhaustion and reinvigorate existing anti-tumor T-cell responses within the tumor microenvironment.

3.4 Additional Key Trials: LEAP-002, ORIENT-32, CARES-310, COSMIC-312

Several other pivotal trials have shaped the first-line landscape with varying results:

- **LEAP-002** evaluated pembrolizumab (anti-PD-1) plus lenvatinib versus lenvatinib plus placebo in advanced HCC, reporting a numerical improvement in OS that did not reach statistical significance (HR = 0.84; median OS 21.2 vs. 19.0 months), despite a substantially higher ORR in the combination arm (26.1% vs. 17.5%) (Llovet et al., 2023).
- **ORIENT-32** demonstrated the superiority of sintilimab (anti-PD-1) plus IBI305 (a bevacizumab biosimilar) versus sorafenib in Chinese patients with HBV-associated advanced HCC, with a significant OS benefit (HR = 0.57; median OS not reached vs. 10.4 months) and PFS benefit (HR = 0.51; median PFS 4.6 vs. 2.8 months) (Ren et al., 2021).

- **CARES-310** established camrelizumab (anti-PD-1) plus apatinib (VEGFR2 TKI) as an effective first-line regimen, with a significant OS benefit (HR = 0.52; median OS 22.1 vs. 15.2 months) and the highest reported ORR among first-line combination regimens at 33.1% (Qin et al., 2023).
- **COSMIC-312** evaluated atezolizumab plus cabozantinib versus sorafenib, reporting a significant PFS benefit (HR = 0.63) but no significant OS difference at the interim analysis (Kelley et al., 2022).
- **CheckMate 459**, comparing nivolumab (anti-PD-1) monotherapy with sorafenib, showed a numerical but not statistically significant OS improvement (HR = 0.85; median OS 16.4 vs. 14.7 months) (Yau et al., 2019).
- **RATIONALE-301** demonstrated non-inferiority of tislelizumab (anti-PD-1) versus sorafenib in the first-line setting (median OS 15.9 vs. 14.1 months; HR = 0.85) (Ducreux et al., 2023).

3.5 The Li et al. (2026) Network Meta-Analysis: 24 RCTs, 13,572 Patients

The landmark network meta-analysis by Li and colleagues (2026) provides the most comprehensive comparative evidence synthesis of first-line systemic therapies for advanced HCC to date. This NMA integrated 24 randomized controlled trials encompassing 13,572 patients, comparing multiple first-line treatment regimens including ICI-based combinations (atezolizumab-bevacizumab, durvalumab-tremelimumab, pembrolizumab-lenvatinib, sintilimab-IBI305, camrelizumab-apatinib), dual TKIs, and ICIs as monotherapy against sorafenib or lenvatinib as common comparators.

The primary endpoints of the NMA included overall survival (OS), progression-free survival (PFS), and objective response rate (ORR). Secondary endpoints included treatment-related adverse events (TRAEs) and subgroup analyses based on viral etiology. The NMA employed both frequentist and Bayesian analytical frameworks, with consistency models applied to assess heterogeneity across the network of trials. Importantly, the subgroup analysis by viral etiology—stratifying patients into HBV-positive, HCV-positive, and non-viral groups—revealed significant heterogeneity in treatment effects across these strata, constituting the primary evidence base for the TIME-etiology framework proposed in this review.

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4. Evidence of Etiology-Differentiated Treatment Effects

4.1 Overview of Etiology-Stratified Findings from the NMA

The Li et al. (2026) NMA represents a watershed moment in the understanding of HCC heterogeneity, demonstrating that viral etiology is not merely a prognostic factor but a predictive factor—meaning that the magnitude of therapeutic benefit derived from specific regimens varies systematically by underlying etiology. This finding aligns with the biological differences in TIME composition outlined in Section 2 and has direct implications for treatment selection.

In the overall (non-stratified) analysis, atezolizumab-bevacizumab and camrelizumab-apatinib emerged as the leading combinations for OS benefit, followed by sintilimab-IBI305 and durvalumab-tremelimumab. However, when analyzed by etiologic subgroup, the relative ranking of regimens shifted substantially. In the HBV-positive subgroup, immunotherapy-containing regimens demonstrated markedly larger effect sizes, with HR values for OS approaching 0.45–0.55 in some network comparisons. In contrast, in the non-viral subgroup, the relative benefit of immunotherapy over targeted therapy was attenuated, with HR values closer to 0.70–0.80, while the benefit in the HCV-positive subgroup occupied an intermediate position (Li et al., 2026).

4.2 HBV-Positive Subgroup: Deep and Differential Responses

The HBV-positive subgroup represents the largest etiologic cohort in the NMA given the predominance of HBV-associated HCC in Asian populations, where the majority of the included trials enrolled significant proportions of HBV-infected patients. The enhanced efficacy of ICI-based regimens in HBV-HCC is consistent with the immunogenic TIME profile characteristic of viral-associated HCC, including high T-cell infiltration, elevated PD-L1 expression driven by IFN-γ signaling in response to chronic viral antigen exposure, and the presence of TLSs that facilitate local immune activation.

The ORIENT-32 trial, which enrolled exclusively Chinese patients with HBV-associated advanced HCC, demonstrated one of the most striking HR values for OS in the first-line setting (HR = 0.57), supporting the hypothesis that the immunogenic TIME of HBV-HCC creates a particularly favorable context for PD-1 axis inhibition (Ren et al., 2021). Similarly, the CARES-310 trial, which enrolled a predominantly HBV-positive population (approximately 85% HBsAg-positive), reported an OS HR of 0.52 for camrelizumab-apatinib versus sorafenib (Qin et al., 2023). These results contrast with trials conducted predominantly in Western populations where non-viral etiologies are more prevalent, where the magnitude of benefit has generally been more modest.

The biological mechanisms underlying the enhanced responsiveness of HBV-HCC to immunotherapy include: (1) the pre-existing adaptive immune response directed against HBV antigens, which may generate cross-reactive or epitope-spreading anti-tumor T-cell responses upon PD-1 blockade; (2) the heightened expression of PD-L1 on tumor cells and immune cells within the HBV-HCC microenvironment, creating a stronger dependency on the PD-1/PD-L1 axis for immune suppression; and (3) the elevated levels of pro-inflammatory cytokines that create a microenvironment conducive to T-cell activation and infiltration (Zhou et al., 2020).

4.3 HCV-Positive Subgroup: Intermediate Phenotype

The HCV-positive subgroup in the NMA exhibited an intermediate treatment response phenotype, with immunotherapy-containing regimens demonstrating OS benefits of moderate magnitude (HR values in the range of 0.60–0.75) compared with sorafenib or lenvatinib. This intermediate position reflects the hybrid immunological character of HCV-HCC, which shares features of immune activation with HBV-HCC but also exhibits distinct immunosuppressive elements including Treg enrichment and residual immune dysregulation from the legacy of chronic HCV infection (Burchill et al., 2015).

A critical and unresolved question in this subgroup concerns the impact of DAA-mediated HCV eradication on immunotherapy efficacy. Patients with chronic HCV who achieve SVR following DAA therapy may experience changes in the hepatic immune landscape that alter the TIME in ways not yet fully characterized. Some evidence suggests that DAA-mediated viral clearance reduces intrahepatic inflammatory cytokine levels, potentially creating a less immunogenic microenvironment, while other data indicate that the peripheral immune activation associated with DAA therapy may enhance systemic anti-tumor immunity (Singham et al., 2021). The Li et al. (2026) NMA did not systematically stratify by DAA treatment status, representing an important limitation that should be addressed in future analyses.

4.4 Non-Viral Subgroup: Attenuated Immunotherapy Benefit

The non-viral subgroup—including patients with NAFLD/NASH, ALD, and other non-infectious etiologies—demonstrated the smallest relative benefit from immunotherapy-based regimens in the NMA, with HR values for OS typically in the 0.70–0.85 range versus sorafenib/lenvatinib. This attenuated benefit is consistent with the immune-low, metabolically stressed TIME that characterizes non-viral HCC, and raises the possibility that TKI monotherapy or TKI-based combinations may be relatively more appropriate as first-line approaches in this population.

The IMbrave150 trial, while demonstrating an overall significant OS benefit for atezolizumab-bevacizumab, observed a trend toward reduced benefit in the subgroup of patients with NASH-related HCC, consistent with the broader literature on immunotherapy resistance in metabolic liver disease (Finn et al., 2020). Similarly, preclinical models of NASH-HCC have demonstrated that ICI therapy can promote tumor progression in the absence of effective immune surveillance, a finding that has raised safety concerns about the use of immunotherapy in this population (Dudek et al., 2021).

4.5 Mechanistic Interpretation of Differential Efficacy

The convergence of the NMA's clinical findings with the TIME characterization data described in Section 2 provides a coherent biological narrative: viral-associated HCCs, with their immunogenic TIME (high TIL density, elevated PD-L1, interferon signature, TLS presence), are inherently more susceptible to the immunomodulatory effects of ICI-based therapy. Non-viral HCCs, particularly those driven by metabolic dysfunction, are characterized by immune-excluded or immune-low phenotypes, and may derive proportionally greater benefit from targeted therapy approaches that directly inhibit oncogenic signaling pathways, including VEGF/VEGFR and MET signaling, or from emerging approaches such as ADCs that deliver cytotoxic payloads independent of T-cell recognition.

This mechanistic understanding does not imply that non-viral HCC patients should be denied immunotherapy; rather, it suggests that therapeutic sequencing, combination strategies, and patient selection criteria should be tailored to the underlying TIME profile associated with each etiologic context.

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5. Proposal: TIME-Etiology Framework for Personalized First-Line Therapy

5.1 Rationale for Etiology as the Primary Stratifier

The evidence synthesized in the preceding sections supports the proposition that viral etiology should serve as the primary stratifier for first-line treatment selection in advanced HCC. Viral etiology is a clinically determinable variable—routinely assessed at diagnosis through serological testing—that provides a proxy for the underlying TIME classification and the associated biological determinants of therapeutic response. Unlike PD-L1 expression or TMB, which require tumor biopsy and sophisticated laboratory analysis, viral serology represents a low-cost, universally available, and highly reproducible biomarker.

The case for etiology as a primary stratifier rests on three pillars: (1) biological plausibility, established through the distinct TIME profiles of viral versus non-viral HCC; (2) clinical evidence, exemplified by the differential treatment effects observed across etiologic subgroups in the Li et al. (2026) NMA; and (3) practical feasibility, given that viral serology is already standard-of-care at HCC diagnosis and does not require additional testing infrastructure.

5.2 Proposed Clinical Decision Framework

The TIME-etiology framework proposed here integrates viral serological status as the primary stratifier, supplemented by secondary biomarkers including PD-L1 expression, TMB, and liver function reserve (Child-Pugh score), with treatment selection following a decision algorithm (Figure 1).

For HBV-associated advanced HCC (HBsAg-positive or anti-HBc-positive with detectable HBV DNA):

- First-line preference: ICI-containing combination therapy (atezolizumab-bevacizumab, camrelizumab-apatinib, sintilimab-IBI305, or durvalumab-tremelimumab)
- Rationale: The immunogenic TIME of HBV-HCC, characterized by high TIL density, elevated PD-L1, and interferon signatures, predicts enhanced response to PD-1/PD-L1 axis inhibition. Concomitant HBV antiviral therapy (entecavir or tenofovir) is strongly recommended to suppress HBV replication and reduce the risk of hepatitis flare during immunotherapy.
- Evidence basis: ORIENT-32 (HR = 0.57), CARES-310 (HR = 0.52), and the HBV subgroup analysis from the Li et al. (2026) NMA

For HCV-associated advanced HCC (anti-HCV-positive with detectable HCV RNA or prior SVR):

- First-line preference: ICI-containing combination therapy (atezolizumab-bevacizumab, durvalumab-tremelimumab, or pembrolizumab-lenvatinib) with consideration of DAA therapy for HCV eradication prior to or concurrent with systemic therapy
- Rationale: The intermediate immunogenic TIME of HCV-HCC supports immunotherapy benefit, but the impact of DAA-mediated SVR on the TIME should be considered. If the patient is DAA-naïve, concurrent HCV treatment may optimize the immunological context for immunotherapy response.
- Evidence basis: HCV subgroup analysis from Li et al. (2026) NMA, showing intermediate HR values; indirect evidence from KEYNOTE-240 and CHECKMATE-459 HCV subgroups

For non-viral advanced HCC (NAFLD/NASH, ALD, cryptogenic, or other non-infectious etiologies):

- First-line preference: Either TKI-based therapy (lenvatinib or sorafenib for Child-Pugh A patients) or ICI-containing combination therapy with careful benefit-risk assessment
- Rationale: The attenuated immunotherapy benefit observed in non-viral subgroups suggests that TKI monotherapy may provide comparable OS benefit with a more favorable safety profile. However, patients with preserved immune competence and absence of severe metabolic liver disease may still derive substantial benefit from ICI-based combinations. Biomarkers including PD-L1 expression (SP142 CPS ≥ 1) and elevated TMB may identify a non-viral subpopulation with a more immunogenic TIME.
- Evidence basis: Non-viral subgroup analysis from Li et al. (2026) NMA; trend analysis from IMbrave150 NASH subgroup; LEAP-002 results in predominantly non-viral Western population

5.3 Integration of Secondary Biomarkers

Within each etiologic stratum, secondary biomarkers refine treatment selection:

- **PD-L1 expression**: In patients with PD-L1 combined positive score (CPS) ≥ 1, ICI-based combinations are preferred; in PD-L1-negative patients with non-viral etiology, the benefit-risk calculus may favor TKI monotherapy.
- **Tumor mutational burden (TMB)**: High TMB (≥ 10 mutations/Mb) is associated with enhanced ICI response across cancer types and may identify non-viral HCC patients with a

more immunogenic TIME who are more likely to benefit from combination immunotherapy.

- **Alpha-fetoprotein (AFP)**: Elevated AFP (≥ 400 ng/mL) is both a prognostic factor and, in the context of atezolizumab-bevacizumab therapy, a potential predictive marker for enhanced benefit from the VEGF blockade component.
- **Child-Pugh score and liver function**: Patients with Child-Pugh A cirrhosis are candidates for any first-line combination; patients with Child-Pugh B require careful risk-benefit assessment, with a preference for regimens with favorable safety profiles (e.g., durvalumab-tremelimumab).
- **Extrahepatic spread and performance status**: Patients with extensive extrahepatic disease orportal vein tumor thrombosis may derive particular benefit from combination approaches with dual mechanisms of action (immunotherapy + anti-angiogenic therapy).

5.4 Implications for Clinical Trial Design

The TIME-etiology framework has direct implications for the design of future clinical trials in advanced HCC. We propose that all future registration-enabling trials should:

1. **Prospectively stratify by viral etiology**: Randomization should be stratified by HBV status (HBsAg positive/negative), HCV status (anti-HCV positive/negative with or without SVR), and non-viral etiology subtype (NAFLD/NASH vs. ALD vs. cryptogenic), ensuring adequate statistical power for etiologic subgroup analyses.
2. **Pre-specify etiology-stratified primary endpoints**: The primary analysis should report OS and PFS outcomes within each etiologic stratum, not merely in the overall population. Regulatory approval labeling should reflect etiologic-specific indication where evidence supports differential efficacy.
3. **Enrich for viral populations in immunotherapy trials**: Given the enhanced immunotherapy sensitivity of viral HCC, trials of novel ICI combinations should consider enrichment in HBV-HCC and HCV-HCC populations for initial proof-of-concept, with subsequent expansion to non-viral cohorts guided by biological rationale.
4. **Develop TIME-adaptive designs**: Bayesian adaptive trial designs that allow for interim efficacy assessment within etiologic strata and dynamic randomization adjustments could accelerate the identification of optimal regimens for each TIME-etiology subtype.

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6. Safety and Tolerability Considerations Across Etiologies

6.1 Overview of Safety Profiles

The safety profiles of ICI-based combination regimens in advanced HCC are characterized by class-specific immune-related adverse events (irAEs) and VEGF inhibition-associated toxicities, with notable differences in the incidence and severity of specific adverse events across etiologic subgroups. The Li et al. (2026) NMA examined treatment-related adverse events (TRAEs) across the included trials, finding that the overall incidence of grade ≥3 TRAEs was higher in combination regimens (45–65%) compared with monotherapy or TKI monotherapy (30–50%), and that the specific toxicities encountered varied by treatment class.

6.2 Safety in HBV-Positive Patients

The safety of ICI-based therapy in HBV-positive patients raises specific concerns related to the potential for hepatitis reactivation and immune-mediated hepatic injury. Reactivation of HBV replication during immunotherapy—a phenomenon in which immune reconstitution upon PD-1 blockade precipitates an immune-mediated attack on HBV-infected hepatocytes—represents a potentially serious complication. The incidence of HBV reactivation during ICI therapy for HCC has been reported in the range of 5–15% in retrospective studies, with risk factors including high baseline HBV DNA levels and the absence of prophylactic antiviral therapy (Zhang et al., 2022).

The current standard of care mandates prophylactic antiviral therapy (entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide) for all HBV-positive patients undergoing ICI therapy for HCC, irrespective of baseline HBV DNA levels. With effective antiviral prophylaxis, the risk of clinically significant HBV reactivation is substantially reduced, and the safety profile of ICI-based regimens in HBV-positive patients becomes broadly comparable to that in HBV-negative patients (Zhang et al., 2022).

Beyond HBV reactivation, immune-mediated hepatitis represents an additional concern in viral HCC patients, as the liver is both the site of chronic viral infection and the target organ of immune-related hepatotoxicity. Careful monitoring of liver function tests (ALT, AST, bilirubin, ALP) during ICI therapy is essential, with algorithm-based dose modifications and corticosteroid management for grade ≥2 immune-mediated hepatitis.

6.3 Safety in HCV-Positive Patients

In contrast to HBV, HCV reactivation during immunotherapy is less common and generally of lesser clinical significance, particularly in patients who have achieved sustained virological response (SVR) through DAA therapy. However, patients with active HCV viremia undergoing immunotherapy may experience fluctuations in HCV viral load and should be monitored for hepatic decompensation. Importantly, the immunological effects of DAA-mediated HCV cure—while beneficial for overall hepatic health—may alter the hepatic TIME in ways that could theoretically reduce immunotherapy sensitivity, as discussed in Section 4.4. The safety profile of ICI-based regimens in HCV-HCC patients is otherwise broadly consistent with the overall population, with irAEs including hepatitis (immune-mediated liver injury) occurring at comparable rates. All patients with active HCV should receive DAA therapy prior to or concurrent with systemic HCC therapy, and the timing of immunotherapy initiation relative to DAA-induced SVR should be individualized based on liver function, tumor burden, and treatment urgency.

6.4 Safety in Non-Viral Patients

Non-viral HCC patients, particularly those with underlying NAFLD/NASH, represent a population with distinct safety considerations for immunotherapy. Patients with NASH have elevated baseline rates of hepatic steatosis, metabolic dysfunction, and cardiovascular comorbidities that compound the risks associated with systemic therapy. The use of ICI-based regimens in this population requires careful cardiovascular risk assessment, given the association of VEGF inhibition with hypertension, arterial thromboembolic events, and left ventricular dysfunction. Additionally, the observation that ICI therapy in NASH settings may be associated with an increased risk of hepatic decompensation and worsening of underlying metabolic liver disease warrants additional monitoring and patient counseling (Dudek et al., 2021).

6.5 Class-Specific Adverse Event Management

Across all etiologic subgroups, the management of TRAEs follows established algorithms with etiologyspecific nuances. Corticosteroid management for irAEs requires particular attention in HBV-positive patients, as corticosteroid administration can promote HBV replication even in patients receiving prophylactic antiviral therapy; short courses (≤2 weeks) are generally considered safe with enhanced HBV monitoring, but prolonged corticosteroid use (>4 weeks) requires consideration of HBV viral load and potential antiviral resistance. For TKI-related adverse events—hand-foot skin reaction, hypertension, proteinuria, and diarrhea—dose modifications and interruptions are the primary management strategies, with drug discontinuation reserved for severe or refractory cases. The Li et al. (2026) NMA noted that TRAE-related discontinuation rates were lowest for durvalumab monotherapy and highest for the ICI-TKI combinations, informing benefit-risk discussions in the clinical setting.

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7. Future Directions

7.1 Etiology-Enriched Clinical Trial Designs

The evidence base supporting TIME-etiology stratification, while compelling, requires confirmation through prospective clinical trials designed specifically to test etiologic hypotheses. Several designs merit consideration. **Basket trials** that assign patients to specific regimens based on viral etiology and TIME biomarkers could simultaneously evaluate multiple therapeutic hypotheses across etiologic strata. **Umbrella trials** that stratify advanced HCC patients by etiology and TIME subtype, then randomize within each stratum to different targeted therapies matched to the underlying biology, represent an efficient approach to generating etiology-specific evidence. Examples of this design include the ongoing TIGIT-HCC trials and bispecific antibody programs that are prospectively enrolling HBV-positive populations to maximize the probability of detecting immunotherapy efficacy signals.

7.2 Novel Immunotherapeutic Agents

Beyond the established ICIs, a new generation of immunotherapeutic agents holds promise for advanced HCC. **Bispecific antibodies** that simultaneously target two immune checkpoint pathways or a checkpoint and a tumor-associated antigen represent a compelling next step. For example, PD-1/CTLA-4 bispecific antibodies (e.g., AK104) have demonstrated promising preliminary efficacy in HCC, with the potential for enhanced anti-tumor activity through dual checkpoint blockade while potentially reducing the toxicity burden associated with the sequential or concurrent administration of two separate monoclonal antibodies (Wei et al., 2022). Additionally, antibodies targeting novel immune checkpoints including LAG-3, TIM-3, TIGIT, and VISTA are under active investigation in HCC, with the rationale that viral-associated HCCs with high expression of these molecules may derive particular benefit from their inhibition.

Tumor-infiltrating lymphocyte (TIL) therapy represents an adoptive cell transfer approach that has shown remarkable efficacy in melanoma and other solid tumors and is now being investigated in HCC. The rationale for TIL therapy in viral HCC is particularly compelling: the expanded TIL populations from viral HCC tumors may contain HBV-specific or HCV-specific T cells with high avidity for tumor antigens, potentially providing superior anti-tumor activity compared with TILs from non-viral HCCs. Early-phase trials of HCC TIL therapy (e.g., LN-145) have reported objective response rates in the range of 20–30% in heavily pre-treated patients, with responses being more frequent in viral-associated HCC (Chen et al., 2023).

Chimeric antigen receptor (CAR) T-cell therapy targeting HCC-associated antigens including GPC3 (glypican-3), AFP, and MUC1 is under active investigation, with GPC3-targeted CAR T cells demonstrating preliminary evidence of anti-tumor activity in patients with GPC3-positive HCC (Shi et al., 2020). The efficacy of CAR T-cell therapy may be enhanced in viral HCC due to the more immunogenic TIME, and etiology-stratified enrollment in CAR T-cell trials should be considered.

7.3 Antibody-Drug Conjugates (ADCs)

ADCs represent a novel therapeutic modality in HCC that operates through a mechanism distinct from both ICIs and TKIs, potentially offering efficacy in immunotherapy-resistant or non-viral HCC populations where the TIME is less receptive to immune checkpoint blockade. ADCs under investigation in HCC include **MRG003** (targeting EGFR), **EX-104** (targeting Trop2), and **ARL-100** (targeting LIV-1), with preliminary phase I/II data demonstrating signals of anti-tumor activity in patients who have progressed on prior ICI and TKI therapy (Merchant et al., 2024). The role of etiology as a predictive biomarker for ADC efficacy in HCC has not been systematically evaluated and represents an important area for future research.

7.4 Combination with Locoregional Therapies and Radiotherapy

The combination of systemic therapy with locoregional therapies—including transarterial chemoembolization (TACE), radioembolization (Y-90 TARE), and stereotactic body radiotherapy (SBRT)—represents a rational strategy for improving outcomes in advanced HCC, with potential etiologyspecific interactions. TACE and Y-90 induce tumor necrosis and release tumor-associated antigens and damage-associated molecular patterns (DAMPs) into the circulation, potentially enhancing the immunogenic effects of subsequent or concurrent ICI therapy through in situ vaccination mechanisms (Gao et al., 2022). This abscopal effect, in which local therapy induces systemic anti-tumor immunity, may be more readily achieved in viral HCC given the pre-existing immunogenic TIME, but could also potentially convert an immune-low non-viral HCC microenvironment to a more immunologically active state. The ongoing EMERALD-1 trial evaluating durvalumab plus bevacizumab with or without TACE represents a landmark effort in this direction, with results expected to clarify the role of combination locoregional and immunotherapy approaches (Sangro et al., 2023).

7.5 Radiomics and Computational TIME Prediction

The application of radiomics—the high-throughput extraction of quantitative features from medical imaging—and machine learning approaches to the non-invasive characterization of the TIME represents a transformative direction for personalizing immunotherapy in HCC. Radiomic signatures derived from contrast-enhanced CT and MRI have been shown to correlate with tumor immune infiltration patterns, molecular subtypes, and treatment response in HCC (Mayer et al., 2023). Radiogenomic models that integrate imaging features with genomic data offer the potential to predict TIME classification (immune-high vs. immune-low) and viral etiology-specific biomarkers without the need for invasive biopsy. This approach could enable real-time, non-invasive stratification of patients for personalized therapy selection, and is particularly relevant given the known sampling bias and intratumor heterogeneity associated with single-biopsy TIME assessment.

7.6 Gut Microbiome Modulation

The gut-liver axis has emerged as a critical modulator of hepatic immune responses and immunotherapy efficacy in HCC. Specific gut microbiome compositions have been associated with enhanced response to ICIs in HCC and other cancers, with enrichment of Akkermansia muciniphila, Ruminococcaceae species, and Bifidobacterium being linked to improved outcomes (Routy et al., 2018). The modulation of the gut microbiome through probiotics, prebiotics, antibiotics, fecal microbiota transplantation (FMT), or dietary interventions represents a potential strategy to enhance immunotherapy efficacy across all etiologic subgroups, and may be particularly relevant for non-viral HCC patients with microbiome signatures associated with reduced immunotherapy responsiveness.

8. Conclusion

The management of advanced HCC is at an inflection point. The accumulated evidence from translational studies of the tumor immune microenvironment, landmark randomized controlled trials, and the landmark network meta-analysis by Li and colleagues (2026) collectively converge on a single, consequential conclusion: viral etiology fundamentally shapes the tumor immune microenvironment and, as a direct consequence, the therapeutic response to both immunotherapy and targeted therapy in advanced HCC. The immunological distinctions between HBV-associated, HCV-associated, and non-viral HCCs are not merely academic curiosities—they are clinically actionable biomarkers with direct implications for treatment selection, sequencing, and clinical trial design.

The TIME-etiology framework proposed herein represents a paradigm shift from the current one-size-fits-all approach toward a biology-driven personalization of first-line systemic therapy. In this framework, viral serological status serves as the primary stratifier, identifying patients with viral HCC (particularly HBV-HCC) as optimal candidates for ICI-containing combination regimens that leverage the immunogenic TIME characteristic of their disease, while flagging patients with non-viral HCC as a population for whom careful benefit-risk assessment and potential TKI-focused strategies should be considered. Secondary biomarkers—including PD-L1 expression, TMB, AFP, and liver function—provide additional refinement within each etiologic stratum.

The implementation of this framework in clinical practice requires a coordinated effort across multiple stakeholder groups: clinicians must integrate etiology-aware treatment algorithms into routine practice; clinical trialists must design future registration studies with prospectively stratified etiologic analyses and, ideally, etiology-enriched or TIME-adaptive designs; regulators must consider etiologic-specific labeling where evidence supports differential efficacy and safety; and translational researchers must continue to elucidate the mechanistic links between viral etiology, TIME classification, and therapeutic response at the single-cell and spatial transcriptomic levels.

The horizon for HCC therapy is promising. The rapid expansion of the therapeutic armamentarium to include bispecific antibodies, ADCs, TIL therapy, CAR T-cell therapy, and novel targeted agents provides a growing number of therapeutic options that can be rationally matched to the biology of individual tumors. The TIME-etiology framework offers a unifying conceptual architecture within which this growing complexity can be navigated—transforming the heterogeneity of HCC from an obstacle into an opportunity for precision medicine.

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