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The Impact of Viral, Molecular, and Immunological Factors on Hepatocellular Carcinoma Recurrence After Curative Resection

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and remains a leading cause of cancer-related mortality worldwide. Curative liver resection offers an effective treatment option for patients with preserved liver function and resectable tumors; however, postoperative recurrence remains the principal challenge, occurring in up to 70% of patients within five years. Tumor recurrence results from a complex interplay between residual microscopic disease, de novo hepatocarcinogenesis, and the biological characteristics of both the tumor and the underlying liver. Increasing evidence indicates that viral factors, molecular alterations, and the host immune response play pivotal roles in determining recurrence risk following curative resection. Understanding these mechanisms is essential for improving risk stratification, optimizing postoperative surveillance, and developing personalized therapeutic strategies.

Aim: This review aims to provide a comprehensive and contemporary overview of the viral, molecular, and immunological determinants of hepatocellular carcinoma recurrence after curative resection. It highlights the influence of chronic hepatitis B virus and hepatitis C virus infections, viral replication status, and antiviral therapy, together with key molecular pathways including genomic alterations, oncogenic signaling, angiogenesis, circulating biomarkers, and epigenetic regulators. In addition, the review discusses the role of the tumor immune microenvironment, immune checkpoint pathways, inflammatory mediators, and immune cell populations in recurrence, while examining emerging biomarker-based prediction models and their potential application in precision medicine.

Conclusion: Recurrence after curative resection remains the greatest obstacle to long-term survival in patients with hepatocellular carcinoma. Current evidence demonstrates that postoperative recurrence is driven by a multifactorial interaction between persistent viral activity, tumor-specific molecular abnormalities, and dysregulation of the host immune response. Integration of virological, molecular, immunological, and clinicopathological factors provides a more accurate prediction of recurrence than conventional clinical parameters alone and represents the foundation of personalized postoperative management. Advances in multi-omics technologies, liquid biopsy, artificial intelligence, and immune profiling are expected to refine recurrence prediction and identify patients who may benefit from individualized surveillance and adjuvant therapies. Future prospective studies and standardized biomarker-guided approaches are required to translate these discoveries into routine clinical practice and improve long-term outcomes following curative resection for hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma; Curative resection; Hepatitis B virus; Tumor microenvironment; Biomarkers.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed cancer and the third leading cause of cancer-related mortality worldwide, accounting for a substantial global health burden. Despite remarkable advances in surveillance programs, diagnostic imaging, surgical techniques, and systemic therapies, HCC continues to exhibit poor long-term outcomes because of its high propensity for recurrence after curative treatment. Surgical resection remains one of the principal curative options for patients with preserved liver function, localized tumors, and adequate future liver remnant. Nevertheless, postoperative recurrence develops in approximately 50–70% of patients within five years, significantly limiting overall survival and emphasizing the need for improved understanding of the biological mechanisms underlying disease relapse. [1]

Recurrence following curative resection is a heterogeneous process resulting from two distinct mechanisms. Early recurrence, generally occurring within the first two years after surgery, is primarily attributed to intrahepatic metastasis arising from residual microscopic tumor dissemination, vascular invasion, or aggressive tumor biology. In contrast, late recurrence is more commonly associated with multicentric hepatocarcinogenesis developing within chronically diseased liver tissue, particularly in patients with persistent viral hepatitis, advanced fibrosis, or cirrhosis. Differentiating these mechanisms is clinically important because they are influenced by different biological pathways and require distinct preventive and surveillance strategies. [2]

Chronic viral hepatitis remains the dominant etiological factor for HCC worldwide, with hepatitis B virus (HBV) and hepatitis C virus (HCV) accounting for the majority of cases. Persistent viral replication promotes chronic hepatic inflammation, oxidative stress, genomic instability, and progressive fibrosis, thereby creating a pro-oncogenic hepatic microenvironment. Even after apparently curative tumor resection, ongoing viral activity may continue to drive hepatocarcinogenesis and contribute to the development of recurrent disease. The introduction of potent nucleos(t)ide analogues for HBV and direct-acting antiviral agents for HCV has substantially altered the natural history of chronic viral hepatitis; however, recurrence remains a major concern, highlighting the complex interaction between viral persistence and tumor biology. [3]

In addition to viral factors, accumulating evidence has identified numerous molecular alterations that influence postoperative recurrence. Genetic mutations involving TP53, CTNNB1, and TERT promoter regions, together with dysregulation of signaling pathways such as Wnt/β-catenin, PI3K/AKT/mTOR, and vascular endothelial growth factor (VEGF), contribute to tumor proliferation, angiogenesis, invasion, and metastatic potential. Furthermore, epigenetic modifications, microRNAs, long non-coding RNAs, and circulating tumor DNA have emerged as promising biomarkers capable of identifying patients at increased risk of recurrence. These molecular signatures offer opportunities for more precise prognostic assessment and may facilitate the development of personalized postoperative therapeutic strategies. [4]

The tumor immune microenvironment has also emerged as a critical determinant of HCC recurrence. The balance between antitumor immune surveillance and immune evasion is regulated by complex interactions among cytotoxic T lymphocytes, regulatory T cells, tumor-associated macrophages, natural killer cells, dendritic cells, and immune checkpoint molecules such as programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1). Chronic hepatic inflammation resulting from viral hepatitis further modifies this immune landscape by promoting persistent immune activation, cytokine dysregulation, and progressive immune exhaustion. These immunological alterations not only facilitate tumor recurrence but also influence responsiveness to emerging immunotherapeutic strategies. [5]

Traditional prognostic indicators, including tumor size, tumor number, microvascular invasion, histological differentiation, alpha-fetoprotein (AFP), and liver function status, remain important predictors of postoperative outcome. However, these clinicopathological parameters alone do not fully explain the marked heterogeneity in recurrence patterns observed among patients with apparently similar disease characteristics. Integrating viral activity, molecular biomarkers, and immunological profiles with conventional prognostic models offers a more comprehensive approach to individualized risk assessment and postoperative management, representing an important step toward precision hepatology. [6]

Although substantial progress has been made in understanding the biology of HCC recurrence, important knowledge gaps remain regarding the relative contributions and interactions of viral, molecular, and immunological determinants. Most currently available prediction models rely predominantly on clinicopathological variables and fail to incorporate emerging biomarkers that may substantially improve prognostic accuracy. Furthermore, standardized biomarker-guided surveillance strategies and personalized adjuvant therapeutic approaches have not yet been fully established, limiting their routine clinical implementation.

Therefore, a comprehensive synthesis of current evidence is needed to bridge these gaps and facilitate translation of biological discoveries into clinical practice.

Accordingly, this review aims to critically examine the impact of viral infections, molecular alterations, and immunological mechanisms on hepatocellular carcinoma recurrence following curative resection. It also discusses emerging biomarkers, prediction models, and evolving strategies for individualized postoperative surveillance and targeted interventions, with the goal of improving long-term outcomes and advancing precision management for patients with HCC.

2. Epidemiology and Patterns of Hepatocellular Carcinoma Recurrence After Curative Resection

Hepatocellular carcinoma (HCC) is characterized by one of the highest postoperative recurrence rates among solid malignancies, making recurrence the principal determinant of long-term survival following curative resection. Although advances in surgical techniques, perioperative care, and patient selection have significantly reduced postoperative morbidity and mortality, recurrence continues to affect approximately 50–70% of patients within five years after surgery. This high recurrence rate reflects the unique biological behavior of HCC, which develops in a chronically diseased liver that remains susceptible to ongoing carcinogenesis even after complete tumor removal. Consequently, postoperative recurrence represents not only a marker of tumor aggressiveness but also a manifestation of the persistent oncogenic environment within the liver. [7]

The incidence of recurrence varies considerably according to geographic region, underlying liver disease, tumor characteristics, and postoperative management. In East Asia and sub-Saharan Africa, where chronic hepatitis B virus (HBV) infection remains highly prevalent, recurrence is frequently associated with persistent viral replication and intrahepatic metastasis. In contrast, hepatitis C virus (HCV)-related HCC predominates in Japan, Southern Europe, and parts of North America, where chronic inflammation, advanced fibrosis, and multicentric hepatocarcinogenesis play more prominent roles. Increasingly, metabolic dysfunction-associated steatotic liver disease (MASLD), formerly nonalcoholic fatty liver disease, has emerged as an important etiological factor for HCC recurrence, particularly in Western countries, reflecting the growing global burden of obesity, diabetes mellitus, and metabolic syndrome. [8]

Recurrence after curative resection is generally classified into early and late recurrence because these entities differ substantially in their biological mechanisms, prognostic implications, and preventive strategies. Early recurrence, typically occurring within two years after surgery, is predominantly attributed to occult intrahepatic metastases originating from the primary tumor. It is closely associated with aggressive pathological features such as microvascular invasion, satellite nodules, poor tumor differentiation, elevated alpha-fetoprotein (AFP) levels, and large tumor size. These patients generally exhibit poorer overall survival because recurrence reflects dissemination of biologically aggressive tumor clones that escaped complete surgical eradication. [9]

Late recurrence, occurring more than two years after curative resection, is considered a consequence of de novo hepatocarcinogenesis arising within chronically injured hepatic parenchyma. Persistent viral hepatitis, advanced fibrosis or cirrhosis, chronic hepatic inflammation, and continuous regenerative activity contribute to the emergence of independent primary tumors. Unlike early recurrence, late recurrence is more closely associated with the severity of underlying liver disease than with the biological characteristics of the original tumor. Consequently, effective control of chronic liver disease through antiviral therapy, fibrosis regression, and lifestyle modification plays an essential role in reducing the incidence of late postoperative recurrence. [10]

Several clinicopathological factors consistently influence recurrence risk following curative resection. Tumor size exceeding 5 cm, multiple tumor nodules, microvascular invasion, poor histological differentiation, incomplete tumor capsule, elevated serum AFP, and positive surgical margins have all been associated with increased recurrence rates. Similarly, impaired liver function, portal hypertension, severe fibrosis, and active viral replication adversely affect long-term outcomes by promoting both metastatic spread and multicentric tumor development. The coexistence of multiple adverse prognostic factors substantially increases recurrence risk, underscoring the need for individualized postoperative surveillance and risk stratification. [11]

Recent advances in molecular oncology have demonstrated that recurrence cannot be fully explained by conventional clinicopathological variables alone. Distinct genomic alterations, epigenetic modifications, circulating tumor DNA, and immune signatures have been shown to differentiate patients with apparently similar pathological features but markedly different clinical outcomes. Likewise, persistent HBV DNA integration, viral mutations, immune checkpoint activation, and chronic inflammatory signaling contribute to biological heterogeneity that is not captured by traditional staging systems. These findings have stimulated

growing interest in integrating molecular and immunological biomarkers with established clinical predictors to improve recurrence prediction and guide personalized postoperative management. [12]

The timing and pattern of recurrence also influence therapeutic decision-making and patient prognosis. Solitary intrahepatic recurrence may remain amenable to repeat resection, local ablation, or liver transplantation in carefully selected patients, whereas multifocal disease, vascular invasion, or extrahepatic metastasis often necessitates systemic therapy. Consequently, accurate identification of patients at high risk for recurrence is essential not only for optimizing surveillance intervals but also for selecting individuals who may benefit from adjuvant therapies or enrollment in clinical trials evaluating novel preventive strategies. Understanding the epidemiological and biological patterns of HCC recurrence therefore provides the foundation for exploring the viral, molecular, and immunological mechanisms that drive disease relapse after curative resection.

3. Viral Factors Influencing Hepatocellular Carcinoma Recurrence After Curative Resection

Chronic viral hepatitis remains the most important etiological factor for hepatocellular carcinoma (HCC) worldwide and continues to exert a profound influence on postoperative recurrence even after complete tumor resection. Persistent infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) promotes chronic hepatic inflammation, hepatocyte injury, regenerative proliferation, and progressive fibrosis, creating a pro-carcinogenic hepatic environment that persists despite removal of the primary tumor. Consequently, viral activity contributes not only to de novo hepatocarcinogenesis but also to tumor progression through interactions with molecular signaling pathways and the host immune response. Recognition of these mechanisms has emphasized the importance of optimal antiviral therapy as an integral component of postoperative HCC management. [13]

3.1 Hepatitis B Virus Infection

HBV remains the leading cause of HCC in many regions of Asia and sub-Saharan Africa and accounts for a substantial proportion of HCC-related mortality worldwide. Unlike most oncogenic viruses, HBV can directly promote hepatocarcinogenesis through integration of viral DNA into the host genome, resulting in chromosomal instability, activation of oncogenes, disruption of tumor suppressor genes, and persistent genomic alterations. In addition, viral proteins, particularly hepatitis B virus X protein (HBx), regulate multiple intracellular signaling pathways involved in cell proliferation, apoptosis, angiogenesis, epithelial-mesenchymal transition, and immune evasion. These direct oncogenic effects explain why HBV-associated recurrence may occur even in patients without advanced cirrhosis. [14]

Serum HBV DNA level is one of the strongest independent predictors of postoperative recurrence. High preoperative viral load has consistently been associated with both early and late recurrence, reflecting enhanced viral replication, sustained hepatic inflammation, and continued carcinogenic activity. Persistent viremia following resection further increases recurrence risk by promoting multicentric tumor development and facilitating survival of residual malignant cells. Therefore, quantitative HBV DNA assessment before and after surgery has become an essential component of postoperative risk stratification and long-term surveillance. [15]

The widespread use of potent nucleos(t)ide analogues, including entecavir and tenofovir, has significantly improved the prognosis of patients undergoing curative resection for HBV-related HCC. Effective viral suppression reduces hepatic inflammation, slows fibrosis progression, decreases the incidence of de novo hepatocarcinogenesis, and improves overall and recurrence-free survival. Current international guidelines recommend long-term antiviral therapy for patients with HBV-related HCC regardless of baseline viral load because suppression of viral replication provides sustained protection against postoperative recurrence while preserving liver function for potential future treatments. [16]

3.2 Hepatitis C Virus Infection

HCV remains an important cause of HCC recurrence, particularly in regions where chronic hepatitis C has historically been prevalent. Unlike HBV, HCV is an RNA virus that does not integrate into the host genome; instead, hepatocarcinogenesis results primarily from chronic necroinflammatory injury, oxidative stress, immune-mediated hepatocyte destruction, and progressive fibrosis leading to cirrhosis. Persistent inflammatory signaling and repeated cycles of hepatocyte death and regeneration generate an environment conducive to genetic mutations and malignant transformation, thereby increasing the likelihood of recurrent HCC even after successful surgical treatment. [17]

The introduction of direct-acting antiviral (DAA) therapy has revolutionized the treatment of chronic HCV infection, achieving sustained virological response rates exceeding 95%. Viral eradication is associated with reduced hepatic inflammation,

stabilization or regression of fibrosis, and improved liver function. Several large cohort studies have demonstrated that sustained virological response after curative HCC treatment significantly lowers the risk of late recurrence and improves overall survival, although it does not completely eliminate recurrence because molecular and epigenetic alterations induced during chronic infection may persist despite viral clearance. Consequently, continued surveillance remains mandatory even after successful antiviral therapy. [18]

3.3 Occult HBV Infection and Viral Reactivation

Occult HBV infection, characterized by persistence of HBV DNA in hepatic tissue despite negative hepatitis B surface antigen (HBsAg), has emerged as a potential contributor to HCC recurrence. Low-level viral persistence may maintain chronic hepatic inflammation and genomic instability, thereby promoting hepatocarcinogenesis even in patients without overt HBV infection. Although the clinical significance of occult HBV varies across populations, increasing evidence suggests that it should be considered in recurrence risk assessment, particularly in endemic regions and among patients receiving immunosuppressive therapies. [19]

HBV reactivation following curative resection represents another clinically important issue. Surgical stress, postoperative immunosuppression, and subsequent systemic therapies may facilitate renewed viral replication, leading to hepatitis flares, hepatic decompensation, and potentially increased recurrence risk. Prophylactic antiviral therapy and regular monitoring of HBV DNA levels are therefore recommended in susceptible patients to prevent viral reactivation and preserve hepatic reserve during postoperative follow-up. [20]

3.4 Emerging Viral Determinants of Recurrence

Beyond conventional virological markers, several emerging viral biomarkers have demonstrated prognostic significance. HBV DNA integration patterns, quantitative hepatitis B surface antigen (HBsAg), hepatitis B core-related antigen (HBcrAg), and serum HBV RNA have all been associated with postoperative recurrence and may better reflect persistent viral transcriptional activity than serum HBV DNA alone. Viral genetic mutations, particularly within the basal core promoter and pre-S regions, have also been linked to increased oncogenic potential and poorer postoperative outcomes. These novel biomarkers may improve recurrence prediction when incorporated into comprehensive prognostic models. [21]

Although hepatitis D virus (HDV) infection represents a relatively uncommon cause of HCC globally, it accelerates hepatic fibrosis, increases inflammatory activity, and markedly elevates the risk of hepatocarcinogenesis in patients with chronic HBV infection. Data regarding HDV and postoperative HCC recurrence remain limited; however, available evidence suggests that advanced liver disease and persistent viral activity contribute to unfavorable long-term outcomes. Future prospective studies are needed to clarify the impact of HDV and other emerging hepatotropic viruses on recurrence following curative resection. [22]

Overall, viral factors remain fundamental determinants of HCC recurrence after curative surgery. Persistent viral replication, chronic hepatic inflammation, viral genomic integration, and virus-induced immune dysregulation interact with tumor-specific molecular alterations to promote both early metastatic recurrence and late multicentric hepatocarcinogenesis. Consequently, comprehensive postoperative management should combine effective antiviral therapy with individualized surveillance and integration of virological biomarkers into recurrence prediction models, thereby supporting a precision medicine approach to long-term care of patients with HCC.

4. Molecular Factors Associated with Hepatocellular Carcinoma Recurrence

Molecular alterations are increasingly recognized as major determinants of hepatocellular carcinoma (HCC) recurrence following curative resection. Although conventional clinicopathological characteristics such as tumor size, vascular invasion, and histological differentiation remain valuable prognostic indicators, they do not fully explain the marked heterogeneity in postoperative outcomes among patients with similar clinical profiles. Advances in genomic sequencing, transcriptomics, epigenetics, and liquid biopsy have identified numerous molecular biomarkers associated with tumor aggressiveness, metastatic potential, and recurrence. These biomarkers provide important insights into tumor biology and may facilitate individualized postoperative surveillance and therapeutic decision-making. [23]

4.1 Genomic Alterations and Driver Mutations

HCC is characterized by considerable genomic heterogeneity resulting from the accumulation of somatic mutations during

chronic liver injury and hepatocarcinogenesis. Several driver mutations influence tumor proliferation, invasion, angiogenesis, and metastatic behavior, thereby contributing to postoperative recurrence. The coexistence of multiple genetic alterations often reflects increased genomic instability and is associated with more aggressive disease phenotypes. Comprehensive genomic profiling has therefore emerged as an important tool for identifying patients at high risk of recurrence and for guiding precision oncology strategies. [24]

Among the most frequently mutated genes in HCC, **TP53** plays a central role in regulating cell-cycle arrest, DNA repair, apoptosis, and genomic integrity. Loss-of-function TP53 mutations impair these protective mechanisms, allowing accumulation of additional genetic abnormalities and promoting uncontrolled cellular proliferation. TP53-mutated tumors are commonly associated with poor differentiation, microvascular invasion, larger tumor size, and reduced recurrence-free survival after surgical resection. These observations have established TP53 mutation as one of the most important molecular predictors of aggressive tumor behavior. [25]

Mutations involving **CTNNB1**, the gene encoding β-catenin, represent another major molecular subtype of HCC. Aberrant activation of the Wnt/β-catenin signaling pathway enhances hepatocyte proliferation, inhibits apoptosis, and facilitates tumor progression. Although CTNNB1-mutated tumors often exhibit relatively well-differentiated histology, activation of this pathway contributes to immune exclusion within the tumor microenvironment and may influence recurrence risk as well as responsiveness to immune checkpoint inhibitors. Consequently, molecular characterization of β-catenin signaling has become increasingly relevant in postoperative prognostic assessment and treatment selection. [26]

Mutations of the **telomerase reverse transcriptase (TERT) promoter** are among the earliest genetic events in hepatocarcinogenesis and are detected in a substantial proportion of HCCs. TERT activation promotes telomere maintenance, cellular immortalization, and sustained tumor growth. When combined with TP53 or CTNNB1 mutations, TERT promoter alterations have been associated with increased tumor aggressiveness, earlier recurrence, and poorer long-term survival. These findings suggest that integrated genomic profiling provides greater prognostic value than evaluation of individual mutations alone. [27]

4.2 Dysregulated Molecular Signaling Pathways

Several intracellular signaling pathways contribute to HCC recurrence by regulating cell proliferation, migration, angiogenesis, and resistance to apoptosis. The **Wnt/β-catenin pathway** is one of the most extensively investigated and promotes tumor growth through activation of genes involved in cell-cycle progression and stem-cell maintenance. Persistent activation of this pathway has been linked to postoperative recurrence and resistance to immunotherapy, highlighting its potential as both a prognostic biomarker and therapeutic target. [28]

The **PI3K/AKT/mTOR signaling pathway** also plays a crucial role in hepatocarcinogenesis by enhancing cellular proliferation, protein synthesis, angiogenesis, and metabolic adaptation. Dysregulation of this pathway has been associated with increased recurrence risk, resistance to apoptosis, and poor overall survival. In parallel, overexpression of **vascular endothelial growth factor (VEGF)** stimulates neovascularization, facilitating tumor growth and intrahepatic metastasis. Elevated VEGF expression has consistently been correlated with microvascular invasion, early postoperative recurrence, and unfavorable prognosis, providing the biological rationale for antiangiogenic therapies in advanced HCC. [29]

Another important mechanism contributing to recurrence is **epithelial-mesenchymal transition (EMT)**, a process whereby epithelial tumor cells acquire mesenchymal characteristics that enhance motility, invasiveness, and metastatic potential. EMT is mediated by multiple signaling pathways, including transforming growth factor-β (TGF-β), Wnt/β-catenin, Notch, and Hedgehog signaling. Increased expression of EMT-related transcription factors such as Snail, Slug, Twist, and ZEB1 has been associated with vascular invasion, circulating tumor cell dissemination, and early postoperative recurrence. [30]

4.3 Epigenetic Alterations and Non-Coding RNAs

Epigenetic modifications contribute significantly to HCC progression without altering the underlying DNA sequence. Aberrant DNA methylation, histone modifications, and chromatin remodeling regulate the expression of oncogenes and tumor suppressor genes involved in proliferation, apoptosis, angiogenesis, and immune escape. These reversible alterations are increasingly recognized as potential therapeutic targets and biomarkers for recurrence prediction. Their dynamic nature also makes them attractive candidates for monitoring disease progression during postoperative surveillance. [31]

MicroRNAs (miRNAs) represent one of the best-studied classes of non-coding RNAs in HCC. Dysregulated expression of miR-21, miR-122, miR-221, miR-224, and several other miRNAs has been associated with tumor proliferation, epithelial-mesenchymal transition, vascular invasion, and recurrence after curative resection. Likewise, **long non-coding RNAs (lncRNAs)**, including HULC, HOTAIR, MALAT1, and MEG3, regulate multiple oncogenic pathways and have demonstrated independent prognostic value in predicting recurrence-free survival. Integration of these RNA biomarkers into predictive models may substantially improve individualized postoperative risk assessment. [32]

4.4 Liquid Biopsy and Emerging Molecular Biomarkers

Recent advances in liquid biopsy have expanded opportunities for noninvasive postoperative monitoring of HCC recurrence. Circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), extracellular vesicles, and circulating non-coding RNAs provide real-time information regarding minimal residual disease and evolving tumor biology. Detection of postoperative ctDNA has been associated with microscopic residual disease and significantly increased risk of early recurrence, often preceding radiological evidence of relapse by several months. These technologies offer considerable promise for early detection of recurrence and dynamic assessment of therapeutic response. [33]

Multi-omics approaches integrating genomic, transcriptomic, proteomic, metabolomic, and epigenomic data are expected to further enhance prediction of HCC recurrence. Combined molecular signatures have consistently demonstrated greater prognostic accuracy than individual biomarkers, reflecting the biological complexity of hepatocarcinogenesis. As sequencing technologies become more accessible and analytical methods continue to evolve, comprehensive molecular profiling is likely to become an integral component of precision hepatology, enabling personalized surveillance strategies and selection of targeted adjuvant therapies following curative resection. [34]

5. Immunological Factors and the Tumor Microenvironment

The tumor immune microenvironment has emerged as a critical determinant of hepatocellular carcinoma (HCC) recurrence following curative resection. Beyond genetic and viral influences, the balance between effective antitumor immune surveillance and tumor-induced immune evasion plays a pivotal role in determining whether residual malignant cells are eliminated or progress to clinically detectable recurrence. Chronic liver disease, persistent viral hepatitis, and continuous hepatic inflammation profoundly alter the composition and function of immune cells within the liver, creating an immunosuppressive microenvironment that favors tumor progression. Consequently, increasing attention has focused on identifying immune biomarkers capable of predicting recurrence and guiding postoperative therapeutic strategies. [35]

5.1 The Tumor Immune Microenvironment

The liver possesses a unique immunological environment characterized by continuous exposure to dietary antigens, microbial products, and viral pathogens through the portal circulation. Under physiological conditions, this environment promotes immune tolerance to prevent excessive inflammatory injury. During hepatocarcinogenesis, however, persistent inflammation and chronic antigenic stimulation remodel the hepatic immune landscape, resulting in impaired immune surveillance and enhanced tumor immune escape. The HCC microenvironment consists of complex interactions among tumor cells, stromal cells, hepatic stellate cells, endothelial cells, fibroblasts, and multiple populations of innate and adaptive immune cells. These interactions regulate tumor growth, angiogenesis, invasion, and metastatic dissemination, thereby influencing postoperative recurrence risk. [36]

5.2 Cytotoxic T Lymphocytes and Regulatory T Cells

Cytotoxic $CD8^+$ T lymphocytes represent the principal effector cells responsible for recognizing and eliminating malignant hepatocytes. High intratumoral infiltration by functional $CD8^+$ T cells has consistently been associated with prolonged recurrence-free survival and improved overall survival following curative resection. These cells exert antitumor activity through direct cytotoxicity mediated by perforin and granzyme release, as well as production of interferon-γ and tumor necrosis factor-α, which inhibit tumor proliferation and promote immune activation. Reduced $CD8^+$ T-cell infiltration or functional exhaustion, conversely, is associated with increased postoperative recurrence and poorer clinical outcomes. [37]

In contrast, regulatory T cells (Tregs) suppress antitumor immune responses by inhibiting cytotoxic T-cell proliferation and cytokine production. Increased infiltration of FOXP3-positive Tregs within HCC tissue has been associated with immune suppression, enhanced tumor progression, microvascular invasion, and early postoperative recurrence. Tregs also contribute to immune checkpoint activation through interactions with programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated

antigen-4 (CTLA-4), further weakening host antitumor immunity. Consequently, an elevated Treg-to-$CD8^+$ T-cell ratio has emerged as a strong immunological predictor of unfavorable prognosis after curative resection. [38]

5.3 Tumor-Associated Macrophages and Natural Killer Cells

Tumor-associated macrophages (TAMs) constitute one of the most abundant immune cell populations within the HCC microenvironment and exhibit remarkable functional plasticity. Classically activated M1 macrophages exert antitumor effects through production of pro-inflammatory cytokines and enhanced antigen presentation, whereas alternatively activated M2 macrophages promote angiogenesis, extracellular matrix remodeling, immune suppression, and tumor invasion. A predominance of M2-polarized macrophages has consistently been associated with vascular invasion, tumor progression, and increased recurrence following surgical resection, making TAM polarization an attractive therapeutic target. [39]

Natural killer (NK) cells provide rapid innate immune responses against transformed hepatocytes without prior antigen sensitization. Their antitumor activity depends on recognition of stress-induced ligands expressed by malignant cells and subsequent release of cytotoxic granules. In HCC, both the number and functional activity of NK cells are frequently diminished because of chronic viral infection, persistent inflammation, and immunosuppressive cytokine signaling. Reduced NK-cell infiltration has been associated with increased recurrence and inferior postoperative survival, highlighting their essential role in controlling minimal residual disease after curative surgery. [40]

5.4 Immune Checkpoint Pathways

Immune checkpoint molecules have become central to understanding immune escape in HCC. Programmed death-1 (PD-1) expressed on activated T lymphocytes interacts with programmed death ligand-1 (PD-L1) expressed on tumor cells and antigen-presenting cells, leading to T-cell exhaustion, reduced cytokine production, and impaired cytotoxic function. Increased PD-L1 expression within HCC tissue has consistently been associated with aggressive tumor behavior, early recurrence, and reduced survival after curative resection. Similarly, CTLA-4 suppresses early T-cell activation by competing with CD28 for binding to costimulatory molecules on antigen-presenting cells, thereby contributing to immune tolerance and tumor progression. These observations provide the biological basis for immune checkpoint inhibition as a strategy to reduce recurrence in high-risk patients. [41]

5.5 Cytokines, Chronic Inflammation, and Immune Escape

Chronic hepatic inflammation remains a central mechanism linking viral hepatitis, liver fibrosis, and HCC recurrence. Persistent production of inflammatory cytokines, including interleukin-6 (IL-6), interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and tumor necrosis factor-α (TNF-α), promotes hepatocyte proliferation, angiogenesis, epithelial-mesenchymal transition, and resistance to apoptosis. Simultaneously, these mediators suppress effective antitumor immunity by enhancing Treg expansion, inducing macrophage polarization toward the M2 phenotype, and promoting T-cell exhaustion. Elevated circulating levels of these cytokines have been associated with increased recurrence risk and poorer postoperative prognosis. [42]

Tumor cells further evade immune destruction through multiple complementary mechanisms, including downregulation of major histocompatibility complex class I molecules, secretion of immunosuppressive cytokines, recruitment of myeloid-derived suppressor cells, metabolic reprogramming, and induction of immune checkpoint pathways. Chronic HBV and HCV infections amplify these mechanisms by maintaining continuous antigenic stimulation and immune dysfunction, thereby facilitating persistence of residual tumor cells after surgery. Understanding these complex interactions has become increasingly important with the emergence of immunotherapy as a component of HCC management. [43]

5.6 Emerging Immunological Biomarkers and Therapeutic Implications

Advances in immunology have identified numerous biomarkers with potential value for predicting postoperative recurrence. Immune gene expression signatures, spatial immune profiling, multiplex immunohistochemistry, single-cell RNA sequencing, circulating immune cell phenotyping, and cytokine profiling provide increasingly detailed characterization of the tumor immune microenvironment. Integration of these biomarkers with molecular, virological, and clinicopathological data has demonstrated improved prognostic accuracy compared with conventional staging systems alone. [44]

The growing success of immune checkpoint inhibitors and combination immunotherapy has further emphasized the clinical importance of postoperative immune profiling. Patients with high-risk immune signatures may benefit from future adjuvant

immunotherapeutic strategies aimed at eliminating minimal residual disease and preventing recurrence. As precision immuno-oncology continues to evolve, incorporation of comprehensive immune biomarkers into individualized postoperative surveillance and treatment algorithms is expected to play an increasingly important role in improving long-term outcomes following curative resection for hepatocellular carcinoma. [45]

6. Clinicopathological Predictors and Integrated Risk Assessment for Hepatocellular Carcinoma Recurrence

Although viral, molecular, and immunological biomarkers have substantially improved understanding of hepatocellular carcinoma (HCC) recurrence, conventional clinicopathological characteristics remain the cornerstone of postoperative prognostic assessment. These readily available parameters continue to guide clinical decision-making because they reflect both tumor biology and the severity of underlying liver disease. However, individual predictors often lack sufficient discriminatory power, highlighting the importance of integrated risk assessment models that combine clinical, pathological, and biological variables to identify patients at greatest risk of recurrence following curative resection. [46]

6.1 Tumor-Related Predictors

Tumor morphology remains one of the strongest determinants of postoperative outcome. Larger tumor diameter, multifocal disease, absence of a complete tumor capsule, poor histological differentiation, and satellite nodules have consistently been associated with increased recurrence rates. Larger tumors are more likely to exhibit aggressive biological behavior, increased angiogenesis, and microscopic dissemination before surgical removal. Likewise, multifocal tumors frequently represent either intrahepatic metastases or multicentric carcinogenesis, both of which significantly increase the likelihood of postoperative relapse. Histological grading further reflects tumor aggressiveness, with poorly differentiated tumors demonstrating greater proliferative capacity, enhanced invasiveness, and reduced recurrence-free survival compared with well-differentiated lesions. [47]

Among pathological variables, **microvascular invasion (MVI)** is widely recognized as one of the most powerful independent predictors of early recurrence. Microscopic invasion of small portal or hepatic venous branches indicates dissemination of malignant cells beyond the primary tumor, increasing the probability of residual microscopic disease despite apparently complete surgical excision. Numerous studies have demonstrated that patients with MVI experience significantly higher rates of early intrahepatic recurrence and poorer long-term survival. Consequently, MVI has become an essential component of postoperative prognostic models and plays an important role in identifying candidates for intensified surveillance and emerging adjuvant therapies. [48]

6.2 Liver-Related Predictors

The condition of the underlying liver substantially influences recurrence, particularly late recurrence resulting from multicentric hepatocarcinogenesis. Advanced fibrosis and cirrhosis create a chronic inflammatory and regenerative environment that favors continuous malignant transformation of hepatocytes. Persistent viral hepatitis, clinically significant portal hypertension, impaired hepatic reserve, and ongoing hepatic necroinflammation further amplify this carcinogenic process. Consequently, patients with advanced chronic liver disease remain at elevated risk for developing new primary HCC even after successful resection of the original tumor, emphasizing the importance of long-term surveillance regardless of initial pathological findings. [49]

Assessment of liver function also contributes significantly to postoperative prognostic evaluation. Traditional scoring systems such as the Child–Pugh classification and the Model for End-Stage Liver Disease (MELD) score remain useful for estimating hepatic reserve, while newer indices including the albumin-bilirubin (ALBI) grade provide more objective assessment of liver function without subjective variables. Poor hepatic functional reserve not only limits therapeutic options in the event of recurrence but is also associated with increased postoperative complications, reduced tolerance to adjuvant therapies, and inferior overall survival. [50]

6.3 Serum Biomarkers

Serum biomarkers continue to play an important role in predicting recurrence because they are inexpensive, widely available, and easily incorporated into routine clinical practice. Alpha-fetoprotein (AFP) remains the most extensively studied biomarker in HCC. Elevated preoperative AFP levels, incomplete postoperative normalization, or progressive AFP elevation during follow-up have all been associated with increased recurrence risk and poorer survival. AFP reflects both tumor burden and biological aggressiveness and may identify patients with microscopic residual disease even when postoperative imaging findings are

negative. [51]

Additional circulating biomarkers have demonstrated complementary prognostic value. Protein induced by vitamin K absence or antagonist-II (PIVKA-II), also known as des-γ-carboxy prothrombin, has been associated with vascular invasion, tumor progression, and early recurrence. Likewise, inflammatory indices derived from routine laboratory investigations—including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and C-reactive protein (CRP)—reflect the balance between systemic inflammation and host immune competence. Elevated inflammatory markers consistently correlate with more aggressive tumor biology and reduced recurrence-free survival, supporting their inclusion in integrated prognostic models. [52]

6.4 Integrated Prognostic Models

Recognizing the limitations of individual predictors, numerous prognostic models have been developed to improve recurrence risk stratification. Widely used staging systems such as the Barcelona Clinic Liver Cancer (BCLC) classification, American Joint Committee on Cancer (AJCC) TNM staging system, and the Hong Kong Liver Cancer (HKLC) classification provide valuable prognostic information but rely predominantly on clinical and pathological variables. Although these systems effectively guide treatment allocation, they do not adequately capture the biological heterogeneity responsible for substantial variability in postoperative outcomes among patients with similar disease stages. [53]

Recent predictive models increasingly incorporate viral activity, molecular biomarkers, immune signatures, radiological characteristics, and artificial intelligence-based algorithms alongside conventional clinicopathological factors. Machine learning techniques capable of integrating high-dimensional clinical, imaging, pathological, and molecular datasets have demonstrated promising improvements in recurrence prediction compared with traditional statistical models. Such precision-based approaches may facilitate individualized surveillance schedules, optimize patient selection for adjuvant therapies, and improve long-term clinical outcomes through earlier identification of patients at highest risk of recurrence. [54]

Overall, clinicopathological predictors remain fundamental components of postoperative HCC management, but their prognostic value is substantially enhanced when combined with virological, molecular, and immunological biomarkers. Integrated risk assessment models represent an important step toward precision hepatology, allowing clinicians to move beyond conventional staging systems and adopt personalized strategies for surveillance, prevention, and treatment of recurrence after curative resection.

7. Biomarker-Based Prediction Models and Strategies to Reduce Hepatocellular Carcinoma Recurrence

Accurate prediction of hepatocellular carcinoma (HCC) recurrence after curative resection is essential for tailoring postoperative surveillance, selecting candidates for adjuvant therapy, and improving long-term survival. Traditional prediction models based solely on clinicopathological characteristics provide valuable prognostic information but often fail to capture the complex biological heterogeneity of HCC. Recent advances in biomarker discovery, high-throughput molecular technologies, and computational modeling have enabled the development of more comprehensive prediction systems that integrate viral, molecular, immunological, radiological, and pathological data. These integrated models offer greater prognostic precision and support the transition toward personalized postoperative management. [55]

7.1 Biomarker-Based Prediction Models

Several prognostic models have incorporated circulating biomarkers to improve prediction of postoperative recurrence. Alpha-fetoprotein (AFP) remains the most widely used serum biomarker and is frequently combined with tumor size, tumor number, and microvascular invasion to estimate recurrence risk. Additional biomarkers, including protein induced by vitamin K absence or antagonist-II (PIVKA-II), circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), inflammatory indices, and immune-related biomarkers, have demonstrated complementary prognostic value. These biomarkers provide dynamic information regarding minimal residual disease and tumor biology that cannot be obtained from conventional pathological assessment alone. [56]

Multi-omics technologies have further transformed recurrence prediction by integrating genomic, transcriptomic, proteomic, metabolomic, and epigenomic datasets into unified prognostic signatures. Artificial intelligence (AI) and machine learning algorithms are capable of analyzing these complex datasets alongside radiological and clinical variables, generating individualized recurrence risk profiles with greater accuracy than traditional statistical models. Although many of these models

remain under clinical validation, they represent an important advance toward precision hepatology and individualized postoperative care. [57]

Radiomics has emerged as another promising approach for recurrence prediction. Quantitative analysis of preoperative computed tomography (CT) and magnetic resonance imaging (MRI) can identify imaging features associated with tumor heterogeneity, vascular invasion, and biological aggressiveness that are not appreciable by visual interpretation alone. When combined with pathological findings and molecular biomarkers, radiomic signatures have demonstrated encouraging predictive performance for both early and late postoperative recurrence, supporting their incorporation into future multidisciplinary prognostic models. [58]

7.2 Antiviral Therapy and Control of Underlying Liver Disease

Effective management of the underlying liver disease remains one of the most important strategies for reducing HCC recurrence. In patients with chronic hepatitis B virus (HBV) infection, long-term treatment with potent nucleos(t)ide analogues such as entecavir or tenofovir suppresses viral replication, decreases hepatic inflammation, slows fibrosis progression, and significantly reduces both recurrence and liver-related mortality. Likewise, sustained virological response following direct-acting antiviral therapy for hepatitis C virus (HCV) decreases the incidence of de novo hepatocarcinogenesis and improves long-term survival, although continued surveillance remains necessary because recurrence risk is not completely eliminated. [59]

Beyond antiviral therapy, optimization of liver health contributes substantially to recurrence prevention. Management of metabolic dysfunction-associated steatotic liver disease (MASLD), control of diabetes mellitus, treatment of obesity, avoidance of excessive alcohol consumption, and prevention of progressive fibrosis all reduce chronic hepatic inflammation and may lower the risk of late multicentric recurrence. Preservation of hepatic functional reserve is equally important because it allows patients to undergo repeat curative treatment should recurrence occur. [60]

7.3 Adjuvant Systemic and Locoregional Therapies

The role of adjuvant therapy after curative resection has evolved considerably in recent years. Historically, no systemic therapy consistently demonstrated a survival benefit in preventing postoperative recurrence. However, advances in immunotherapy and targeted therapy have renewed interest in adjuvant treatment for patients with high-risk pathological features such as microvascular invasion, large tumors, or multifocal disease. Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway, alone or in combination with antiangiogenic agents, are currently being investigated in several clinical trials and have shown encouraging preliminary results in reducing recurrence risk among selected patients. [61]

Locoregional approaches may also benefit carefully selected high-risk patients. Postoperative transarterial chemoembolization (TACE) has demonstrated improved recurrence-free survival in individuals with vascular invasion or large tumors by eliminating residual microscopic disease. Radiofrequency ablation, microwave ablation, stereotactic body radiotherapy, and selective internal radiation therapy may provide effective treatment for isolated recurrent lesions detected during surveillance. Selection of these modalities should be individualized according to tumor burden, liver function, and patient performance status within a multidisciplinary treatment framework. [62]

7.4 Personalized Surveillance and Future Perspectives

Postoperative surveillance remains fundamental for the early detection of recurrent HCC, when potentially curative interventions remain feasible. Current recommendations generally include serial measurement of serum AFP together with contrast-enhanced CT or MRI every three to six months during the first two postoperative years, followed by individualized long-term surveillance according to recurrence risk. Future surveillance protocols are expected to incorporate dynamic biomarkers such as ctDNA, immune profiling, and AI-assisted imaging analysis, allowing earlier identification of recurrence before conventional radiological evidence becomes apparent. [63]

The future of recurrence prevention lies in precision medicine. Integration of virological characteristics, molecular alterations, immune signatures, radiomics, digital pathology, and multi-omics technologies will enable individualized prediction models capable of identifying patients most likely to benefit from intensified surveillance or adjuvant treatment. Continued multicenter prospective studies are required to validate these biomarkers across diverse patient populations and establish standardized clinical algorithms. Such advances are expected to improve recurrence-free survival, optimize resource utilization, and ultimately enhance long-term outcomes following curative resection for hepatocellular carcinoma. [64]

8. Future Perspectives

The management of hepatocellular carcinoma (HCC) recurrence is rapidly evolving from conventional clinicopathological risk stratification toward precision oncology. Advances in molecular biology, immunology, artificial intelligence (AI), and multi-omics technologies have substantially improved understanding of the mechanisms driving recurrence after curative resection. Future strategies will likely focus on integrating these complementary disciplines into individualized predictive models capable of identifying patients at greatest risk of recurrence, facilitating personalized surveillance protocols and targeted postoperative interventions. Such an approach has the potential to improve recurrence-free survival while minimizing unnecessary investigations and treatment-related toxicity. [65]

One of the most promising developments is the application of **multi-omics profiling**, which combines genomic, transcriptomic, epigenomic, proteomic, metabolomic, and microbiome data to comprehensively characterize tumor biology. Unlike single biomarkers, multi-omics platforms capture the complex interactions among viral infection, molecular alterations, immune responses, and host metabolic pathways. Integration of these datasets may enable clinicians to identify biologically distinct HCC subtypes associated with specific recurrence patterns and therapeutic vulnerabilities, thereby supporting truly personalized postoperative management. [66]

Liquid biopsy is expected to become an integral component of postoperative surveillance. Circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), extracellular vesicles, circulating microRNAs, and tumor-derived methylation signatures offer minimally invasive approaches for detecting minimal residual disease and monitoring tumor evolution in real time. Because these biomarkers may identify molecular relapse months before radiological recurrence becomes apparent, they could facilitate earlier therapeutic intervention and improve opportunities for repeat curative treatment. Continued refinement of assay sensitivity, standardization of analytical methods, and prospective validation are necessary before widespread clinical implementation. [67]

Artificial intelligence and machine learning are also transforming HCC management by integrating high-dimensional clinical, laboratory, pathological, radiological, and molecular datasets into highly accurate predictive algorithms. Deep learning models applied to contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and whole-slide digital pathology can identify subtle imaging and histopathological features associated with recurrence risk that are beyond human interpretation. When combined with viral biomarkers and immune signatures, AI-driven models have demonstrated superior predictive performance compared with traditional staging systems, supporting their future incorporation into routine clinical practice. [68]

The expanding role of **precision immunotherapy** represents another major area of investigation. Immune checkpoint inhibitors targeting programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), together with novel cellular therapies, therapeutic vaccines, and bispecific antibodies, are being evaluated as adjuvant strategies following curative resection. Future treatment selection will likely depend on comprehensive immune profiling, allowing identification of patients most likely to respond to immunomodulatory therapies while avoiding unnecessary toxicity in those unlikely to benefit. Biomarker-guided immunotherapy therefore represents an important step toward individualized postoperative care. [69]

Advances in antiviral management are expected to further reduce recurrence among patients with virus-related HCC. Development of therapies capable of achieving functional cure for chronic hepatitis B virus (HBV) infection, together with continued optimization of hepatitis C virus (HCV) eradication strategies, may substantially decrease chronic hepatic inflammation and subsequent multicentric hepatocarcinogenesis. Simultaneously, growing recognition of metabolic dysfunction-associated steatotic liver disease (MASLD) as a leading cause of HCC underscores the importance of comprehensive metabolic risk modification, including weight reduction, glycemic control, lipid management, and antifibrotic therapies, as components of recurrence prevention. [70]

Future clinical research should prioritize large multicenter prospective studies that validate emerging biomarkers across geographically and etiologically diverse populations. Standardization of biomarker assays, harmonization of recurrence definitions, and integration of molecular endpoints into randomized clinical trials will be essential for translating laboratory discoveries into routine clinical practice. Furthermore, incorporation of patient-reported outcomes, health-economic analyses, and quality-of-life assessments will ensure that emerging surveillance and therapeutic strategies remain clinically meaningful and cost-effective. International collaboration will be critical for establishing globally applicable evidence-based

recommendations. [71]

Ultimately, the future management of HCC recurrence will depend on multidisciplinary precision medicine, integrating hepatology, oncology, surgery, pathology, radiology, virology, molecular biology, immunology, and computational sciences. Comprehensive risk stratification based on viral, molecular, immunological, and clinicopathological characteristics will enable individualized surveillance schedules, early detection of recurrence, and selection of personalized adjuvant therapies. Such an integrated approach has the potential to significantly reduce recurrence, improve long-term survival, and redefine the standard of care for patients undergoing curative resection for hepatocellular carcinoma. [72]

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