Predictors of Hepatocellular Carcinoma Recurrence After Curative Liver Resection: A Comprehensive Review

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Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and remains a leading cause of cancer-related mortality worldwide. Surgical resection is considered one of the most effective curative treatment modalities for patients with preserved liver function and resectable tumors. Despite significant advances in surgical techniques, perioperative care, and patient selection, postoperative recurrence remains the major obstacle to long-term survival, occurring in more than half of patients within five years after curative hepatectomy. HCC recurrence is a multifactorial process influenced by complex interactions among tumor biology, underlying liver disease, patient characteristics, and surgical factors. Identification of reliable predictors of recurrence is therefore essential for risk stratification, individualized surveillance, and optimization of postoperative therapeutic strategies.

Aim: This review aims to provide a comprehensive overview of the clinicopathological, biochemical, radiological, and surgical factors associated with hepatocellular carcinoma recurrence following curative liver resection. It examines the mechanisms underlying early and late recurrence, evaluates established and emerging prognostic predictors, and discusses their clinical significance in guiding patient selection, postoperative surveillance, and individualized management. Additionally, the review highlights current prognostic models and identifies existing knowledge gaps that warrant further investigation.

Conclusion: Recurrence after curative liver resection remains the principal determinant of long-term outcomes in patients with hepatocellular carcinoma. Numerous predictors have been identified, including tumor size and multiplicity, microvascular invasion, poor histological differentiation, elevated serum alpha-fetoprotein levels, satellite nodules, resection margin status, liver functional reserve, severity of underlying cirrhosis, and etiological factors such as chronic hepatitis B and hepatitis C infections. Increasing evidence also supports the prognostic value of inflammatory biomarkers, molecular signatures, and advanced imaging-based prediction models in refining recurrence risk assessment. Because HCC recurrence results from the interplay between aggressive tumor behavior and the carcinogenic hepatic microenvironment, accurate prediction requires a multidimensional approach integrating tumor-related, liver-related, patient-related, and treatment-related variables. Improved risk stratification may facilitate personalized surveillance protocols, timely implementation of adjuvant therapies, and early detection of recurrent disease, ultimately improving long-term survival. Future prospective multicenter studies incorporating molecular biomarkers, artificial intelligence-based prediction tools, and precision medicine approaches are needed to develop standardized prognostic models and optimize postoperative management for patients undergoing curative liver resection.

Keywords: Hepatocellular carcinoma; Liver resection; Recurrence; Prognostic factors.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, accounting for approximately 75–90% of all primary liver cancers, and represents one of the leading causes of cancer-related mortality worldwide. According to recent global cancer statistics, HCC ranks among the most frequently diagnosed malignancies and is responsible for a substantial proportion of cancer deaths, particularly in regions with a high prevalence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Although the incidence of viral hepatitis-related HCC has declined in some countries owing to effective antiviral therapies and vaccination programs, the global burden of HCC continues to increase because of the rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), obesity, diabetes mellitus, and alcohol-associated liver disease. These epidemiological changes have made HCC an increasingly important public health challenge requiring multidisciplinary management strategies. **[1]**

Curative liver resection remains one of the primary treatment options for patients with early-stage HCC who have preserved liver function, adequate future liver remnant, and technically resectable tumors. Advances in preoperative imaging, perioperative care, anesthetic management, surgical techniques, and postoperative support have substantially improved operative safety, with mortality rates in specialized centers falling below 3%. Compared with non-curative therapies, surgical resection provides excellent local tumor control and favorable long-term survival in carefully selected patients, particularly those without clinically significant portal hypertension or advanced hepatic dysfunction. Consequently, hepatectomy continues to play a central role in the management of resectable HCC despite the emergence of liver transplantation, local ablative therapies, and systemic treatments. **[2]**

Despite these advances, postoperative recurrence remains the greatest obstacle to long-term survival following curative liver resection. Reported recurrence rates range from 50% to 70% within five years, making recurrence the principal cause of treatment failure and cancer-related mortality after surgery. HCC recurrence is generally classified as early recurrence, typically occurring within two years of resection and largely reflecting occult intrahepatic metastasis from the primary tumor, and late recurrence, which is considered a de novo tumor arising within the chronically diseased liver. This distinction is clinically important because the biological mechanisms, prognostic implications, and preventive strategies differ substantially between the two recurrence patterns. **[3]**

The development of recurrent HCC is a complex, multifactorial process involving interactions between tumor biology, the underlying hepatic microenvironment, patient-related characteristics, and treatment-related factors. Aggressive tumor features such as large tumor size, multiple lesions, microvascular invasion, satellite nodules, poor histological differentiation, and elevated serum alpha-fetoprotein (AFP) levels have consistently been associated with increased recurrence risk. Simultaneously, chronic hepatic inflammation, advanced fibrosis or cirrhosis, active viral replication, metabolic dysfunction, and impaired liver function create a carcinogenic environment that promotes multicentric hepatocarcinogenesis even after complete removal of the primary tumor. These interacting mechanisms explain why recurrence remains common despite apparently curative surgery. **[4]**

Increasing attention has therefore been directed toward identifying reliable predictors of recurrence that can improve risk stratification and guide individualized postoperative management. Numerous clinicopathological variables, biochemical markers, radiological characteristics, histopathological findings, inflammatory indices, and molecular biomarkers have been investigated as prognostic indicators. More recently, advances in genomics, transcriptomics, radiomics, artificial intelligence, and machine learning have facilitated the development of integrated prediction models capable of estimating individualized recurrence risk with greater accuracy than conventional staging systems alone. These evolving approaches have the potential to optimize surveillance intensity, identify candidates for adjuvant therapies, and enable earlier detection of recurrent disease. **[5]**

Risk prediction has become increasingly important in the era of precision medicine. Patients identified as having a high probability of recurrence may benefit from intensified imaging surveillance, prolonged

antiviral therapy, closer monitoring of tumor biomarkers, enrollment in clinical trials, or consideration of emerging adjuvant systemic and immunotherapeutic strategies. Conversely, patients with favorable prognostic profiles may avoid unnecessary investigations and associated healthcare costs. Therefore, accurate identification of recurrence-associated factors has significant implications not only for prognosis but also for individualized treatment planning and resource allocation within hepatology and oncology practice. **[6]**

Although numerous studies have examined prognostic factors for HCC recurrence, considerable heterogeneity exists regarding study populations, recurrence definitions, underlying liver disease etiology, surgical techniques, pathological assessment, and follow-up protocols. Furthermore, many available prognostic models have been developed using retrospective single-center cohorts and have not undergone adequate external validation. This variability has limited their widespread clinical implementation and highlights the need for comprehensive evaluation of the available evidence to distinguish consistently validated predictors from emerging biomarkers that require further investigation. **[7]**

This review provides a comprehensive analysis of the current evidence regarding predictors of hepatocellular carcinoma recurrence after curative liver resection. It examines tumor-related, liver-related, patient-related, biochemical, histopathological, and surgical determinants of recurrence, discusses the biological mechanisms underlying early and late relapse, evaluates established and emerging prognostic models, and highlights future directions aimed at improving individualized risk prediction, postoperative surveillance, and long-term clinical outcomes.

Aim of the Review

This review aims to comprehensively evaluate the clinicopathological, liver-related, patient-related, biochemical, and surgical factors associated with hepatocellular carcinoma recurrence following curative liver resection, while examining their prognostic significance, underlying mechanisms, and clinical applications in postoperative risk stratification and surveillance.

Research Gap

Despite substantial progress in identifying predictors of hepatocellular carcinoma recurrence, no universally accepted prognostic model accurately integrates tumor biology, underlying liver disease, molecular biomarkers, and treatment-related variables into routine clinical practice. Most available evidence is derived from retrospective studies with heterogeneous patient populations and inconsistent definitions of recurrence. Consequently, large prospective multicenter studies are needed to validate integrated prediction models and establish standardized strategies for individualized postoperative surveillance and recurrence prevention.

2. Epidemiology and Global Burden of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the predominant primary liver malignancy, accounting for approximately 75–90% of all primary liver cancers. It represents a major global health challenge because of its high incidence, aggressive biological behavior, and poor long-term prognosis. According to the Global Cancer Observatory (GLOBOCAN), liver cancer is among the most frequently diagnosed cancers worldwide and remains one of the leading causes of cancer-related death. The close similarity between incidence and mortality rates reflects the aggressive nature of HCC and the fact that many patients are diagnosed at advanced stages when curative treatment options are no longer feasible. Despite improvements in surveillance programs and therapeutic modalities, the global burden of HCC continues to increase, particularly in low- and middle-income countries where viral hepatitis remains highly prevalent. **[8]**

The geographical distribution of HCC varies considerably across the world, largely reflecting differences in the prevalence of chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, aflatoxin exposure, alcohol consumption, and metabolic risk factors. Eastern Asia and sub-Saharan Africa continue to report the highest incidence rates, primarily because of endemic HBV infection acquired early in life and limited access to comprehensive screening and antiviral treatment. In contrast, North America and many European countries have experienced changing epidemiological

patterns characterized by declining HCV-related HCC following the introduction of direct-acting antiviral therapy, alongside a progressive increase in HCC associated with metabolic dysfunction-associated steatotic liver disease (MASLD) and obesity. **[9]**

Chronic viral hepatitis remains the single most important etiological factor for HCC worldwide. Chronic HBV infection is responsible for nearly half of all HCC cases globally and remains the dominant cause in many Asian and African countries. HBV promotes hepatocarcinogenesis through persistent hepatic inflammation, repeated cycles of hepatocyte injury and regeneration, viral DNA integration into the host genome, and direct oncogenic effects of viral proteins. Unlike many other etiologies, HBV-related HCC may develop even in the absence of cirrhosis, emphasizing the unique carcinogenic potential of chronic HBV infection. The implementation of universal HBV vaccination and potent nucleos(t)ide analogue therapy has significantly reduced HCC incidence in several endemic regions; however, HBV continues to account for a substantial proportion of HCC-related morbidity and mortality worldwide. **[10]**

Hepatitis C virus remains another major contributor to hepatocellular carcinoma, particularly in Western countries, Japan, and Egypt, where HCV infection has historically been highly prevalent. HCV-associated carcinogenesis occurs predominantly through chronic necroinflammation, progressive fibrosis, and cirrhosis rather than direct viral oncogenic activity. The widespread introduction of direct-acting antiviral agents has dramatically increased rates of sustained virological response and reduced the long-term risk of HCC development. Nevertheless, patients with advanced fibrosis or established cirrhosis remain at persistent risk of hepatocarcinogenesis even after successful viral eradication, highlighting the importance of continued surveillance in this population. **[11]**

In recent years, metabolic dysfunction-associated steatotic liver disease has emerged as one of the fastest-growing causes of HCC worldwide. The increasing prevalence of obesity, type 2 diabetes mellitus, insulin resistance, dyslipidemia, and metabolic syndrome has contributed to a marked rise in MASLD-related cirrhosis and HCC, particularly in developed nations. Unlike viral hepatitis, HCC associated with MASLD may occur in both cirrhotic and non-cirrhotic livers, although the risk is substantially greater in patients with advanced fibrosis. This epidemiological transition is expected to reshape the global landscape of HCC over the coming decades, making metabolic liver disease an increasingly important focus for prevention and early detection strategies. **[12]**

Alcohol-associated liver disease remains another major etiological factor contributing to HCC development. Chronic excessive alcohol consumption induces oxidative stress, hepatic inflammation, fibrosis, and cirrhosis, thereby creating a pro-carcinogenic hepatic microenvironment. Furthermore, alcohol frequently acts synergistically with chronic HBV, HCV infection, and metabolic syndrome, accelerating hepatic fibrosis and substantially increasing the risk of malignant transformation. As patterns of alcohol consumption continue to evolve globally, alcohol-related HCC is expected to remain a significant contributor to the overall burden of liver cancer. **[13]**

The prognosis of HCC is influenced by both tumor stage and underlying liver function at diagnosis. In regions with established surveillance programs targeting high-risk populations, increasing numbers of tumors are detected at an early stage, allowing potentially curative treatment with surgical resection, liver transplantation, or local ablation. Conversely, many patients worldwide continue to present with advanced disease because of inadequate surveillance, limited healthcare access, or asymptomatic tumor progression. Consequently, substantial disparities persist in survival outcomes between countries with well-developed liver cancer screening programs and those with limited diagnostic resources. **[14]**

The changing epidemiology of hepatocellular carcinoma has important implications for postoperative recurrence following curative liver resection. As the etiological profile shifts from predominantly viral hepatitis to increasing contributions from metabolic dysfunction, alcohol-related liver disease, and aging populations with multiple comorbidities, the biological mechanisms underlying recurrence are also evolving. Understanding these epidemiological trends provides essential context for interpreting recurrence risk factors and developing individualized surveillance and prevention strategies tailored to diverse patient populations. **[15]**

3. Mechanisms and Patterns of Hepatocellular Carcinoma Recurrence

Hepatocellular carcinoma (HCC) recurrence after curative liver resection is a complex biological process resulting from the interaction between aggressive tumor characteristics and the chronically diseased hepatic microenvironment. Despite complete macroscopic tumor removal with histologically negative margins, microscopic residual disease or the development of new primary tumors frequently leads to recurrence. This high recurrence rate distinguishes HCC from many other solid malignancies and remains the principal limitation of surgical treatment. Understanding the biological mechanisms underlying recurrence is essential for identifying prognostic factors, developing effective surveillance strategies, and designing interventions that reduce the likelihood of tumor relapse. **[16]**

Clinically, HCC recurrence is broadly categorized into early recurrence and late recurrence, as these two patterns differ in their pathogenesis, associated risk factors, and prognostic implications. Early recurrence is generally defined as recurrence occurring within the first two years after curative resection and is primarily attributed to intrahepatic metastasis originating from the primary tumor. In contrast, late recurrence develops more than two years after surgery and is considered a de novo hepatocarcinogenic event arising from the chronically injured liver. Distinguishing between these recurrence patterns is important because they reflect different biological processes and require different preventive and surveillance strategies. **[17]**

Early recurrence is predominantly driven by aggressive tumor biology. Microscopic intrahepatic metastases may already exist at the time of surgery but remain undetectable using conventional imaging modalities. Tumor cells disseminate through the portal venous system, invade adjacent hepatic parenchyma, and subsequently proliferate to form recurrent lesions. Consequently, pathological features such as microvascular invasion, satellite nodules, poor histological differentiation, multiple tumors, and large tumor size are consistently associated with an increased risk of early postoperative recurrence. These characteristics reflect enhanced invasive potential and greater metastatic capacity of the primary tumor. **[18]**

Microvascular invasion (MVI) is considered one of the most important mechanisms contributing to early recurrence. Histologically, MVI is characterized by the presence of malignant cells within small portal or hepatic venous branches surrounding the primary tumor. This finding indicates that tumor dissemination has occurred before surgical resection, increasing the likelihood of residual microscopic disease despite complete removal of the visible tumor. Numerous studies have demonstrated that MVI is independently associated with shorter recurrence-free survival and poorer overall survival, making it one of the strongest pathological predictors incorporated into modern prognostic models. **[19]**

Late recurrence differs fundamentally from early recurrence because it usually represents multicentric carcinogenesis rather than metastatic spread. Chronic liver diseases—including hepatitis B virus infection, hepatitis C virus infection, alcohol-associated liver disease, and metabolic dysfunction-associated steatotic liver disease (MASLD)—produce persistent hepatic inflammation, oxidative stress, fibrosis, and regenerative nodules that create a carcinogenic microenvironment. Continuous cycles of hepatocyte injury and regeneration promote accumulation of genetic and epigenetic alterations, allowing new primary HCC lesions to develop independently after successful resection of the original tumor. Consequently, liver-related factors exert a greater influence on late recurrence than tumor-related characteristics. **[20]**

The hepatic tumor microenvironment plays a pivotal role in both recurrence patterns. Chronic inflammation activates hepatic stellate cells, macrophages, neutrophils, and lymphocytes, resulting in secretion of inflammatory cytokines, chemokines, and growth factors that promote angiogenesis, extracellular matrix remodeling, epithelial-mesenchymal transition, and tumor cell proliferation.

Simultaneously, progressive fibrosis alters hepatic architecture and creates a hypoxic environment that favors malignant transformation. These biological processes explain why patients with advanced fibrosis or cirrhosis remain susceptible to recurrent HCC even after apparently curative treatment. **[21]**

Host immune responses also influence recurrence risk. Effective antitumor immune surveillance mediated by cytotoxic T lymphocytes and natural killer cells can eliminate residual malignant cells following surgery. However, chronic viral hepatitis, cirrhosis, and prolonged inflammation frequently induce immune exhaustion and immunosuppressive signaling pathways that permit survival and proliferation of residual tumor cells. Increased expression of immune checkpoint molecules, expansion of regulatory T cells, and accumulation of tumor-associated macrophages have all been implicated in promoting postoperative recurrence. These observations provide a biological rationale for investigating adjuvant immunotherapeutic strategies following curative liver resection. **[22]**

The mechanisms underlying HCC recurrence are therefore multifactorial and involve a dynamic interplay between residual microscopic tumor burden, intrinsic tumor aggressiveness, chronic liver injury, immune dysregulation, and continuous hepatocarcinogenesis. Early recurrence primarily reflects dissemination of the original tumor, whereas late recurrence is largely driven by persistent liver disease and the development of new primary tumors. Recognition of these distinct biological pathways is fundamental for interpreting recurrence-associated prognostic factors discussed in subsequent sections and supports the development of individualized surveillance protocols and targeted preventive strategies following curative liver resection. **[23]**

4. Tumor-Related Predictors of Hepatocellular Carcinoma Recurrence

Tumor-related characteristics are among the strongest and most consistently validated predictors of hepatocellular carcinoma (HCC) recurrence following curative liver resection. These factors primarily reflect the intrinsic biological aggressiveness of the tumor and largely determine the risk of early postoperative recurrence through intrahepatic metastatic spread. Numerous studies have demonstrated that pathological features of the primary tumor—including tumor size, tumor number, microvascular invasion, satellite nodules, histological differentiation, capsule integrity, vascular invasion, and serum tumor biomarkers—are independently associated with recurrence-free survival and overall survival. Comprehensive assessment of these variables is therefore fundamental for postoperative risk stratification and individualized surveillance planning. **[24]**

4.1 Tumor Size

Tumor size is one of the most extensively studied prognostic factors in HCC. Larger tumors are associated with more aggressive biological behavior, increased vascular invasion, higher rates of satellite lesions, and greater metastatic potential. As tumor diameter increases, the likelihood of microscopic intrahepatic dissemination also rises, predisposing patients to early postoperative recurrence. Although various cut-off values have been proposed, including 3 cm, 5 cm, and 10 cm, most clinical studies consistently demonstrate that tumors exceeding 5 cm carry a significantly greater risk of recurrence and reduced disease-free survival compared with smaller lesions. Larger tumors are also more likely to exhibit poor differentiation and microscopic vascular invasion, further amplifying their adverse prognostic impact. **[25]**

4.2 Tumor Number

The presence of multiple HCC nodules is another well-established predictor of recurrence after liver resection. Multifocal tumors may represent either intrahepatic metastases from the primary lesion or independent multicentric carcinogenesis within the chronically diseased liver. Regardless of the underlying mechanism, multiple tumors indicate a greater overall tumor burden and increased biological aggressiveness. Patients with multifocal disease generally experience lower recurrence-free survival and overall survival than those with solitary tumors, even after apparently complete resection. Consequently, tumor multiplicity is incorporated into several staging systems and prognostic models used for treatment selection and postoperative risk assessment. **[26]**

4.3 Microvascular Invasion

Microvascular invasion (MVI) is widely regarded as one of the most powerful pathological predictors

of postoperative recurrence. It is defined by the presence of tumor emboli within small portal venous or hepatic venous branches adjacent to the primary lesion and reflects early metastatic dissemination before surgery. Patients with MVI exhibit significantly higher rates of early recurrence, shorter recurrence-free survival, and poorer long-term survival than those without vascular invasion. Although MVI can only be confirmed histopathologically after resection, increasing efforts are being directed toward developing preoperative imaging and biomarker-based prediction models capable of identifying patients at high risk for occult vascular invasion. **[27]**

4.4 Macrovascular Invasion

Macrovascular invasion, involving major branches of the portal vein or hepatic veins, represents one of the most advanced manifestations of tumor progression and is associated with an extremely poor prognosis. Although patients with gross vascular invasion are less frequently candidates for curative resection, selected individuals with limited vascular involvement may still undergo surgery in specialized centers. Even after complete resection, macrovascular invasion markedly increases the likelihood of residual microscopic disease, intrahepatic metastasis, and early postoperative recurrence. Consequently, vascular invasion remains an important determinant of recurrence risk and postoperative survival. **[28]**

4.5 Histological Differentiation

Histological tumor grade reflects the degree of cellular differentiation and biological aggressiveness of HCC. Poorly differentiated tumors demonstrate higher proliferative activity, increased genomic instability, greater invasive capacity, and enhanced metastatic potential compared with well-differentiated lesions. Numerous pathological studies have identified poor differentiation as an independent predictor of early recurrence and reduced long-term survival following liver resection. Conversely, well-differentiated tumors generally exhibit slower growth, lower rates of vascular invasion, and more favorable postoperative outcomes. Histological grading therefore provides important prognostic information that complements conventional clinical and radiological assessment. **[29]**

4.6 Satellite Nodules and Intrahepatic Metastasis

Satellite nodules are small tumor foci located adjacent to the primary HCC lesion and usually represent intrahepatic metastatic spread through microscopic vascular channels. Their presence indicates advanced local tumor dissemination and strongly predicts early recurrence after surgery. Patients with satellite nodules frequently have concomitant microvascular invasion, larger primary tumors, and poorer histological differentiation, all of which contribute to adverse oncological outcomes. Detection of satellite lesions during pathological examination should therefore prompt intensified postoperative surveillance because of the substantially increased risk of early tumor relapse. **[30]**

4.7 Tumor Capsule and Capsular Invasion

The fibrous capsule surrounding many hepatocellular carcinomas may act as a partial barrier limiting local tumor spread. Complete encapsulation has generally been associated with less aggressive tumor behavior and improved postoperative prognosis. In contrast, incomplete capsule formation or capsular invasion reflects greater invasive potential and facilitates extension of malignant cells into surrounding hepatic parenchyma. Several studies have reported that disruption of the tumor capsule is associated with increased recurrence rates, although its independent prognostic significance may vary after adjustment for tumor size and vascular invasion. Nevertheless, assessment of capsular integrity remains an important component of pathological evaluation following liver resection. **[31]**

4.8 Serum Alpha-Fetoprotein and Other Tumor Biomarkers

Serum alpha-fetoprotein (AFP) remains the most widely used biomarker for HCC diagnosis and prognosis. Elevated preoperative AFP concentrations, particularly persistent levels exceeding established clinical thresholds, have consistently been associated with larger tumors, vascular invasion, poor differentiation, and increased postoperative recurrence. Furthermore, failure of AFP levels to normalize after curative resection may indicate residual microscopic disease or early recurrence before radiological detection. Other biomarkers, including des-gamma-carboxy prothrombin (PIVKA-II) and AFP-L3, have demonstrated additional prognostic value and may improve recurrence prediction when

combined with conventional clinicopathological variables. Ongoing research into circulating tumor DNA, microRNAs, and other molecular biomarkers may further refine postoperative risk stratification in the future. **[32]**

5. Liver-Related Predictors of Hepatocellular Carcinoma Recurrence

Liver-related factors play a pivotal role in hepatocellular carcinoma (HCC) recurrence after curative liver resection because the majority of patients develop HCC in the setting of chronic liver disease. Unlike tumor-related predictors, which primarily influence early recurrence through intrahepatic metastasis, liver-related factors are more strongly associated with late recurrence by promoting multicentric hepatocarcinogenesis within the chronically injured liver. Persistent hepatic inflammation, progressive fibrosis, cirrhosis, impaired liver function, and ongoing viral replication create a pro-oncogenic microenvironment that predisposes patients to the development of new primary tumors even after complete surgical removal of the index lesion. Consequently, evaluation of the underlying liver condition is essential for accurate postoperative risk stratification and long-term surveillance. **[33]**

5.1 Liver Cirrhosis

Liver cirrhosis is one of the most important predictors of postoperative HCC recurrence. Continuous hepatocyte injury and regeneration in cirrhotic livers lead to genomic instability, accumulation of somatic mutations, and progressive remodeling of the hepatic microenvironment, all of which facilitate de novo carcinogenesis. Numerous studies have demonstrated that patients with cirrhosis experience significantly higher rates of late recurrence than those without cirrhosis, even when complete tumor resection has been achieved. Furthermore, cirrhosis limits hepatic functional reserve, often restricting the extent of surgical resection and reducing the ability to tolerate repeat curative treatment if recurrence occurs. Therefore, the severity of cirrhosis has important prognostic implications extending beyond recurrence alone. **[34]**

5.2 Degree of Hepatic Fibrosis

Advanced hepatic fibrosis is closely associated with an increased risk of postoperative recurrence independent of established cirrhosis. Progressive fibrosis promotes chronic inflammation, extracellular matrix remodeling, activation of hepatic stellate cells, and production of profibrotic cytokines, thereby establishing an environment favorable for malignant transformation. Histological fibrosis staging has consistently demonstrated that patients with advanced fibrosis have poorer recurrence-free survival than those with minimal fibrosis. Non-invasive methods such as transient elastography and serum fibrosis biomarkers have also shown promise in predicting recurrence risk by estimating the severity of underlying hepatic fibrosis before surgery. **[35]**

5.3 Liver Functional Reserve

Preserved liver function is a prerequisite for curative liver resection and remains an important determinant of postoperative outcomes. Assessment of hepatic functional reserve using the Child-Pugh classification, Model for End-Stage Liver Disease (MELD) score, Albumin-Bilirubin (ALBI) grade, and indocyanine green retention testing helps identify patients who can safely undergo hepatectomy while minimizing postoperative liver failure. Beyond surgical safety, impaired liver function has been associated with increased recurrence and reduced overall survival because it reflects advanced chronic liver injury and limits the feasibility of repeat resection, local ablation, or systemic therapies following recurrence. Recent studies suggest that the ALBI grade may provide more objective prognostic information than conventional Child-Pugh classification in patients undergoing curative resection. **[36]**

5.4 Portal Hypertension

Clinically significant portal hypertension represents another adverse prognostic factor in patients undergoing liver resection. Elevated portal venous pressure reflects advanced architectural distortion of the liver caused by fibrosis and cirrhosis and is associated with impaired hepatic reserve, increased perioperative morbidity, and reduced long-term survival. Patients with portal hypertension often require more conservative hepatic resections to preserve liver function, which may limit surgical margins in selected cases. Additionally, portal hypertension serves as an indirect marker of advanced chronic liver disease, contributing to persistent hepatocarcinogenesis and increased risk of late recurrence following

apparently curative surgery. **[37]**

5.5 Chronic Hepatitis B Virus Infection

Chronic hepatitis B virus (HBV) infection remains a major determinant of HCC recurrence, particularly in endemic regions. Persistent viral replication promotes chronic hepatic inflammation, integration of viral DNA into the host genome, activation of oncogenic signaling pathways, and continuous hepatocyte regeneration, all of which contribute to recurrent carcinogenesis. High preoperative HBV DNA levels have consistently been associated with increased postoperative recurrence and poorer survival. Conversely, effective suppression of viral replication with nucleos(t)ide analogue therapy significantly reduces recurrence risk and improves long-term outcomes after liver resection. Consequently, antiviral therapy has become an essential component of postoperative management in HBV-related HCC. **[38]**

5.6 Chronic Hepatitis C Virus Infection

Hepatitis C virus (HCV) infection also contributes substantially to postoperative recurrence through persistent hepatic inflammation and progressive fibrogenesis. Although HCV lacks direct oncogenic activity comparable to HBV, chronic infection promotes cirrhosis and creates a carcinogenic hepatic environment conducive to multicentric tumor development. The widespread use of direct-acting antiviral agents has dramatically improved sustained virological response rates and reduced the incidence of de novo HCC. Nevertheless, patients with advanced fibrosis or established cirrhosis remain at measurable risk of recurrence even after successful viral eradication, emphasizing the need for lifelong surveillance in this population. **[39]**

5.7 Etiology of Chronic Liver Disease

Beyond viral hepatitis, the underlying cause of chronic liver disease influences recurrence risk after hepatectomy. Patients with metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-associated liver disease, autoimmune hepatitis, and hereditary metabolic disorders each exhibit distinct biological pathways leading to hepatocarcinogenesis. Increasing evidence suggests that MASLD-related HCC is associated with persistent metabolic inflammation, insulin resistance, oxidative stress, and lipotoxicity, all of which may contribute to postoperative recurrence. As the global epidemiology of HCC shifts toward metabolic liver disease, careful consideration of disease etiology will become increasingly important in postoperative risk assessment and surveillance strategies. **[40]**

5.8 Future Perspective on Liver-Related Risk Stratification

Contemporary evidence indicates that recurrence after curative liver resection cannot be adequately predicted by tumor characteristics alone. Integration of liver-related variables—including fibrosis severity, portal hypertension, hepatic functional reserve, viral activity, and underlying disease etiology—provides a more comprehensive assessment of recurrence risk. Emerging biomarkers of hepatic inflammation, fibrosis progression, and liver regeneration, together with advanced imaging techniques and molecular profiling, are expected to further improve individualized prediction models. Such integrated approaches may facilitate personalized surveillance protocols and targeted interventions aimed at reducing late recurrence while preserving long-term liver function and patient survival.

6. Patient-Related Predictors of Hepatocellular Carcinoma Recurrence

Patient-related characteristics substantially influence the risk of hepatocellular carcinoma (HCC) recurrence following curative liver resection. Although tumor biology remains the primary determinant of early recurrence, host factors affect hepatic carcinogenesis, immune surveillance, liver regeneration, and tolerance to chronic liver injury, thereby contributing to both early and late postoperative recurrence. Demographic characteristics, metabolic comorbidities, nutritional status, lifestyle factors, and performance status have all been investigated as potential prognostic indicators. Comprehensive assessment of these variables complements tumor- and liver-related predictors and facilitates individualized postoperative risk stratification. **[41]**

6.1 Age

The relationship between patient age and HCC recurrence remains controversial. Younger patients frequently present with biologically aggressive tumors, particularly in regions where chronic hepatitis B virus infection is endemic, and several studies have reported higher rates of early recurrence in

younger individuals because of more invasive tumor characteristics. Conversely, elderly patients often exhibit reduced physiological reserve, multiple comorbidities, and impaired hepatic regenerative capacity, which may adversely affect long-term survival. Current evidence suggests that chronological age alone is not an independent determinant of recurrence; rather, recurrence risk is influenced by the interaction between age, tumor biology, liver function, and overall health status. Therefore, treatment decisions should be guided by comprehensive clinical assessment rather than age alone. **[42]**

6.2 Sex

Sex-related differences have been observed in both the incidence and recurrence of HCC. Men develop HCC considerably more frequently than women, largely because of higher exposure to viral hepatitis, alcohol consumption, smoking, and metabolic risk factors, as well as the influence of androgen signaling on hepatocarcinogenesis. Estrogen is believed to exert protective anti-inflammatory and antifibrotic effects that may partially explain the lower incidence of HCC among women. However, after curative liver resection, the independent effect of sex on recurrence remains inconsistent across studies, suggesting that differences are largely mediated through underlying etiological and biological factors rather than sex itself. **[43]**

6.3 Diabetes Mellitus

Diabetes mellitus is one of the most consistently reported patient-related predictors of HCC recurrence. Chronic hyperglycemia, insulin resistance, and hyperinsulinemia stimulate cellular proliferation through activation of insulin-like growth factor signaling pathways while simultaneously promoting oxidative stress, chronic inflammation, and hepatic fibrogenesis. Diabetic patients frequently have coexisting metabolic dysfunction-associated steatotic liver disease (MASLD), obesity, and advanced fibrosis, all of which contribute to an increased risk of de novo hepatocarcinogenesis following resection. Several meta-analyses have demonstrated that diabetes is independently associated with shorter recurrence-free survival and poorer overall survival after curative hepatectomy, emphasizing the importance of optimal glycemic control during postoperative follow-up. **[44]**

6.4 Obesity and Metabolic Syndrome

Obesity and metabolic syndrome have emerged as increasingly important predictors of HCC recurrence in parallel with the global rise in metabolic liver disease. Excess adipose tissue promotes chronic low-grade inflammation, adipokine dysregulation, insulin resistance, oxidative stress, and lipotoxicity, thereby creating a pro-carcinogenic hepatic environment. Patients with metabolic syndrome often exhibit multiple overlapping risk factors, including hypertension, diabetes, dyslipidemia, and MASLD, which collectively accelerate fibrosis progression and increase recurrence risk. Recent evidence suggests that obesity-related inflammatory pathways may contribute to both early tumor progression and late multicentric recurrence, making metabolic optimization an important component of postoperative management. **[45]**

6.5 Nutritional Status and Sarcopenia

Nutritional status has emerged as an important determinant of outcomes following liver resection. Sarcopenia, characterized by progressive loss of skeletal muscle mass and function, is common among patients with chronic liver disease and has been associated with increased postoperative complications, reduced tolerance to treatment, and poorer long-term survival. Mechanistically, sarcopenia reflects systemic inflammation, protein-energy malnutrition, hormonal imbalance, and impaired immune function, all of which may facilitate tumor progression and recurrence. Assessment of skeletal muscle mass using cross-sectional imaging and implementation of perioperative nutritional support and exercise programs may improve postoperative recovery and potentially reduce recurrence risk in vulnerable patients. **[46]**

6.6 Lifestyle Factors

Lifestyle behaviors continue to influence recurrence after curative liver resection. Persistent alcohol consumption promotes ongoing hepatic inflammation, oxidative injury, and fibrosis progression, thereby increasing the likelihood of late multicentric HCC recurrence. Cigarette smoking has also been associated with adverse oncological outcomes through induction of oxidative stress, DNA damage, and

chronic systemic inflammation. Conversely, maintenance of a healthy body weight, regular physical activity, abstinence from alcohol, smoking cessation, and adherence to balanced dietary patterns may improve liver health and reduce progression of chronic liver disease. Although prospective evidence remains limited, lifestyle modification is increasingly recognized as an integral component of comprehensive postoperative care. **[47]**

6.7 Performance Status and Comorbidities

Baseline functional status and associated medical comorbidities influence both recurrence and overall survival following hepatectomy. Patients with poor Eastern Cooperative Oncology Group (ECOG) performance status, cardiovascular disease, chronic kidney disease, chronic pulmonary disease, or severe metabolic disorders generally experience inferior long-term outcomes because these conditions limit tolerance to surgery, reduce eligibility for repeat curative therapies, and increase non-cancer-related mortality. Furthermore, systemic inflammation and immune dysfunction associated with chronic comorbid conditions may contribute to tumor recurrence. Comprehensive preoperative optimization and multidisciplinary management are therefore essential to maximize postoperative outcomes. **[48]**

6.8 Clinical Implications of Patient-Related Factors

Patient-related predictors should not be considered in isolation but rather integrated with tumor-related and liver-related characteristics to provide individualized estimates of recurrence risk. Incorporating demographic variables, metabolic comorbidities, nutritional assessment, and functional status into prognostic models improves risk stratification and supports personalized surveillance schedules, targeted lifestyle interventions, and optimization of chronic disease management. As precision medicine continues to evolve, combining patient-related clinical characteristics with molecular biomarkers and advanced predictive algorithms may further enhance the ability to identify patients at highest risk of recurrence and improve long-term outcomes following curative liver resection. **[49]**

7. Surgical and Perioperative Predictors of Hepatocellular Carcinoma Recurrence

Surgical and perioperative factors significantly influence the risk of hepatocellular carcinoma (HCC) recurrence after curative liver resection. Although recurrence is primarily determined by tumor biology and the underlying hepatic microenvironment, operative strategy and perioperative management can affect residual microscopic disease, postoperative liver regeneration, inflammatory responses, and long-term oncological outcomes. Careful preoperative planning, meticulous surgical technique, and optimization of perioperative care are therefore essential to maximize recurrence-free survival while preserving adequate liver function. **[50]**

7.1 Surgical Margin Width

The adequacy of the surgical margin remains one of the most extensively investigated operative predictors of HCC recurrence. A negative (R0) resection margin is the primary objective of curative hepatectomy because residual microscopic tumor cells may serve as a source of early recurrence. Several studies have suggested that wider resection margins, particularly those exceeding 1 cm, are associated with lower recurrence rates by reducing the likelihood of leaving occult microscopic satellite lesions or vascular tumor emboli adjacent to the primary tumor. However, the optimal margin width remains controversial, especially in patients with cirrhosis, where preservation of functional liver parenchyma must be balanced against oncological radicality. Contemporary evidence suggests that achieving a tumor-free margin is more important than achieving a predetermined margin distance, particularly when liver functional reserve is limited.

7.2 Anatomical Versus Non-Anatomical Liver Resection

The choice between anatomical and non-anatomical liver resection has been widely debated. Anatomical resection involves removal of the entire hepatic segment supplied by the portal venous branch feeding the tumor, thereby theoretically eliminating microscopic portal venous tumor spread. In contrast, non-anatomical (wedge) resection removes the tumor with an adequate surrounding margin while preserving maximal liver parenchyma. Numerous retrospective studies and several meta-analyses have demonstrated improved recurrence-free survival following anatomical resection, particularly for solitary tumors

measuring ≤5 cm and in patients with preserved liver function. However, overall survival differences are less consistent, as the benefit of wider oncological clearance may be offset by increased postoperative liver dysfunction in selected patients. Consequently, the choice of surgical approach should be individualized according to tumor characteristics, liver reserve, and future liver remnant volume.

7.3 Intraoperative Blood Loss

Excessive intraoperative blood loss has consistently been associated with adverse oncological outcomes following hepatectomy. Significant hemorrhage may impair surgical visualization, prolong operative time, increase postoperative complications, and contribute to systemic inflammatory and immunosuppressive responses that facilitate tumor recurrence. Furthermore, excessive blood loss often reflects technically complex resections involving larger tumors, vascular invasion, or advanced cirrhosis. Modern hepatic surgical techniques, including low central venous pressure anesthesia, meticulous vascular control, ultrasonic dissectors, bipolar energy devices, and vascular stapling systems, have substantially reduced intraoperative bleeding and improved perioperative outcomes.

7.4 Perioperative Blood Transfusion

Perioperative blood transfusion has been repeatedly identified as an independent predictor of HCC recurrence and reduced long-term survival. Several mechanisms have been proposed, including transfusion-related immunomodulation, suppression of natural killer cell activity, altered T-cell function, and enhanced inflammatory cytokine production, all of which may facilitate survival of residual malignant cells. Patients requiring transfusion frequently undergo more extensive resections or experience greater intraoperative blood loss, making it difficult to distinguish the independent effect of transfusion from underlying surgical complexity. Nevertheless, current evidence supports restrictive transfusion strategies whenever clinically appropriate to minimize unnecessary exposure to allogeneic blood products.

7.5 Operative Time

Prolonged operative duration has also been associated with poorer postoperative outcomes. Longer procedures often indicate technically demanding surgery resulting from larger tumors, vascular reconstruction, severe cirrhosis, adhesions from previous interventions, or complex anatomical resections. Extended operative time may increase physiological stress, inflammatory activation, and postoperative complications, all of which can adversely affect immune function and delay recovery. Although operative duration itself may not directly cause recurrence, it serves as an important surrogate marker of operative complexity and should be considered when interpreting postoperative prognosis.

7.6 Minimally Invasive Versus Open Liver Resection

Laparoscopic and robotic liver resections have become increasingly adopted for selected patients with early-stage HCC. Compared with conventional open surgery, minimally invasive hepatectomy is associated with reduced intraoperative blood loss, lower postoperative pain, shorter hospital stay, faster recovery, and decreased surgical stress without compromising oncological principles. Numerous comparative studies have demonstrated similar recurrence-free and overall survival between minimally invasive and open liver resection when appropriate patient selection criteria are applied. Therefore, the choice of surgical approach should primarily depend on tumor location, surgeon expertise, liver function, and technical feasibility rather than concerns regarding oncological adequacy.

7.7 Postoperative Complications

Major postoperative complications may adversely influence long-term oncological outcomes by delaying recovery, impairing liver regeneration, and postponing treatment of recurrent disease. Complications such as post-hepatectomy liver failure, bile leakage, intra-abdominal infection, and sepsis induce prolonged systemic inflammation and immunosuppression, potentially facilitating tumor progression. Several studies have reported that patients experiencing severe postoperative complications have significantly shorter recurrence-free survival than those with uncomplicated recoveries. Accordingly, enhanced recovery protocols, meticulous perioperative care, and early recognition and treatment of complications may contribute not only to improved short-term outcomes but also to better long-term prognosis.

7.8 Clinical Implications of Surgical Predictors

Surgical and perioperative variables represent modifiable determinants of HCC recurrence that

complement tumor- and liver-related prognostic factors. Careful patient selection, meticulous operative planning, achievement of negative surgical margins, minimization of blood loss and transfusion, preservation of adequate liver function, and prompt management of postoperative complications collectively improve oncological outcomes after curative hepatectomy. Future advances in image-guided surgery, fluorescence navigation, artificial intelligence-assisted operative planning, and precision hepatic surgery may further optimize surgical quality and reduce recurrence risk. Integrating operative variables into comprehensive prognostic models alongside clinicopathological and molecular biomarkers will likely enhance individualized postoperative risk assessment and guide personalized surveillance strategies.

8. Histopathological and Molecular Predictors of Hepatocellular Carcinoma Recurrence

Histopathological evaluation remains the gold standard for assessing the biological behavior of hepatocellular carcinoma (HCC) following curative liver resection. While conventional clinicopathological parameters such as tumor size and vascular invasion provide valuable prognostic information, microscopic pathological features offer a more comprehensive understanding of tumor aggressiveness and metastatic potential. In recent years, advances in molecular pathology have further improved recurrence prediction by identifying genetic, epigenetic, and immunological biomarkers associated with tumor progression. Integration of histopathological and molecular characteristics into prognostic models has the potential to enhance individualized risk assessment beyond traditional staging systems. **[51]**

8.1 Histological Tumor Grade

Histological differentiation is one of the most consistently validated pathological predictors of HCC recurrence. According to the Edmondson-Steiner grading system, poorly differentiated tumors exhibit marked cellular atypia, increased mitotic activity, architectural disorganization, and loss of hepatocellular characteristics, reflecting aggressive biological behavior. Numerous studies have demonstrated that poor histological differentiation is independently associated with increased rates of microvascular invasion, intrahepatic metastasis, early postoperative recurrence, and reduced overall survival. Conversely, well-differentiated tumors generally exhibit slower growth, lower metastatic potential, and more favorable long-term outcomes following curative resection. Therefore, histological grading remains an essential component of postoperative prognostic assessment. **[52]**

8.2 Microvascular and Lymphovascular Invasion

Microvascular invasion (MVI) is considered the most powerful histopathological predictor of early HCC recurrence. Microscopically, tumor emboli within small portal venous or hepatic venous branches indicate dissemination of malignant cells beyond the primary lesion before surgery. Several meta-analyses have consistently identified MVI as an independent predictor of both recurrence-free and overall survival. The severity of vascular invasion, including the number of invaded vessels and the distance from the primary tumor, appears to further influence prognosis. Although lymphatic invasion is less common in HCC than vascular invasion, its presence similarly reflects aggressive tumor biology and has been associated with poor postoperative outcomes. **[53]**

8.3 Satellite Nodules and Microscopic Intrahepatic Metastasis

The presence of satellite nodules surrounding the primary tumor represents microscopic intrahepatic metastatic spread and is strongly associated with early recurrence following liver resection. Satellite lesions frequently coexist with microvascular invasion and poor histological differentiation, indicating advanced local tumor dissemination before surgery. Histopathological identification of these lesions suggests that complete macroscopic tumor removal may not eliminate all malignant foci, thereby increasing the likelihood of early postoperative relapse. Consequently, patients with satellite nodules require intensive postoperative surveillance because of their substantially elevated recurrence risk. **[54]**

8.4 Tumor Capsule Integrity

The pathological characteristics of the tumor capsule also influence recurrence risk. Complete fibrous encapsulation may restrict local tumor extension and serve as a protective barrier against microscopic invasion into adjacent hepatic parenchyma. In contrast, incomplete capsule formation, capsular disruption, or direct extracapsular invasion reflects increased invasive potential and has been associated with higher recurrence rates. Although capsule integrity alone is rarely an independent prognostic factor after multivariable adjustment, it provides valuable complementary information when interpreted alongside tumor size, vascular invasion, and histological grade. **[55]**

8.5 Tumor Necrosis and Histological Growth Pattern

Histological evidence of spontaneous tumor necrosis has shown variable prognostic significance in HCC. Extensive necrosis may reflect rapid tumor proliferation exceeding vascular supply and has been associated with aggressive tumor behavior in some studies. In addition, different histological growth patterns, including expansive, infiltrative, and replacement growth, have distinct biological characteristics. Infiltrative tumors are particularly associated with vascular invasion, poor differentiation, and early recurrence because of their tendency to invade surrounding hepatic tissue without forming a distinct boundary. Recognition of these microscopic growth characteristics contributes to a more accurate assessment of postoperative recurrence risk. **[56]**

8.6 Molecular Biomarkers

Recent advances in molecular oncology have identified numerous biomarkers associated with HCC recurrence. Gene expression signatures related to cell proliferation, angiogenesis, epithelial-mesenchymal transition, and immune regulation have demonstrated prognostic value in predicting postoperative relapse. Alterations in genes such as **TP53**, **CTNNB1**, **TERT**, and regulators of the Wnt/β-catenin pathway have been associated with aggressive tumor behavior and reduced recurrence-free survival. In addition, dysregulated microRNAs, circulating tumor DNA (ctDNA), and exosomal nucleic acids are emerging as promising non-invasive biomarkers capable of detecting minimal residual disease and predicting recurrence before radiological evidence becomes apparent. Although these molecular markers remain largely investigational, they represent important advances toward precision oncology in HCC. **[57]**

8.7 Immunohistochemical Markers

Immunohistochemistry has become an increasingly valuable tool for evaluating tumor biology. Elevated expression of proliferative markers such as Ki-67 is consistently associated with increased cellular proliferation, early recurrence, and poor survival. Similarly, overexpression of angiogenic factors including vascular endothelial growth factor (VEGF), as well as markers associated with epithelial-mesenchymal transition and cancer stem cells such as EpCAM, CD133, and glypican-3, has been linked to aggressive disease and unfavorable outcomes. Immune checkpoint proteins, particularly programmed death-ligand 1 (PD-L1), are also being investigated as prognostic biomarkers because of their association with immune evasion and potential responsiveness to immunotherapy. **[58]**

8.8 Future Perspectives in Molecular Risk Stratification

The future of recurrence prediction following curative liver resection lies in integrating conventional histopathological assessment with molecular profiling and artificial intelligence-based predictive models. Combining clinicopathological characteristics with genomic alterations, transcriptomic signatures, proteomic biomarkers, immune profiling, and radiomic features may substantially improve the accuracy of individualized recurrence prediction. Prospective multicenter validation of these integrated models is still required before routine clinical implementation. Nevertheless, advances in molecular pathology are expected to facilitate precision surveillance strategies, improve patient selection for adjuvant therapies, and ultimately reduce recurrence-related mortality after curative resection of hepatocellular carcinoma. **[59]**

9. Prognostic Models, Risk Stratification, and Future Directions

Accurate prediction of hepatocellular carcinoma (HCC) recurrence following curative liver resection is essential for optimizing postoperative surveillance, identifying patients who may benefit from adjuvant therapies, and improving long-term survival. Although numerous clinicopathological predictors have been

independently associated with recurrence, no single variable adequately captures the complex biological interactions underlying tumor relapse. Consequently, considerable efforts have been directed toward developing prognostic models that integrate multiple tumor-related, liver-related, patient-related, and molecular factors into comprehensive risk stratification systems. These models aim to provide individualized estimates of recurrence risk and facilitate precision-based postoperative management. **[60]**

9.1 Conventional Staging Systems

Several staging systems have been developed to predict prognosis in patients with HCC, including the Barcelona Clinic Liver Cancer (BCLC) staging system, the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) classification, the Cancer of the Liver Italian Program (CLIP) score, the Japan Integrated Staging (JIS) score, and the Hong Kong Liver Cancer (HKLC) staging system. While these classifications are valuable for treatment allocation and overall survival prediction, their ability to accurately predict postoperative recurrence is relatively limited because they primarily focus on tumor burden and liver function rather than microscopic pathological features and biological behavior. Consequently, recurrence-specific prediction models have increasingly been developed to overcome these limitations. **[61]**

9.2 Clinicopathological Prediction Models

Numerous prognostic nomograms have combined conventional clinicopathological variables to estimate recurrence risk following curative hepatectomy. Commonly incorporated variables include tumor size, tumor number, microvascular invasion, histological differentiation, serum alpha-fetoprotein (AFP), liver cirrhosis, resection margin status, and liver function indices. Compared with individual prognostic factors, these multivariable models provide superior predictive accuracy because they account for the cumulative contribution of multiple risk determinants. Several externally validated nomograms have demonstrated excellent discrimination for recurrence-free survival and are increasingly being adopted to guide individualized follow-up strategies in specialized centers. **[62]**

9.3 Biomarker-Based Risk Stratification

The incorporation of serum biomarkers into prognostic models has significantly improved recurrence prediction. Alpha-fetoprotein remains the most widely used biomarker; however, combining AFP with protein induced by vitamin K absence-II (PIVKA-II), AFP-L3 fraction, inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), and albumin-based nutritional indices enhances prognostic performance. More recently, circulating tumor DNA, circulating tumor cells, exosomal microRNAs, and gene-expression signatures have demonstrated promising predictive value for identifying minimal residual disease and early postoperative recurrence before radiological evidence becomes apparent. These advances are moving recurrence prediction toward a precision medicine approach based on individualized biological profiling. **[63]**

9.4 Artificial Intelligence and Radiomics

Artificial intelligence (AI) and radiomics have emerged as rapidly evolving technologies capable of transforming postoperative risk prediction in HCC. Radiomic analysis extracts quantitative imaging features from computed tomography (CT), magnetic resonance imaging (MRI), and contrast-enhanced ultrasound that are not detectable by visual interpretation alone. Machine learning algorithms integrate these imaging features with clinical, pathological, and laboratory variables to generate individualized recurrence prediction models with high predictive accuracy. Deep learning techniques have further improved the ability to identify occult microvascular invasion, tumor heterogeneity, and aggressive biological phenotypes preoperatively. Although these technologies remain under active investigation, they hold considerable promise for improving surgical planning and postoperative surveillance. **[64]**

9.5 Personalized Surveillance Strategies

Risk stratification should directly influence postoperative surveillance intensity. Patients classified as high risk because of unfavorable clinicopathological or molecular characteristics require more frequent follow-up using cross-sectional imaging and serial tumor marker assessment during the first two postoperative years, when recurrence risk is greatest. Conversely, patients with favorable prognostic profiles may undergo less intensive surveillance without compromising early detection. Personalized surveillance

protocols based on validated recurrence prediction models may improve resource utilization while increasing the likelihood of detecting recurrent disease at a stage amenable to curative treatment. **[65]**

9.6 Emerging Adjuvant Therapeutic Strategies

The recognition that recurrence is driven by both residual microscopic disease and ongoing hepatocarcinogenesis has stimulated interest in postoperative adjuvant therapies. Long-term antiviral treatment for hepatitis B virus infection has already demonstrated significant reductions in recurrence following curative resection. In addition, immune checkpoint inhibitors, molecular targeted therapies, antiangiogenic agents, cancer vaccines, and adoptive cellular immunotherapy are currently being investigated as adjuvant treatments for patients at high risk of recurrence. Although several clinical trials have reported encouraging preliminary results, further evidence is required before these approaches become standard components of postoperative management. **[66]**

9.7 Research Gaps and Future Perspectives

Despite significant advances in recurrence prediction, several important challenges remain unresolved. Most available prognostic models have been developed using retrospective single-center cohorts with heterogeneous patient populations and variable follow-up protocols. External validation across diverse geographic regions and disease etiologies is still limited, particularly for patients with metabolic dysfunction-associated steatotic liver disease. Future research should focus on developing universally applicable prediction models that integrate clinicopathological characteristics, molecular biomarkers, radiomic features, immune profiling, and artificial intelligence into standardized clinical decision-support systems. Large prospective multicenter studies are essential to validate these integrated approaches and determine their impact on long-term patient outcomes. **[67]**

9.8 Clinical Implications

The future management of hepatocellular carcinoma following curative liver resection will increasingly rely on individualized recurrence prediction rather than conventional staging alone. Comprehensive integration of tumor biology, liver function, patient characteristics, surgical variables, molecular biomarkers, and advanced computational technologies offers the opportunity to identify patients at highest risk of recurrence with greater precision. Such personalized risk assessment will facilitate tailored surveillance schedules, early therapeutic intervention, appropriate selection for adjuvant treatments, and ultimately improve recurrence-free and overall survival. As precision hepatology continues to evolve, validated multidisciplinary prediction models are expected to become an integral component of routine postoperative care for patients undergoing curative liver resection. **[68]**

Conclusion

Recurrence following curative liver resection remains the principal challenge in the management of hepatocellular carcinoma (HCC), significantly limiting long-term survival despite advances in surgical techniques and perioperative care. The risk of recurrence is determined by a complex interplay of tumor-related, liver-related, patient-related, surgical, histopathological, and molecular factors. Tumor characteristics such as microvascular invasion, tumor size, multiplicity, and poor differentiation primarily influence early recurrence, whereas chronic liver disease, cirrhosis, fibrosis, and persistent hepatic inflammation contribute predominantly to late multicentric recurrence. Recent developments in molecular biomarkers, artificial intelligence, radiomics, and integrated prognostic models have enhanced the ability to identify patients at high risk for recurrence and support personalized postoperative surveillance and therapeutic strategies. Future research should focus on prospective validation of comprehensive prediction models that combine clinical, pathological, radiological, and molecular data to improve individualized risk assessment. A multidisciplinary precision medicine approach integrating optimized surgical management, treatment of underlying liver disease, biomarker-guided surveillance, and effective adjuvant therapies offers the greatest potential to reduce recurrence and improve long-term outcomes following curative liver resection.

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