Hepatocellular Carcinoma: Understanding Disease Development, Diagnostic Perspectives, and Management Strategies

Carcinoma hepatocelular: compreensão do desenvolvimento da doença, perspectivas diagnósticas e estratégias de tratamento

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer-related mortality worldwide. Its development is associated with chronic hepatitis B and C infections, alcohol consumption, metabolic dysfunction-associated steatotic liver disease, diabetes and other environmental and metabolic factors. This chapter offers an overview of HCC epidemiology, risk factors, molecular pathogenesis, diagnosis, staging, management, surveillance and future perspectives. HCC involves genetic and epigenetic modifications, chronic inflammation, oxidative stress, fibrosis and cirrhosis. Dysregulation of major signalling pathways, including MAPK/ERK, Wnt/β-catenin, PI3K/AKT/mTOR, Hippo-YAP/TAZ and p53, enhances

tumour development, progression and therapeutic resistance, and the tumour microenvironment further contributes to immune evasion and recurrence. Early diagnosis remains challenging because initial symptoms are often absent or nonspecific. Diagnostic approaches include serum alpha-fetoprotein measurement, ultrasonography, contrast-enhanced computed tomography, magnetic resonance imaging and, when indicated, histopathological examination. The Barcelona Clinic Liver Cancer classification guides treatment decisions by integrating tumour characteristics, liver function and patient performance status. Treatment options comprise surgical resection, liver transplantation, locoregional therapies, targeted agents and immune checkpoint inhibitors. Regular surveillance with ultrasonography, with or without alpha-fetoprotein, supports early detection and post-treatment monitoring. Despite significant advances, late diagnosis, tumour heterogeneity, recurrence and unequal access to healthcare remain major challenges. Future research should emphasize molecular profiling, personalized medicine, novel biomarkers, improved surveillance and multidisciplinary care to improve clinical outcomes and reduce HCC-related morbidity and mortality.

Keywords: hepatocellular carcinoma, hepatitis B virus, hepatitis C virus, fibrosis, cirrhosis.

Resumo

O carcinoma hepatocelular (CHC) é o câncer primário de fígado mais comum e uma das principais causas de mortalidade por câncer no mundo. Seu desenvolvimento está associado às infecções crônicas pelos vírus das hepatites B e C, ao consumo de álcool, à doença hepática esteatótica associada à disfunção metabólica, ao diabetes e a outros fatores ambientais e metabólicos. Este capítulo apresenta uma visão geral da epidemiologia, dos fatores de risco, da patogênese molecular, do diagnóstico, do estadiamento, do tratamento, da vigilância e das perspectivas futuras do CHC. O CHC envolve modificações genéticas e epigenéticas, inflamação crônica, estresse oxidativo, fibrose e cirrose. A desregulação de importantes vias de sinalização, como MAPK/ERK, Wnt/β-catenina, PI3K/AKT/mTOR, Hippo-YAP/TAZ e p53, favorece o desenvolvimento e a progressão tumoral e a resistência terapêutica, e o microambiente tumoral contribui ainda para a evasão imune e a recidiva. O diagnóstico precoce continua difícil, porque os sintomas iniciais costumam ser ausentes ou inespecíficos. As abordagens diagnósticas incluem a dosagem sérica de alfafetoproteína, a ultrassonografia, a tomografia computadorizada com contraste, a ressonância magnética e, quando indicado, o exame histopatológico. A classificação Barcelona Clinic Liver Cancer orienta as decisões terapêuticas ao integrar as características do tumor, a função hepática e o estado funcional do paciente. As opções de tratamento incluem ressecção cirúrgica, transplante hepático, terapias locorregionais, agentes-alvo e inibidores de checkpoints imunológicos. A vigilância regular por ultrassonografia, com ou sem alfafetoproteína, favorece a detecção precoce e o acompanhamento após o tratamento. Apesar de avanços significativos, o diagnóstico tardio, a heterogeneidade tumoral, a recidiva e a desigualdade no acesso aos serviços de saúde continuam sendo grandes desafios. Pesquisas futuras devem priorizar a caracterização molecular, a medicina personalizada, novos biomarcadores, o aprimoramento da vigilância e o cuidado multidisciplinar, a fim de melhorar os desfechos clínicos e reduzir a morbidade e a mortalidade associadas ao CHC.

Palavras-chave: carcinoma hepatocelular, vírus da hepatite B, vírus da hepatite C, fibrose, cirrose.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a major global health concern. The World Health Organization estimates that approximately 239,000 people died from cirrhosis and hepatocellular carcinoma caused by hepatitis C virus (HCV) infection, that 47 million people worldwide live with chronic HCV infection and that 0.9 million new infections occur each year (World Health Organization, 2026b). People with hepatitis B virus (HBV) or HCV infection, excessive alcohol consumption or non-alcoholic fatty liver disease (NAFLD) are more likely to develop the disease. Long-term liver injury, chronic inflammation, progressive fibrosis and, finally, cirrhosis all contribute to its development.

Early detection of HCC remains challenging because signs and symptoms may be nonspecific or absent. People at high risk should undergo ultrasound and serum alpha-fetoprotein testing every six months. Advanced imaging methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), show the characteristic patterns of blood flow of the tumour, and a biopsy may be needed when the diagnosis remains unclear. Staging systems such as the Barcelona Clinic Liver Cancer (BCLC) classification guide clinical decisions. Treatment depends on liver function, tumour size and the patient's overall health: transarterial chemoembolization is frequently the preferred option for intermediate-stage tumours, systemic agents are the main choice for advanced disease, and palliative care remains essential as the disease progresses (Fite & Makary, 2024).

This chapter is a narrative review of the current literature on HCC, covering its epidemiology, risk factors, molecular pathogenesis, diagnosis, staging, treatment and surveillance. Relevant literature was identified in scientific databases, including PubMed, Scopus and Google Scholar, alongside established clinical practice guidelines and recommendations from the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and the Barcelona Clinic Liver Cancer (BCLC) group. The review primarily covers literature published between 2015 and 2026, with earlier landmark studies included where relevant to provide historical and scientific context.

Epidemiology and risk factors

Epidemiology of hepatocellular carcinoma

HCC is the fifth most commonly diagnosed cancer worldwide and the second leading cause of cancer death. About 72% of all cases occur in Asia, where incidence rates are particularly high in China, Vietnam, Laos, Cambodia, Mongolia and Thailand. While HBV remains the primary cause in many developing countries, chronic alcohol consumption, HCV

infection and the growing incidence of metabolic syndrome increasingly contribute to HCC in high-income countries (Singh et al., 2025).

Global burden and mortality

According to WHO estimates for 2024, 240 million people were living with chronic HBV infection and around 0.9 million new infections occur each year. The WHO also reports that 1.1 million deaths were caused by HBV-related cirrhosis and hepatocellular carcinoma (World Health Organization, 2026a). The widespread use of direct-acting antiviral agents (DAAs) has greatly reduced HCV-related disease, and national vaccination programmes, such as Taiwan's HBV immunization initiative, have contributed significantly to lower HCC mortality. In North America, Europe and Australia, non-viral aetiologies, such as metabolic dysfunction-associated steatohepatitis (MASH) and alcohol-related liver disease (ALD), now account for most cases (Singh et al., 2025).

In both developed and developing regions, NAFLD has become a major cause of HCC. It accounted for 0% to 3% of cases in the 1990s and rose to between 12% and 29% in Europe and North America during the 2010s. In Japan, the proportion of non-viral HCC rose from 10% to 32.5% (Cho et al., 2011; Dyson et al., 2014; Myers et al., 2021; Pais et al., 2017; Tateishi et al., 2019). Other Asian countries are undergoing similar changes, and NAFLD is quickly replacing viral hepatitis as the main cause of liver disease (Yip et al., 2022). Between 2016 and 2030, the number of people with HCC in China is projected to rise by 86% and the number of new cases by 82%. In India, metabolic dysfunction-associated steatotic liver disease (MASLD) has replaced HBV as the principal cause of HCC (Estes et al., 2020; Prabhakar et al., 2023). A multicentre study of 354 patients with MASLD-related HCC treated between 2007 and 2018 compared patients with and without cirrhosis and found that about 60% of them had cirrhosis and 35% did not (Vitellius et al., 2024). Alcohol consumption and hepatitis B or C infection were the next most common causes. In South America, the proportion of HCC linked to NAFLD rose from 9% to 37% in ten years (Farah et al., 2023).

Risk factors

A systematic review of 12 studies showed that older age, male sex, hypertension and diabetes are significantly associated with an increased risk of HCC in NAFLD. Patients with both NAFLD and diabetes have a nearly 2.27-fold higher likelihood of developing HCC, whereas active smoking and dyslipidaemia were not statistically significant. These findings highlight the need for targeted health education and preventive services for older people, men and NAFLD patients with diabetes or hypertension (Yin et al., 2024).

Tumour cells constantly change their genotypic and epigenetic profiles, which leads to phenotypic alterations that allow adaptation to environmental stress and therapeutic challenges. These changes may occur in different tumour nodules or even within the same lesion, resulting in substantial intratumoral heterogeneity. HCC rarely harbours mutations in clinically actionable genes; instead, it frequently carries mutations in tumour suppressors that cannot be directly targeted, such as TP53 or ARID1/2, alterations of TERT/TERC and of components of the JAK-STAT axis, such as JAK1, IL6R and IL6ST. Other dysregulated pathways involved in hepatocarcinogenesis include PI3K/AKT/mTOR, MYC, oxidative stress regulators (KEAP1, NFE2L2), RAS/RAF/MAPK kinase and MET signalling (Yin et al., 2024).

Pathogenesis of hepatocellular carcinoma

Molecular and genetic mechanisms

With the development of molecular technologies, researchers have identified a variety of signalling pathways and genetic and epigenetic alterations that are abnormally expressed during the onset and spread of HCC. Tumorigenesis results from the abnormal activation or dysregulation of signal transduction pathways in the liver, which affects the proliferation, survival, differentiation and apoptosis of parenchymal liver cells. Research into the intricate network of pathways in HCC is therefore necessary to identify more effective molecular markers that can target the entire tumour (Safri et al., 2024).

In human HCC, the MAPK/ERK signalling cascade is frequently activated, primarily by growth factors such as EGF and TGF-β rather than only by RAS and RAF mutations. This activation may also result from the suppression of negative regulators or the enhancement of positive modulators. Hepatocyte growth factor (HGF), released by hepatic stellate cells, activates the MAPK/ERK pathway through its receptor, HGFR. In addition, certain non-coding RNAs, including miR-4510 and miR-30a (downregulated) and miR-330-5p and miR-487 (upregulated), along with specific long non-coding RNAs, contribute to the regulation and promotion of tumorigenesis through this pathway (Borlak et al., 2005).

Dysregulated Wnt/β-catenin signalling plays a crucial role in the development of HCC, with gain-of-function mutations in *CTNNB1* and loss-of-function mutations in *AXIN1* found in approximately 35% of cases. These mutations can stabilize β-catenin, leading to its nuclear translocation and to gene expression profiles that differ according to the virus type (HCV or HBV). Besides genetic mutations, epigenetic factors such as DNA methylation and histone modifications also contribute to aberrant Wnt/β-catenin activation. Elevated Wnt ligands in liver cancer cells encourage immune cell infiltration, while downregulated Wnt inhibitors further facilitate this signalling. However, Wnt/β-catenin activation alone may not be sufficient

for HCC progression, which probably requires additional signals from oncogenic partners such as c-Met and K-RasV12 (Audard et al., 2007; Cieply et al., 2009; Song et al., 2018).

The Wnt/β-catenin pathway also influences the tumour microenvironment, and autophagy plays a critical role in both liver function and disease. Recent findings indicate that autophagy can inhibit HepG2 cell proliferation by interfering with GPC3/Wnt/β-catenin signalling. Conversely, it also promotes metastasis and glycolysis in HCC cells by activating this pathway and enhancing the expression of MCT1, which facilitates lactic acid transport. Despite the strong association between Wnt/β-catenin activation and HCC, its effects depend on genetic alterations and additional oncogenic signals, which suggests that other genetic changes or pathways may affect tumour development and treatment resistance (Srivastava et al., 2026).

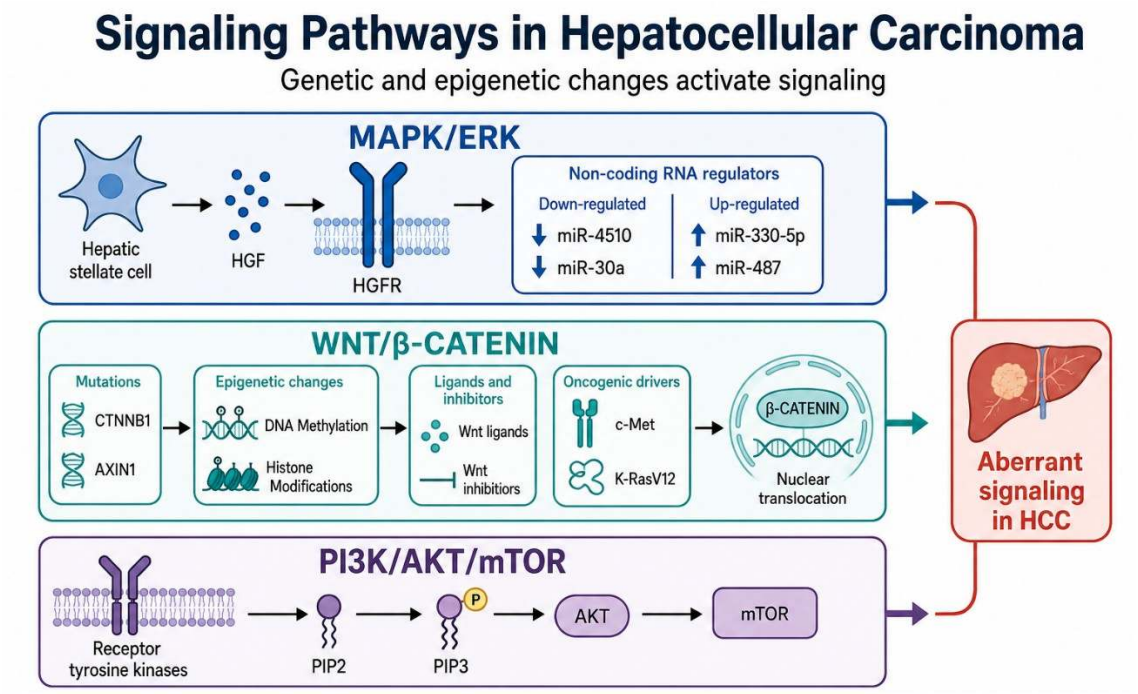
The PI3K/AKT/mTOR signalling pathway plays a crucial role in HCC development by regulating key cellular processes such as proliferation, apoptosis and metabolism. It is often activated through receptor tyrosine kinases, resulting in the conversion of PIP2 into PIP3, which recruits and activates AKT. Up to 50% of HCC cases show dysregulation of this pathway, which is linked to aggressive tumour behaviour and poor prognosis. Despite its therapeutic importance and ongoing studies of multikinase inhibitors and direct PI3K/AKT/mTOR inhibitors, single-agent mTOR inhibition has shown limited clinical benefit, owing to pathway crosstalk and adaptive resistance. Further research is needed to identify the patients who might benefit from targeted therapies and to explore combination treatments (Srivastava et al., 2026).

The Hippo signalling pathway regulates cell growth and is implicated in diseases such as HCC. Its key components include MST1/2, LATS1/2, YAP and TAZ. YAP, a crucial transcriptional co-activator, is often overexpressed in HCC because of mutations or alterations in the pathway, promoting cancer cell survival and proliferation (Valero et al., 2015). YAP activation occurs early in HCC development and is found in 54% to over 70% of tumours, although Hippo mutations are rare. Regulatory mechanisms that sustain YAP signalling include mechanotransduction and GPCR signalling (Xu et al., 2009). TAZ, like YAP, promotes cancer progression by regulating growth-related genes. Preclinical studies suggest that targeting the Hippo-YAP/TAZ pathway could be therapeutic for HCC, and therapies that modulate pathway activity are under evaluation (Bala et al., 2025).

The tumour suppressor p53, together with p63 and p73, is crucial for genomic stability and cell cycle regulation, particularly in HCC. Alterations in the p53 pathway, such as *TP53* mutations or increased levels of inhibitors such as MDM2, are prevalent in HCC and affect the DNA damage response and chemosensitivity. Common *TP53* mutations occur at specific codons and lead to loss or gain of function, with implications for therapy (Anzola et al., 2004; Kunst et al., 2016). Targeted treatments, such as TACE combined with recombinant

adenovirus p53, and small molecules (e.g., Nutlins, RITA, MIRA-1, PRIMA-1 and RETRA) aim to reactivate p53 or counteract its mutants. The expression of various p53 isoforms complicates treatment, as these can shift from tumour suppressor to oncogenic roles. Understanding these mechanisms may support new therapeutic strategies for HCC and related cancers (Shi et al., 2008). The main signalling pathways involved in HCC are shown in Figure 1.

Figure 1
Major signalling pathways involved in the development and progression of hepatocellular carcinoma (HCC)



The figure shows three key pathways in hepatocarcinogenesis. MAPK/ERK: hepatocyte growth factor (HGF), released by hepatic stellate cells, binds to its receptor (HGFR) and initiates downstream signalling; the pathway is also influenced by dysregulated non-coding RNAs (downregulation of miR-4510 and miR-30a and upregulation of miR-330-5p and miR-487). Wnt/β-catenin: the pathway is affected by mutations in *CTNNB1* and *AXIN1*, by epigenetic modifications such as DNA methylation and histone modifications and by changes in Wnt ligands, inhibitors and oncogenic drivers, including c-Met and K-RasV12; these alterations stabilize β-catenin and promote its translocation into the nucleus, where it regulates genes involved in cell proliferation and tumour development. PI3K/AKT/mTOR: activation through receptor tyrosine kinases converts phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3), followed by AKT activation and downstream mTOR signalling. Aberrant activation and interaction of these pathways contribute to HCC initiation, progression, survival and tumour growth. Source: prepared by the authors (2026).

The role of persistent inflammation

Chronic hepatic inflammation creates a self-sustaining pathological cycle that worsens liver damage and promotes tumour formation. The process begins when continuous exposure to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activates pattern recognition receptors (PRRs) on liver cells. HMGB1 is an essential DAMP that increases the capacity of HCC cells to invade other

tissues and metastasize. Anticancer treatments may intensify inflammatory signals by inducing immunogenic cell death. Inflammatory cytokines, reactive oxygen species (ROS) and oxidative stress work together to accelerate hepatocyte turnover, destabilize the genome and modify immune protection. In chronic liver disease, weakened antioxidant defences promote hepatocyte migration, fibrosis and metastatic activity. In HBV, HCV or HDV infection, mitochondrial dysfunction, activation of endoplasmic reticulum stress pathways and impaired generation and clearance of ROS all aggravate oxidative stress. Moreover, metabolic dysregulation may promote hepatocarcinogenesis through inflammation-mediated mechanisms (Galasso et al., 2024).

Progression of fibrosis and cirrhosis

Chronic lobular and portal inflammation kills hepatocytes, destroys the parenchyma and severely damages the hepatic microvasculature, blocking small portal, hepatic and arterial branches. This ischaemic damage causes ductular reactions, the collapse of hepatocellular plates and gradual structural changes. Repeated episodes of injury and vascular dysfunction, which may persist for years, produce irreversible changes in the parenchyma. As fibrosis regresses, enzymes such as matrix metalloproteinases (MMPs) break down components of the extracellular matrix, while tissue inhibitors of metalloproteinases (TIMPs) block MMP activity. About nine types of MMPs contribute to matrix degradation, including collagenases (which degrade type I and III collagen), gelatinases or type IV collagenases, and stromelysins (which degrade laminin, gelatin and type IV collagen). Hepatic stellate cells and Kupffer cells release TIMPs, which bind irreversibly to MMPs and keep matrix turnover in check (Lee, 2023).

Next-generation sequencing has revealed numerous potential HCC driver genes, and viral hepatitis (HBV/HCV) remains responsible for nearly 70% of cases. Although nucleos(t)ide analogues and direct-acting antivirals reduce viral replication, HCC may still arise. Genetic and epigenetic factors, including microRNAs, contribute to the transition from cirrhosis to HCC. Despite substantial progress, further clarification is needed on the immune checkpoints and kinase inhibitor targets that influence cirrhosis-associated carcinogenic pathways (Kanda et al., 2019).

Carcinogenesis associated with hepatitis B and C viruses

Cirrhosis is a primary precursor of HCC; however, HBV and, less frequently, HCV can initiate hepatocarcinogenesis in the absence of cirrhosis, which highlights their intrinsic oncogenic properties. HBV, a DNA virus, and HCV, an RNA virus, promote malignant transformation through distinct molecular mechanisms involving complex virus-host interactions. HCC advances through successive genetic modifications that lead to malignant

transformation and unregulated cell proliferation. Although many mechanistic pathways have been identified, most derive from limited human studies or experimental models, and their direct applicability to clinical disease is not yet fully confirmed. Consequently, despite decades of research, a comprehensive model of the molecular pathogenesis of virus-associated HCC has yet to be established (Fung et al., 2009).

Non-viral risk factors (NAFLD, alcohol, aflatoxins and others)

A variety of non-viral factors play a role in the onset of HCC. Diabetes and a higher body mass index are two major metabolic risks that increase the likelihood of non-alcoholic steatohepatitis (NASH). Other factors include iron overload disorders, excessive alcohol consumption, smoking, oral contraceptives, exposure to aflatoxins and pesticides, and chewing betel quid, which is common in some low-income areas. Genetic and metabolic disorders, such as Wilson disease, α-1 antitrypsin deficiency, porphyrias and autoimmune hepatitis, as well as *Schistosoma japonicum* infection (especially in HBsAg-positive individuals), also increase the risk of HCC. Exposure to thorotrast is another known carcinogenic factor, and the risk is also higher in people with congestive hepatopathy, primary biliary cirrhosis or a family history of liver cancer. Understanding these non-viral causes is essential to improve prevention and identify modifiable risk factors, and a multilayered prevention strategy is expected to reduce the incidence of non-viral HCC and its economic and clinical consequences (Hamed & Ali, 2013).

Tumour microenvironment and immune evasion

HCC has a high recurrence rate and is difficult to treat because its tumour microenvironment (TME) suppresses the immune system. The TME combines chronic inflammation, abnormal angiogenesis and uncontrolled remodelling of the extracellular matrix, all of which help the tumour escape immune control. Interactions between tumour cells, stromal components and immune cells abrogate effective antitumour immunity. Understanding TME-based immune evasion is crucial to improve therapeutic response, particularly to immunotherapy, and interventions that modulate the TME could help overcome immune suppression. Cancer immunoediting, with its elimination, equilibrium and escape phases, expresses the dynamic interplay between tumour development and the immune response. In the elimination phase, immune cells kill cancer cells; in the equilibrium phase, immune control keeps residual tumour cells in check; and in the escape phase, cancer cells proliferate unchecked after acquiring mechanisms that circumvent immune detection. Progressive HCC is associated with chronic inflammation, persistent neoantigen exposure, reduced T-cell cytotoxicity and disturbances in the metabolic and gut microbial microenvironments. Tumour-infiltrating immunosuppressive cells, exhausted T cells, soluble

cytokines and dysregulated signalling pathways all promote immune evasion and resistance to immunotherapy. Together, these features make the hepatic TME a central determinant of treatment failure and tumour progression (Chen et al., 2023).

Diagnosis of hepatocellular carcinoma

Clinical presentation and symptoms

HCC often causes no signs or symptoms in its early stages. It may cause pain or discomfort in the right upper abdomen, a feeling of fullness, abdominal swelling or a palpable mass, and physical examination may reveal an enlarged liver. HCC can also lead to unintentional weight loss, loss of appetite, fatigue or weakness and, sometimes, fever (Dimitroulis et al., 2017). It may cause jaundice, sometimes with itching, ascites, leg swelling, confusion due to encephalopathy or bleeding from oesophageal varices; these signs may indicate that cirrhosis is also present. HCC can also produce paraneoplastic effects, such as low blood glucose, high blood calcium or an increased red blood cell count (Charach et al., 2017).

In people with cirrhosis, multiphasic CT or MRI can show the typical features of HCC, such as arterial phase hyperenhancement (APHE) and washout in the delayed phase. The Liver Imaging Reporting and Data System (LI-RADS), used in the United States, relies on these features to classify lesions and guide clinical management. The AASLD recommends that people at risk undergo abdominal ultrasound, or MRI or CT, every six months (Yang & Heimbach, 2020).

Laboratory markers

Current guidelines recommend that individuals with cirrhosis or chronic hepatitis B (CHB) undergo abdominal ultrasonography every six months, with or without serum alpha-fetoprotein (AFP) testing. Evidence from cohort studies and randomized clinical trials in Asian CHB populations shows that such surveillance markedly improves early detection, facilitates access to curative treatment and improves overall survival. A meta-analysis published in 2018 showed that combining AFP with ultrasound detects early-stage HCC more often (63%) than ultrasound alone (45%), and cost-effectiveness models indicate that this combination is the most economically advantageous screening method in most scenarios.

Despite these benefits, early detection still faces challenges. Risk stratification tools remain insufficient, and many patients are diagnosed late, when they have fewer treatment options and are less likely to receive curative therapy. In high-risk groups, competing mortality from the underlying liver disease also affects outcomes. Only about 30% of patients

in Europe are diagnosed at an early stage. In the United States, the five-year survival rate is above 70% for early-stage HCC but below 5% for advanced disease.

Des-gamma-carboxy prothrombin (DCP) and lectin-reactive AFP (AFP-L3) are two other biomarkers often used to monitor HCC, and their performance varies according to the aetiology and stage of the disease. Apart from DCP and AFP, both supported by Japanese guidelines, no additional biomarker has been validated in phase III trials or approved for routine clinical use. This limitation reflects the biological heterogeneity of HCC, whose diverse biochemical pathways produce distinct biomarker profiles (Shahini et al., 2023).

Imaging modalities

Ultrasound and contrast-enhanced ultrasound (CEUS)

In contrast-enhanced ultrasound (CEUS), gas-filled microbubbles are surrounded by a shell of cross-linked albumin or a lipid monolayer. These microbubbles emit strong harmonic signals from inside the blood vessels, which improves visualization. CEUS harmonic imaging is particularly useful for detecting small residual or recurrent HCC lesions because it can capture contrast signals even from very slow-moving microbubbles. Vilana et al. found that CEUS with SonoVue had a sensitivity of 27% for detecting residual tumour one day after radiofrequency ablation (RFA), higher than contrast-enhanced CT, which detected only 20% of cases (Minami & Kudo, 2015). Conventional ultrasound is used for surveillance in patients at risk, and a suspicious lesion usually requires further assessment with contrast-enhanced imaging. Because ultrasound sometimes does not provide adequate images, alternative surveillance modalities may be considered (Singal et al., 2023).

Contrast-enhanced CT and MRI

Contrast-enhanced CT or MRI is the recommended first-line examination for diagnosis and allows a non-invasive diagnosis in high-risk patients. Multiphase contrast-enhanced CT shows how a lesion behaves across the phases after contrast injection (Cannella, 2025). The classic HCC pattern is arterial phase hyperenhancement, with washout and an enhancing capsule in the portal venous and delayed phases. These major features are combined with lesion size to reach a definitive diagnosis (Cannella et al., 2024).

Dynamic contrast-enhanced MRI

Dynamic contrast-enhanced MRI is an alternative to CT. It may use extracellular or hepatobiliary contrast agents and adds sequences, such as diffusion-weighted imaging, that help to differentiate lesions (Nowicki et al., 2017; Sangro et al., 2025). A recent meta-analysis showed that MRI and CT have similar diagnostic performance, although MRI is generally preferred for small lesions. Intra-individual studies suggest that MRI with

extracellular contrast agents may perform better than MRI with hepatobiliary agents for the diagnosis of HCC (Cannella et al., 2024).

Role of biopsy and histopathology

The decision to restrict liver biopsy in suspected HCC is largely based on concern about procedural risks and may influence both the diagnostic and the therapeutic approach. The literature on biopsy describes how the procedure should be performed and how the adequacy of samples should be assessed. Pain is the most frequent complication and may affect up to 84% of patients. Less frequent complications include perforation, bile peritonitis and pneumothorax, and fatal outcomes are estimated at between 1 in 2,500 and 1 in 10,000 procedures. Bleeding, which may be delayed, occurs in approximately 1 in 500 procedures. Ultrasound guidance makes it possible to obtain small tissue samples more safely and lowers the risk of complications. The patient's interests must come first, and informed consent is essential. Patients with advanced HCC usually receive multikinase inhibitors such as sorafenib and are rarely biopsied beforehand. A biopsy describes the current state of the tumour rather than predicting its course, and without tissue samples it is more difficult to identify molecular targets and to stratify patients. A growing number of studies have used in-depth genomic profiling of tumour tissue and the surrounding liver parenchyma to tailor treatment, but biomarker-based studies remain scarce. Trials such as METIV-HCC and JET-HCC, which evaluated tivantinib in patients with high MET expression, showed no survival benefit, highlighting the limits of precision oncology in HCC and the importance of current efforts to personalize treatment (Di Tommaso et al., 2019).

The histological diagnosis of HCC depends on a combination of architectural features. The most common pattern is trabecular, in which tumour cells form plates or cords separated by sinusoid-like spaces; pseudoglandular (acinar) and solid patterns may also appear in the same tumour (Nakashima & Kojiro, 1987). Diagnosis becomes difficult when early lesions are subtle. They may show increased cell density, crowded nuclei, thin trabeculae and, sometimes, pseudoglandular structures. Kondo's summary of early HCC lists thin trabeculae, hypercellularity, cytoplasmic hyperstainability and microacinar formation (Kondo & Wada, 1987; Kondo, 2009). Distinguishing HCC from a high-grade dysplastic nodule can be extremely challenging on a biopsy specimen. Because early HCC has a vaguely nodular appearance and is well differentiated, whereas progressed HCC is distinctly nodular and mostly moderately differentiated, pathologists must correlate these findings with clinical and imaging data (El Jabbour et al., 2019; Schlageter et al., 2014).

Staging systems

The Okuda staging system classifies patients according to tumour size and liver condition. It remains useful for identifying patients whose disease is too advanced for clinical trials, but it is of limited value for deciding which patients should be treated, even in Okuda stage I. The Child-Pugh classification has shortcomings, particularly in early-stage HCC, when surgery may be appropriate. The TNM staging system is commonly applied by oncologists when patients undergo tumour resection or orthotopic liver transplantation (OLT). TNM mainly describes the tumour and does not take cirrhosis into account, although it is an important prognostic factor; research indicates that TNM classifies many early-stage cases as advanced disease, which reduces its accuracy in predicting outcomes. Many new prognostic models have been proposed, but they can be difficult to apply because they rely on small samples or retrospective designs. Ultimately, treatment decisions must be based on clinical judgement, tumour biology and a thorough understanding of the behaviour of the disease beyond simple staging (Llovet et al., 1999). The Barcelona Clinic Liver Cancer (BCLC) staging classification is summarized in Table 1.

Table 1
Barcelona Clinic Liver Cancer (BCLC) staging classification of hepatocellular carcinoma: clinical characteristics and stage-specific treatment approaches

Stage	Classification	Main clinical characteristics	General treatment approach
0	Very early	A single tumour ≤2 cm, with no vascular invasion or extrahepatic spread, preserved liver function and no cancer-related symptoms (Reig et al., 2022).	Ablation, resection or transplantation may be considered according to liver function and individual circumstances (Reig et al., 2026).
A	Early	A single tumour of any size, or up to three tumours each ≤3 cm, without macrovascular invasion, extrahepatic spread or cancer-related symptoms; liver function is preserved (Reig et al., 2022).	Potentially curative options include resection, transplantation and local ablation (Chevallier et al., 2023).
B	Intermediate	Multifocal HCC beyond stage A: more than three nodules, or up to three nodules with at least one >3 cm, without vascular invasion or extrahepatic spread; Eastern Cooperative Oncology Group performance status of 0 (Mauro & Forner, 2022; Reig et al., 2026).	Selected patients may be considered for transplantation, transarterial chemoembolization (TACE) or systemic therapy, depending on tumour distribution and liver function (Mauro & Forner, 2022; Tsilimigras et al., 2022).
C	Advanced	Macrovascular invasion, extrahepatic spread and/or cancer-related symptoms with a performance status of 1-2 and sufficiently preserved liver function (Díaz-González et al., 2016).	Systemic therapy is generally considered for eligible patients (Reig et al., 2026).
D	End stage	Severe liver dysfunction or poor cancer-related performance status, without a suitable transplantation option (Díaz-González et al., 2016; Reig et al., 2022).	Best supportive care focuses on symptom management and quality of life; transplantation eligibility requires individual assessment (Reig et al., 2026).

Source: prepared by the authors (2026), based on the sources cited.

Management of hepatocellular carcinoma

Liver transplantation may treat both the carcinoma and the underlying cirrhosis. In patients whose initial tumour burden exceeds the transplant criteria, locoregional treatment can be used to reduce tumour size before eligibility for transplantation is reassessed (Hobeika et al., 2024). First-line immune-based combinations include atezolizumab-bevacizumab, tremelimumab-durvalumab and nivolumab-ipilimumab, and the choice depends on suitability and availability. When immune-based combinations cannot be used, sorafenib or lenvatinib may be considered. The optimal sequence of treatments after immunotherapy is still being studied (Albarrak & Al-Shamsi, 2023; Lonardo et al., 2026). Before starting atezolizumab-bevacizumab, patients should be assessed for bleeding risk, including endoscopy to look for varices; if there is a bleeding risk or another reason to avoid bevacizumab, a different treatment plan may be preferable (Singal et al., 2023). Treatment response, liver function and performance status should be checked regularly, because these factors change over time, affect the balance of benefits and risks and determine which treatment options remain available.

Surveillance and follow-up

Surveillance aims to detect HCC early, when treatment can still cure the disease. The AASLD recommends surveillance for adults with cirrhosis because it improves survival. Surveillance is typically offered when the annual risk of developing HCC is at least 1.5%, which includes patients with cirrhosis and some people with hepatitis B who do not have cirrhosis. Patients with Child-Pugh class C cirrhosis are usually not included, because of their short survival, unless they are on the transplant waiting list. Overall, 80% to 90% of HCC cases occur in patients with chronic liver disease.

The standard approach is ultrasound, with or without alpha-fetoprotein (AFP), every six months (Heimbach et al., 2018). The AASLD, EASL, APASL and NCCN all recommend this interval, but they differ on whether AFP is required (Hanouneh et al., 2019). A 2026 clinical practice update of the American Gastroenterological Association (AGA) maintains liver ultrasound plus AFP as the preferred approach for people at sufficient risk, because the effectiveness of ultrasound alone varies in practice and adding AFP increases sensitivity at some loss of specificity (Hanouneh et al., 2019).

Cross-sectional imaging, such as CT or MRI, is not currently recommended for surveillance. However, abbreviated MRI is being studied for patients in whom liver ultrasound is limited, such as those with NAFLD-related cirrhosis.

Nodules detected during surveillance are examined with multiphasic imaging. For lesions classified as LI-RADS category 4 or higher, the AASLD advises multidisciplinary

discussion; a biopsy may be indicated in some cases, or the lesion may be rescanned after three months. Lesions smaller than one centimetre are usually monitored with ultrasound and AFP every three to six months, and if a lesion shows no growth on two follow-up scans, routine six-month surveillance can resume. False-positive or indeterminate results lead to additional imaging, biopsies, anxiety and costs, so surveillance should not be extended to low-risk groups (Hanouneh et al., 2019). Surveillance is underused among non-white patients and people with lower socioeconomic status (Harris et al., 2019).

Follow-up after treatment is important because recurrence is frequent even after successful treatment, reaching 60% to 70% within five years after surgery. As there is no firm evidence on the optimal frequency of follow-up, current practice relies on guidelines and expert opinion. During the first two years, when the risk of recurrence is highest, imaging and AFP tests are performed every three to six months, and some experts suggest CT or MRI every three to four months. After two years without recurrence, the interval is extended to every six to twelve months (Kim, 2020). The main goal of this schedule is to detect recurrence early, when more treatment options, including repeat treatment, are available.

Challenges and future directions

About 75% of all deaths from HCC and almost 50% of all deaths from cirrhosis and chronic liver disease (CLD) occur in the Asia-Pacific region. Chronic hepatitis B remains the main cause, but MASLD affects almost a third of adults in the region, partly because of genetic traits specific to these populations. Excessive alcohol consumption is causing liver disease in a growing number of people, and drug-induced liver injury is still poorly understood. The lack of agreement on the definition of acute-on-chronic liver failure makes it even harder to describe the spread of disease. A significant number of CLD cases remain undiagnosed, and current treatment and vaccination efforts are inadequate (Mak et al., 2024).

Although further research in different populations is needed, HCC risk calculators could help identify patients who require surveillance in resource-limited settings. To help low- and middle-income countries (LMICs) cope with the rising number of cancer cases, it is also necessary to map and expand the cancer workforce. The Asian National Cancer Centers Alliance seeks to support cancer prevention by promoting the World Code Against Cancer, and the burden of HCC in the Asia-Pacific region is expected to decrease as access to antiviral therapy and HCC surveillance expands.

Conclusion

Hepatocellular carcinoma remains a complex clinical challenge that requires continuous improvements in prevention, clinical evaluation and patient management. A clear

understanding of the biological mechanisms underlying liver tumour development and progression can help identify promising therapeutic targets and more effective interventions. Public awareness, the monitoring of viral hepatitis, attention to lifestyle-related factors and timely medical evaluation are essential to reduce the burden of the disease. Collaboration among researchers, clinicians and healthcare policymakers is equally important to translate scientific discoveries into practical benefits. Ultimately, integrating innovative research with equitable healthcare services offers considerable potential to improve patient survival and quality of life.

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Use of artificial intelligence. Paperpal was used only to draw Figure 1. The figure was created by the authors, who checked its content for scientific accuracy.

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