***Review Paper:***

# Liver Cancer: An Integrative Review of Pathogenesis, Diagnosis and Treatment

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## *Abstract*

*Liver cancer, specifically Hepatocellular carcinoma (HCC) represents significant global health concerns, characterized by high mortality rates and complex pathophysiological mechanisms. This review provides a comprehensive examination of liver cancer epidemiology, identifying important risk factors including chronic infections with Hepatitis viruses, excessive consumption of alcohol and non-alcoholic fatty liver disease. The review examines the molecular mechanisms involved in the progression of liver cancer, emphasizing the impact of genetic alterations, microenvironment of the tumor and prolonged inflammation.*

*In addition, it evaluates contemporary diagnostic techniques, highlighting the advantages of advanced imaging methods while acknowledging the shortcomings of conventional biomarkers. Treatment options are also being studied including surgical options, liver transplantation and systemic therapies including targeted and immunotherapy approaches. Despite significant progress in these areas, the overall prognosis for liver cancer remains unfavourable, indicating a pressing need for further research into innovative treatment strategies.*

**Keywords:** Hepatocellular carcinoma (HCC), Risk factors, Molecular mechanisms, Diagnostic techniques, Prognosis, Targeted therapy.

## Introduction

Cancer is characterized by uncontrolled proliferation and expansion of atypical cells capable of invading and damaging normal tissue. Malignant cells disseminate throughout various regions of the body via the circulatory and lymphatic systems. It has the potential to develop in nearly any organ or tissue within the body, resulting in various types of cancer, each with distinct symptoms and treatment options. Hepatocellular carcinoma, a highly aggressive neoplasm often associated with cirrhosis and chronic liver conditions, arises within the liver, which plays a crucial role in numerous biological functions including protein synthesis, detoxification and production of biochemicals necessary for digestion.

Liver cancer primarily manifests in two predominant forms: hepatocellular carcinoma (HCC), which develops from hepatocytes, the principal liver cell type and cholangiocarcinoma, which originates in the bile ducts.

This malignancy, especially HCC, poses a considerable public health challenge globally, given its widespread occurrence in numerous nations[54]. It is acknowledged as the fourth most significant factor contributing to cancer mortality worldwide, with projections from the World Health Organization indicating that liver cancer could result in over one million deaths by the year 2030.

Additionally, it stands as the second primary contributor to cancer-related fatalities among men, with an incidence ratio of HCC in males compared to females being 2.8:1[35]. Several risk factors are associated with the onset of liver cancer including viral infections such as hepatitis viruses[30], intake of alcohol[26], non-alcoholic fatty liver disease[52] and tobacco use.

Research has demonstrated that aflatoxin exposure results in DNA mutations and adduct formation[22,28]. The overall prognosis for liver cancer is unfavourable, with only 5% to 15% of individuals who qualify for surgical excision procedures, primarily due to diminished hepatic regenerative ability and the lack of cirrhosis. Right hepatectomy is linked to a higher occurrence of complications following surgery when compared to left hepatectomy. In cases of advanced liver cancer, treatment modalities including trans arterial chemoembolization had demonstrated a progression in the 2-year survival rates among patients diagnosed with HCC at the intermediate phase by 23% relative to conservative management. Additionally, the oral kinase inhibitor sorafenib is indicated for advanced HCC; however, it is ineffectual in less than one third of patients and resistance to the drug often emerges within six months of initiating treatment[22,29].

Liver cancer develops through various cellular mechanisms including disruption of the cell cycle and apoptosis, molecular pathways linked to inflammation and fibrogenesis processes. These mechanisms constitute significant molecular targets for developing innovative pharmacological therapies[29].

Sorafenib, has been authorized for the intervention of hepatic carcinoma and serves as the primary therapeutic option for advanced Hepatocellular Carcinoma (HCC). Although it significantly improves overall survival, resistance to antiproliferative therapy emerges, preventing the drug from halting disease progression[69].

## Classification of Liver cancer

### Primary Liver Cancer

Primary hepatic carcinoma is characterized as a neoplasm originating from the hepatic parenchyma. The predominant forms of primary liver carcinoma include Hepatocellular carcinoma (HCC) and Cholangiocarcinoma.

**Hepatocellular carcinoma:** HCC represents the principal form of primary hepatic malignancy, constituting 75–85% of all cases of liver malignancy[15,41]. This malignancy arises from hepatocytes, which are the primary functional cells within the hepatocytes. Common causes of HCC are frequently linked with chronic liver conditions including Cirrhosis due to Hepatitis B viruses, NAFLD and long-term alcohol intake[15]. The pathophysiology of HCC is driven by a complex relationship between genetic changes and various environmental factors leading to uncontrolled cell proliferation and malignancy[6].

Hepatocellular carcinoma (HCC) is frequently present without symptoms during its initial phases, complicating early detection and often leading to diagnoses at more advanced stages where treatment alternatives are restricted. The existing therapeutic strategies for HCC encompass surgical excision, liver transplantation, local ablation techniques and systemic interventions including targeted therapies and immunotherapeutic strategies[43,56].

**Cholangiocarcinoma:** Cholangiocarcinoma, commonly referred to as bile duct cancer, originates from the epithelial cells associated with the bile ducts. Despite its infrequent occurrence, this malignancy is characterized by its aggressive behaviour and unfavourable prognosis. Cholangiocarcinoma is categorized into three types according to its anatomical site: distal, perihilar and intrahepatic. Intrahepatic Cholangiocarcinomas (ICCs), which occur within the liver, accounts for approximately 10-15% of all primary liver malignancies[60]. Various risk factors have been identified for cholangiocarcinoma including chronic inflammatory conditions such as primary sclerosing cholangitis, infections caused by liver flukes and congenital liver anomalies[32].

Symptoms of cholangiocarcinoma, including abdominal pain and jaundice etc. are typically observed in the progressed stages of the disease. Diagnosis often involves histological analysis of biopsy samples and imaging techniques such as MRIs and CT scans[25]. Treatment options for cholangiocarcinoma are limited and include chemotherapy, radiation therapy and surgical resection, though overall survival statistics persist at a low level[13].

### Secondary Liver Cancer

Secondary liver cancer, referred to as metastatic liver cancer, arises when malignant cells from a primary tumor in a different organ disseminate to the liver. These secondary cancers arise when cells from the primary tumor detach and are transported via the lymphatic or circulatory systems to the liver, where they establish new tumors. This process is known as metastasis.

**Metastatic liver cancer:** Cancer cells that arise from a primary tumor located in a different organ and subsequently disseminate to the liver are referred to as secondary liver cancers or liver metastases. These metastatic tumors can develop months or years after the initial tumour's formation. They represent a significant clinical challenge due to the liver's role in various essential bodily functions and the complexity of treating metastatic disease.

### Risk factors and Etiology

**Hepatitis viruses:** Infections resulting from Hepatitis viruses (HBV and HCV) are primary factors in the global incidence of HCC, accounting for approximately 75% of hepatic cancer cases worldwide. The emergence of Hepatitis B virus is notably elevated in East Asia, while Hepatitis C Virus is mainly found in Mediterranean areas. A notable geographic correlation exists between the prevalence of chronic HBV infections and the occurrence of hepatocellular carcinoma (HCC), with HBV estimated to be responsible for approximately 54% of liver cancer cases. While the majority of liver cancer cases associated with hepatitis B virus (HBV) are found in low and middle-income nations, epidemiological studies reveal that individuals infected with HCV exhibit a 20–30% higher likelihood of developing hepatocellular carcinoma (HCC) in comparison to those who are not infected. Investigations carried out in the US have revealed the correlation of HBV and the occurrence of hepatic cancer. HCV contributes to approximately 33% of liver cancer cases worldwide[30,47,71].

**Non-Alcoholic Fatty Liver Disease:** NAFLD is a widespread chronic liver disorder, impacting around 25.2% of individuals worldwide. The progression of this disease may lead to serious complications including Hepatocellular Carcinoma, Non-Alcoholic Steatohepatitis and Cirrhosis. Recent studies have highlighted NAFLD as a significant contributor to the incidence of HCC. Between the years 2004 and 2009, the incidence of HCC cases linked to NAFLD in the United States was by 9%, while the rate of incidence standing at 44 cases for every 100,000 individuals, has been observed annually for the diagnosis of NAFLD[47,68].

**Cigarette and Tobacco smoking:** A substantial body of research has established a notable correlation between cigarette and tobacco use and the incidence of liver cancer. Current smokers exhibit a higher relative risk of elevating liver cancer when contrasted to individuals with a prior history of smoking. A detailed meta-analysis found that current smokers face a relative risk of 1.51 while former smokers have a relative risk of 1.12 in relation to individuals who have never smoked[34,47].

**Alcohol consumption:** Previous research has demonstrated a notable correlation between excessive alcohol intake and an elevated occurrence of primary liver carcinoma. The

relative risk (RR) of hepatitis cancer is 1.16 for those who drink three times or more per day and 1.22 for those who drink six times or more per day compared to non-drinkers. A prospective cohort study conducted in eight European countries found that past and present alcohol use contributed to 33% and 18% of liver cancer cases respectively[47,59].

**Aflatoxin:** Aflatoxin-contaminated food serves as a significant risk element for the emergence of HCC. Aflatoxin is a carcinogenic and toxic compound generated by the Aspergillus species, which can contaminate various food items including maize, peanuts and nuts. Regions like East Asia, especially Sub-Saharan Africa and South China exhibit elevated levels of aflatoxin exposure. In these high-exposure areas, the co-occurrence of aflatoxin and HBV markedly heightens the chance of encountering HCC[28,47,63].

**Genetic factors:** Research has established a familial clustering of liver cancer with common lifestyle factors including tobacco use and alcohol consumption attributed to familial transmission of hepatitis viruses. Genetic susceptibility and hereditary disorders such as hemochromatosis, elevate the likelihood of developing hepatocellular carcinoma (HCC). Individuals who have a familial predisposition to liver cancer are twice as likely to develop the condition when compared to those lacking a similar family history[47,66].

**Obesity and Diabetes:** Numerous research has established a correlation between overweight status and obesity with an elevated risk of multiple forms of cancer, including HCC. Specifically, individuals classified as obese exhibit an 89% increased likelihood of developing liver cancer, whereas those who are overweight, face a 17% heightened risk in comparison to individuals maintaining a normal weight. The relationship between liver cancer and obesity is notably more pronounced in males than in females. Furthermore, obesity is known to affect genes associated with insulin resistance, the onset of type-2 diabetes and NAFLD. A variety of epidemiological investigations have indicated a significant correlation between type-2 diabetes and an elevated incidence of HCC[36,47].

**Pathogenesis and Molecular mechanism**

Hepatocellular carcinoma (HCC) develops through complex interactions among environmental, genetic and epigenetic factors. Understanding these mechanisms is critical for establishing effective treatment modalities and preventive measures.

**Genetic mutations and alterations:** Genetic mutations are crucial contributors to the onset of liver cancer. Commonly altered genes in hepatocellular carcinoma (HCC) encompass AX1N1, CTNNB1 and TP53 (beta-catenin)[33]. These mutations disrupt essential biological functions, contributing to cancer development. TP53 mutations are frequently identified in HCC, responsible for encoding a tumor suppressor protein that serves a significant role in regulating apoptosis and the cell cycle. Mutations in this gene can impair its tumor-suppressive functions, leading to uncontrolled cell proliferation[61]. A frequently observed genetic modification in hepatocellular carcinoma pertains to the CTNNB1 gene, which encodes for beta-catenin, an essential element of the Wnt signalling cascade.

Alterations in CTNNB1 can result in the subsequent accumulation of beta-catenin within the nuclear compartment, consequently triggering oncogenic transcriptional pathways[27]. Similarly, AXIN1 mutations are critical in HCC development. AXIN1 acts as a crucial element within the beta-catenin destruction complex and mutations within this gene can interfere with the regulation of beta-catenin. This disruption may lead to abnormal cell proliferation and cancer progression[33].

**Chronic liver disease and Inflammation:** Chronic liver conditions including Hepatitis infections, along with prolonged alcohol intake, significantly increase the likelihood of developing HCC through mechanisms that include chronic inflammation and the progression of cirrhosis[15]. Inflammatory mediators and cytokines produced during chronic liver injury induce oxidative stress and DNA damage, promoting carcinogenesis[4]. Chronic inflammation activates the NF-kB pathway, which supports cell survival and proliferation, thus aiding tumor development[23].

**Epigenetic changes:** Significant contributions to liver cancer development arise from epigenetic changes, notably through processes including modifications of histones and DNA methylation. Global hypomethylation and hypermethylation of tumor suppressor genes can result in gene expression abnormalities and HCC. For example, hypermethylation of the p16INK4a gene, which regulates the cell cycle, has been observed in HCC patients[64].

**Oncogenic pathways:** Various oncogenic signalling pathways are integral to the etiology of liver cancer particularly the MAPK, Wnt/β-catenin pathways and PI3K/Akt. The Wnt/β-catenin pathway, as previously highlighted, is important for the initiation of liver tumors[48]. Meanwhile, the PI3K/Akt pathway is crucial in the modulation of cellular metabolism, proliferation and programmed cell death, all of which are essential processes in the progression of cancer[70]. The MAPK pathway, often activated by growth factor signalling, promotes cell survival and proliferation[10].

**Tumor microenvironment:** The tumor microenvironment in hepatocellular carcinoma (HCC) comprises of extracellular matrix components, fibroblasts and immune cells that interact with tumor cells, influencing cancer progression. Interactions between tumor cells and the stroma can promote angiogenesis, tissue remodelling and immune evasion. Synthesis of pro-angiogenic factors including VEGF, within the tumor microenvironment facilitates both tumor proliferation and the process of metastasis[63].

## Diagnosis and Screening

**Alpha-protein serology and Radiologic imaging:** Evaluation of HCC typically involves radiological imaging and Alpha-fetoprotein (AFP) serology. Due to the infrequency of HCC in patients without hepatic cirrhosis, this discussion predominantly focuses on instances where cirrhosis is present. With the high sensitivity and specificity of modern MRI, biopsies are rarely required[45]. Currently, no blood test has proven reliable for HCC diagnosis[41]. AFP levels lack the necessary sensitivity and specificity for diagnosing HCC, as elevated alpha-fetoprotein (AFP) concentrations can arise in various conditions including hepatitis C virus (HCV) infection and intrahepatic cholangiocarcinoma[1]. Thus, HCC diagnosis relies primarily on radiologic appearance, with AFP serology not recommended for diagnostic purposes[55,67].

**Ultrasound for HCC screening:** Ultrasonography is the main technique used to screen for hepatocellular carcinoma (HCC). Nevertheless, the AASLD recommends the use of two imaging techniques when ultrasound is added, due to its insufficient sensitivity and specificity in identifying small HCCs[1,9]. Contrast-enhanced ultrasonography demonstrates improved diagnostic features; However, reliance on operator skill has hindered its widespread adoption. A consensus meeting held in 2009 by the AHPBA determined that CE-US was not a feasible option for surveillance, primarily due to this limitation[45].

A 1997 European study illustrated the unreliability of ultrasound (US) for screening HCC in cirrhotic patients. The study involved a cohort of 43 patients exhibiting multiple hepatic lesions, all of whom underwent MRI, CT and US examinations within a two-week period. The US detected only 1 out of 50 regenerating nodules, 2 out of 6 benign lesions and 2 out of 16 HCCs, highlighting its inadequacy for HCC screening, especially for small lesions where sensitivity was found to be as low as 14%[38,45,62].

**MRI and MDCT for HCC detection:** Multidetector computed tomography employs ionizing radiation and iodinated contrast agents to improve the visualization of the liver across arterial, portal and hepatic venous phases. However, MDCT has drawbacks including nephrotoxicity from the contrast agent and significant radiation exposure, with two CT scans resulting in about 40 mSV of radiation, comparable to 2.4 kilometres from Hiroshima's ground zero[17]. Despite these drawbacks, CT scanning detects HCC in cirrhotic livers with a sensitivity of approximately 70% (ranging from 65% to 78%). It is more widely accepted and less labour-intensive than MRI[45].

Magnetic resonance imaging, unlike MDCT, offers non-invasive, non-radioactive imaging with high sensitivity and specificity. MRI provides a detailed tissue-by-tissue image of the body. For lesions that exceed 2 cm in size, MRI exhibits a sensitivity rate - 100%, specificity - 99% and an overall accuracy - 99.1%. Additionally, in numerous large-scale studies, the sensitivity for the detection of Small HCCs has been noted to exceed 90%[37]. MRI's superiority in detecting small HCCs is evident when compared to CT, which detects only about 50% of small HCCs with sensitivity dropping to 36% in some series.

Recent studies indicate that MRI can detect liver lesions transcending 2 cm size with an accuracy rate surpassing 99%, thereby reducing the necessity for liver biopsy to obtain pathological confirmation. Considering the elevated specificity, diagnostic accuracy and sensitivity observed, the incorporation of additional imaging techniques is improbable to yield significant benefits and it is advisable to refrain from pursuing biopsy for pathological correlation[45].

### Clinical features and Staging

**Clinical manifestations:** Hepatocellular carcinoma (HCC) presents with a range of clinical manifestations depending on the disease stage. HCC is usually asymptomatic, which often delays diagnosis in its early stage[40]. As malignancy progresses, individuals may experience significant unintended weight loss and persistent abdominal discomfort, particularly in the upper right quadrant[14].

Advanced stages of HCC are often present with jaundice due to impaired bilirubin filtration by the liver, leading to yellowing of the skin and sclera[24]. Ascites, characterized by abdominal distension and discomfort, is another common symptom indicative of advanced disease[21]. Hepatic encephalopathy, presenting as altered mental status and cognitive impairment, can occur due to severe liver failure[8,21]. Furthermore, portal hypertension represents a significant complication in HCC patients, potentially causing variceal bleeding from dilated veins in the stomach or esophagus[20].

### Staging systems

Numerous staging frameworks have been established to predict the outcomes associated with Hepatocellular carcinoma, with the Barcelona clinic liver cancer and tumor-node metastasis systems being the most widely used. These systems account for factors such as tumor size, underlying liver disease severity, metastasis presence and tumor extension into adjacent structures, reflecting the variability of HCC and regional differences in treatment eligibility[39].

**TNM staging:** In 2010, the TNM staging system for HCC underwent revisions that emphasized the significance of tumor dimensions and the level of vascular invasion as vital prognostic determinants. Notably, liver fibrosis score was an important prognostic marker in this setting, independent of tumor grade or the presence of cirrhosis.

Survival rates over a five-year duration for TNM stages I, II and III were observed to be 55%, 37% and 16%. Furthermore, the predictive validity of the TNM system was prospectively confirmed in individuals who have received a liver transplant or surgical intervention for HCC. However,

its applicability is limited in patients with incurable HCC, reducing its utility in this population[39].

**BCLC staging system:** The BCLC staging system categorizes patients according to their initial liver function, performance status, the existence of vascular invasion and the extent of extrahepatic tumor dissemination, as determined by the Child-Pugh classification. The system is clinically relevant, linking each BCLC stage to specific treatment options: potential curative options including surgical or local resection, or liver transplantation are recommended for stage 0 and stage A stages; Trans - arterial chemoembolization is indicated for stage B stages; Sorafenib is used for advanced (stage C) stages characterized by extrahepatic spread or vascular invasion. Best supportive care is recommended for stage D patients who exhibit cirrhosis and poor performance status. In a study involving 244 individuals with hepatocellular carcinoma and cirrhosis, research indicated that the BCLC staging system provided better prognostic classification[9,39].

**Treatment modalities of Liver cancer**

**Surgical resection:** Regardless of tumor size, surgery is regarded as the most efficacious therapeutic approach for individuals diagnosed with early-stage tumors (BCLC 0-A) that do not exhibit cirrhosis. However, tumor growth continues to act as a negative prognostic factor. Recent developments have paved the way for the creation of novel approaches focused on the management of individuals suffering from Hepatocellular carcinoma (HCC), classified under BCLC stages B and C, that take into account factors such as residual liver volume, liver function reserve and overall tumor burden. Several scoring systems are used to assess liver function including model for end-stage liver disease and Child-Buck-Turcot.

However, these systems often overlook patient performance status, resulting in variable prognostic accuracy. The recently introduced serum bilirubin/cholinesterase (BILCHE) scoring system shows promise in effectively identifying low-risk patients who experience surgical complications. Ultimately, surgical resection is only beneficial for patients, as high rates of recurrence are often observed because of the appearance of microvascular invasion and dissemination. Adjuvant treatments like immunotherapy or internal radiation therapy have shown promise in reducing tumor recurrence and improving overall survival post-resection[46,50].

**Liver transplant:** In cases of liver cirrhosis accompanied by tumor lesions that satisfy the Milan criteria, liver transplantation is acknowledged as the most suitable solution for addressing critical liver conditions. These criteria specify either a solitary tumor exceeding 5 cm in size or with a limit of three tumors, each measuring 3 cm or less. Following the establishment of these standards, a remarkable overall survival rate of 75% has been recorded over a span of five years, alongside a tumor recurrence rate of merely 15%. Despite criticisms of the MC for being overly restrictive, tumors exceeding these criteria have a poorer prognosis due to higher recurrence and new tumor development risks. Research suggests expanding the criteria (UCSF, UCLA), although further validation is needed[31,45].

**Immunotherapy:** Immunotherapy constitutes an innovative approach for treating HCC, stemming from the understanding that tumor cells can escape the detection of immune by expressing Programmed Cell Death Ligand-1. This ligand interacts PD-1 receptor found on activated T cells, leading to their inactivation. The human monoclonal antibody nivolumab targets PD-1, thereby interfering with PD-L1 interaction and enhancing T cell activation against malignancies. In addition, tremilimumab works by blocking CTLA-4, a cytotoxic T-lymphocyte antigen that allows T cells to continue attacking tumor cells. Ongoing clinical trials are comparing the efficacy of those immunotherapeutic dealers, both as monotherapies and in mixture with Trans arterial chemoembolization (TACE) or different healing procedures for HCC[31,46]. Immunotherapy can lead to adverse effects including fatigue, diarrhea, itching and skin rash and elevated aspartate/alanine aminotransferase levels, leading to liver function deterioration. Cardiovascular effects and "pseudo progression," where immune cell infiltration causes a delayed antitumoral response, have also been observed[12,19,33].

**Ablation:** Ablation involves injecting ethanol into the tumor or using intratumor radiofrequency to create a 3 cm necrotic area. A standard treatment approach for individuals with tumors measuring below 2 cm who are ineligible for surgical options or unable to proceed with surgery is outlined. Recently, microwave ablation has been used for larger tumors, demonstrating greater necrosis potential than radiofrequency. However, these ablative techniques are primarily successful for small tumors, with recurrence rates similar to surgical excision[19,31].

**Chemoembolization:** Trans arterial chemoembolization (TACE) combines the localized administration of chemotherapeutic agents with embolization techniques, making it a preferred approach for patients diagnosed with elevated Hepatocellular carcinoma, especially BCLC classified as stage B. The utilization of drug-eluting beads facilitates controlled release. therapeutic agents, thereby increasing drug concentration at the tumor site while decreasing systemic exposure. Radioactive isotopes like Yttrium-90 are being explored as alternatives to chemotherapy drugs in this approach (radioembolization, RE). The primary benefit of radioembolization (RE) compared to trans arterial chemoembolization (TACE) lies in its ability to reduce ischemic damage to the tumor and surrounding liver tissue through the use of tiny microspheres. This technique is particularly advantageous in patients who maintain adequate liver function and lack extrahepatic or vascular tumor invasion[19].

**Chemotherapy:** Systemic chemotherapy is considered the main therapeutic strategy for individuals with advanced and metastasized HCC, aiming to extend overall survival. Tyrosine kinase inhibitors (TKIs) including sorafenib (Sor), have been used as first-line therapy, demonstrating anti-proliferative and anti-angiogenic effects. Although sorafenib extends overall survival and halts disease progression, it has serious side effects that may necessitate discontinuation including diarrhea, dermatological events like hand-foot skin reaction (HFSR) and hypertension[42,57]. Lenvatinib, another anti-angiogenic TKI, has shown comparable or superior efficacy to Sor and is considered a first-line alternative, though it also has significant adverse consequences such as diarrhea, anorexia and hypertension[49].

Regorafenib, has received approval for use as a subsequent treatment strategy for patients who cannot endure Sorafenib. Additionally, compounds targeting specific molecular pathways in hepatocarcinogenesis or addressing epigenetic dysregulation, such as Axitinib, Apatinib, Tivantinib and Everolimus, are under investigation. Research indicates that combination therapy, which employs multiple pharmacological agents, demonstrates superior effectiveness relative to monotherapy, though combining Sorafenib with TKIs or mTOR inhibitors did not increase efficacy and led to higher toxicity[57]. Systemic administration of various cytotoxic substances including doxorubicin, cisplatin, epirubicin and 5-fluorouracil, has been implemented, yet these agents are associated with significant side effects. Combining systemic therapies like Sor with TACE or similar treatments may enhance benefits but will also increase toxicity[57].

**Oncolytic virus therapy:** Recent advances in cancer treatment have focused more on oncolytic virus therapy which represents an innovative and promising approach. This treatment method involves the usage of genetically changed or evidently happening viruses that selectively ruin cancer cells even as stimulating the immune machine, thereby sparing normal tissues from harm. Recent research has confirmed that the use of 2nd-technology oncolytic herpes simplex virus type-1 in combination with granulocyte macrophage colony-stimulating thing results in reduction of tumor boom and improvement in malignant cancer lesions, associated with typical survival prices. Drastically, this 2d-technology oncolytic herpes simplex virus type-1 is the primary to acquire regulatory approval in both America and Europe. Present day clinical trials are comparing diverse oncolytic viruses inclusive of vaccinia virus JX-594 for hepatocellular carcinoma, adenovirus CG0070 producing GM-CSF. Oncolytic virotherapy has emerged as an ability treatment for cancer, especially hepatocellular carcinoma[18,58].

**Prognosis and Survival rates**

Hepatocellular carcinoma (HCC), commonly known as liver cancer, generally has a poor prognosis due to several critical factors. Early diagnosis is paramount; particularly in instances where it remains localized to the liver without evidence of metastasis, surgical interventions such as partial hepatectomy or liver transplantation are often viable and can significantly improve patient outcomes[11]. The existence of chronic Hepatitis (B or C) or cirrhosis infections further complicates treatment, exacerbates liver dysfunction and adversely affects prognosis[53]. Tumor features, including dimensions, count and the occurrence of satellite lesions or vascular invasion, significantly influence prognostic outcomes. Individuals diagnosed with extensive blood vessel invasion or multifocal tumors tend to have a poorer prognosis[2,11].

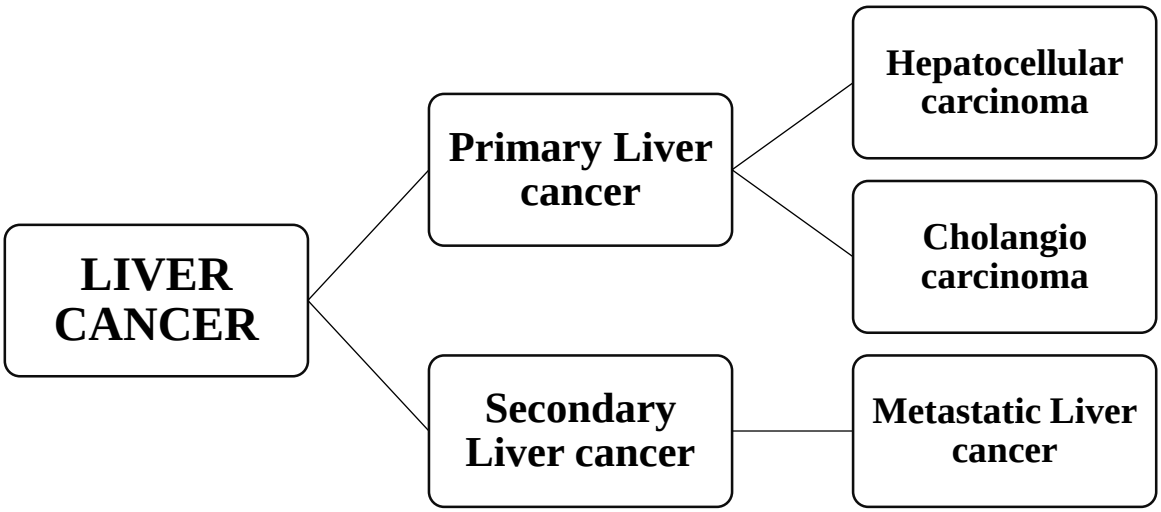


**Fig. 1: Classification of Hepatic tumors**

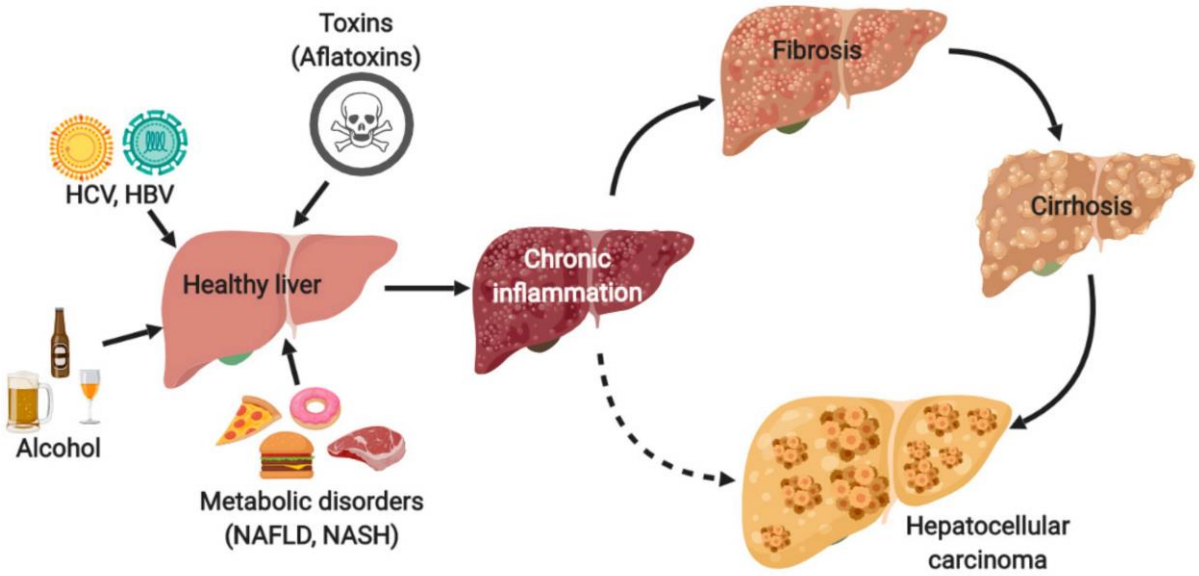


**Fig. 2: Several factors that contribute to risk and mechanisms of Hepatocellular carcinoma[16]**

Genetics and biomarkers are additional factors influencing prognosis. Recent research has identified numerous genetic alterations and molecular markers associated with more severe disease and resistance to conventional treatments[53]. For instance, mutations in the TP53 and CTNNB1 genes have been linked to poorer outcomes. Liver function is evaluated using assessment tools such as by the model for End-Stage Liver Disease score and Child-Pugh score, impacting treatment options and survival[3].

Due to late-stage detection, the survival rate over a five-year period for patients identified with liver cancer continues to be significantly low, averaging around 20% in Western countries, compared to many other malignancies[35]. However, early detection significantly improves survival rates when the disease is still localized. For certain patients, the advent of new therapeutic strategies including checkpoint inhibitors and targeted therapies such as sorafenib and lenvatinib, has led to better outcomes[3]. Advances in personalized medicine and early detection techniques are expected to further enhance survival rates and overall well-being of individuals diagnosed with liver cancer[41].

## Challenges and Future directions

**Challenges:** The treatment and management of liver cancer, particularly hepatocellular carcinoma (HCC), are fraught with significant challenges. A major obstacle encountered is the identification of the disease during its later stages. Liver cancer in its early stages typically shows no discernible symptoms, posing challenges for early identification. As a result, a significant number of patients receive their diagnosis late in the course of the disease, at which point therapeutic modalities are often less effective[2,44]. The heterogeneity of HCC further complicates its management. The disease can arise from various etiologies, making it challenging to develop a one-size-fits-all treatment approach[7]. Moreover, the underlying liver disease, such as cirrhosis, often results in impaired liver function and limits therapeutic options, adding another layer of complexity to treatment.

While advanced therapies like targeted treatments and immune checkpoint inhibitors have shown promise, they are not without challenges. These treatments can have severe side effects and are not universally effective due to the genetic variability among tumors. Additionally, the high cost of these advanced therapies, especially in resource-limited settings, restricts access to potentially life-saving treatments[43]. The creation and assessment of trustworthy biomarkers for the prompt detection and ongoing observation of liver cancer persist as a major obstacle. Although several promising biomarkers have been identified, their sensitivity and specificity often fall short of what is required for consistent clinical application, leading to potential false positives or negatives that can complicate diagnosis and treatment decisions[49]. Addressing these challenges necessitates a multifaceted approach, including improved screening techniques, tailored treatment protocols according to the genetic makeup of tumors and the development of more accessible and affordable therapies[2,43].

### Future directions

**Enhancing precision medicine:** Precision medicine holds the promise of revolutionizing liver cancer treatment by tailoring therapeutic strategies to the distinct biological features of each patient's tumor. Researchers are identifying unique biomarkers in liver cancers that can guide individualized therapeutic regimens. This approach aims to minimize side effects and improve outcomes by selecting treatments that patients are most likely to respond to. For instance, ongoing research is focusing on the genetic

characteristics of liver cancers to develop more precise therapies[31].

**Advancements in Immunotherapy:** Immunotherapy, a treatment modality that utilizes the immune system's mechanisms to combat cancerous cells, is progressively becoming a crucial component in the management of liver cancer. Ongoing investigations are exploring the integration of immunotherapies with various therapeutic modalities such as trans arterial embolization. This combination aims to simultaneously target the tumour and enhance the immune response, thereby improving treatment efficacy[33,43].

**Innovative biomarkers for the early detection of diseases:** Early diagnosis of HCC significantly improves survival rates. Researchers are developing new blood-based biomarkers that offer greater sensitivity and specificity than current methods like ultrasonography and AFP (alpha-fetoprotein) testing. Biomarkers such as Glypican-3 and DCP (des-gamma carboxy prothrombin) are in various stages of validation and show promise for earlier and more accurate diagnosis of liver cancer[51].

**Innovative therapies and techniques:** Novel therapeutic approaches, including virus-based therapies and targeted treatments, are under investigation. Targeted therapies, such as ramucirumab and sorafenib, aim to inhibit specific proteins involved in cancer development, thereby halting tumor growth. Additionally, early results from virus therapy, which uses modified viruses to selectively kill cancer cells, are promising. These innovative treatments aim to provide new viable options for patients with advanced liver cancer[49].

**Improving surgical outcomes:** Efforts are underway to improve outcomes for liver cancer patients by improving surgical techniques and incorporating adjuvant treatment approaches. Research focuses on increasing the safety and efficacy of partial hepatectomies and liver transplants. Additionally, the use of neoadjuvant therapy treatments given before surgery to shrink tumors and facilitate resection, is being investigated. These efforts aim to reduce post-operative recurrence rates and to expand the eligibility for curative surgery[5,50].

**Role of APOBEC3B in liver cancer:** The APOBEC3B enzyme, part of the APOBEC family of cytidine deaminases, has been implicated in instances of liver carcinoma linked with the Hepatitis B virus infection. Ongoing research is exploring the molecular pathways through which APOBEC3B contributes to liver cancer development. Elucidating these mechanisms has the potential to uncover new therapeutic targets and methodologies aimed at the prevention and clinical management of liver cancer[65].

## Conclusion

Hepatic carcinoma, particularly Hepatocellular carcinoma, presents a serious public health concern because of its substantial rates of occurrence and fatality globally. The etiology of hepatic cancer is complex, driven by a multifaceted interaction of environmental, lifestyle and hereditary factors, complicating both its prevention and treatment. Despite advancements in diagnostic imaging and therapeutic interventions, the overall prognosis for liver cancer remains poor, especially at advanced stages.

Effective management of liver cancer necessitates a multifaceted approach, including robust screening programs for high-risk populations, ongoing research into molecular targets for innovative therapies and comprehensive strategies to address subclinical adverse conditions including hepatitis viruses and lifestyle choices. Future research should focus on enhancing early detection methods and developing personalized treatment plans to elevate the rates of survival and life quality metrics pertinent to patients with liver cancer.

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