# Comprehensive Review of Hepatocellular Carcinoma: Epidemiological Trends, Risk Factors, and Mechanisms of Carcinogenesis

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## Abstract

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide, often arising in the context of chronic liver diseases like cirrhosis, with significant contributions from hepatitis B virus (HBV), hepatitis C virus (HCV), and metabolic dysfunction-associated fatty liver disease (MAFLD). The disease's high mortality rate and complex etiology underscore the need for improved diagnostic and therapeutic strategies. Methods: This review synthesizes current epidemiological data and research on HCC. We analyzed global and regional incidence and mortality rates, assessed the role of major risk factors, including HBV, HCV, and MAFLD, and evaluated recent advancements in diagnostic and therapeutic approaches. Data were sourced from recent literature, including epidemiological studies and clinical trials. Results: The incidence of HCC continues to rise globally, with significant regional variations. HBV and HCV infections remain major contributors to HCC, with HBV's integration into the host genome playing a critical role in carcinogenesis. MAFLD, now a prominent risk factor in high-income countries, is expected to impact global HCC rates increasingly. Despite advances in diagnostic techniques such as precision medicine and liquid biopsies, early detection remains challenging, and recurrence rates after treatment are high. Conclusion: The growing burden of HCC highlights the urgent need for enhanced screening methods and novel treatments. Continued research into the disease's etiology and improved therapeutic approaches are essential to reducing incidence and improving patient outcomes. Enhanced early detection and personalized treatment strategies are critical to addressing the ongoing challenges in HCC management.

**Keywords:** Hepatocellular carcinoma, chronic liver disease, HBV, HCV, MAFLD

***Significance*** | To improve early detection, personalized treatments, and prevention strategies for hepatocellular carcinoma (HCC).

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## Introduction

Hepatocellular carcinoma (HCC) is a malignant liver tumor that ranks among the deadliest forms of cancer worldwide (Chakraborty & Sarkar, 2022; Kar et al., 2024). Despite advancements in medical research, the prevalence and mortality of HCC continue to rise, making it a significant public health challenge (Shah & Sarkar, 2024). As the most common type of primary liver cancer, HCC accounts for approximately 90% of liver cancer cases, contributing to a staggering 906,000 new diagnoses and 830,000 deaths globally in 2020 alone (Foglia, Turato, & Cannito, 2023). With an estimated 750,000 new cases annually, HCC has become the sixth most prevalent cancer in humans, and its extremely high fatality rate places it as the third leading cause of cancer-related deaths, claiming

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around 700,000 lives each year (Wang et al., 2023, Tufael et al. 2024). The aggressive nature of HCC, combined with limited treatment options, particularly in advanced stages, underscores the urgency of early detection and intervention (Lazzaro & Hartshorn, 2023). HCC predominantly develops in the context of chronic liver diseases, such as cirrhosis, which is often linked to hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol abuse, and more recently, metabolic dysfunction-associated fatty liver disease (MAFLD) (Panneerselvam et al., 2023). Men are disproportionately affected, with HCC incidence rates significantly higher among males compared to females (McGlynn, Petrick, & El-Serag, 2021). In India, for example, the age-standardized death rate due to HCC is 6.8 per 100,000 males and 5.1 per 100,000 females (Daher, Dahan, & Singal, 2023). Furthermore, in the United States, the incidence of HCC has tripled over the past four decades, with projections for 41,210 new cases in 2023 (Kim & Viatour, 2020).

Although the rate of increase has plateaued since 2015, the overall burden remains high, driven by geographical variations in the etiological risk factors (Frager & Schwartz, 2020). The epidemiological landscape of HCC reflects not only the rising prevalence of liver disease but also significant shifts in the global population's lifestyle, dietary habits, and socioeconomic conditions (Chiang et al., 1987; Petrick et al., 2020). Projections based on data from the GLOBOCAN 2020 database indicate that the annual number of new liver cancer cases could rise by 55% by 2040, with a possible 1.4 million cases by that year (Angulo, 2002). These alarming statistics highlight the growing need for comprehensive screening and early detection strategies (Han, Baik, & Kim, 2023). The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend biannual abdominal ultrasounds for individuals at high risk, such as those with cirrhosis or chronic liver disease, often accompanied by alpha-fetoprotein (AFP) monitoring (Daher et al., 2023). However, even with these guidelines in place, early-stage HCC remains difficult to detect, with ultrasound sensitivity as low as 47%, leading to delays in diagnosis and treatment (Huang et al., 2021).

Although surgical resection and liver transplantation offer curative potential for early-stage HCC, less than 20% of cases are diagnosed at this stage (Zheng et al., 2022). Once the disease has metastasized, survival rates plummet, with fewer than 10% of patients surviving beyond five years (Kim et al., 2021). While advancements in targeted therapies, including the use of tyrosine kinase inhibitors (TKIs) and immunotherapy, have improved treatment outcomes, recurrence rates remain high up to 70% following curative-intent therapy (Yu et al., 2022). Moreover, limited liver donor availability further complicates the potential for liver transplantation, underscoring the need for alternative therapeutic options (Kouroumalis, Tsomidis, & Voumvouraki, 2023).

The advent of precision medicine offers hope in the fight against HCC (Oura et al., 2022). With the rapid evolution of genome sequencing technologies, bioinformatics, and artificial intelligence, researchers are increasingly able to tailor treatments to individual patients based on their genetic profile and disease characteristics (Liu, Tsai, & Hsu, 2021). Precision medicine, combined with innovative diagnostic tools such as liquid biopsies, molecular imaging, and nanotechnology, holds promise for improving early detection and prognosis (Huang et al., 2023). Furthermore, breakthroughs in immunotherapy and gene-targeted treatments have opened new avenues for combating the disease, although challenges related to therapeutic resistance and disease recurrence persist (Must et al., n.d.).

In light of HCC's complex and multifactorial nature, ongoing research into its pathogenesis, treatment options, and preventive strategies is essential (Zunica et al., 2022). As the global burden of HCC continues to rise, fueled by evolving risk factors such as MAFLD, there is an urgent need for novel diagnostic techniques, personalized therapies, and public health interventions that can reduce the incidence and improve outcomes for patients afflicted by this devastating disease (Milosevic et al., 2023).

**Epidemiology**

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths globally and ranks as the sixth most common type of cancer. Liver cancer, primarily driven by HCC, is the second most frequent cause of cancer deaths after lung cancer, accounting for 85–90% of all primary liver malignancies (Chakraborty & Sarkar, 2022; Lazzaro & Hartshorn, 2023). The development of HCC is strongly associated with underlying chronic liver diseases, including cirrhosis and hepatic fibrosis, particularly in individuals with liver damage caused by excessive alcohol consumption and chronic infections such as hepatitis B virus (HBV) and hepatitis C virus (HCV) (Shah & Sarkar, 2024; Panneerselvam et al., 2023). An estimated 257 million people worldwide approximately 3.5% of the global population are living with chronic HBV infection, significantly elevating their risk of developing HCC (Foglia, Turato, & Cannito, 2023) as shown in table 1.

HCC exhibits a marked geographic variation in its incidence, with low- to middle-income countries, particularly those in Eastern Asia and sub-Saharan Africa, bearing the brunt of the disease burden. These regions account for approximately 85% of HCC cases globally (Wang et al., 2023; Zheng et al., 2022). According to data from Globocan 2018, the cumulative incidence risk of hepatitis C in North America was estimated at 3.4 per 100,000 women and 6.6 per 100,000 men. In Canada, the incidence of HCC was projected to be around 12 cases per 100,000 people, highlighting the significant disease burden in high-income regions as well (Carcinoma et al., 2022; Renne et al., 2021). By 2020, liver cancer had age-standardized

incidence and mortality rates of 9.5 and 8.7 per 100,000 people, respectively, with the highest rates observed in regions such as Eastern Asia (17.8 new cases, 16.1 deaths), Northern Africa (15.2 new cases, 14.5 deaths), and South-Eastern Asia (13.7 new cases, 13.2 deaths) (Yang et al., 2019; Frager & Schwartz, 2020).

Differences influence the geographical variation in HCC incidence in regional etiological factors. In Asia and sub-Saharan Africa, chronic HBV infection is the predominant risk factor, while in the United States and Europe, HCV, alcohol abuse, and metabolic dysfunction-associated fatty liver disease (MAFLD) are major contributors (Ducreux et al., 2023; Kim & Viatour, 2020). Since the 1980s, HCC cases have been on the rise in the United States, with over 40,000 new cases predicted in 2020. Globally, it is projected that the number of new HCC cases will increase by 55% between 2020 and 2040, reaching an estimated 1.4 million new diagnoses by 2040 (Petrick et al., 2020; Valle Tovo et al., 2023).

Age at diagnosis varies significantly by region. In high-income countries such as Japan, North America, and Europe, HCC is typically diagnosed in older adults, with median onset ages above 60 years. In contrast, in parts of Asia and most African countries, HCC is often diagnosed between the ages of 30 and 65. The median age of HCC diagnosis is 59 years in South Korea and 52 years in China, while it is 69 years in Japan, 65 years in Europe, and 62 years in North America (McGlynn et al., 2021). These findings were reported in the HCC BRIDGE study, which analyzed data from 18,031 patients across 42 sites in 14 countries (Chiang et al., 1987).

In terms of gender, men are generally at a higher risk of developing HCC than women, as reflected in the higher age-standardized incidence rates (ASIRs) for males in Eastern Asia (26.8 per 100,000) and South-Eastern Asia (21.0 per 100,000). Conversely, regions such as Western Asia (5.4 per 100,000) and South-Central Asia (3.4 per 100,000) report lower incidence rates for males. For females, the highest incidence rates are seen in Melanesia (8.9 per 100,000) and Eastern Asia (8.7 per 100,000), with South-Central Asia having the lowest rates (1.7 per 100,000) (Milosevic et al., 2023; Han, Baik, & Kim, 2023). Interestingly, the male-to-female ratio of HCC incidence is less pronounced in certain regions. For example, in countries like Uganda, Costa Rica, Ecuador, and Colombia, the male-to-female ratio of liver cancer incidence is close to 1:1 (Ohkuma, Peters, & Woodward, 2018).

Research suggests that gender differences in HCC incidence may be related to hormonal influences, with testosterone promoting HCC development, while estrogen has a protective effect. Estrogen is believed to exert its protective role by inhibiting interleukin-6 (IL-6), a pro-inflammatory cytokine implicated in liver inflammation and carcinogenesis. This estrogen-mediated suppression of IL-6 may explain the lower HCC incidence in women (Khan et al., 2020; Kim et al., 2021).

To viral hepatitis and alcohol-related liver disease, non-alcoholic fatty liver disease (NAFLD), now reclassified as MAFLD, is emerging as a significant risk factor for HCC, particularly in high-income countries. A retrospective cohort study of European primary care databases involving 136,703 NAFLD patients and matched controls revealed that the incidence of HCC was significantly higher in patients with NAFLD, with an incidence rate of 3% per 1,000 person-years and a hazard ratio of 3.51 compared to controls (Yu et al., 2022; Kouroumalis, Tsomidis, & Voumvouraki, 2023). As global demographics shift and lifestyle-related liver diseases like MAFLD become more prevalent, the incidence of HCC is expected to rise further, posing a substantial threat to public health worldwide (Huang, El-Serag, & Loomba, 2021; Liu, Tsai, & Hsu, 2021). Continued research into the epidemiology, prevention, and treatment of HCC is critical to mitigating this growing global health challenge (Zunica, Heintz, Axelrod, & Kirwan, 2022; Angulo, 2002; Daher, Dahan, & Singal, 2023; Huang, Mathurin, Cortez-Pinto, & Loomba, 2023; Oura, Morishita, Tani, & Masaki, 2022).

**Etiology of HCC**

Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infections are among the most significant risk factors for the development of hepatocellular carcinoma (HCC). For patients with chronic HBV or HCV infection, particularly those who have progressed to cirrhosis, the annual risk of developing HCC is estimated to be between 2% and 5% (Chakraborty & Sarkar, 2022; Lazzaro & Hartshorn, 2023). In Canada, data from the Canadian Liver Foundation in 2013 estimated that approximately 500,000 people were infected with either HBV or HCV, highlighting the extensive burden of these infections (Shah & Sarkar, 2024).

**Hepatitis B Virus (HBV) and HCC Risk**

HBV is a DNA virus that causes a chronic necro inflammatory condition in the liver, increasing the likelihood of genetic mutations within liver cells (Panneerselvam et al., 2023). Over time, these mutations contribute to the development of hepatocellular carcinoma. HBV's ability to incorporate its DNA into the host genome is a key factor in the oncogenic process, as the viral DNA can disrupt normal cellular functions and promote uncontrolled cell growth (Foglia, Turato, & Cannito, 2023). In fact, studies of tumor tissue from HBV carriers frequently show evidence of HBV DNA integrated into the genome (Wang et al., 2023). Chronic HBV infection follows a fluctuating course, driven by the complex interplay between viral replication and the host's immune response (Zheng et al., 2022). HBV is transmitted through contact with blood, semen, or other bodily fluids, and it is one of the few known viruses that can directly cause liver cancer (Carcinoma et al., 2022).

Globally, HBV is responsible for an estimated 265,000 deaths from liver cancer annually (René et al., 2021). Among individuals chronically infected with HBV, the lifetime risk of developing HCC is between 10% and 25% (Yang et al., 2019). As of 2015, it was estimated that 257 million people worldwide were infected with HBV (Frager & Schwartz, 2020). Between 2015 and 2030, HBV-related complications such as cirrhosis, acute hepatitis, chronic hepatitis, and HCC are expected to cause 20 million deaths, with HCC accounting for 5 million of those fatalities (Ducreux et al., 2023).

The global distribution of HBV infections varies widely. Regions with the highest prevalence include the Western Pacific (6.2%) and Africa (6.1%), while the Americas have a much lower prevalence (0.7%) (Kim & Viatour, 2020). Notably, in the U.S., the risk of HCC is relatively low in individuals under the age of 40, particularly among African Americans (Petrick et al., 2020). HBV-associated HCC occurs most commonly in populations with a high prevalence of chronic HBV infection (Valle Tovo et al., 2023).

**HBV Treatment and Prevention**

Nucleos(t)ide analogs (NAs) are commonly used to treat chronic HBV infection, with the goal of reducing viral replication, improving liver histology, and decreasing the risk of progression to HCC (Milosevic et al., 2023). Although NA therapy can significantly reduce the short- and medium-term risk of HCC, it does not completely eliminate the risk (Han, Baik, & Kim, 2023). Studies have shown that patients treated with the first-generation NA, lamivudine, experience a reduced incidence of HCC (Angulo, 2002). Preventive measures, such as the hepatitis B vaccination, have had a profound impact on reducing the incidence of HCC, particularly when administered at birth (Daher, Dahan, & Singal, 2023). For instance, Taiwan's 30-year evaluation of its neonatal HBV vaccination program demonstrated an 80% reduction in HCC incidence and a 92% decrease in liver cancer mortality among cohorts born after the program's implementation (Huang, El-Serag, & Loomba, 2021).

HBV can be transmitted horizontally, through contact with infected blood or bodily fluids, and vertically, from mother to child during childbirth (Liu, Tsai, & Hsu, 2021). Vaccination programs have been particularly effective in preventing vertical transmission, significantly reducing the risk of chronic HBV infection and subsequent HCC development (Zunica et al., 2022).

**Hepatitis C Virus (HCV) and HCC Risk**

HCV, unlike HBV, is an RNA virus and does not integrate into the host's genome (Yu et al., 2022). Despite this, HCV infection is strongly associated with HCC, accounting for approximately one-third of all HCC cases (Kouroumalis, Tsomidis, & Voumvouraki, 2023). HCV infection leads to chronic inflammation and liver damage over time, and several factors can increase the risk of HCC in individuals with chronic HCV infection (Chakraborty & Sarkar, 2022). These include the duration of infection, co-infection with HIV or HBV, male sex, Hispanic ethnicity, HCV genotype 3, insulin resistance, obesity, and diabetes (Huang, Mathurin, Cortez-Pinto, & Loomba, 2023). Approximately 55%–85% of individuals with HCV will develop chronic hepatitis C (CHC), and 20%–30% of those with CHC will progress to cirrhosis (Milosevic et al., 2023). Among individuals with cirrhosis, the annual incidence of HCC ranges from 1% to 4% (Kim et al., 2021).

Globally, HCV affects around 71 million people, with the highest prevalence found in the Eastern Mediterranean region (2.3%) and the lowest prevalence in Southeast Asia (0.4%) (Ohkuma, Peters, & Woodward, 2018). In North America, Europe, Japan, and parts of Central Asia and Northern Africa, including Egypt, HCV-related HCC remains a major health concern (Huang, El-Serag, & Loomba, 2021). In Canada, estimates from 2007 reported that over 242,500 individuals were living with HCV, and approximately 7,900 new infections occurred annually (Chakraborty & Sarkar, 2022).

**HCV Treatment and Prevention**

While there is currently no vaccine for HCV, antiviral therapies have proven highly effective in treating the infection and reducing the risk of HCC (Khan et al., 2020). The goal of treatment is to achieve a sustained virologic response (SVR), which is defined as the absence of detectable HCV RNA in the blood 24 weeks after completing antiviral therapy (Zunica et al., 2022). Once SVR is achieved, the infection is considered cured, and the risk of progression to liver disease and HCC is greatly reduced (Huang, El-Serag, & Loomba, 2021). However, the risk of HCC persists even after successful HCV eradication, particularly in patients with advanced liver disease, raising ongoing concerns about HCC recurrence and the need for long-term surveillance (Shah & Sarkar, 2024).

**Non-Alcoholic Fatty Liver Disease**

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent liver diseases worldwide, affecting approximately 30% of the global population (Yu et al., 2022). NAFLD occurs in individuals who do not consume excessive amounts of alcohol and is closely linked to metabolic conditions such as obesity, insulin resistance, and type 2 diabetes (Liu, Tsai, & Hsu, 2021). The risk of developing NAFLD is significantly elevated in obese individuals, with studies indicating a 4.6-fold increased likelihood compared to those with a healthy body mass index (BMI) (Zunica et al., 2022).

NAFLD has become the most common chronic liver disease and represents a growing risk factor for hepatocellular carcinoma (HCC) (Angulo, 2002). NAFLD is responsible for approximately 20% of HCC cases, and its contribution to the global HCC burden

is expected to rise in the coming decade (Huang et al., 2021). Despite this growing concern, population-based studies exploring the link between NAFLD and HCC are limited (McGlynn, Petrick, & El-Serag, 2021).

NAFLD was first introduced as a medical term in 1986 by Schaffner and is characterized by the presence of steatosis (fat accumulation) in more than 5% of hepatocytes, often driven by insulin resistance (Daher et al., 2023). The disease affects around one-third of the population, with the highest prevalence observed in North America, Europe, and the Middle East (Kouroumalis, Tsomidis, & Voumvouraki, 2023). For instance, NAFLD affects an estimated 64 million Americans and has become the second leading cause of liver transplants related to HCC in the U.S. (McGlynn, Petrick, & El-Serag, 2021). Conversely, Africa has the lowest prevalence of NAFLD (Huang et al).

**Alcohol**

Alcohol consumption is a significant contributor to global morbidity and mortality, playing a direct role in the development and progression of over 200 diseases and injuries (Rehm et al., 2009). While alcohol itself does not cause genetic mutations, chronic excessive alcohol intake—defined as consuming more than 40 grams of pure alcohol per day over an extended period—increases the risk of cirrhosis (Bellentani et al., 2010). The development of cirrhosis due to alcohol is a key precursor to hepatocellular carcinoma (HCC), with alcohol-related cirrhosis posing a much higher risk for HCC than cirrhosis caused solely by hepatitis C virus (HCV) infection (Feng et al., 2020).

**Alcohol-Related Liver Disease (ALD) and Its Progression**

Alcohol-related liver disease (ALD) encompasses a spectrum of liver conditions, including liver steatosis (fatty liver), alcoholic hepatitis, steatohepatitis, and cirrhosis (Gao & Bataller, 2011). ALD results from chronic excessive alcohol consumption, which leads to liver damage through various mechanisms. The liver, the primary organ responsible for metabolizing ethanol, is particularly susceptible to damage from alcohol's byproducts, such as acetaldehyde and reactive oxygen species (Gao et al., 2019). Additionally, alcohol consumption increases the production of lipopolysaccharides (LPS), further exacerbating liver damage through inflammation and oxidative stress (Szabo & Mandrekar, 2009).

In the U.S. and Europe, alcoholic cirrhosis is the second most common risk factor for HCC (World Cancer Research Fund, 2018). A meta-analysis conducted by the World Cancer Research Fund, which reviewed 19 studies involving 5,650 participants, found a statistically significant 4% increase in HCC risk for every additional 10 grams of alcohol consumed daily (relative risk 1.04, 95% CI 1.02–1.06) (World Cancer Research Fund, 2018). In Canada, alcohol consumption has steadily risen, with the per capita intake increasing from 7.6 liters (16 grams of pure alcohol per day) in 2000 to 8.2 liters (18 grams of pure alcohol per day) in 2010 (Canadian Institute for Health Information, 2011). This rise in alcohol consumption has been positively correlated with an increase in alcohol-related liver disease (Canadian Institute for Health Information, 2011).

**Global Impact of Alcohol Consumption**

According to the World Health Organization's (WHO) Global Status Report on Alcohol and Health (2018), over two billion people worldwide consume alcohol, with an average daily intake of 32.8 grams of pure alcohol. Between 1990 and 2017, global per capita alcohol consumption increased, and projections suggest this trend will continue until at least 2030 (World Health Organization, 2018). In 2016 alone, alcohol consumption was responsible for 132.6 million disability-adjusted life years (DALYs) and three million deaths worldwide (World Health Organization, 2018). Among individuals aged 15 to 49, alcohol-related diseases and injuries contributed to 12% of male deaths and 4% of female deaths globally (World Health Organization, 2018).

**Mechanisms of Alcohol-Induced Liver Damage**

Alcohol metabolism in the liver produces toxic substances, including acetaldehyde, which directly damages liver cells (Cederbaum, 2012). Additionally, excessive alcohol consumption generates oxidative stress and promotes inflammation, leading to progressive liver injury (Moreau et al., 2016). The accumulation of lipopolysaccharides (LPS) from gut bacteria is another factor that exacerbates liver inflammation (Wang et al., 2015). These processes collectively contribute to the development of cirrhosis and, eventually, HCC in individuals with chronic alcohol use (Gao & Bataller, 2011).

**Challenges in Diagnosing and Treating ALD**

One of the key challenges in managing ALD is the lack of reliable biochemical tests or early symptoms that can help diagnose the disease before significant liver damage occurs (Schaffner & Gores, 2011). ALD is often only diagnosed at later stages, such as alcoholic hepatitis or cirrhosis, when the liver damage is already extensive (Schaffner & Gores, 2011). Despite these challenges, several therapeutic approaches are being studied to prevent and treat ALD. These include drugs targeting oxidative stress, microRNA modulation, gut microbiota manipulation, and mesenchymal stem cell-based therapies (Wang et al., 2019).

**Metabolic Syndrome, Diabetes, and Obesity**

Emerging evidence consistently links metabolic syndrome a cluster of conditions that includes hypertension, insulin resistance,

**Table 1**. Overview of hepatocellular carcinoma (HCC), including key statistics, risk factors, diagnostic challenges, and emerging strategies.

| **Characteristic** | **Details** |
|---|---|
| Prevalence | HCC is the sixth most common cancer worldwide, with approximately 750,000 new cases annually. |
| Mortality | It is the third leading cause of cancer-related deaths, with around 700,000 deaths each year. |
| Geographic Distribution | Predominantly high in Eastern Asia and sub-Saharan Africa; accounts for ~85% of global cases. |
| Risk Factors | Chronic liver diseases (cirrhosis, HBV, HCV), alcohol abuse, MAFLD. |
| Gender Disparity | Higher incidence in males; differences in rates observed between regions. |
| Age of Onset | Varies by region; typically, older in high-income countries and younger in parts of Asia and Africa. |
| Diagnostic Challenges | Early-stage HCC often difficult to detect; ultrasound sensitivity ~47%. |
| Treatment Options | Surgical resection, liver transplantation, targeted therapies (TKIs, immunotherapy), with limitations and high recurrence rates. |
| Emerging Strategies | Precision medicine, liquid biopsies, molecular imaging, nanotechnology. |
| Future Projections | Annual new cases may rise by 55% by 2040, potentially reaching 1.4 million. |

abdominal obesity, and atherogenic dyslipidemia to an elevated risk of hepatocellular carcinoma (HCC) (Jung et al., 2014). A 2014 meta-analysis highlighted that individuals with metabolic syndrome face an 81% higher risk of developing HCC compared to those without it (Jung et al., 2014). There is some indication that treating dyslipidemia, a key component of metabolic syndrome, with statins may lower the risk of HCC by 37–42% (Yoshida et al., 2019). Metabolic syndrome is widespread, with significant portions of affected individuals presenting with hypertension (47.5%), type 2 diabetes (42%), and obesity (47%) (Jung et al., 2014). These conditions collectively contribute to a higher likelihood of developing liver diseases such as HCC (Jung et al., 2014).

**Obesity and Its Role in Liver Disease**

Obesity is characterized by the chronic accumulation of excess body fat, driven by a combination of factors including genetics, environmental influences, comorbidities, and certain medications (such as hormone therapy) (Lavie et al., 2014). By 2020, over 700 million adults worldwide more than 15% of the global adult population were classified as obese, with projections indicating a rapid increase in the coming years (World Health Organization, 2021).

Obesity is a well-established independent risk factor for numerous diseases, including type 2 diabetes (T2D), which is strongly associated with the development of liver cancer (Kauffmann et al., 2021). Approximately 75% of T2D cases are linked to obesity, underscoring the global obesity epidemic's profound impact on the rising prevalence of diabetes (Kauffmann et al., 2021). The term "diabesity" has been coined to describe the close relationship between diabetes and obesity, highlighting how these two conditions frequently co-occur and exacerbate each other's effects on health (Kauffmann et al., 2021).

**Diabetes and Its Connection to HCC**

Diabetes increases the risk of developing HCC by two to three times, with men showing a notably higher risk than women (Huang et al., 2019). Type 2 diabetes, in particular, is a major public health concern globally, contributing significantly to the rise in HCC cases (Huang et al., 2019). While diabetes is a recognized risk factor for liver cancer, treatment for T2D plays a critical role in modifying this risk. For instance, studies suggest that metformin, a common diabetes medication, may reduce the risk of HCC (Nair et al., 2019). In contrast, treatments involving insulin or sulfonylureas have been associated with an increased risk of liver cancer (Nair et al., 2019).

**Obesity and HCC Across the Lifespan**

While it is well known that obesity in adulthood raises the risk of developing liver cancer, several studies point to the impact of obesity earlier in life. Research from the U.S. and Sweden indicates that obesity during early adulthood is associated with a two to three-fold increased risk of HCC (Renehan et al., 2008). Similarly, a Danish study found that a one-unit increase in body mass index (BMI) z-score at ages 7 or 13 is associated with a 20–30% higher risk of liver cancer later in life (Barker et al., 2013).

Furthermore, cohort studies conducted in the U.S. and Europe have shown that individuals with a high waist circumference have a two-fold higher risk of HCC (Kawasaki et al., 2014). This increased risk persists even when other measures, such as body mass index (BMI) or hip circumference, are considered (Kawasaki et al., 2014). This suggests that central obesity, particularly the accumulation of visceral fat around the abdomen, may be a more significant risk factor for liver cancer than overall body fat (Kawasaki et al., 2014).

**Pathogenesis of HCC**

Hepatocellular carcinoma (HCC) represents a multifaceted global health challenge, with its pathogenesis involving a complex interplay of genetic, epigenetic, and environmental factors (Llovet et al., 2016). Central to the development of cancer, chronic inflammation is a well-established indicator of carcinogenesis (Coussens & Werb, 2002). This association was first articulated by Rudolf Virchow in the 19th century, who proposed that cancer arises from sites of chronic inflammation, observing leukocytes in malignant tissues (Virchow, 1863).

The development of HCC is an intricate process that is still not fully understood (Schulze et al., 2016). Various forms of cell death, including necroptosis, apoptosis, and autophagy-dependent cell death, are linked to HCC progression (Finkel, 2015; Galluzzi et al., 2015). Additionally, non-programmed forms of cell death such as necrosis and pyroptosis also contribute to the disease's advancement (Vanden Berghe et al., 2014). Both genetic mutations and epigenetic modifications play significant roles in HCC development. Notably, mutations in the p53 tumor suppressor gene and alterations in the TERT promoter are critical in HCC pathogenesis (Huang et al., 2016; Smith et al., 2018).

Several key signaling pathways are frequently disrupted in HCC and are crucial for molecular classification. These include the MAP kinase, AKT/mTOR, and Wnt/β-catenin pathways, which are commonly altered in HCC and significantly impact disease progression (Lee et al., 2015; Zhao et al., 2017).

Environmental factors such as excessive alcohol consumption, viral hepatitis infections (hepatitis B and C), and poor dietary habits contribute significantly to the development of HCC (El-Serag, 2012; Yang et al., 2019). Chronic liver damage, often resulting from prolonged endoplasmic reticulum (ER) stress, is a precursor to HCC (Hernandez-Gea & Friedman, 2011). Chronic liver damage is usually present long before the onset of cancer and is primarily associated with risk factors including excessive alcohol use, nonalcoholic fatty liver disease (NAFLD), metabolic syndrome, and

persistent viral infections (Rossi et al., 2020, Tufael et al., 2024). These conditions cause liver damage and inflammation, setting the stage for a multi-step progression from chronic inflammation to fibrosis, cirrhosis, and eventually carcinoma (Kakizaki et al., 2018). Notably, while most HCC cases arise in the context of cirrhosis, about 12% of patients develop HCC in the absence of cirrhosis, underscoring the complexity of the disease (Sangiovanni et al., 2010).

Inflammation is a pivotal pathogenetic element in HCC, regardless of the underlying liver disease (Zhu & Wang, 2017). Dying hepatocytes, whether through regulated or accidental mechanisms, release inflammatory mediators such as HMGB1 and HDGF, which trigger an inflammatory response (Hsu et al., 2015). This response is mediated by inflammasomes, particularly the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain containing 3 (NLRP3) inflammasome (Man & Kanneganti, 2015). NLRP3 activation is primarily driven by mitochondrial ATP generation in injured cells (Wen et al., 2019). Cathepsin B from lysosomes is also involved in triggering the NLRP3 inflammasome, highlighting its role in the inflammatory process (Bae et al., 2015).

Controlled cell death mechanisms such as apoptosis and autophagy are critical in HCC biology (Galluzzi et al., 2016). Autophagy initially acts as a tumor suppressor during HCC induction but can transition to a tumor-promoting role as the disease progresses (Rautou et al., 2010). Autophagy is closely linked to both chemotherapy resistance and apoptosis induction in HCC (Mizushima et al., 2011). Recently, ferroptosis a newly identified form of regulated cell death has emerged as a significant factor in HCC, though its role and mechanisms are still under investigation (Dixon et al., 2012; Yang & Stockwell, 2016).

## Conclusion

Hepatocellular carcinoma (HCC) remains a significant global health challenge due to its rising prevalence, high mortality rates, and limited treatment options. Despite advancements in medical research, early detection remains difficult, with ultrasound sensitivity being low and many cases diagnosed at advanced stages. Chronic liver diseases, such as cirrhosis, hepatitis B and C infections, and metabolic disorders, are primary risk factors, and the geographical distribution of HCC reflects regional variations in these factors. While surgical resection and liver transplantation offer curative potential, the high recurrence rates and limited donor availability necessitate alternative therapies. Emerging strategies, including precision medicine, liquid biopsies, and advanced imaging technologies, offer hope for improved patient outcomes. However, the rising global burden of HCC underscores the need for continued research, public health interventions, and personalized treatment approaches to combat this devastating disease.

## Author contributions

T.H. conceptualized the project and developed the methodology. M.U.P. conducted a formal analysis and drafted the original writing. T.J. contributed to the methodology. A.I. and K.A. conducted investigations, provided resources, visualized the data, and contributed to reviewing and editing the writing.

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## Competing financial interests

The authors have no conflict of interest.

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