Hepatocellular carcinoma in patients without cirrhosis

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Abstract

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, the sixth most common cancer worldwide, and the third leading cause of cancer-related death. Cirrhosis is the predominant risk factor for HCC, driven by major etiologies including hepatitis B and C, excessive alcohol consumption, and metabolic dysfunction-associated steatotic liver disease (MASLD). While approximately 80% of HCC cases occur in patients with cirrhosis, its incidence among individuals without cirrhosis has significantly increased, particularly in developed countries, driven by the rising prevalence of MASLD. The prevalence of patients with non-cirrhotic HCC varies geographically, yet data on this subgroup remain limited. Consequently, screening and clinical management guidelines for patients with non-cirrhotic HCC are underdeveloped. Current surveillance is typically not recommended for non-cirrhotic populations, except for individuals with hepatitis B, and diagnostic criteria like Liver Imaging Reporting and Data System are designed explicitly for cirrhotic or hepatitis B-associated HCC. Furthermore, treatment strategies for non-cirrhotic HCC are often extrapolated from studies focused on patients with cirrhosis, leading to gaps in knowledge regarding treatment efficacy, survival outcomes, and etiological variability in non-cirrhotic cohorts. Thus, emerging evidence must be reviewed to guide the development of enhanced diagnostic and therapeutic strategies for patients with non-cirrhotic HCC. To address these gaps, we comprehensively reviewed the epidemiology, clinical and genetic characteristics, diagnostic modalities, and therapeutic approaches for patients with non-cirrhotic HCC.

Core Tip: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, and the incidence of HCC among individuals without cirrhosis is on the rise, correlating with increasing rates of obesity and metabolic syndrome. Targeted surveillance is advised for high-risk groups, especially those with chronic hepatitis B infection, while it remains unrecommended for individuals with metabolic dysfunction-associated steatotic liver disease. Liver biopsy is the only diagnostic method available for this population, highlighting the need for further non-invasive diagnostic tools. This review summarizes the epidemiology, clinical and genetic characteristics, diagnostic methods, and treatment options for patients with non-cirrhotic HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver neoplasia and the sixth leading cause of cancer-related mortality worldwide. Its prevalence varies across regions and is influenced by factors such as underlying liver disease (LD) etiology, genetic predisposition, and environmental risk factors[1]. While the majority of HCC cases arise in cirrhotic livers, a significant proportion (approximately 15%-20%) occurs in individuals without cirrhosis[2-4]. A recent epidemiological study showed a rising prevalence of non-cirrhotic HCC, particularly among individuals with metabolic dysfunction-associated steatotic LD (MASLD)[5]. This trend parallels the increasing rates of obesity and metabolic risk factors in Western countries and is further supported by studies highlighting an increasing prevalence of incidental HCC in individuals who underwent liver transplantation (LT) due to MASLD[5-7].

Current guidelines recommend biannual surveillance for individuals with liver cirrhosis[8-10]. However, individuals without cirrhosis typically do not undergo such surveillance, often resulting in diagnosis at more advanced tumor stages, which complicates clinical management. Furthermore, the lack of consensus and the limited studies on this specific population highlight the urgent need for improved risk stratification and early detection strategies.

This review provides a comprehensive overview of the current literature on the epidemiology, clinical and genetic characteristics, diagnostic modalities, and therapeutic approaches for HCC in non-cirrhotic individuals. Notably, HCC in individuals without cirrhosis represents a distinct clinical entity, with unique patterns in tumor presentation, diagnosis, treatment, prognosis, and epidemiology compared to HCC in patients with cirrhosis.
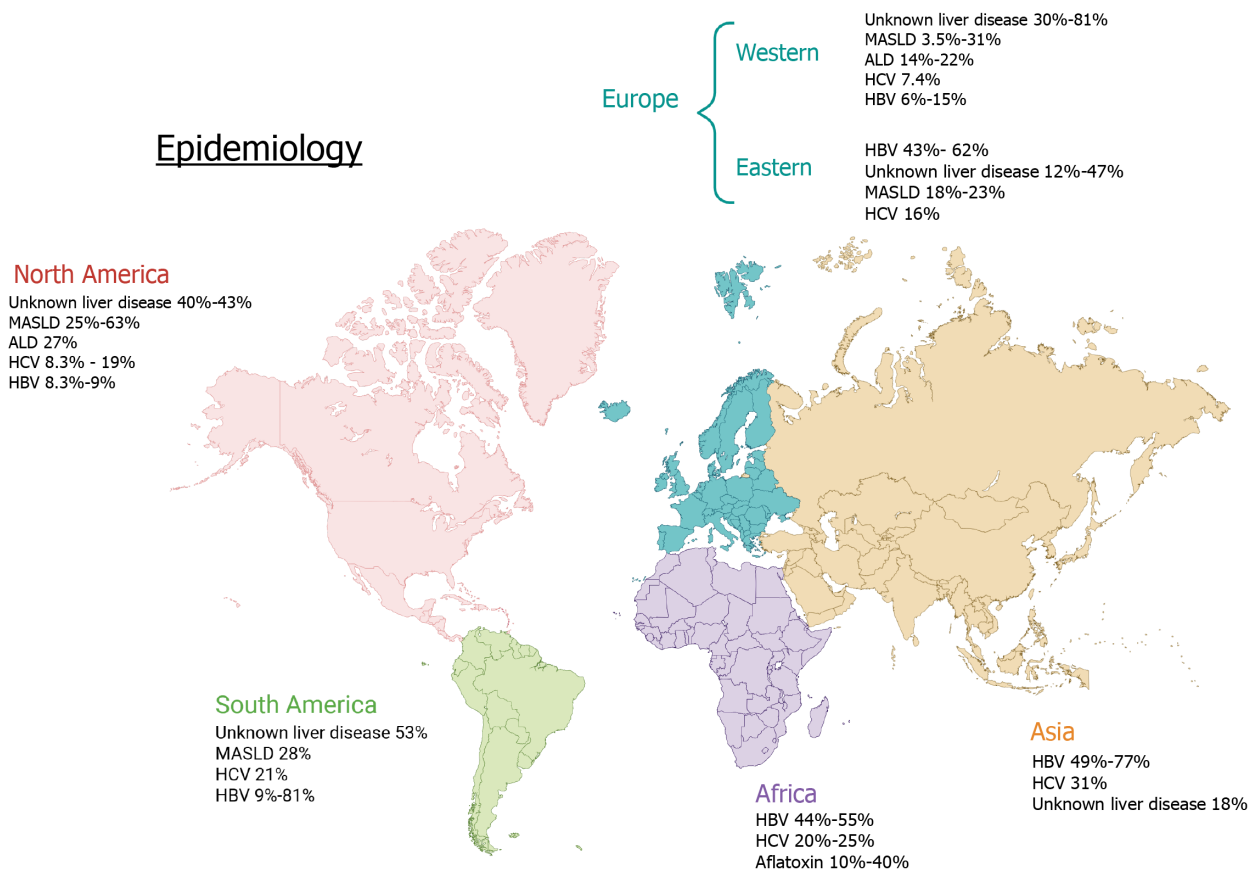
EPIDEMIOLOGY

Risk factors for HCC in individuals without cirrhosis vary across regions and populations. This section summarizes regional trends (Figure 1).

North America

Two multicenter studies conducted in the United States reported that the most common etiology of HCC in individuals without cirrhosis was LD of unknown origin. The first study (2000-2014) found that 43% of cases had unknown etiology, followed by MASLD (26%), with hepatitis C virus (HCV) and hepatitis B virus (HBV) accounting for 8.6% and 8.3% of cases, respectively[11]. The second study (2000-2015) reported similar results: 40% unknown etiology, 25% MASLD, and 8.3% HBV, with a higher contribution from HCV (19%)[12]. A study in the United States Veterans Health Administration (2005-2015) noted a higher prevalence of metabolic syndrome in patients with non-cirrhotic HCC, especially those with MASLD or no known LD[13]. In Mexico, a single-center study (2008-2018) found that MASLD was the leading cause of non-cirrhotic HCC (63%), followed by alcohol LD (ALD) (27%) and HBV (9%)[14]. Another United States-based study analyzing MASLD cases (2015-2020) found that 15% of MASLD individuals developed HCC without cirrhosis, with a prevalence of 4.6 per 10000[15] (Figure 2A).

Europe

In Western Europe, LD of unknown origin is also the most reported etiology for non-cirrhotic HCC. A nationwide study in Iceland (1998-2017) found that 35% of cases had unknown etiology, followed by metabolic syndrome/metabolic dysfunction-associated steatohepatitis (MASH) (31%) and ALD (22%). Viral hepatitis did not appear to be a significant

Epidemiology

Europe

Western
Unknown liver disease 30%-81%
MASLD 3.5%-31%
ALD 14%-22%
HCV 7.4%
HBV 6%-15%

Eastern
HBV 43%- 62%
Unknown liver disease 12%-47%
MASLD 18%-23%
HCV 16%

North America
Unknown liver disease 40%-43%
MASLD 25%-63%
ALD 27%
HCV 8.3% - 19%
HBV 8.3%-9%

South America
Unknown liver disease 53%
MASLD 28%
HCV 21%
HBV 9%-81%

Africa
HBV 44%-55%
HCV 20%-25%
Aflatoxin 10%-40%

Asia
HBV 49%-77%
HCV 31%
Unknown liver disease 18%

Figure 1 Geographic distribution of hepatocellular carcinoma in non-cirrhotic liver based on different etiologies. ALD: Alcohol-associated liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MASLD: Metabolic dysfunction-associated steatotic liver disease. Created in BioRender (Supplementary material).

etiology in this population during the study period[16]. In Sweden (2008-2018), 81% of cases were of unknown etiology, with 7.4% HCV and 3.5% MASLD[17]. Two studies from the Netherlands (2005-2012 and 2009-2020) reported similar patterns: Unknown etiology (30%-33%), MASLD (22%-28%), ALD (16%), and HBV (7%-15%)[18,19].

By contrast, in Eastern Europe, particularly Turkey, chronic HBV was identified as the predominant cause of non-cirrhotic HCC. The first Turkish study (2009-2019) reported HBV in 61% of cases, followed by MASLD or unknown LD (23%) and HCV (16%)[20]. The second Turkish study (2016-2020) found similar trends, with 62% HBV, 18% MASLD, and 12% unknown etiology[21]. The third Turkish study (2011-2021) observed nearly equal proportions of unknown etiology (47%) and HBV (43%)[22] (Figure 2B).
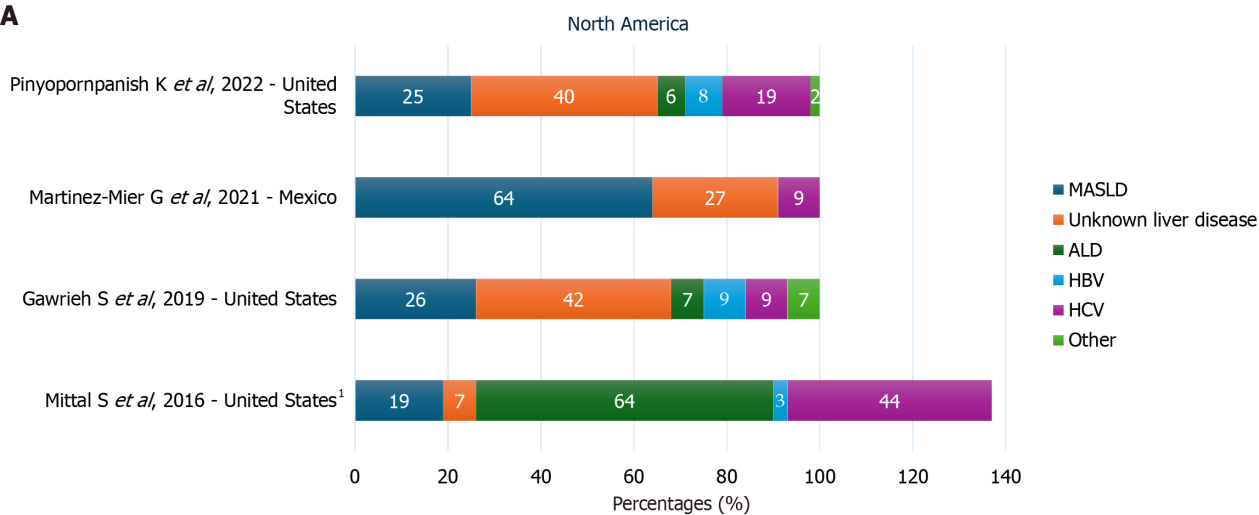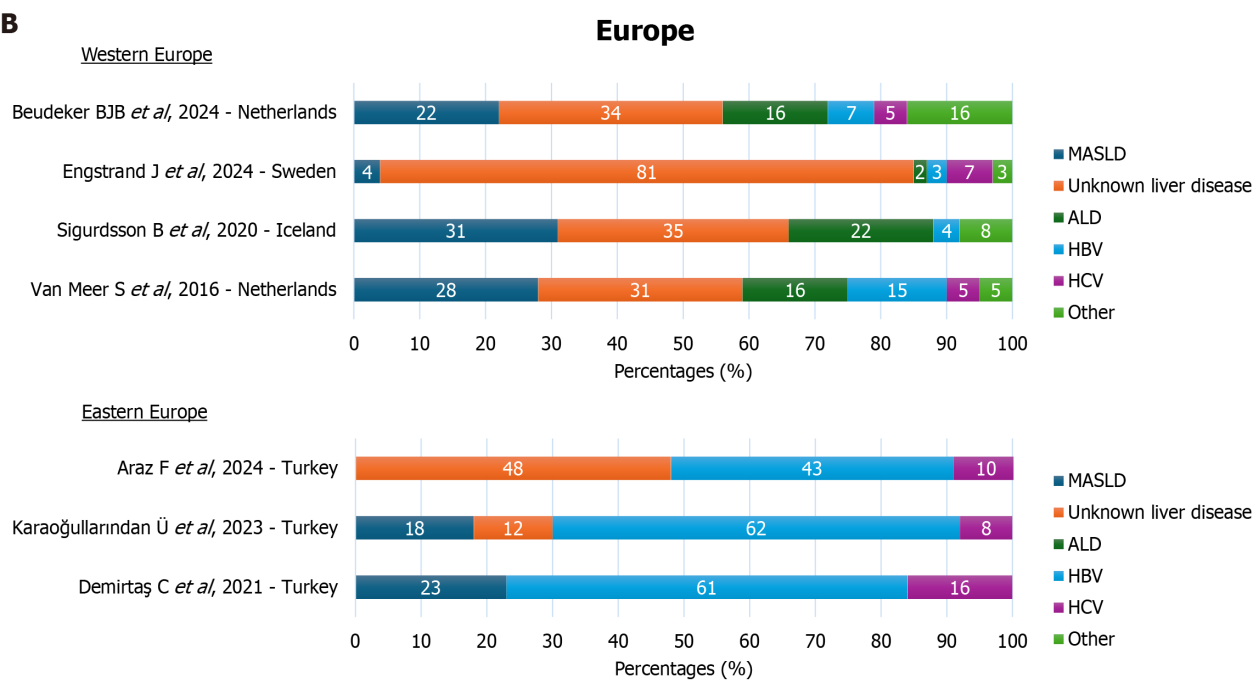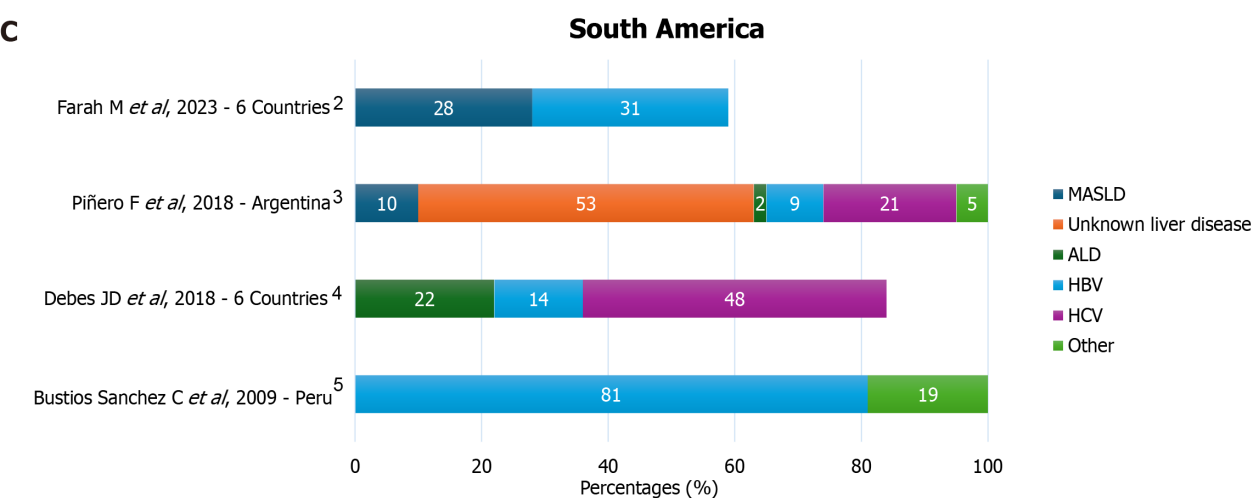
South America
A multinational study by the South American Liver Research Network, analyzing data from 2019 to 2021 across Argentina, Peru, Ecuador, Chile, and Colombia, identified HBV as the most common etiology of non-cirrhotic HCC (31%), followed by MASLD (28%)[23]. Another multinational study (2005-2015) involving Argentina, Brazil, Colombia, Ecuador, and Uruguay reported HCV and ALD as the leading risk factors for HCC in all countries except Peru, where HBV accounted for 34% of cases[24]. Supporting this, an earlier Peruvian study (2007-2008) found HBV in 81% of non-cirrhotic HCC cases[25]. In Argentina, a multicenter study (2009-2016) reported unknown LD as the most common etiology in individuals without cirrhosis (53%), followed by HCV (21%) and MASLD (10%)[26] (Figure 2C).

A major limitation in studies reporting high HCV-related HCC prevalence is the inconsistent definition of "non-cirrhotic" and the frequent absence of liver fibrosis staging. Without proper fibrosis assessment, individuals with advanced fibrosis (*e.g.*, F3) may be misclassified as non-cirrhotic. As HCV-associated HCC risk increases in advanced fibrosis, these findings must be interpreted with caution. Prospective studies with standardized definitions and fibrosis staging are needed to more accurately characterize HCC risk factors in these populations.

Asia
A study from Korea (2000-2009) showed that about 59% of individuals without cirrhosis with HCC had chronic HBV infection, regardless of whether the infection was active[27]. Similarly, a study from Taiwan (2009-2011) reported that 49% of non-cirrhotic HCC cases were HBV-positive, followed by HCV (31%), and no underlying LD (18%)[28] (Figure 2D).

HBV infection, particularly genotypes B and C, is a well-established risk factor, even in the absence of cirrhosis, due to its direct oncogenic mechanisms[29,30]. By contrast, HCV increases the risk of HCC in patients with advanced fibrosis

A

North America

B

Europe

Western Europe

Eastern Europe

C

South America

D
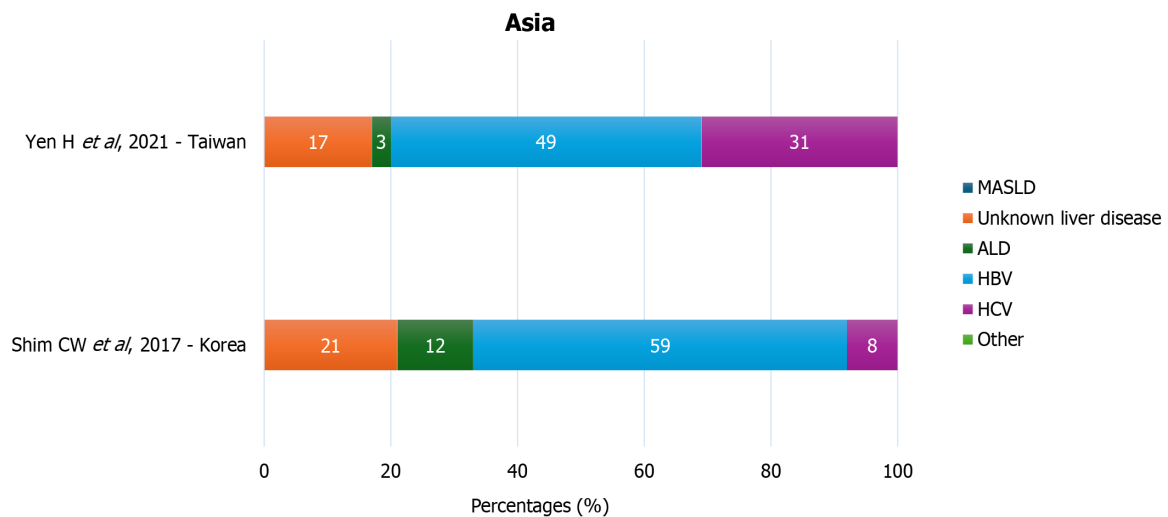
Figure 2 Summary of percentage by etiology of hepatocellular carcinoma in individuals without cirrhosis from studies conducted. A: North America; B: Europe; C: Summary of percentage by etiology of individuals with hepatocellular carcinoma (HCC) from studies conducted in South America; D: Asia. [1] Risk factor distribution was not mutually exclusive as many patients had more than one risk factor, and the percentage sum was more than 100%; [2]Percentage of non-cirrhotic HCC by country: Peru 31%, Ecuador 28%, Chile 26%, Brazil 12%, Argentina 7%, Colombia 4%. Limitation of the study: The reported etiology was combined with that of individuals with cirrhosis; [3]The data were inferred from the individuals with cirrhosis available status, but no confirmation of non-cirrhosis was reported in the study; [4]Countries included in the analysis: Peru, Ecuador, Brazil, Argentina, Colombia, Uruguay. No data on the number of individuals without cirrhosis were available. The study's limitation was that the reported etiology was combined with that of individuals with cirrhosis; [5]Only data available on hepatitis B virus (HBV) infection in non-cirrhosis available. ALD: Alcohol-associated liver disease; HCV: Hepatitis C virus; MASLD: Metabolic dysfunction-associated steatotic liver disease.

[31], and true non-cirrhotic HCC in patients with HCV infection is considered rare.

Worldwide

Aflatoxin exposure is a recognized risk factor for HCC, even in the absence of cirrhosis. The proportion of HCC cases linked to aflatoxin exposure varies widely by region, from as low as 3% in Latin America to as high as 40% in parts of Africa. This risk is particularly elevated in Sub-Saharan Africa, Southeast Asia, and China, where HBV and aflatoxin exposure are common[32].

Hereditary factors also contribute to non-cirrhotic HCC, although they account for a small proportion of cases. These include Wilson's disease, glycogen storage disease, alpha-1 antitrypsin deficiency, hereditary hemochromatosis, acute hepatic porphyria, hypercitrulinemia, and Budd-Chiari syndrome[33-37].

Healthcare professionals should consider these uncommon etiologies, especially in patients without conventional risk factors or with clinical features suggestive of metabolic or hereditary LD, or with exposure to high-risk regions.

In North America and Western Europe, the leading risk factors for non-cirrhotic HCC are LD of unknown etiology and MASLD. The adoption of the new nomenclature for MASLD and MASH raises an important question: Will the reclassification of cardiometabolic risk factors reduce the proportion of cases previously labeled as "unknown?" The updated nomenclature emphasizes the role of cardiometabolic conditions, such as obesity, type 2 diabetes (T2DM), hypertension, and dyslipidemia, which were not explicitly accounted for under NAFLD but are now recognized contributors to HCC [38,39]. This standardization may enhance diagnostic accuracy and support future research in identifying MASLD and MASH as leading causes of HCC[40].

Conversely, Asia and South America report higher prevalence of viral hepatitis, particularly HBV, as the leading risk factor for non-cirrhotic HCC. While antiviral therapies significantly reduce HCC risk, it does not eliminate it[41-44]. Additionally, HBV vaccination significantly reduces HCC risk. Current guidelines recommend universal vaccinations for newborns and unvaccinated high-risk adults. Ongoing screening and surveillance remain crucial for early detection and HCC prevention in at-risk populations.

HCV is frequently identified as the second or third most common etiology of HCC across different populations. However, the accuracy of these findings is limited by misclassification due to retrospective data and reliance on indirect cirrhosis assessments. Many studies use International Classification of Diseases codes, non-invasive scores, or clinical indicators such as esophageal varices, ascites, features of portal hypertension, Child-Pugh scores, elastography findings, or limited liver biopsy data. Patients with advanced fibrosis (*e.g.*, F3 stage) but without overt cirrhotic-related complications may have been misclassified as non-cirrhotic, leading to incomplete or inaccurate risk assessments.

Accurate assessment of fibrosis status is essential for diagnosis, risk stratification, and characterization of HCC in individuals without cirrhosis. Mittal *et al*[13] proposed a classification system to identify individuals without cirrhosis using laboratory and imaging data. The model had two probability levels: Level 1 (indicating a very high probability of absence of cirrhosis) requires histological confirmation *via* liver biopsy. Level 2 (high probability of absence of cirrhosis) required the following criteria: Aspartate transaminase to platelet ratio index score < 1; no imaging features suggestive of cirrhosis on abdominal imaging within 3 years prior to HCC diagnosis; and at least two of the following three laboratory

values within 6 months before and 4 weeks after diagnosis-albumin > 3.5 g/dL, platelet count > 200000/μL, or international normalized ratio < 1.1. Level 2 was externally validated by Gawrieh *et al*[11] using liver biopsy as the reference standard, demonstrating an area under the receiver operating characteristic of 0.80 (95% confidence interval: 0.74-0.86), with 62% sensitivity and 98% specificity. These findings support the utility of this model in accurately classifying patients without cirrhosis when biopsy is not feasible, and its potential to enhance early detection and prognostic evaluation in future studies.

PATHOGENESIS

Inflammatory mechanism

Inflammatory processes arising from various pathways of cellular injury play a significant role in initiating hepatic carcinogenesis. Hepatocyte injury promotes the recruitment of immune cells that secrete pro-inflammatory cytokines, including interleukin 1 (IL-1), IL-6, IL-18, and tumor necrosis factor alpha (TNF-α), with TNF-α identified as the most critical factor in HCC development[45]. These cytokines activate transcription factors such as nuclear factor kappa B (NF-kB) and signal transducer and activator of transcription 3 (STAT3), which drive hepatocyte proliferation, survival, and tumor progression.

In individuals with cirrhosis, chronic inflammation contributes to a pro-carcinogenic environment through persistent hepatocyte damage and regeneration, facilitating tumor initiation and progression. Genomic studies have demonstrated that sustained inflammatory stress can induce hepatocytes to dedifferentiate into progenitor-like cells, which can subsequently undergo malignant transformation[46] (Figure 3).

In individuals without cirrhosis with MASH, elevated levels of IL-6 and TNF-α stimulate STAT3 activation, promoting hepatic progenitor cell expansion, cellular transformation, and dysplastic changes in hepatocytes[47]. This inflammatory signaling facilitates tumor invasion and metastasis, correlating with clinical outcomes[48]. While inflammation remains a key contributor to tumorigenesis in non-cirrhotic HCC, the underlying mechanisms are more closely associated with metabolic dysregulation than with fibrosis-driven injury.

MASLD

HCC development in MASLD is multifactorial, with insulin resistance (IR) and oxidative stress playing key roles. The "two-hit" hypothesis suggests that IR constitutes the first hit, followed by oxidative stress as the second hit, which induces lipid peroxidation and cytokine-mediated hepatocellular injury. IR upregulates insulin-like growth factor 1 (IGF-1), activating phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, which promote cell proliferation and inhibit apoptosis[49]. The PI3K pathway contributes to tumorigenesis through cyclin D1-mediated cell cycle progression, mouse double minute 2 homolog p53 inhibition, and mammalian target of rapamycin-driven cellular growth[50]. The MAPK pathway facilitates fibrosis and oncogenesis *via* transcriptional activation of *c-fos* and *c-jun*, which trigger the Wnt/β-catenin signal cascade[51]. The multiple parallel hit theory suggests that MASH development and its progression to HCC result from multiple factors including oxidative stress, genetic variations, abnormal lipid metabolism, mitochondrial dysfunction, immune response alterations, and gut microbiota imbalances[52] (Figure 4).

Obesity is a well-known risk factor for various types of cancer, including HCC[53,54]. Individuals with obesity often present an imbalance of adipokines, characterized by elevated leptin levels and reduced adiponectin levels, promoting IR and inflammation[55]. Leptin stimulates IGF-1 expression and enhances *c-jun* and *c-fos*, activation, thereby amplifying the risk of HCC development in both individuals with and without cirrhosis[56,57].

Hepatitis viral infection

HBV integrates its genome into the hepatocyte genome, resulting in chromosomal rearrangement and genomic instability. HBV encodes the hepatitis B virus X protein (HBx) protein, which is genotoxic and interacts with the tumor suppressor p53, inhibiting its function. Additionally, the HBx protein activates various pathways, including Ras, Raf, MAPK, extracellular signal-regulated kinase, and c-Jun N-terminal kinase, which regulate cell proliferation[58].

By contrast, the HCV does not integrate into the hepatocyte genome. Instead, it causes direct cellular damage through a neuroinflammatory process mediated by viral factors. Repeated cycles of hepatocyte death and regeneration allow for mutations to accumulate that can lead to tumorigenesis[58]. Key viral proteins such as nonstructural protein 5A (NS5A) and NS3 induce oxidative stress and activate NF-kB and MAPK signaling, enhancing inflammatory cytokine release and impairing apoptosis. Transcription factors such as Notch and transforming growth factor beta (TGF-β) are upregulated, with TGF-β playing an important role in promoting tumor invasion and metastasis through induction of oncogene expression[59].

Although both HBV and HCV are associated with HCC development in individuals with cirrhosis, only HBV can initiate carcinogenesis in the absence of cirrhosis through direct genomic integration and oncogenic activation. HCV-associated HCC, by contrast, typically requires advanced fibrosis or cirrhosis.

Aflatoxin B1

Aflatoxin B1, a mycotoxin produced by *Aspergillus flavus*, is a potent hepatocarcinogen. Upon ingestion, it is metabolized in the liver into a reactive epoxide that forms DNA adduct, leading to DNA strand breaks, base modifications, and oxidative damage. Aflatoxin B1 has been shown to induce mutations in the tumor protein p53 (*TP53*) tumor suppressor gene, which are strongly associated with HCC development, even in the absence of cirrhosis[60].
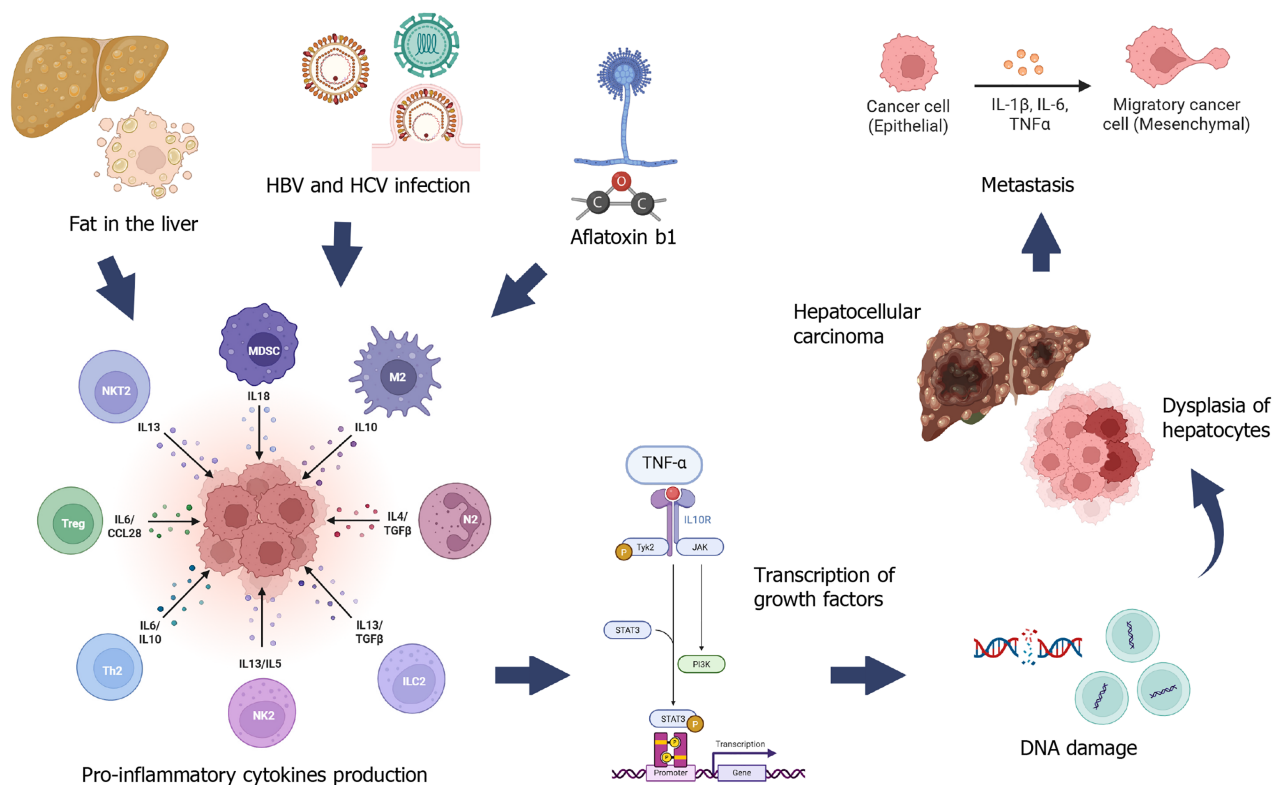
Figure 3 Inflammatory mechanism in hepatic carcinogenesis and metastasis. IL: Interleukin; HBV: Hepatitis B virus; HCV: Hepatitis C virus; TNF-α: Tumor necrosis factor alpha. Created in BioRender (Supplementary material).

Alcohol

Excessive alcohol consumption plays a multifaceted role in liver carcinogenesis. Ethanol is converted to acetaldehyde, a genotoxic compound that forms DNA adducts and induces mutations[61]. Cytochrome P450 2E1-mediated metabolism of ethanol generates reactive oxygen species, leading to oxidative stress and hepatocyte injury. Additionally, alcohol impairs immune surveillance by suppressing the activity of natural killer cells and cytotoxic T cells[62].

Chronic inflammation, caused by endotoxins such as lipopolysaccharides, activates toll-like receptor 4, promoting tumorigenesis and carcinogenesis[63]. Alcohol has a synergistic effect with metabolic disorders and viral hepatitis, compounding HCC risk. It also disrupts gut microbiota, increases intestinal permeability, and promotes microbial translocation to the liver, further aggravating inflammation[64].

Recent findings implicate the activation of inflammasomes in ALD. Oxidative stress from alcohol stimulates the nucleotide-binding domain, leucine-rich-repeat family, pyrin domain-containing-3 inflammasome, leading to IL-1β and IL-18β secretion, immune cell recruitment, and hepatic inflammation. Interferon-inducible protein 2 inflammasome activation further contributes to immune dysregulation and fibrosis progression[64]. Despite these known pathways, the precise mechanisms underlying alcohol-related HCC in individuals without cirrhosis remain incompletely understood.

CLINICAL AND GENETIC CHARACTERISTICS

Clinical characteristics

The prevalence of HCC in individuals without cirrhosis ranges from 3.5% to 37.3%, depending on the study population and comparison groups[11-13,17-22,28,65-72] (Table 1).

Individuals without cirrhosis with HCC are generally diagnosed at an older age compared to their cirrhotic counterparts[11,12,17,22,65,68,69,71]. However, conflicting research suggests that patients without cirrhosis may be younger than their cirrhotic counterparts[25,72,73], and other studies have found no significant age differences between the two groups[19,21,66]. This age variability appears to be influenced by differences in underlying population characteristics. Studies reporting a younger age of HCC onset often involve populations with a high prevalence of HBV infection, where routine surveillance enables earlier detection. In contrast, individuals with risk factors such as MASLD, obesity, or metabolic syndrome are typically diagnosed at an older age due to the lack of established screening protocols in these populations.

Several studies have reported that individuals with non-cirrhotic HCC have a higher prevalence of comorbidities, including hypertension, coronary artery disease, hyperlipidemia, T2DM, and metabolic syndrome, compared to their cirrhotic counterparts[12,13,65,68]. However, a few studies have described a lower prevalence of T2DM than in patients

| Ref.	Population	Prevalence (%)	General characteristics	Tumor characteristics	Outcome
Gawrieh *et al*[11]	605 HCC non-cirrhotic; 4539 HCC cirrhotic	11.7	Older age, lower prevalence of T2DM and obesity	Large tumor size, higher prevalence of advanced tumor stage, being outside the Milan criteria, and vascular invasion	Better OS at 1 and 3 years, but no difference at 5 years
Pinyopornpanish *et al*[12]	290 HCC non-cirrhotic; 1947 HCC cirrhotic	13	Older age, higher prevalence of HTN, hyperlipidemia	Large tumor size, higher prevalence being outside the Milan criteria. Lower prevalence of vascular invasion	Better OS
Sigurdsson *et al*[16]	49 HCC non-cirrhotic; 152 HCC cirrhotic	N/A	No difference in age between the groups	Large tumor size, lower prevalence of portal vein thrombosis	No difference in OS between the groups
Engstran *et al*[17]	1431 HCC non-cirrhotic; 2828 HCC cirrhotic	34	Older age	Large tumor size, higher prevalence of advanced disease	Worse OS, irrespective of the treatment
Van Meer *et al*[19]	238 HCC non-cirrhotic; 983 HCC cirrhotic	19	No difference in age between the groups	Larger tumor size, higher prevalence of advanced stages	N/A
Karaoğullarından *et al*[21]	82 HCC non-cirrhotic; 138 HCC cirrhotic	37.3	No difference in age between the groups	No difference in tumor size and morphology. Lower prevalence of vascular and portal vein invasion	Better OS at 1, 3, and 5 years
Araz *et al*[22]	42 HCC non-cirrhotic; 146 HCC cirrhotic	22.3	No difference in age between the groups	Large tumor size	Better OS, PFS, and DFS
Yen *et al*[28]	259 HCC non-cirrhotic; 1796 HCC cirrhotic	25.7	Younger age	Large tumor size	Better OS at 5 years
Altshuler *et al*[65]	Unresectable HCC: 264 non-cirrhotic; 1230 cirrhotic	17.7	Older age, higher prevalence of HTN and CAD	Large tumor size, higher prevalence of distant metastasis	No difference in OS or PFS between groups
Chen *et al*[66]	26 HCC-non-cirrhotic; 85 HCC cirrhotic	23.4	No difference in age between the groups	Large tumor size, higher prevalence of vascular invasion, and being outside the Milan criteria.	No difference in OS, RFS, and bleeding-free survival between the groups
Schütte *et al*[68]	93 HCC non-cirrhotic; 571 HCC cirrhotic	14	Older age, higher prevalence of T2DM and HTN	More advanced tumor stage	No difference in OS between the groups
Donica *et al*[69]	4545 HCC non-cirrhotic; 18592 HCC cirrhotic	19.6	Older age	Large tumor size, higher prevalence of localized disease	Better OS
Vitellius *et al*[71]	124 MASLD-HCC non-cirrhotic; 230 MASLD-HCC cirrhotic	35	Older age, lower prevalence of T2DM	Large tumor size, lower prevalence of portal vein thrombosis	Better OS
Pommergaard *et al*[72]	HCC underwent LT: 792 non-cirrhotic; 21995 cirrhotic	3.5	Younger age	Large tumor size	Worse OS

CAD: Coronary artery disease; DFS: Disease-free survival; HCC: Hepatocellular carcinoma; HTN: Hypertension; LT: Liver transplantation; MASLD: Metabolic dysfunction-associated steatotic liver disease; N/A: Not available; OS: Overall survival; PFS: Progression-free survival; RFS: Recurrence-free survival; T2DM: Type 2 diabetes.

without cirrhosis compared to their cirrhotic counterpart[11,71].

Tumor characteristics

Most studies on HCC tumor characteristics have reported that individuals without cirrhosis are more likely to present with a single tumor, but with a larger size at diagnosis compared to their cirrhotic counterparts[11,12,16,17,19,20,22,28,65-67,69,71,72,74,75]. However, a study in Turkey reported no difference in tumor size and morphology between the groups [21]. At diagnosis, patients without cirrhosis often present with more advanced disease and a higher likelihood of metastasis[11,17,20,65,66,68,75,76]. They also show a higher prevalence of cases falling outside the Milan criteria[11,12,66,74,76], which dictate LT eligibility as a single tumor ≤ 5 cm, or up to three tumors each ≤ 3 cm, with no extrahepatic spread or major vessel involvement[77]. By contrast, a few studies have reported a lower prevalence of vascular infiltration and portal vein invasion in patients without cirrhosis compared to cirrhotic counterparts[78] (Table 1).
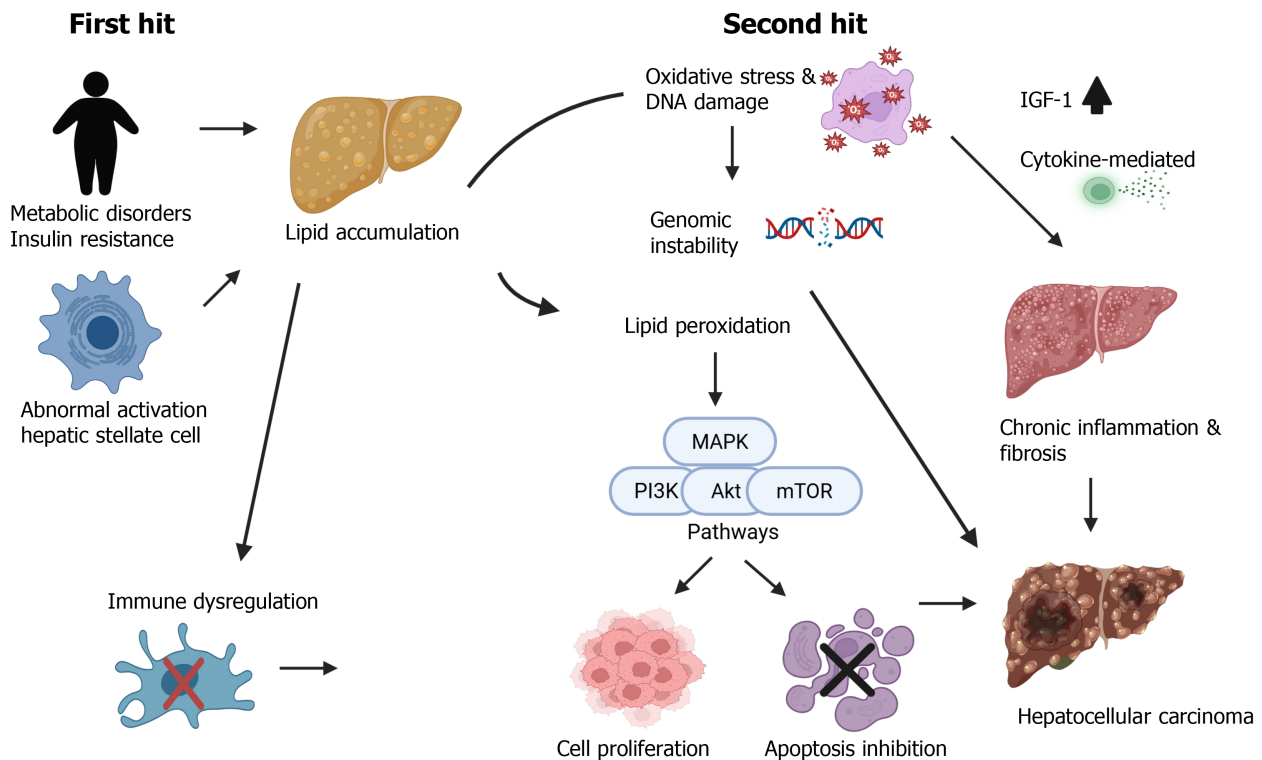
Figure 4 Hypothesis of the development of hepatocellular carcinoma in individuals with metabolic dysfunction-associated steatotic liver disease. Akt: Protein kinase B; IGF-1: Insulin-like growth factor-1; MAPK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinase. Created in BioRender (Supplementary material).

Genetic characteristics

An Italian study found a significant association between the membrane-bound *O*-acyltransferase 7 (*MBOAT7*) gene variant (rs641738) and increased risk of HCC in individuals with MASLD, identifying the T allele as the risk allele, particularly among those without advanced fibrosis (F0-F2)[78] HCV and ALD have also been shown to increase HCC risk in individuals without cirrhosis carrying the T allele, suggesting that the role of *MBOAT7* in carcinogenesis extends beyond MASLD.

Mutations in telomerase reverse transcriptase (*TERT*) promoter are the most commonly reported mutation in non-cirrhotic liver with HCC[79], especially for individuals with MASLD[80]. One study utilizing high-throughput sequencing for genome- and transcriptome-wide profiling of non-cirrhotic HCC found mutations in *TERT* (55%), *TP53* (28%), beta-catenin (*CTNNB1*) (21%), and apolipoprotein B (13%), similar to those found in cirrhotic counterparts. Despite high *TERT* expression, most tumors showed shortened telomeres. In individuals without cirrhosis, CTNNB1 mutations led to downregulated β-catenin expression—a mechanism distinct from that seen in cirrhosis. The study concludes that cirrhotic and non-cirrhotic HCC share similar genomic landscapes during tumor progression[81].

SURVEILLANCE AND DIAGNOSIS

Current guidelines do not recommend routine surveillance for all individuals with non-cirrhotic HCC. Instead, they specify subgroups of patients without cirrhosis who may warrant surveillance[82-86] (Table 2).

HCC diagnosis in non-cirrhotic livers differs from that in individuals with cirrhosis. Currently, liver biopsy remains the only valid method for diagnosing HCC in patients without cirrhosis (Figure 5). Non-invasive imaging techniques, such as computed tomography scans or magnetic resonance imaging, are not recommended for diagnosing HCC in patients without cirrhosis, although they are commonly used in those with cirrhosis.

Scores and staging systems

Several studies evaluating HCC in both individuals with and without cirrhosis apply the same scoring and staging systems to assess liver function, guide treatment selection, and predict prognosis. However, the applicability and validity of these systems in individuals without cirrhosis remain unclear and warrant further discussion. Commonly used systems include the tumor-node-metastasis (TNM), Cancer of the Liver Italian Program, Barcelona Clinic Liver Cancer (BCLC), Japan Integrated Staging, and Hong Kong Liver Cancer (HKLC) systems. Among these, the BCLC system is the most widely used and validated, though primarily in cirrhotic populations.

Table 2 Recommendations for hepatocellular carcinoma screening and surveillance by medical societies

Medical societies	Cirrhotic individuals		Non-cirrhotic individuals		Both populations	
	At-risk population	Additional notes	At-risk population	Additional notes	Surveillance tests	Frequency
EASL[8]	Individuals with Child-Pugh A and B, or Child-Pugh C if awaiting LT	N/A	Chronic HBV infection with PAGE-B score ≥ 10	No current recommendation for individuals with chronic liver disease and advanced fibrosis without cirrhosis	Ultrasound ± AFP	Every 6 months
AASLD[9]	Individuals with Child-Pugh A or B with any etiology, and Child-Pugh C if awaiting LT	CT or MRI is suggested if limited liver visualization with ultrasound	Chronic HBV infection: From endemic countries (women > 50 years old and men > 40 years old); From Africa at an earlier age; Family history of HCC; PAGE-B Score ≥ 10	Same as the cirrhotic population	Ultrasound ± AFP	Every 6 months
AGA[10]	All individuals with cirrhosis	CT or MRI is suggested if limited liver visualization with ultrasound	N/A	Screening should be considered in advanced liver fibrosis	Ultrasound ± AFP	Every 6 months
NCCN[86]	Individuals with Child-Pugh A or B with any etiology, and Child-Pugh C if awaiting LT	CT or MRI is suggested if limited liver visualization with ultrasound	Chronic HBV infection: Asian women > 50 years old and men > 40 years old); Family history of HCC; African/North American Blacks	Same as the cirrhotic population	Ultrasound ± AFP	Every 6 months
ESMO[85]	All individuals with cirrhosis	N/A	Chronic HBV infection with moderate to high HCC risk score at the onset of nucleoside analogue therapy	N/A	Ultrasound ± AFP	Every 6 months
BSG[84]	All individuals with cirrhosis	N/A	Chronic HBV infection: From endemic countries (women > 50 years old and men > 40 years old); Family history of HCC; African Black people	No current recommendation for individuals with non-cirrhotic MASLD	Ultrasound + AFP	Every 6 months
APASL[82]	All individuals with cirrhosis	N/A	Chronic HBV infection: From endemic countries (women > 50 years old and men > 40 years old); Family history of HCC; African individuals > 20 years old	No current recommendation for chronic HCV individuals with bridging fibrosis	Ultrasound ± AFP	Every 6 months
JSH[83]	All individuals with cirrhosis	Individuals with cirrhosis type B and C should undergo dynamic CT/MRI every 6-12 months, which is optional	Individuals with chronic HBV and HCV	N/A	Ultrasound + tumor marker	Every 6 months for chronic hepatitis B/C and non-viral cirrhosis; Every 3-4 months for cirrhosis types B and C

AASLD: American Association for the Study of Liver Disease; AFP: Alpha fetoprotein; AGA: American Gastroenterological Association; APASL: Asia-Pacific Association for the Study of the Liver; BSG: British Society of Gastroenterology; CT: Computed tomography; EASL: European Association for the Study of the Liver; ESMO: European Society of Medical Oncology; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; JSH: Japanese Society of Hepatology; LT: Liver transplantation; MRI: Magnetic resonance imaging; N/A: Not available; NAFLD: Non-alcoholic fatty liver disease; NCCN: National Cancer Comprehensive Network; PAGE-B: Platelet-age-gender-hepatitis B virus.

The BCLC system, originally developed for patients with chronic LD, particularly cirrhosis[87], was updated in 2022 to incorporate features more applicable to non-cirrhotic individuals[88]. It utilizes tumor burden, liver function, and performance status. While individuals without cirrhosis typically have preserved liver function, they may still fall into BCLC stages 0, A, B, or C depending on tumor size, vascular invasion, and extrahepatic spread. Nonetheless, a key limitation is that the BCLC system lacks stratified criteria designed explicitly for patients without cirrhosis and has not been well validated in this subgroup. Prognosis and recurrence patterns may also differ between cirrhotic and non-cirrhotic HCC.

The Child-Pugh score was originally designed to assess cirrhosis severity and predict outcomes in patients undergoing surgery or treatment for portal hypertension[89,90]. It has not been validated in patients without cirrhosis, where preserved liver function can lead to underestimation of clinical features such as ascites and encephalopathy, resulting in
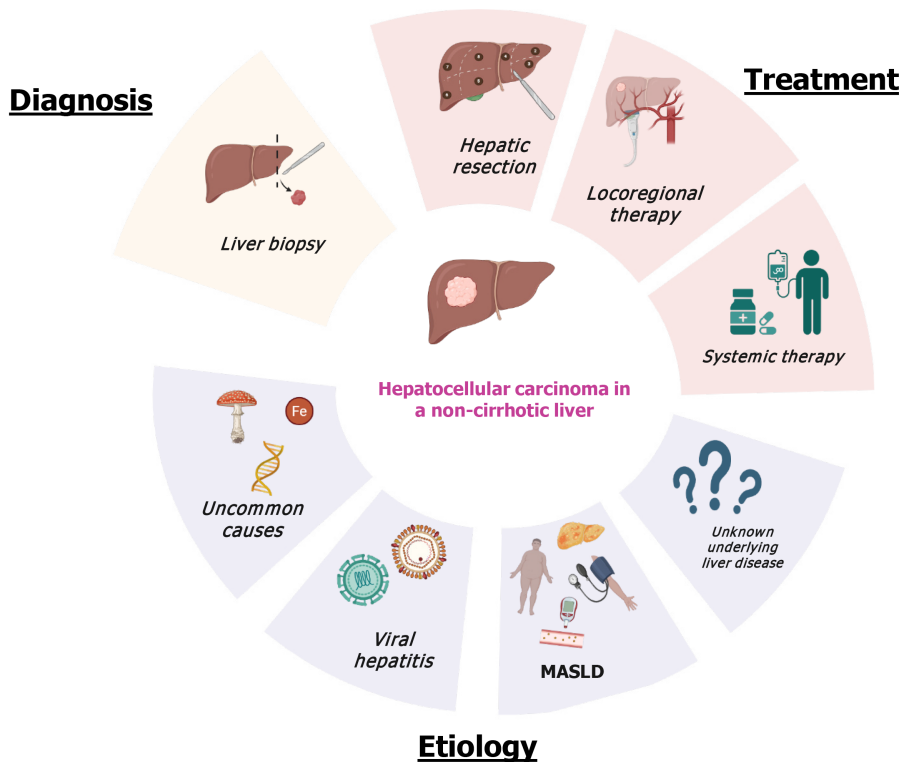
Figure 5 Graphical abstract summarizing the etiology, treatments, and diagnosis of hepatocellular carcinoma in individuals without cirrhosis. MASLD: Metabolic dysfunction-associated steatotic liver disease. Created in BioRender (Supplementary material).

potential misclassification as Class A.

The TNM staging system evaluates tumor characteristics, such as size, number, vascular invasion, lymph node involvement, and distant metastases, without accounting for liver function[91-93]. This makes it applicable to both individuals with and without cirrhosis[94,95].

The HKLC system, developed in a population largely affected by HBV, incorporates more aggressive treatment strategies[96]. While it may include individuals with and without cirrhosis, it uses the Child-Pugh score to assess liver function, making it difficult to determine whether patients without cirrhosis were explicitly included.

This section highlights the key features, limitations, and gaps in current scoring and staging systems as they apply to individuals with non-cirrhotic HCC. For a comprehensive comparison, refer to Table 3.

New diagnostic approaches

Currently, there is no consensus on reliable biomarkers or diagnostic tools, other than liver biopsy, for diagnosing HCC in individuals without cirrhosis. However, numerous ongoing studies are exploring the potential approaches in this population.

A case-control study evaluated bifucosylated tetra-antennary haptoglobin glycan (BiFc-Tetra-glycan) and alpha-fetoprotein (AFP) levels in individuals without cirrhosis with and without HCC. BiFc-tetra-glycan demonstrated a sensitivity of 71% and specificity of 96% for detecting HCC, whereas AFP exhibited a lower sensitivity (43%) but a higher specificity (99%)[97].

Another study assessed the utility of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) to distinguish between HCC with and without cirrhosis. NLR showed no significant differences between the groups, but PLR was significantly higher in individuals without cirrhosis, with borderline predictive performance with area under the curve AUC of 0.66[98].

DNA methylation markers (DMMs), including homeobox A1, C-type lectin domain family 11 member A, *AK055957*, and testis-specific Y-encoded-like protein 5, have been evaluated in liver tissue from individuals with non-cirrhotic HCC. Four of these DMMs were elevated and present in 73.1% of patients with non-cirrhosis, compared to AFP > 20 ng/mL in only 40%. The combination of the four DMMs achieved a sensitivity of 78%, a specificity of 80%, and an AUC of 0.85 in distinguishing HCC from benign or hepatitis-related lesions[99].

Diagnosing HCC in individuals without cirrhosis is challenging due to the absence of universally validated biomarkers and limited sample sizes of existing studies. As artificial intelligence (AI) continues to advance, integrating machine learning tools with clinical data may enhance diagnostic accuracy, interpretability, and real-world applicability[100]. These technologies hold promise for improving early detection, prognostic assessment, and personalized treatment planning in non-cirrhotic HCC. Existing studies indicate that AFP has low sensitivity in individuals without cirrhosis, limiting its reliability as a diagnostic maker in this population. Emerging biomarkers and AI-driven tools represent key innovations in the diagnostic landscape, but prospective studies involving larger, more diverse cohorts are needed to

Table 3 Summary of the scores and stage systems in individuals with non-cirrhotic hepatocellular carcinoma

	Controversies	Limitations	Research hotspots
Scores and stage systems			
BCLC	New update in 2022, introducing more flexibility and personalized treatment decisions with no strictly stage-based approach could be advantageous for individuals without cirrhosis	Primarily focus on individuals with underlying chronic liver disease, especially with cirrhosis. Not validated in non-cirrhotic individuals	Studies validated the BCLC stage systems in non-cirrhotic individuals with HCC, which evaluate treatment options, long-term outcomes, and explicitly stratified categories for those individuals are needed
Child-Pugh	The use of ascites and encephalopathy may be underestimated due to the common presentation of preserved liver functions observed in individuals without cirrhosis	Designed to evaluate the severity and prognosis in individuals with cirrhosis. Not validated in non-cirrhotic individuals	Studies that validate the Child-Pugh score in individuals with HCC without cirrhosis are needed; Creating a new score potentially without ascites and encephalopathy is needed to compare if the individuals are being underestimated
TNM	It is a valuable staging system for anatomical tumor burden, but is not sufficient alone for accurate HCC treatment guidance or outcomes	Focus on anatomical staging; Best for post-operative prognosis	Studies redefining TNM, evaluating treatment responses, and long-term outcomes are needed
HKLC	Proposed more aggressive treatments with more curative therapy but with potential risk of over-treatment	Developed based on a population predominantly with hepatitis B; Not well validated with other etiologies	Studies validating the stage system in diverse populations with different background etiologies are needed; Studies evaluating treatment options and long-term outcomes are needed
LI-RADS	Only individuals with hepatitis B or cirrhosis benefit from this, but individuals outside these criteria may be leading to a missed diagnosis. No consensus on biopsy, follow-up time, or surveillance in intermediate categories	Designed for individuals with cirrhosis or with HCC-associated hepatitis B; Not well validated with other etiologies	Studies validating the diagnosis in populations with different background etiologies are needed; Studies integrating LI-RADS with biomarkers to improve early HCC detection are needed

BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma; HKLC: Hong Kong liver cancer; LI-RADS: Liver imaging reporting and data system TNM: Tumor-node-metastasis.

validate these approaches and determine their clinical utility.

TREATMENT

Management of HCC in individuals without cirrhosis requires a comprehensive evaluation of etiology, tumor characteristics (macroscopic and microscopic), performance status, and surgical risk. Available treatments include hepatic resection, locoregional therapy, and systemic therapy (Figure 5). Hepatic resection is generally preferred, regardless of underlying etiology. While locoregional and systemic therapy are used in intermediate or advanced diseases stages, data on long-term outcomes remain limited. No clinical trials have stratified outcome by cirrhosis status, which limits the generalizability of findings to non-cirrhotic populations.

Hepatic resection

Hepatic resection is the most common curative treatment for patients without cirrhosis with HCC[12,16,17,19,21,22,28,66,69]. These individuals often present with preserved liver function, absence of portal hypertension, and lower risk of multifocal disease, making them more suitable surgical candidates. The majority presents with large, solitary tumors amenable to resection over LT or locoregional therapy.

Surgical procedures include anatomical resections (segmentectomy, sectionectomy, hemihepatectomy, extended hepatectomy) and non-anatomical (wedge) resections[101-103]. Postoperative outcomes are categorized using the R classification: R0 indicates no residual tumor (curative), R1 indicates microscopic residual tumor, and R2 indicates gross residual disease[104].

A study comparing surgical procedures for HCC in individuals without cirrhosis of various etiologies (MASH, viral hepatitis, and ALD) found that patients with MASH underwent more extensive liver resections and fewer segmental resections than other groups. These patients experienced higher rates of surgical complications, such as bile leaks, but had lower rates of non-surgical complications[105]. Another study, excluding individuals with viral hepatitis, reported higher rates of hemihepatectomy and extended hepatectomy, with 88% achieving R0 resection. Achieving R0 status was associated with improved cumulative survival (an increase by 4% at 1 year and 12% at 3 years)[106]. A German study found 50% of patients with non-cirrhotic HCC of various etiologies underwent extended hepatectomy, 87% achieved R0 resection, and 41% underwent lymphadenectomy at the hepatic hilus (median: Two lymph nodes removed)[107]. A Taiwanese study also reported a higher incidence of extensive hepatectomy with lower rates of postoperative hepatic decompensation[66].

A Korean study on hepatitis C-related HCC compared resection outcomes in individuals with and without cirrhosis. They found that individuals without cirrhosis had a higher rate of anatomic resections (96%) and major hepatectomies, but lower rates of laparoscopic surgery. No significant differences were found in transfusion rates, blood loss, operative

time, postoperative mortality, or hospital stay[108]. Another study similarly reported no differences in hepatic venous pressure gradients, postoperative complications, or length of admission between the two groups[75].

A multicenter European study compared anatomical liver resection (ALR)-removal of the tumor with the corresponding liver segment-to non-ALR (NALR), which preserves more parenchyma. ALR was performed more frequently (71%) than NALR (29%). Postoperative outcomes showed no significant difference in intensive care unit stay (average 5 days), but moderate to life-threatening complications were more frequent in the NALR group, while ALR had a higher incidence of liver insufficiency[102].

Hepatic resection is the preferred treatment for HCC in non-cirrhotic livers, regardless of the underlying etiology. However, the choice of surgical technique and patient-specific risk factors significantly influence complication risk, highlighting the importance of individualized treatment planning.

Locoregional therapy

While hepatic resection remains the primary treatment for HCC in individuals without cirrhosis, several studies have reported the use of locoregional and systemic therapies in patients with non-cirrhotic HCC.

Locoregional treatments, including transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and radiofrequency ablation (RFA), are commonly used in patients with cirrhosis with early to intermediate-stage HCC [109,110]. Systemic therapy is typically reserved for more advanced diseases[111,112]. However, the efficacy of these therapies in patients without cirrhosis remains unclear and warrants further investigation.

A nationwide study in Iceland found that 41% of individuals with non-cirrhotic HCC received non-surgical treatments, including TACE, RFA, and sorafenib, although, none underwent LT[16]. In a United States study for individuals with non-cirrhotic HCC, 33% received TACE, 20% TARE, and 19% systemic therapy[65]. A Turkish study reported 63% of individuals with non-cirrhotic HCC received palliative treatment, of whom 70% received TACE, 23% systemic therapy, and 7% TARE[20]. Similarly, in Mexico, 35% of patients without cirrhosis received non-surgical therapy: 26% systemic (sorafenib), 23% RFA, and 12% TACE. This study identified that older patients (> 70 years) with multiple comorbidities (*e.g.*, hypertension, diabetes) were more likely to receive RFA, although no significant difference in survival was found between RFA and TACE[14]. By contrast, a Scottish study found improved survival with TACE in patients without cirrhosis compared to those with cirrhosis, with no differences observed for other treatments[70].

Despite these findings, direct comparative data on locoregional therapies in non-cirrhotic HCC are limited. Without standardized guidelines, treatment decisions-whether curative, palliative, or as a bridge to surgery-vary by institutional protocols and resource availability.

Systemic therapy

Systemic therapy is recommended for patients with advanced-stage HCC (BCLC stage C). particularly those who are ineligible for locoregional therapies or have failed initial treatment. According to European Association for the Study of the Liver guidelines[8], individuals with advanced HCC, preserved lived function (Child-Pugh class A), and Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 should receive systemic therapy, including at least one programmed cell death protein 1/program cell death ligand 1 inhibitor, unless contraindicated. This recommendation applies regardless of tumor size, location, or number of lesions. The presence or absence of cirrhosis significantly influences tolerance to systemic therapies (Table 4).

The Sorafenib HCC Assessment Randomized Protocol (SHARP), a Phase 3 study, demonstrated the efficacy of sorafenib in patients with advanced HCC[113]. A Phase 2 randomized, double-blind, placebo-controlled trial conducted in the Asia-Pacific region[114] confirmed sorafenib's effectiveness. The REFLECT trial, a Phase 3 multinational randomized non-inferiority study, established that lenvatinib is non-inferior to sorafenib for unresectable HCC[115]. Recently, IMBRAVE150 showed that atezolizumab plus bevacizumab significantly improved overall and progression-free survival compared to sorafenib in untreated patients with locally advanced or metastatic HCC[116]. Similarly, the HIMALAYA trial demonstrated that a combination of durvalumab and tremelimumab as first-line therapy for advanced HCC resulted in superior overall survival (OS) *vs* sorafenib[117].

A recent Phase 3 trial, camrelizumab plus rivoceranib *vs* sorafenib as first-line therapy for unresectable HCC (CARES-310), found that camrelizumab plus rivoceranib improved OS compared to sorafenib, particularly among individuals with HBV infection[118]. Interestingly, the median OS in the sorafenib arm was higher than that in the SHARP study, potentially due to differences in population characteristics, including the proportion of patients without cirrhosis.

It is important to note that all systemic therapy trials primarily included patients with compensated cirrhosis (Child-Pugh class A) and an ECOG performance status of 0-1 (Table 5). As a result, the efficacy and safety of these treatments in individuals without cirrhosis remain poorly understood. Additionally, previous studies did not adequately address the inappropriate application of the Child-Pugh score, which was specifically designed for patients with cirrhosis, thereby limiting the applicability of these findings to non-cirrhotic individuals in real-world settings. This raises concerns about extrapolating such results to non-cirrhotic populations, whose treatments and outcomes remain unclear.

Patients with recurrent HCC after LT are often excluded from clinical trials. However, several descriptive studies suggest that systemic therapies such as sorafenib, regorafenib, and lenvatinib may provide some clinical benefit in patients without cirrhosis[8,119-121]. By contrast, immunotherapy is generally not recommended in this population due to the risk of allograft rejection and immune-related complications.

Table 4 Clinical comparison of individuals with and without cirrhosis with hepatocellular carcinoma in systemic therapy

	Cirrhotic	Non-cirrhotic
Liver function	Impaired (Child-Pugh A, B, C)	Preserved
Therapeutic flexibility	Limited	Higher freedom for the TKI and IO combination
Toxicity risk	High (decompensation, bleeding, and encephalopathy)	Low (better tolerance)
Clinical trial inclusion	Most Child-Pugh A (B or C are typically excluded)	No well-classified
TKI use	Reduced dose in Child-Pugh B, and avoided in Child-Pugh C	Full dose (according to guidelines)
IO	Can be used in Child-Pugh A, but has uncertain use in Child-Pugh B or C	Well tolerated (first-line treatment)
Treatment goals	Controlling the tumor while maintaining liver function	Aggressive tumor control; Potential cure
Liver transplant eligibility	Yes, it is within the criteria (*e.g.*, Milan criteria)	Usually not applicable
Prognosis	Hepatic functional reserve is more critical than tumor stage	Determined by tumor size and stage

IO: Immunotherapy; TKI: Tyrosine kinase inhibitor.

Table 5 Summary of available clinical trials on systemic therapy in individuals with hepatocellular carcinoma

Clinical trials	Treatment	Child-Pugh score	Cirrhosis status reported?	Key notes
SHARP[113]	Sorafenib *vs* placebo	Only A	Not mentioned, but approximately 95% with cirrhosis	First trial to show OS benefit with systemic therapy in advanced HCC
REFLECT[115]	Lenvatinib *vs* sorafenib	Only A	Reported, but not explained	Individuals with more than 50% liver involvement or main portal vein invasion were excluded
IMBRAVE150[116]	Atezolizumab + bevacizumab *vs* sorafenib	Only A	Not mentioned, but primarily cirrhotic	Untreated high-risk variceal individuals were excluded
HIMALAYA[117]	Durvalumab +/- tremelimumab *vs* sorafenib	Only A	Not specified	Primarily MASLD or viral causes, without subclassifying for cirrhosis
CARES-310[118]	Camrelizumab + rivoceranib *vs* sorafenib	Only A (A5 & A6)	Most had cirrhosis	Excluded patients at high risk for GI bleeding, including varices

CARES-310: Camrelizumab plus rivoceranib as first-line therapy for unresectable hepatocellular carcinoma; GI: Gastrointestinal; HCC: Hepatocellular carcinoma; MASLD: Metabolic dysfunction-associated steatotic liver disease; OS: Overall survival; SHARP: Sorafenib hepatocellular carcinoma assessment randomized protocol.

OUTCOMES

The literature presents mixed findings on survival outcomes individuals with HCC, with and without cirrhosis, across metrics such as regarding OS, recurrence-free survival (RFS), disease-free survival (DFS), and progression-free survival (PFS).

Multiple studies have reported no significant difference in OS between individuals with and without cirrhotic HCC[16, 18,20,65,66,68,70,75]. Among these, outcome variability was observed for other survival endpoints. For instance, a study on unresectable HCC found similar PFS between groups[65], while another showed no significant differences in RFS or variceal bleeding-free survival following resection[66]. A Dutch study examining cryptogenic HCC found it associated with worse outcomes compared to viral or non-viral etiologies; however, OS remained comparable between cirrhotic and non-cirrhotic individuals. Independent predictors of survival in non-cirrhotics included age, tumor stage, and treatment strategy[18].

Conversely, several studies have reported superior OS in non-cirrhotic individuals[11,12,21,22,28,69,71,76]. A Turkish study found that patients without cirrhosis showed better DFS and PFS, with curative treatment predicting OS and vascular invasion predicting DFS[22]. Another study in the same population identified portal vein thrombosis, elevated AFP, and cryptogenic etiology as independent risk factors for poor survival[21]. A multicenter French study reported that age, liver function, tumor burden, and BCLC classification were significant predictors of OS[71]. Conversely, A Taiwanese study found that age > 70 years, American Joint Committee on Cancer TNM stage III-IV, serum AFP > 200 ng/mL, and non-curative treatment were associated with increased mortality in patients with and without cirrhosis[28].

By contrast, two studies reported worse OS in patients without cirrhosis. A Swedish study identified age, ECOG performance status, tumor size, number of lesions, and treatment modality (*e.g.*, resection or ablation) as key survival predictors[17]. The European Liver Transplant Registry found that individuals without cirrhosis had a higher mortality

risk (hazard ratio = 1.37) compared to cirrhotic counterparts[72].

The variability in outcomes across studies likely reflects differences in study populations, geographic regions, and etiologies. Research from the United States, Europe, and Asia has highlighted the role of ethnic background and underlying LD in shaping outcomes. Additionally, the predominance of retrospective study designs limits control for confounders. Despite this heterogeneity, most studies indicate either improved or similar outcomes in non-cirrhotic patients. Commonly reported independent risk factors include age, tumor burden, AFP levels, and cryptogenic etiology.

CONCLUSION

HCC in individuals without cirrhosis is primarily associated with underlying LD of unknown etiology, MASLD, chronic HBV and HCV infection, and aflatoxin exposure. The prevalence of these risk factors varies by demographic region, raising concerns about the increasing prevalence of HCC associated with MASLD, metabolic syndrome, and obesity – conditions that are rising globally. Current guidelines do not recommend routine HCC surveillance for all individuals without cirrhosis but only advise screening for high-risk populations, including those with chronic hepatitis B and a family history of HCC, particularly among Asian and African populations. Accurate assessment of liver fibrosis status is essential for diagnosing and correctly classifying patients at high risk. Liver biopsy is the only validated method for diagnosing HCC in patients without cirrhosis, highlighting the need to further explore new non-invasive diagnostic tools. Additionally, the absence of valid staging and prognostic models complicates clinical management. The most common treatment performed is hepatic resection, while locoregional therapies, and systemic therapies are used in intermediate or advanced disease stages, data on long-term outcomes remained limited. The interpretation of these results is challenging since evaluating individuals using the BCLC and Child-Pugh scoring systems may underestimate prognosis in this population. Additionally, no clinical trials have differentiated outcomes based on cirrhosis status, making it challenging to apply the results to the non-cirrhotic population. Further research, particularly retrospective studies incorporating diverse cohorts and standardized diagnostic criteria, is essential to improve our understanding and management of HCC in non-cirrhotic individuals.

FOOTNOTES

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