Review

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Management of non-alcoholic fatty liver disease-associated hepatocellular carcinoma

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SUMMARY In recent years, with the decline in HBV and HCV infections, there has been a corresponding reduction in both the morbidity and mortality of virus-associated HCC. Nevertheless, rising living standards, coupled with the increasing prevalence of metabolic disorders like diabetes and obesity, have led to a rapid surge in non-alcoholic fatty liver disease-associated hepatocellular carcinoma (NAFLD-HCC) incidence. The mechanisms underlying the progression from NAFLD to NAFLD-HCC are multifaceted and remain incompletely understood. Current research suggests that genetic predisposition, metabolic dysregulation, lipotoxicity, oxidative stress, and inflammation are key contributing factors. Given the complexity of these mechanisms and the frequent occurrence of metabolic comorbidities like type 2 diabetes mellitus (T2DM) and cardiovascular disease in NAFLD-HCC patients, there is a pressing need for tailored therapeutic strategies, along with novel prevention, monitoring, and treatment approaches that are personalized to the patient's pathophysiology. Due to the limited depth of research, incomplete understanding of pathogenesis, and insufficient clinical data on NAFLD-HCC treatment, current therapeutic approaches largely rely on tumor staging. In this review, we synthesize current research on the pathogenesis, surveillance, diagnosis, treatment, and prevention of NAFLD-HCC, and offer perspectives for future studies, particularly regarding its underlying mechanisms.

Keywords NAFLD-HCC, NAFLD, pathogenesis, diagnosis, treatment

1. Introduction

Hepatocellular carcinoma (HCC) represents the predominant histological subtype of primary liver cancer, comprising the vast majority of cases (*1*). Recent global cancer statistics indicate that HCC exhibits both a high incidence and mortality rate. Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming a leading cause of HCC, driven by the rising prevalence of non-alcoholic fatty liver disease and the declining incidence of chronic viral hepatitis. Current clinical studies suggest that 10~20% of NAFLD patients progress to non-alcoholic steatohepatitis (NASH) , with nearly one-third of those progressing to cirrhosis and potentially HCC (*2*).

The development of NAFLD-HCC is a multifactorial and complex process involving numerous risk factors. Metabolic dysregulation leads to hepatic steatosis, and under the combined influence of genetic predisposition, lipotoxicity, oxidative stress, inflammation, and other mechanisms, NAFLD progresses, leading to hepatic inflammation, fibrosis, and ultimately, the onset of NAFLD-HCC.

The incidence of NAFLD-HCC is steadily rising, highlighting the critical need for a deeper understanding of NAFLD-HCC to enhance treatment outcomes and prognosis. In this review, we summarize the current knowledge on the pathogenesis, diagnosis, surveillance, and treatment of NAFLD-HCC, and offer perspectives for future research, particularly on its underlying mechanisms.

2. Prevalence of NAFLD-HCC

HCC is the most prevalent histological type of primary liver cancer, ranking as the third leading cause of cancer-related deaths globally. It is also the primary cause of mortality in patients with chronic liver disease and cirrhosis, contributing to 7.8% of all cancer-related deaths worldwide (*3*). Globally, morbidity and mortality rates for HCC are two to three times higher in men than in women. Key risk factors for HCC include

chronic hepatitis B and C infections, heavy alcohol use, NAFLD, obesity, T2DM, aflatoxin exposure, and smoking (*4*). The highest incidence and prevalence of HCC currently occur in regions such as East Asia, North Africa, and Southeast Asia, largely due to the high burden of HBV infection, which accounts for over 50% of global HCC cases. By contrast, in North America, Europe, and Australia, non-viral etiologies like NAFLD are responsible for the majority of HCC cases. With rising hepatitis B vaccination rates, antiviral therapies, and increasing obesity rates, the prevalence of HBV-associated HCC has decreased, while NAFLD-HCC has risen from 9.9% to 13.6% (*5*). Globally, the prevalence of NAFLD-HCC is expected to rise in tandem with the increasing incidence of metabolic diseases, including obesity and T2DM. Presently, the highest prevalence of NAFLD-HCC is observed in countries such as the United Kingdom, Germany, Saudi Arabia, Southeast Asia, and Africa. The United States, Canada, Australia, South America, and France show slightly lower rates, while regions like China and Japan report comparatively lower prevalence (Figure 1). The annual incidence of HCC in NASH patients with cirrhosis is estimated at 0.5-2.6%, while in non-cirrhotic NAFLD patients, it is significantly lower, ranging from 0.1 to 1.3 per 1,000 patients per year. Currently, although NAFLD-HCC has a lower incidence compared to HCC from other etiologies, the rising prevalence of obesity, T2DM, and metabolic syndrome suggests that the future burden of NAFLD-HCC will surpass other liver diseases. This highlights the urgent need for a deeper understanding of NAFLD-HCC pathogenesis and the implementation of targeted measures to halt its progression.

3. Pathogenesis of NAFLD-HCC

NAFLD can progress to NAFLD-HCC (Figure 2), a multifactorial process primarily driven by genetic susceptibility, metabolic dysregulation, lipotoxicity, oxidative stress, and inflammation (Figure 3). Additionally, factors such as circadian rhythm disruption, gut microbiota dysbiosis, and alcohol or cigarette use may act as cofactors, potentially contributing to disease progression (*14*).

3.1. Genetic susceptibility

Recent studies increasingly demonstrate that the development of NAFLD and the elevated risk of NAFLD-HCC are linked to genetic polymorphisms in several key genes, including the patatin-like phospholipase domain-containing 3 (PNPLA3), the transmembrane 6 superfamily member 2 (TM6SF2), the membrane bound O-acyltransferase domain-containing 7 (MBOAT7) (*14*), and the 17- beta hydroxysteroid dehydrogenase 13 (HSD17B13) is a protective heritable factor *(15)*.

PNPLA3: The first genome-wide association study(GWAS) on NAFLD, conducted in 2008, identified the rs738409 C>G variant in the *PNPLA3* gene, resulting in an isoleucine-to-methionine substitution at position 148 (p.I148M) (*16*). This variant is a key genetic factor linked to hepatic fat accumulation. Numerous recent studies continue to demonstrate that the PNPLA3 rs738409 C>G variant is strongly associated with NAFLD, hepatic steatosis, and the severity of liver fibrosis in NAFLD, making it the most reliable genetic predictor of inter-individual variability in liver fat content

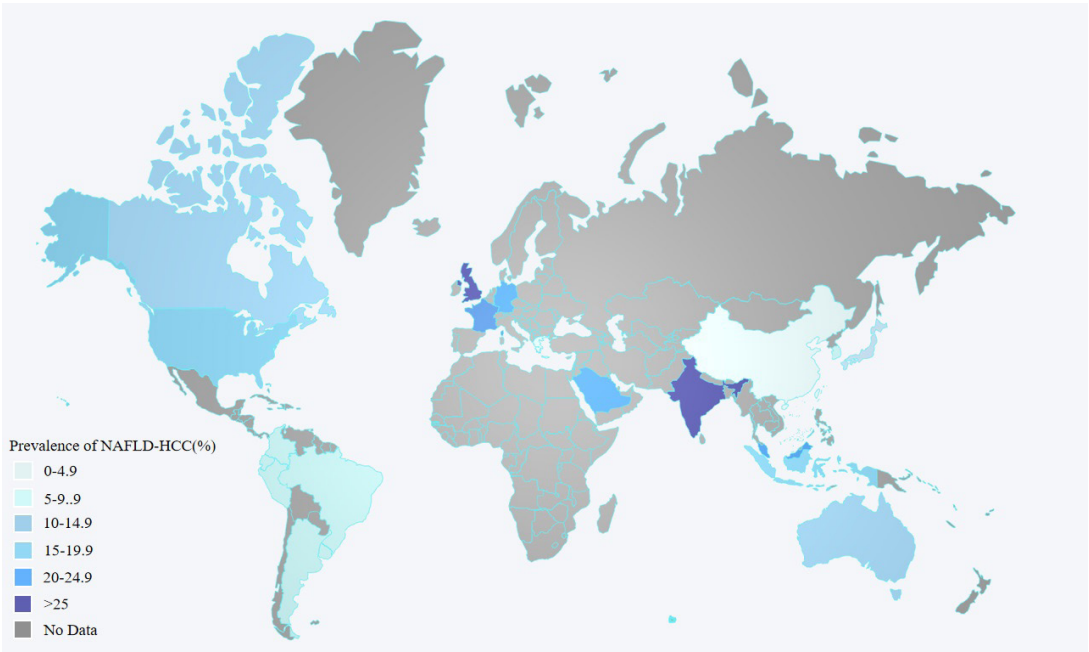

Figure 1. The Prevalence of NAFLD-HCC. The specific data comes from references, but there is still a lack of specific data for many countries (*6-13*).

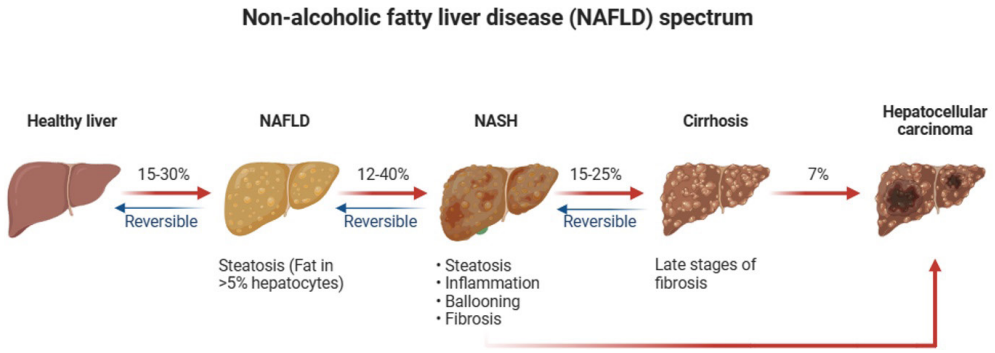

Figure 2. The progression of NAFLD-HCC. Healthy liver, NASH and Cirrhosis of liver can transform each other, but once it progresses to HCC, this progression of the disease is irreversible.

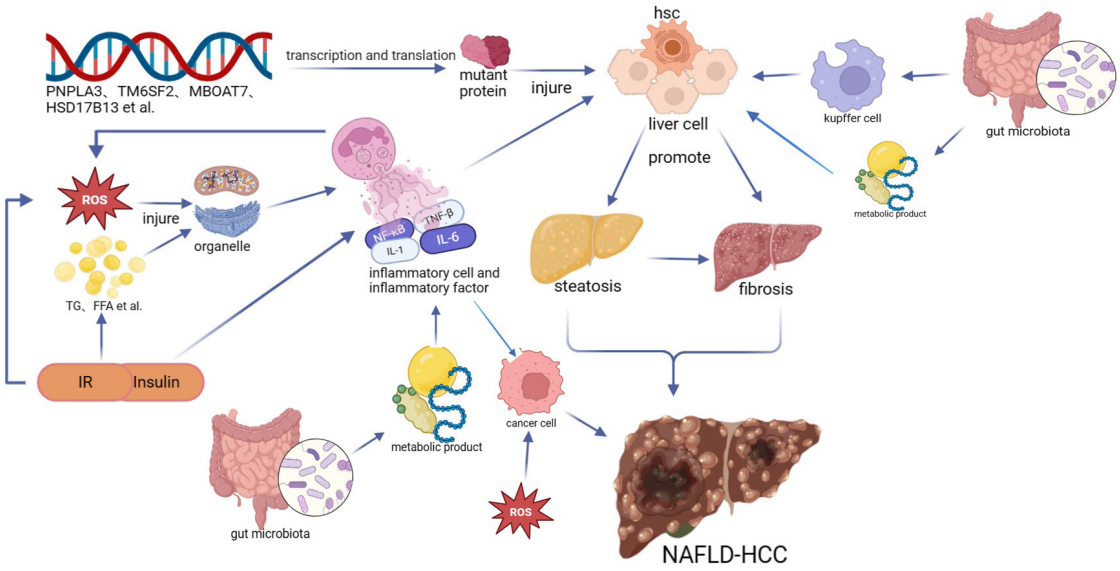

Figure 3. Proposed mechanism of NAFLD-HCC. NAFLD-HCC is mainly associated with genetic susceptibility, metabolic imbalance, lipotoxicity, oxidative stress, and inflammation.

(*17*). The PNPLA3 rs738409 C>G polymorphism is associated not only with hepatic steatosis, steatohepatitis, and fibrosis but also with the development of NAFLD-HCC (*18*). The *PNPLA3* gene encodes a 481-amino acid triacylglycerol lipase, which primarily mediates triglyceride hydrolysis in adipocytes. This enzyme is localized to the surface of the endoplasmic reticulum (ER) and lipid droplets (LD) in hepatocytes, adipocytes, and hepatic stellate cells (HSCs) (*19*). The PNPLA3 mutation impairs triglyceride mobilization and inhibits triglyceride release, leading to hepatic fat accumulation. Excess free fatty acids in hepatocytes disrupt the local liver immune system, triggering hepatic inflammation. Additionally, PNPLA3 mutant proteins may impair retinol release from HSCs, altering liver retinol storage and serum retinol levels, thereby directly promoting hepatic fibrosis and carcinogenesis (*20*).

TM6SF2: A 2014 exome-wide association study identified the rs58542926 C > T variant in the *TM6SF2* gene, resulting in a glutamate-to-lysine substitution at position 167 (p.E167K). This variant is associated with increased serum alanine aminotransferase activity, decreased serum alkaline phosphatase activity, and reduced plasma triglyceride and very low-density lipoprotein levels (*21*). TM6SF2 encodes a protein that plays a crucial role in the regulation of hepatic triglyceride secretion. The E167K variant of the *TM6SF2* gene promotes hepatic lipid accumulation by enhancing hepatic lipid uptake and de novo lipogenesis, while simultaneously reducing β-oxidation and decreasing very low-density lipoprotein secretion (*22*). Individuals carrying the TM6SF2 rs58542926 C>T polymorphism (E167K) exhibit more pronounced hepatic steatosis, inflammation, and fibrosis. Additionally, multiple studies have confirmed the link between this genetic variant and conditions such as hepatic steatosis, NASH, and liver fibrosis (*23*), but the role in hepatocarcinogenesis is unknown.

MBOAT7: The MBOAT7 rs641738 C>T variant has been linked to hepatic fat accumulation, severe

liver injury, and hepatic fibrosis across multiple studies. It is also correlated with disease severity in NAFLD and NAFLD-HCC, particularly in patients without advanced liver fibrosis (*24*). A recent meta-analysis identified the MBOAT7 rs641738 polymorphism as being associated with increased susceptibility to HCC, particularly in Asian populations, where it contributes to hepatocarcinogenesis. The underlying mechanisms, however, warrant further investigation (*25*).

HSD17B13: A 2018 study identified a splice variant (rs72613567) in the *HSD17B13* gene, which encodes hydroxysteroid 17-β dehydrogenase 13, as not being associated with simple steatosis but significantly reducing the risk of NASH and hepatic fibrosis. The variant was also shown to prevent progression to advanced stages of chronic liver disease (*26*). This protective role was further validated by a GWAS study, which found that the protective effect of HSD17B13 was more strongly linked to NAFLD development than to the progression of liver fibrosis (*27*).

As research progresses, many other genes have also been identified as being involved in the development of NAFLD and NAFLD-HCC, including odd-skipped related transcription factor 1, human telomerase reverse transcriptase, programmed cell death protein 1, and ectonucleotide pyrophosphatase/phosphodiesterase 1 (*14*). Research on these genetic variants is enhancing our understanding of NAFLD pathogenesis and improving our capacity to mitigate the risk of HCC development.

3.2. Metabolic imbalance

Metabolic imbalance is primarily associated with fat accumulation, with insulin resistance (IR) and hyperinsulinemia being the most prevalent metabolic features of NAFLD-HCC. In the context of insulin resistance, visceral adipose tissue (AT) becomes resistant to insulin's anti-lipolytic effects, leading to the breakdown of triglycerides (TG) into free fatty acids (FFA) and glycerol. The liver absorbs FFA and converts it into TG, resulting in hepatic TG accumulation and ultimately hepatic steatosis. Additionally, insulin resistance inhibits the β-oxidation of FFA, further exacerbating lipid accumulation in the liver (*28*).

In addition to increased FFA production, enhanced FFA uptake by the liver, inhibition of β-oxidation, and elevated intrahepatic lipogenesis, exogenous lipids from dietary intake also contribute to increased intrahepatic TG levels. Studies have demonstrated that long-term high-fat and high-carbohydrate diets elevate intrahepatic TG production, thereby promoting hepatic steatosis and ultimately facilitating the development of NAFLD-HCC (*29*).

Insulin resistance and hyperinsulinemia have been shown to drive the progression of NAFLD to NAFLD-HCC and contribute to NAFLD-HCC development *via* multiple oncogenic pathways, as evidenced by numerous animal models and human studies (*30*). Insulin and insulin-like growth factor (IGF)-1 increase the risk of hepatocellular carcinoma by promoting cell proliferation and inhibiting apoptosis, among other mechanisms. Hyperglycemia supplies energy for cancer cell growth and proliferation, while chronic hyperglycemia drives glycosylation reactions, producing advanced glycation end products (AGEs), activating nuclear factor κ-B (NF-κB) and inflammatory signaling pathways, promoting reactive oxygen species (ROS) production, and inducing NAFLD-HCC (*31*). Additionally, IR has been shown to promote hepatic neovascularization by stimulating the formation of new blood vessels in the liver (*31*). Through the combined influence of these mechanisms, NAFLD can gradually progress, leading to liver fibrosis and the eventual development of NAFLD-HCC.

3.3. Lipotoxicity

Lipotoxicity refers to the accumulation of toxic lipids resulting from the dysregulation of intracellular lipid composition, primarily including cholesterol, FFA and their derivatives, as well as ceramides (*32*). Lipotoxicity can ultimately result in cellular damage and even cell death by disrupting the function of cellular organelles, such as the endoplasmic reticulum and mitochondria. Additionally, it can dysregulate metabolic and inflammatory pathways by directly altering intracellular signaling mechanisms.

ER is an intracellular organelle responsible for essential functions, including protein folding, lipid synthesis, and calcium storage. Lipotoxicity can lead to ER dysfunction, disrupting the protein folding process. Under ER stress, unfolded or misfolded proteins accumulate, triggering an adaptive mechanism known as the unfolded protein response to restore cellular homeostasis (*33,34*). If ER stress is not alleviated in a timely manner, apoptotic pathways are activated, leading to cell death.

ER stress is closely associated with the development and progression of NAFLD-HCC, increasing the risk of NASH and NAFLD-HCC independently of insulin resistance. ER stress triggers TNF-dependent steatohepatitis, ultimately promoting NAFLD-HCC by stimulating the release of tumor necrosis factor (TNF) from macrophages (*35*).

3.4. Oxidative stress

Oxidative stress refers to tissue damage resulting from an imbalance between oxidants and antioxidants in the body (*36*). Oxidative stress is closely linked to the development and progression of diseases like NAFLD, NASH, and HCC, playing a critical role in promoting liver fibrosis, cirrhosis, and HCC (*37*). The primary driver of oxidative stress is ROS. Under physiological conditions, partially reduced ROS are detoxified to

water, while the body maintains oxidant levels at a relatively low concentration through antioxidant defense mechanisms and repair enzymes (*38*). When redox balance is disrupted, excessive ROS production or impaired clearance can damage cellular macromolecules, including proteins, lipids, and nucleic acids, leading to structural dysfunction, carcinogenesis, and even cell death.

ROS accumulation plays a critical role in the development of chronic inflammation, hepatic fibrosis, necroptosis, and liver carcinogenesis (*39*). ROS accumulation impairs hepatocyte function and induces hepatocyte death by causing mitochondrial dysfunction and altering cell membrane permeability. Additionally, ROS promote the differentiation of HSCs into myofibroblasts, which secrete and accumulate collagen and other extracellular matrix components in the liver. This process is key in the development of liver fibrosis and plays a crucial role in promoting cirrhosis and hepatocellular carcinoma (*40*). When hepatic macrophages (KCs) are activated by specific stimuli, they can further promote this process by producing factors such as transforming growth factor (TGF-β) and platelet-derived growth factor (*41*). Liver sinusoidal endothelial cells (LSECs) protect KCs and HSCs from abnormal activation by toxic molecules in the portal vein. However, ROS accumulation leads to LSEC damage, compromising vascular endothelial function and ultimately resulting in portal hypertension (*42*). In response to oxidative stress, liver cells may develop adaptive survival and proliferation mechanisms, which ultimately promote cancer cell growth and contribute to the progression of NAFLD-HCC.

3.5. Inflammation

Fat accumulation in the liver leads to cellular damage, mitochondrial dysfunction, endoplasmic reticulum stress, oxidative stress, and activation of necrosis. These mechanisms trigger sterile chronic inflammation in the liver, promoting the progression of NASH and facilitating the onset and development of NAFLD-HCC (*43*). Inflammatory cells in chronic inflammation promote vasculogenesis and lymphangiogenesis by releasing various inflammatory factors, including interleukins (IL-6, IL-1), NF-κB, TNF, signal transducer and activator of transcription 3, and TGF-β. These factors cause DNA damage, suppress the immune system, evade host defenses, and promote tumorigenesis and progression through various mechanisms (*44*). Chronic inflammation triggers the release of ROS, cytokines, chemokines, and other mediators, causing DNA damage and promoting tumor proliferation (*45*). As NAFLD progresses, most patients develop chronic liver inflammation. Through these complex mechanisms, NAFLD advances, leading to DNA damage, the formation of new blood vessels and lymphatic vessels, and the eventual emergence of cancer cells, ultimately culminating in NAFLD-HCC.

3.6. Gut microorganisms

Under normal conditions, gut microorganisms maintain a stable balance, supporting various physiological processes such as energy intake, immune regulation, nutrient metabolism, and the integrity of the intestinal mucosal barrier. When this balance is disrupted by gut dysbiosis, it can lead to hepatic inflammation, fibrosis, hepatocyte proliferation, and reduced anti-tumor immunity. Mechanisms such as increased intestinal permeability, bacterial overgrowth, translocation, impaired enterohepatic bile acid circulation, and endotoxemia contribute to the development and progression of chronic liver disease and NAFLD-HCC (*46*). Gut microorganisms play a crucial role in regulating metabolic processes. When gut microbial homeostasis is disrupted, the microbiota can increase hepatic fat accumulation by influencing appetite, enhancing energy extraction from food, and altering the expression of genes involved in fat synthesis and oxidation. This disruption further impairs metabolic homeostasis, contributing to the onset and progression of metabolic disorders.

In cirrhosis, portal hypertension impairs the intestinal mucosal barrier, increasing intestinal permeability and allowing bacteria and bacterial metabolites to enter the liver and bloodstream *via* the portal vein. This leads to elevated endotoxin levels in the blood, which stimulate cytokine production and trigger chronic inflammation in the liver, intestines, and adipose tissue. Inflammatory cells further promote the generation of cancer cells and the progression of NAFLD-HCC by releasing various inflammatory factors and activating multiple pathways.

Disruption of homeostasis between the organism and gut microbiota allows bacterial metabolites, such as lipopolysaccharide from Gram-negative bacteria and lipoteichoic acid from Gram-positive bacteria, to activate immune responses in hepatic macrophages (Kupffer cells) *via* Toll-like receptors and other pattern recognition receptors. This leads to hepatocyte proliferation and hepatic stellate cell activation, ultimately causing hepatic inflammation, liver fibrosis, and the progression of NAFLD-HCC (*47*).

Beyond gut microbes, metabolites in the gut, bloodstream, and liver tissues play a key role in the progression of NAFLD and NAFLD-HCC. These metabolites include amino acids, short-chain fatty acids, and bile acids, which are strongly associated with these conditions. Bile acids, secreted by the liver and undergoing enterohepatic circulation, are influenced by gut microbiota. In obesity-related microbiota, the conversion of chenodeoxycholic acid to the hepatotoxic deoxycholic acid (DCA) is increased, leading to DCA accumulation in the liver. This accumulation induces oxidative damage to mitochondrial structures and promotes hepatocyte proliferation *via* the hepatic

mTOR pathway, contributing to liver fibrosis and HCC development (*48*). Bile acids can modulate the farnesoid X receptor (FXR), and FXR activation helps regulate NAFLD progression by reducing triglyceride levels, inhibiting fatty acid synthesis and uptake in the liver, mitigating inflammatory responses, and alleviating liver fibrosis (*49*).

4. Diagnosis of NAFLD-HCC

Early diagnosis of NAFLD-HCC is crucial for improving treatment outcomes and preventing the severe prognosis commonly associated with this condition. Over the next two decades, the global incidence of HCC is projected to rise by more than 55%, driven by the increasing prevalence of NAFLD (*50*). Current international guidelines recommend that all cirrhotic patients and hepatitis B patients without cirrhosis undergo abdominal ultrasound, with or without alpha-fetoprotein (AFP) testing, every six months (*51*). NAFLD-HCC is typically more monofocal, characterized by larger tumor volume, better differentiation, lower AFP levels, higher body weight, less pronounced early clinical presentation, a higher rate of metabolic complications, and lower rates of cirrhosis and ascites compared to HCC from other causes. Notably, 20%-30% of NAFLD-HCC cases occur in patients without cirrhosis (*52*). Due to the unique characteristics of NAFLD-HCC, current testing faces challenges in improving the early detection rate and enhancing patient survival. Early diagnosis of NAFLD-HCC remains particularly difficult.

Abdominal ultrasonography, a noninvasive and low-cost imaging test with high sensitivity and specificity, is recommended by many guidelines. However, despite its advantages, a meta-analysis highlighted its poor sensitivity for detecting early-stage HCC (*53*). This limitation is even more pronounced in NAFLD-HCC, as the presence of adiposity in NAFLD patients, leading to higher body weight and increased subcutaneous fat, impairs the ultrasound beam, reducing image quality and liver visualization. This hampers lesion detection. Nevertheless, due to its significant benefits, abdominal ultrasonography remains widely used in clinical practice for NAFLD-HCC screening.

According to current guidelines, lesions ≥ 10 mm or AFP levels > 20 ng/mL detected by ultrasound require further evaluation with more sensitive imaging techniques, such as CT, MRI, or contrast-enhanced ultrasound (*54*). MRI offers greater sensitivity and specificity than CT, particularly for detecting HCCs smaller than 1 cm. However, its limited availability, lengthy examination times, and high costs restrict its widespread use in clinical practice (*55*). In 2018, the American College of Radiology and the American Association for the Study of Liver Diseases introduced the Liver Imaging Reporting and Data System (Li-RADS) (*56*), applicable to both CT and MRI. The diagnosis of HCC under Li-RADS is based on factors such as contrast perfusion and excretion, non-rim arterial phase enhancement, lesion size, tumor capsule, and growth rate, to improve lesion characterization.

Liver biopsy is an invasive procedure reserved for cases where imaging, such as CT or MRI, yields uncertain results (*54*), and is less frequently used in clinical practice compared to other diagnostic methods.

The primary serum biomarkers currently used for HCC diagnosis include alpha-fetoprotein (AFP), des-carboxyprothrombin (DCP), and AFP-L3. Numerous additional serum biomarkers for HCC diagnosis are under investigation, such as glypican-3 and adiponectin (*57*), midkine (*58*), and apoptosis inhibitor of macrophages (*59*). Effective monitoring of these serum biomarkers enhances the accuracy of NAFLD-HCC diagnosis, particularly in the absence of imaging.

In conclusion, both imaging techniques and various serum markers play a critical role in diagnosing NAFLD-HCC, particularly when combined to achieve higher sensitivity and specificity. As science and technology advance, additional diagnostic tools, including other serum biomarkers, circulating tumor DNA, genomic glycosylation, and noninvasive saliva biomarkers, show significant potential. However, these methods still require large-scale prospective studies to validate their clinical effectiveness. Moreover, it is crucial to explore more sensitive and specific diagnostic approaches based on the pathogenesis and characteristics of NAFLD-HCC to enable early diagnosis, improve treatment efficacy, and enhance patient prognosis.

5. Treatment of NAFLD-HCC

The pathogenesis of NAFLD-HCC involves multiple pathological processes and remains incompletely understood, contributing to the complexity of its treatment. Managing NAFLD-HCC often requires a multidisciplinary approach, including hepatology, oncology, radiology, and other specialties, to provide combined therapies. Currently, treatment choices for HCC are primarily based on tumor staging, with no significant differences between etiologies (*60*). However, patients with NAFLD-HCC often present with multiple metabolic comorbidities, such as T2DM and cardiovascular disease, which can influence the selection of treatment modalities and impact long-term survival. Therefore, it is crucial to consider the patient's overall condition and tailor treatment options to ensure individualized care.

5.1. Surgical treatment

Surgery remains the most crucial and effective treatment for early-stage liver cancer, primarily including hepatectomy and liver transplantation.

Hepatic resection is the primary curative treatment

for NAFLD-HCC. Patients with BCLC stage 0 and A, as well as CNLC stage IA, IB, and IIA, are prioritized for resection. Additionally, some patients with initially unresectable tumors may become eligible for surgery following conversion therapy (*61*). Retrospective studies have shown no significant differences in 5-year overall survival (OS) and recurrence-free survival (RFS) between NAFLD-HCC patients and those with other etiologies of HCC (Table 1).

Liver transplantation offers a viable treatment option for patients with liver cancer, as it can eliminate both the cancer and underlying liver disease, potentially leading to long-term survival. According to current guidelines, liver transplantation should be considered for patients with HCC who are not candidates for hepatectomy but meet the Milan criteria. These criteria include having either one lesion that is ≥ 2 cm and ≤ 5 cm or up to three lesions, each ≥ 1 cm and ≤ 3 cm, with no evidence of vascular invasion or extrahepatic metastasis (*54*). Many experts argue that the Milan criteria are overly stringent. Recent studies indicate that liver transplantation may be appropriate for certain patients who exceed these criteria or undergo downstaging treatment (*67*), with some patients achieving improved survival outcomes as a result (*68*). Results from the U.S. Multicenter HCC Transplant Consortium indicated no significant difference in the 1-, 3-, and 5-year cumulative incidence of recurrence (3.1%, 9.1%, and 11.5% for NAFLD-HCC *vs* 4.9%, 10.1%, and 12.6% for non-NAFLD-HCC; p = 0.36) and recurrence-free survival (87%, 76%, and 67% *vs* 87%, 75%, and 67%; p = 0.97) between patients with NAFLD-HCC and those with non-NAFLD-HCC (*69*). However, a comprehensive analysis from the European Transplant Registry revealed a lower overall survival rate in NAFLD-HCC compared to HCC associated with alcoholic liver disease (*70*). Numerous studies have explored the long-term prognosis following liver transplantation for NAFLD-HCC (Table 2). Generally, NAFLD-HCC does not significantly affect overall survival compared to HCC from other causes after transplantation (*71*).

5.2. Local treatment

Ablation is a non-surgical treatment modality that utilizes thermal energy to destroy tumor tissue while preserving surrounding healthy liver tissue. It primarily includes radiofrequency ablation (RFA) and microwave ablation (MWA) and is typically applied to patients with BCLC stage 0 or stage A (*60*). In a study involving 520 HCC patients, including 62 with NAFLD-HCC, RFA was identified as an effective treatment modality. There were no significant differences in the 5-year recurrence rate (74% *vs* 77%), overall survival rate (59% *vs* 56%), or recurrence-free survival rate (21% *vs* 18%) between NAFLD-HCC patients and those with other etiologies. Moreover, RFA proved to be both safe and effective for the NAFLD-HCC population (*76*). MWA has been increasingly utilized in the treatment of HCC. Although MWA demonstrates improved efficacy and safety, there is a lack of data regarding the prognosis of NAFLD-HCC patients.

Table 1. Five-year overall survival (OS) and Five-year recurrence-free survival (RFS) in patients with NAFLD-HCC after liver resection

Reference	Patients	Five-year OS.	Five-year RFS.
Koh *et al.* (*62*)	*N* = 996 HCC patients, 844 with non-NAFLD HCC and 152 with NAFLD-HCC	70.1% *vs* 60.9%	45.4% *vs* 40.8%
Jung *et al.* (*63*)	*N* = 426 HCC patients, 32 with NAFLD-HCC, 200 with HBV-HCC, and 194 with HBV/NAFLD-HCC (HBV and NAFLD)	63% *vs* 80%	41% *vs* 55%
Matsumoto *et al.* (*64*)	*N* = 784 HCC patients, 57 with NAFLD-HCC, 727 with virus-related HCC	58.1% *vs* 52.8%	29.6% *vs* 21.3%
Yang *et al.* (*65*)	*N* = 1,483 HCC patients, 96 with NAFLD-HCC and 1,387 with HBV-HCC	51.4% *vs* 55.3%	38.8% *vs* 43.3%
Wakai *et al.* (*66*)	*N* = 225 HCC patients, 17 with NAFLD-HCC, 61 with HBV, and 147 with HCV	59% *vs* 57% *vs* 63%	66% *vs* 39% *vs* 29%

Table 2. Five-year overall survival (OS) and Five-year recurrence rates in patients with NAFLD-HCC after liver transplantation

Reference	Patients	Five-year overall survival.	Five-year recurrence rates.
Rajendran *et al.* (*72*)	*N* = 20,672 HCC patients, 2,071 with NASH-HCC, 18,601 with non-NASH HCC	76.3%	n/a
Lamm *et al.* (*73*)	*N* = 7,461 HCC patients, 1,405 with NASH-HCC, 6,086 with non-NASH HCC	80.71%	5.8%
Holzner *et al.* (*74*)	*N* = 635 HCC patients, 51 with NASH-HCC, 584 with non-NASH HCC	80%	14%
Sadler *et al.* (*75*)	*N* = 929 HCC patients, 60 with NASH-HCC, 869 with non-NASH HCC	80%	13.3%

Transarterial chemoembolization (TACE) is an interventional treatment that involves injecting chemotherapeutic agents directly into a branch of the hepatic artery supplying the tumor and subsequently embolizing that branch, leading to ischemic necrosis of the tumor tissue. Current guidelines recommend TACE as the treatment of choice for patients with BCLC stage B (*51*) and indicate its use in patients with CNLC stage IIB, IIIA, and select IIIB HCC (*77*). While TACE has been extensively studied for HCC treatment, its efficacy and safety in NAFLD-HCC remain less explored. Shamar Young *et al.* conducted TACE on 220 patients, including 30 with NAFLD-HCC, and found that the median OS and treatment-related complications in NAFLD-HCC patients were comparable to those in patients with HCC from other etiologies (*78*). Transarterial radioembolization (TARE) is another intraarterial therapy utilized in Western countries, but its use has not yet become widespread in China. Transarterial radioembolization (TARE) is another intra-arterial therapy utilized in Western countries, but its use has not yet become widespread in China. A retrospective study involving 138 HCC patients treated with TARE, including 30 with NAFLD-HCC, found no significant differences in overall survival and local progression-free survival between NAFLD-HCC and non-NAFLD-HCC patients (*79*).

5.3. Adjuvant therapy

Patients with early-stage NAFLD-HCC can achieve long-term survival following treatments such as hepatectomy or ablation; In one study, the 5-year recurrence rate for NAFLD-HCC patients was approximately 69.6%. Other studies reported a recurrence rate of 44.6% for NAFLD-HCC patients (*80*), However, overall, the recurrence rate remains relatively high. Previous attempts at adjuvant therapy using tyrosine kinase inhibitors yielded unsatisfactory results, failing to significantly enhance recurrence-free survival and overall survival (*81*). However, advancements in systemic therapies and the introduction of immune checkpoint inhibitors (ICIs) are gradually improving the efficacy and safety of adjuvant treatments. The IMbrave050 trial was the first randomized controlled trial to demonstrate positive results, indicating that atilizumab combined with bevacizumab significantly improved recurrence-free survival in patients at high risk of recurrence following hepatectomy or local ablation (*82*). Several ongoing phase III randomized controlled trials are currently underway, notably Keynote-937 (Pembrolizumab), Checkmate-9DX (Nivolumab), EMERALD-2 (Durvalumab +/- bevacizumab), and JUPITER-04 (Toripalimab), among others (*81*). Subsequent studies are anticipated to yield valuable data for the adjuvant treatment of NAFLD-HCC.

5.4. Neoadjuvant therapy

The high recurrence rate of early-stage NAFLD-HCC post-treatment adversely impacts patient prognosis. Adopting neoadjuvant therapy may reduce tumor size, enhance surgical resection rates, eliminate potential micrometastases, and ultimately lower the recurrence rate (*83*). The incorporation of ICIs into neoadjuvant therapy has demonstrated enhanced therapeutic efficacy and safety, a conclusion supported by several trials. A key challenge in neoadjuvant therapy is determining the optimal treatment duration. If the duration is too long, patients may experience lesion progression, immune-related adverse events, and drug toxicity accumulation. Conversely, if the duration is too short, the effectiveness of neoadjuvant therapy may be significantly diminished. Therefore, further studies are needed to establish the optimal treatment duration and identify biomarkers to guide therapeutic decisions (*81,84*). Likewise, neoadjuvant treatment strategies for NAFLD-HCC require further exploration.

5.5. Systemic therapy

Patients with advanced (BCLC stage C) HCC, those ineligible for localized therapy, and early-stage HCC patients who have relapsed or progressed after previous treatments are eligible for systemic therapy (*85*). Due to the limited data on the use of systemic therapy for NAFLD-HCC, treatment approaches in these patients resemble those used for HCC associated with other etiologies. Sorafenib, a multikinase inhibitor and the first systemic treatment for HCC, was found to be more effective in patients with HCV-associated HCC, according to data from the SHARP phase III trial (*86*). Additionally, recent research indicated that patients with NAFLD-HCC had larger tumors and were at a more advanced stage compared to those with other etiology-associated HCC; however, the efficacy of sorafenib was similar in both groups (*87*).

Patients with NAFLD-HCC frequently present with comorbidities such as obesity and T2DM, often resulting in treatment with oral metformin. One study found that HCC patients undergoing long-term metformin treatment experienced worse progression-free survival and overall survival when receiving systemic therapy with sorafenib, compared to HCC patients without T2DM. In contrast, NAFLD-HCC patients treated with insulin demonstrated better responses and longer survival with sorafenib therapy. These results may be attributed to the aggressive nature of tumors induced by long-term metformin treatment and the increased resistance to sorafenib (*88*). However, in patients with NAFLD, metformin reduces body fat accumulation and decreases the risk of progression from NAFLD to HCC.

Recent advances in immunotherapy for HCC have led to the development of more available drugs

for treating advanced NAFLD-HCC, demonstrating improved safety and efficacy. The effectiveness and potential of ICIs in this context have been validated by several clinical trials. Single-agent anti-PD-1/anti-PD-L1 inhibitors show limited efficacy in treating NAFLD-HCC, whereas combination therapies can simultaneously target multiple immune checkpoints, making them the most extensively studied treatment option. The IMbrave150 trial demonstrated that atilizumab in combination with bevacizumab significantly improved overall and progression-free survival compared to sorafenib in patients with advanced NAFLD-HCC who had not received prior systemic therapy; however, 38% of patients experienced severe toxicity (*89*). The phase III HIMALAYA trial demonstrated that the combination therapy of Durvalumab and Tremelimumab resulted in improved overall survival (*90,91*). Both of these regimens have been approved by the FDA as first-line treatment options for patients with advanced HCC. However, the CheckMate 459 phase III randomized clinical trial found that first-line nabulizumab treatment demonstrated better efficacy and safety compared to sorafenib, although it did not significantly improve overall survival in HCC patients (*92*). While it has been demonstrated that the efficacy of immunotherapy diminishes in obese and NAFLD-HCC populations (*93,94*), current research does not allow for the differentiation of therapeutic effects of immunotherapeutic agents across various HCC etiologies.

Current studies suggest that immunotherapy and local therapies (*e.g.*, TACE, ablation, radiation therapy) may exhibit synergistic effects. In a study by Duffy *et al.*, the combination of Tremelimumab and local therapy demonstrated both the feasibility and safety of this approach, as well as improved clinical therapeutic outcomes (*95*). In a study by Zhu *et al.*, the combination of PD-1 inhibitors with TACE demonstrated improved downstaging rates, acceptable survival, and tolerability in patients with intermediate-stage HCC (*96*). Currently, numerous studies are investigating the combination of ICIs with local therapies. This approach is expected to yield more favorable results in the future, and as our understanding of its pathogenesis deepens, treatment options for NAFLD-HCC may become increasingly specialized. However, there is currently a lack of appropriate clinical studies and data on this combination therapy, necessitating further large-scale research in the future.

Overall, the intricate nature of treating NAFLD-HCC demands a comprehensive, multidisciplinary strategy. Surgical resection continues to be the cornerstone of treatment for early-stage NAFLD-HCC patients. Minimally invasive ablation methods, including RFA and MWA, alongside locoregional therapies such as TACE and TARE, provide viable alternatives for patients ineligible for surgery. Nevertheless, given the elevated recurrence rates of NAFLD-HCC, the investigation of adjuvant therapies, particularly immune checkpoint inhibitors, has emerged as a critical research priority. In light of the current paucity of data regarding NAFLD-HCC-specific populations, future research must focus on expanding this knowledge base and refining treatment strategies to deliver more tailored, long-term management plans for affected patients.

6. Prevention of NAFLD-HCC

The development of NAFLD-HCC is primarily linked to metabolic imbalance and fat accumulation. Effective prevention strategies include weight loss and management of related metabolic comorbidities, with lifestyle modifications being the simplest and most feasible approach. According to the practice guidelines from European Association for the Study of the liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity, non-pharmacological treatments — such as adopting a low-calorie, low-fat diet, engaging in moderate physical activity, and achieving weight loss — can reduce liver injury, decrease steatosis, and improve hepatic inflammation and fibrosis (*97*). The safety and therapeutic efficacy of medications like statins, glucagon-like peptide-1 receptor agonists, vitamin E, metformin, and PPAR agonists for managing obesity and T2DM have been supported by various studies (*98*). Therefore, improving metabolic imbalance, reducing body weight, and managing other related comorbidities through these medications are also viable strategies. This pharmacological therapy can help reduce hepatic steatosis, prevent the progression of NAFLD to NAFLD-HCC, and ultimately decrease the incidence of NAFLD-HCC in high-risk populations.

7. Future perspectives

In recent years, as the incidence of HBV and HCV infections has declined, the morbidity and mortality associated with virus-related HCC have also decreased. However, improvements in living standards and the rising prevalence of metabolic diseases such as diabetes mellitus and obesity have contributed to a rapid increase in NAFLD-HCC cases. Several challenges arise in the context of NAFLD-HCC, particularly in prevention efforts aimed at reducing obesity and T2DM prevalence, thereby decreasing NAFLD incidence and preventing its progression to NASH or NAFLD-HCC. Achieving this requires a deeper exploration of the pathogenesis of NAFLD-HCC to uncover its complexities and attain a comprehensive understanding of the condition.

The second challenge involves monitoring high-risk groups for NAFLD-HCC. Early-stage HCC patients tend to have a better prognosis following radical treatment, making early detection of NAFLD-HCC crucial. Achieving this objective requires the development of

more sensitive and specific biomarkers and imaging tests tailored to the pathogenesis and characteristics of NAFLD-HCC, which should be integrated into routine medical examinations to optimize surveillance strategies for NAFLD patients and those at high risk for NAFLD-HCC.

Finally, the treatment of NAFLD-HCC should focus on enhancing the efficacy of treatment modalities while minimizing complications and ensuring safety. While all current treatment options have room for improvement, management should be individualized based on the pathogenesis and characteristics of NAFLD-HCC. Systemic therapy is the recommended approach for unresectable HCC, and further investigation into the development, safety, and therapeutic efficacy of systemic therapies for NAFLD-HCC is necessary. Due to the low representation of NAFLD-HCC patients in completed studies, data on the efficacy and safety of treatment modalities are limited. Therefore, future studies should aim to include a larger proportion of this population to achieve more objective results.

In conclusion, NAFLD-HCC represents a significant challenge; however, our ongoing exploration of its pathogenesis and increasing understanding lead us to believe that future advancements in research will gradually address the issues related to the monitoring and treatment of NAFLD-HCC.

8. Conclusions

In summary, the rising prevalence of NAFLD-HCC presents a significant challenge in the context of improving patient outcomes. The interplay between metabolic imbalances, lifestyle factors, and genetic susceptibility underscores the complexity of NAFLD-HCC pathogenesis. As the understanding of these mechanisms deepens, it becomes increasingly clear that targeted prevention strategies, including lifestyle modifications and early detection methods, are essential in managing high-risk populations.

Moreover, while advancements in immunotherapy and systemic treatments offer new avenues for intervention, the integration of these therapies into clinical practice must be approached with caution. Personalized treatment plans that account for individual metabolic profiles and comorbidities, such as obesity and type 2 diabetes, are critical in optimizing therapeutic outcomes.

Furthermore, the development of sensitive biomarkers and imaging techniques will enhance the monitoring and early detection of NAFLD-HCC, potentially improving prognosis. Despite the current lack of extensive clinical data on effective treatments specifically for NAFLD-HCC, ongoing research and clinical trials are necessary to fill this knowledge gap and refine treatment strategies.

Collectively, addressing the multifaceted challenges of NAFLD-HCC through a comprehensive approach that includes prevention, early detection, individualized treatment, and continued research will be vital in reducing the global burden of this disease and improving patient survival rates.

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