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Review Article

Hepatocellular Carcinoma in Non-alcoholic Fatty Liver Disease: Current Progresses and Challenges

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Abstract

The rising global prevalence of metabolic diseases has increased the prevalence of non-alcoholic fatty liver disease (NAFLD), leading to an increase in cases of NAFLD-related hepatocellular carcinoma (HCC). To provide an updated literature review detailing epidemiology, risk factors, pathogenic pathways, and treatment strategies linked to NAFLD-related HCC, we conducted a literature search on PubMed from its inception to December 31, 2021. About 25% of the global population suffers from NAFLD. The annual incidence of HCC among NAFLD patients is approximately 1.8 per 1,000 person-years. Older age, male sex, metabolic comorbidities, unhealthy lifestyle habits (such as smoking and alcohol consumption), physical inactivity, genetic susceptibility, liver fibrosis, and degree of cirrhosis in NAFLD patients are important risk factors for NAFLD-related HCC. Therefore, low-calorie diet, moderate-intensity exercise, treatment of metabolic comorbidities, and cessation of smoking and alcohol are the main measures to prevent NAFLD-related HCC. In addition, all patients with advanced NAFLD-related fibrosis or cirrhosis should be screened for HCC. Immune suppression disorders and changes in the liver microenvironment may be the main pathogenesis of NAFLD-related HCC. Hepatic resection, liver transplantation, ablation, transarterial chemoembolization, radiotherapy, targeted drugs, and immune checkpoint inhibitors are used to treat NAFLD-related HCC. Lenvatinib treatment may lead to better overall survival, while immune checkpoint inhibitors may lead to worse overall survival. Given the specific risk factors for NAFLD-related HCC, primary prevention is key. Moreover, the same treatment may differ substantially in efficacy against NAFLD-related HCC than against HCC of other etiologies.

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Introduction

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, is prevalent worldwide, especially in Southeast Asia.[1] The main causes of HCC include infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) and chronic alcohol abuse. In the past decade, non-alcoholic fatty liver disease (NAFLD) has emerged in the USA and some European countries as a risk factor for HCC, the incidence of which is increasing.[2,3] Although the prevalence of HCC among patients with NAFLD remains lower than its incidence among patients with chronic HBV or HCV infection, around 25% of the global population has NAFLD, and the prevalence is even higher in high-income areas.[4,5] Thus, the prevalence of NAFLD-related HCC is predicted to increase.[5] This highlights the need to clearly understand the epidemiology, risk factors, pathogenic mechanisms, and effective strategies for preventing and treating NAFLD-related HCC.

Search strategy

PubMed database (https://pubmed.ncbi.nlm.nih.gov/) was systematically searched for publications related to the prevention, screening, and treatment of NAFLD-related HCC, in the presence or absence of non-alcoholic steatohepatitis (NASH). The database was searched from its inception until December 31, 2021. The search terms included "NAFLD" OR "NASH" OR "steatosis" AND "hepatocellular carcinoma". Only research articles and reviews published in English were considered. Studies were screened initially based on titles and abstracts, then retained studies were read in full to determine eligibility. Case reports were excluded. Reference

Keywords: Epidemiology; Hepatocellular carcinoma; Non-alcoholic fatty liver disease; Risk factor; Treatment strategy.

Abbreviations: DFS, disease-free survival; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization.

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lists in relevant literature were searched manually to identify additional studies.

Epidemiology

Several meta-analyses and cohort studies with large samples have shown that 25-30% of the global population suffers from NAFLD, with the highest prevalence in the Middle East and South America, and the lowest in Africa.[6–8] Prevalence of NAFLD has been increasing annually, leading to more frequent NAFLD-related adverse events, including HCC and death. Indeed, the prevalence of NASH, an advanced form of NAFLD, is projected to double by 2030 worldwide.[5]

NAFLD is already the fastest-growing cause of HCC in some developed countries. In 2016, the annual incidence of HCC among NAFLD patients was 1.8 per 1,000 person-years, and the overall mortality was 5.3 per 1,000 person-years.[6,7] The incidence of NAFLD-related HCC varies greatly among NAFLD patients, depending on whether they also have NASH or cirrhosis. Patients with severe fibrosis or cirrhosis are at the highest risk of HCC. For example, the incidence rate of HCC was 0.03 per 100 person-years in patients with NAFLD at a stage earlier than cirrhosis and 3.78 per 100 person-years in patients with cirrhosis.[9] The latter group of patients accounts for 20-50% of HCC cases. Moreover, the incidence of NAFLD-related HCC in patients with non-cirrhotic NAFLD also varies among regions. HCC incidence ranges from 0.1 to 1.3 per 1,000 person-years in patients from the USA and Europe. However, studies from Asia found annual HCC incidences ranges from 0.04% to 0.6%. Interestingly, studies in Asia, USA, and Europe have found that the presence of NASH and fibrosis were associated with a higher HCC incidence in patients with non-cirrhotic NAFLD. In patients with cirrhotic NAFLD, the annual incidence of HCC ranges from 0.7% to 2.6%. Moreover, this data from Asia is consistent with the data from the USA and Europe.[5]

Risk factors for NAFLD-related HCC

Metabolic comorbidities associated with NAFLD include obesity, hyperlipidemia, hypertension, type 2 diabetes, and metabolic syndrome. A relationship between HCC and metabolic diseases such as obesity and type 2 diabetes is well established,[10–14] with diabetes contributing the most to risk of HCC.[14] Metformin treatment and glycemic control significantly reduce the risk of HCC in NAFLD patients with type 2 diabetes.[15] Thus, patients with NAFLD should be screened regularly for diabetes or prediabetes. In addition, the degree of fibrosis is significantly associated with liver-related events and mortality in NAFLD patients,[16] and HCC is more frequent among NAFLD patients with cirrhosis.[17]

Metabolic comorbidities have been strongly associated with older age, lifestyle, and genetic predisposition.[18] For example, the higher body mass index in rural populations is a major cause of the global adult obesity epidemic and a risk factor for NAFLD.[19] Unhealthy lifestyle habits and lack of exercise are common among NAFLD patients.[20] A relationship between lack of exercise and the occurrence of HCC has also been demonstrated.[21] Alcohol consumption is associated with increased mortality in patients with fatty liver disease and metabolic syndrome.[22] Tobacco smoking also increases the risk of NAFLD[23] and the incidence of HCC[24] in the general population. However, we are unaware of studies exploring the relationship between smoking and HCC in NAFLD patients. In addition, there are sex and ethnic differences in the occurrence of NAFLD. Women are at lower risk of NAFLD than men but, once NAFLD is established, women are at a higher risk of severe fibrosis than men, especially after age 50.[25] A meta-analysis found that NAFLD prevalence was highest among Hispanics, but lowest among Blacks in the USA.[26] Occurrence of NAFLD may depend on genetic susceptibility, and appropriate genetic tools may be useful for predicting risk of HCC in patients with NAFLD.[27]

Therefore, older age, male sex, metabolic comorbidities, unhealthy lifestyle habits (such as smoking and alcohol consumption), physical inactivity, genetic susceptibility, liver fibrosis, and degree of cirrhosis in NAFLD patients are important risk factors for NAFLD-related HCC (Fig. 1). Focusing on risk factors that contribute to tumor development will help clarify the mechanisms of HCC and design new prevention and treatment strategies.

Pathogenesis

NAFLD is a metabolic liver disease caused by excessive accumulation of fat in the liver due to diet, metabolism, and other causes. Several metabolic pathways identified by metabolomics and lipidomics have been implicated in NAFLD.[28] Lipotoxicity mediated by free fatty acids and diglycerol can cause insulin resistance and endoplasmic reticulum stress in liver cells, which leads to a chronically inflammatory environment in the liver, resulting in NASH and liver fibrosis which can eventually progress to liver cirrhosis or even HCC.[28] NAFLD is a complex, multifactorial disease, and NASH is a critical first step toward cancer. Although NASH occurs in the context of metabolic alterations, large networks of immune cells are also involved in the evolution of NASH into cirrhosis and HCC.[29] In this way, the intrahepatic microenvironment has a significant impact on the occurrence, development, and prognosis of HCC, and the immune microenvironment of the tumor is closely related to the survival outcome of patients.[30,31] Several groups have investigated the pathogenesis of NAFLD-related HCC, and the mainstream view is that it is related to immune suppression disorders and changes in the liver microenvironment.[30–36] In a mouse model of NASH, $CD8^+$ T cells and natural killer T cells co-promoted the development of HCC.[32] In addition, $CD8^+$ $PD1^+$ T cells in NASH mice can induce hepatocyte cancer transformation by disrupting immune surveillance.[33] Conversely, $CD4^+$ T cells can prevent malignant hepatocyte transformation by restoring immune surveillance.[34] However, the chronic inflammatory environment caused by NAFLD in the liver can inhibit the activation of $CD8^+$ T cells, thus disrupting immune surveillance and promoting the formation of HCC.[35]

The pathogenesis and progression of NAFLD and NAFLD-related HCC are very complex, involving many factors. In addition to disorders of the immune microenvironment and dysregulation of immune surveillance, there are also more and more studies on the pathogenesis of NAFLD-related HCC from the perspectives of gut inflammation and gut dysbiosis, fibrosis caused by chronic inflammation and genetics.[5,12,36–40] Metagenomic and metabolomic studies found that dysregulation is characteristic of the microbiota of patients with NAFLD-related cirrhosis, and the composition and function of the microbiota change with the development of HCC. Moreover, the gut microbiota of NAFLD-related HCC patients has unique microbiome/metabolomic characteristics and modulates peripheral immune responses.[36] In addition, animal experiments have found that dietary cholesterol promotes the formation of NAFLD-related HCC by inducing alteration of gut microbiota and metabolites. Therefore, cholesterol inhibition and gut microbiota regulation may be effective strategies to prevent NAFLD-related HCC.[12] In the field of inflammation, dietary and genetic obesity has been shown to promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression.[38] Moreover, IL-6 leads to activation of signal

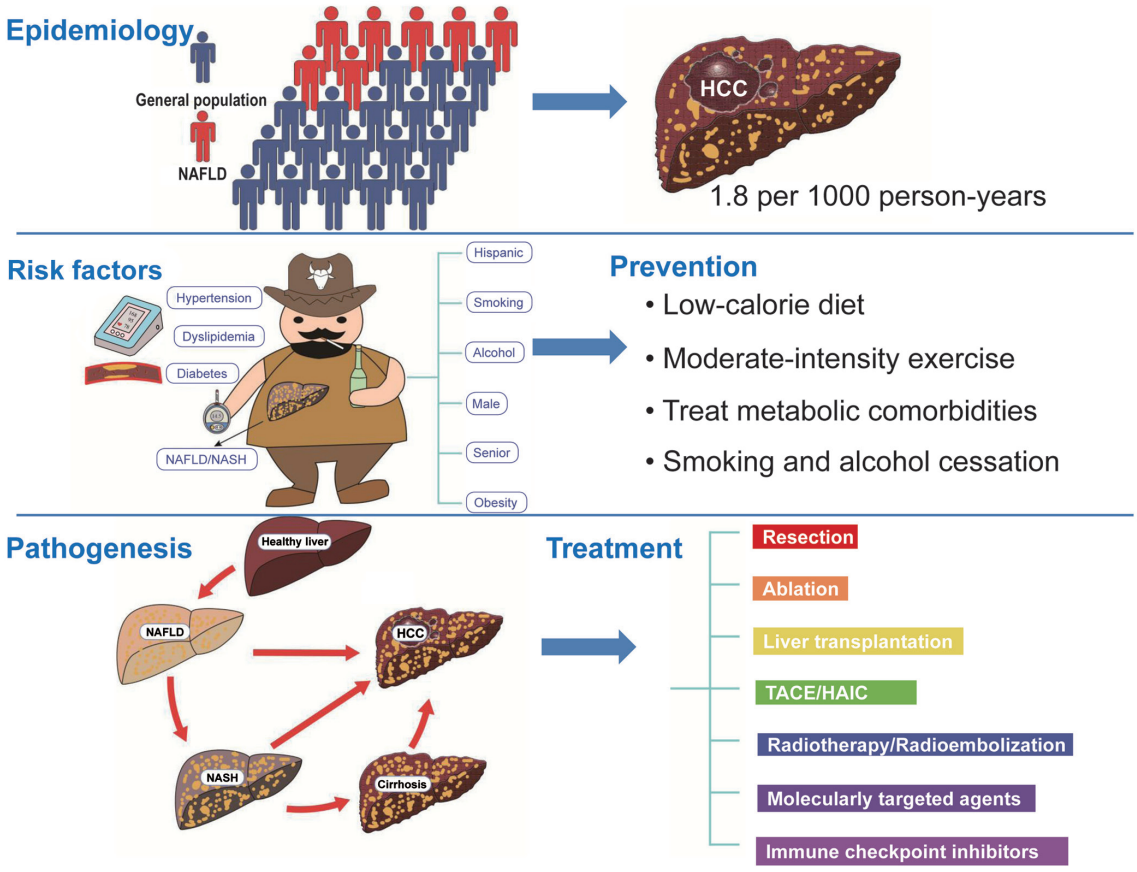

Fig. 1. Epidemiology, risk factors, prevention, pathogenic pathways, and treatment strategies of non-alcoholic fatty liver disease-related HCC. HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TACE, transarterial chemoembolization.

transducer and activator of transcription 3, which stimulates hepatocyte proliferation and malignant transformation.[39] In the field of genetics, many studies found the single nucleotide polymorphism of the patatin-like phospholipase domain-containing 3 (PNPLA3) is associated with an increased risk of advanced fibrosis among patients with a variety of liver diseases and is an independent risk factor for HCC among patients with NASH or alcohol-related cirrhosis.[40] However, further studies are needed to elucidate the mechanisms by which the PNPLA3 mutation contributes to hepatocarcinogenesis. To evaluate the molecular processes underlying hepatocarcinogenesis in this cohort, Pinyol *et al*.[37] collected 80 NASH-related HCC and 125 NASH samples and analyzed the data from expression array and whole exome sequencing. They found NASH-related HCCs display unique molecular features, including higher rates of ACVR2A mutations and the presence of a newly identified mutational signature.

Prevention and surveillance

Due to the popularization of HBV vaccines and growing use of oral antiviral drugs, hepatitis caused by HBV and HCV can be effectively controlled.[41] As a consequence, the prevalence of HBV- or HCV-related HCC is expected to decrease substantially in the future. In contrast, the lack of effective treatments for NAFLD means that the most effective approach is prevention, through alterations in lifestyle and diet. For example, a large multicenter cohort study in Europe suggested a negative association between manual labor and the occurrence of HCC.[42] Another European cohort study found that closer adherence to the Mediterranean diet appears to protect against HCC.[43] Official guidelines about NAFLD recommend the combination of a low-calorie diet and moderate-intensity exercise to keep body weight low.[44–50]

Several cohort studies have suggested that metformin and statins reduce the risk of HCC in patients with type 2 diabetes.[51,52] Aspirin can slow the progression of liver fibrosis in NAFLD patients.[53] Long-term, low-dose aspirin treatment can reduce the risk of HCC in patients with chronic viral hepatitis,[54] and this decrease correlates positively with duration of aspirin use.[55] In principle, medications for NAFLD or NASH, such as liraglutide[56] and namodenoson,[57] should reduce the risk of NAFLD-related HCC, but this remains to be demonstrated in large, multicenter studies with long follow-up.

In terms of HCC surveillance, almost all diagnosis and treatment guidelines recommend that high-risk patients undergo liver ultrasound examination and serum alpha fetoprotein monitoring at least once every six months.[58–62] The onset of HCC is insidious. By the time the disease is discovered, 70% of patients have already reached an intermediate or advanced stage of disease.[63] Therefore, effective monitoring strategies are particularly important, and early diagnosis and treatment can significantly improve prognosis. However, effective monitoring of patients with NAFLD or NASH faces many difficulties. While the prevalence of NAFLD-related HCC is much lower than that of HBV- or HCV-related HCC, the high prevalence of NAFLD translates to

Table 1. Current NAFLD guidelines for the screening, prevention, and diagnosis for HCC among patients with NAFLD

	Asia-Pacific 2017[45]	China 2018[46]	Korean 2021[49]	Japan 2020[48]	EASL 2016[47]	AASLD 2018[44]	AGA 2020[50]
Screening of high-risk subgroups	NASH patients with cirrhosis.	NASH patients with cirrhosis	Patients with cirrhosis due to NAFLD.	Patients with cirrhosis due to NAFLD.	n.d.	Patients with cirrhosis due to NAFLD.	Patients with cirrhosis or advanced liver fibrosis due to NAFLD.
Recommended screening methods	Ultrasound every 6 months.	n.d.	Ultrasound is the primary surveillance test; In overweight or obese patients, CT or MRI can be used instead.	Ultrasound and tumor markers every 6 months.	No recommendation can be currently made on the timing of surveillance and its cost-effectiveness.	Not stated.	Ultrasound; When the quality of ultrasound is suboptimal for screening of HCC (e.g., due to obesity), either CT or MRI should be performed, with or without a-fetoprotein, every 6 months.
Methods to prevent HCC	n.d.	n.d.	Cessation of alcohol drinking and tobacco smoking; Weight loss.	n.d.	Cessation of alcohol drinking in NASH-cirrhosis.	n.d.	Cessation of alcohol drinking and tobacco smoking; Control diabetes, dyslipidemia, and obesity.
Diagnosis criteria of HCC	n.d.	n.d.	Not stated.	n.d.	n.d.	n.d.	Not stated.

AASLD, the American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; CT, computed tomography; EASL, the European Association for the Study of the Liver; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; n.d., not described; MRI, magnetic resonance imaging.

greater costs and effort for generalized screening. In addition, nearly half of patients with NAFLD-related HCC do not develop cirrhosis during disease progression, making monitoring even more challenging.[17] Therefore, effective methods to monitor for NAFLD-related HCC are still lacking.

No NAFLD official guidelines reported the diagnosis criteria of NAFLD-related HCC (Table 1).[44–50] Diagnosis of NAFLD-related HCC is often performed based on clinical symptoms, which explains why the disease is often at an advanced stage when it is diagnosed. Patients with cirrhosis due to NAFLD or NASH are well recognized as high-risk subgroups of HCC in Western and Eastern official guidelines.[44–50] Moreover, patients with advanced liver fibrosis due to NAFLD are also candidates for HCC screening in American Gastroenterological Association guideline.[50] Ultrasound is the primary surveillance test. In overweight or obese patients, either computed tomography or magnetic resonance imaging scan can be used instead.[49,50] Non-enhanced magnetic resonance imaging is a useful diagnostic tool because it is fast, does not require enhanced contrast agent, and offers better specificity and sensitivity than ultrasound.[64] In order to reduce risk of HCC, NAFLD patients should lose weight, control diabetes and dyslipidemia, as well as cease tobacco smoking and drinking alcohol (Table 1).[47,49,50]

Together, these guidelines highlight the need to screen for HCC in all patients with advanced NAFLD-related fibrosis or cirrhosis. They also recommend abstaining from alcohol and smoking, altering one's lifestyle and using appropriate medications in order to optimize the management of diabetes, lipids, and obesity (Fig. 1). Although over 30% of NAFLD-related HCC cases occur in non-cirrhotic NASH patients, the overall risk of HCC occurrence in these patients is relatively low, HCC surveillance is not recommended for non-cirrhotic patients with NAFLD.[44–50]

Treatment

At present, HCC diagnosis and treatment guidelines in various countries and regions recommend different treatment methods depending on tumor stage but not etiology.[58–62] NAFLD-related HCC differs from HCC related to HBV, HCV, or alcohol in terms of pathogenic factors, epidemiology, histological characteristics, tumor stages, and complications. For example, patients with NAFLD-related HCC frequently present some characteristics typical of metabolic syndrome, such as old age, obesity, type 2 diabetes, or cardiovascular complications.[65] These factors are likely to affect the choice of treatment and prognosis of patients. With the increasing prevalence of NAFLD-related HCC, several studies have compared how patients with that or other types of HCC fare after various treatments. These studies, described below, examined outcomes after hepatic resection, local ablation, liver transplantation, transarterial chemoembolization (TACE), radiotherapy, targeted drugs, immunotherapy, and/or postoperative adjuvant therapy (Table 2, Fig. 1). [66–78]

Hepatic resection and local ablation

Hepatic resection is the most important curative treatment for early-stage HCC, and even some patients with intermediate, advanced or recurrent disease can benefit from it.[79–82] Several recent retrospective studies have compared outcomes after hepatic resection to treat NAFLD-related HCC or HCC of other etiologies. Some studies suggested that patients with NAFLD-related HCC had longer survival,[83,84] while others found similar overall survival among patients with HCC of different etiologies.[85,86] Two recently published

Table 2. Comparison of treatment strategies and outcomes in patients with HCC related to NAFLD or other etiologies

Treatment strategy	Studies and patients included	Treatment outcomes	Treatment safety in patients with NAFLD-related HCC
Hepatic resection	One meta-analysis included 15 cohort studies with 7,226 patients;[66] another included 9 cohort studies with 5,579 patients[67]	Better DFS and OS[66,67]	Higher rates of peri- and postoperative complications[67]
Radiofrequency ablation	Two retrospective study with 528[68] or 520 patients[69]	Similar OS	Similar postoperative morbidity[69]
Liver transplantation	One meta-analysis included 9 cohort studies with 717 patients with NASH and 3,520 without[70]	Similar OS	Lower risk of graft failure, but more likely to die from cardiovascular complications or sepsis
Transarterial chemoembolization	One retrospective study with 30 patients with NASH and 190 without[71]	Similar OS	Similar number of complications
Radiotherapy	n.d.	n.d.	n.d.
Radioembolization with yttrium-90	One retrospective study with 87 patients with NAFLD and 67 with HBV[72]	Similar OS	Similar treatment-related toxicity
Tyrosine kinase inhibitors			
Sorafenib	Two retrospective studies with 5,201[73] or 180 patients[74]	Similar OS[73,74]	Similar rate of adverse events[73]
Lenvatinib	Two retrospective studies with 1,232[76] and 530 patients[75]	Better PFS[75,76] and OS[76]	Similar rate of grade 3/4 adverse events;[76] more frequent hypothyroidism and urine protein conditions[75]
Immune checkpoint inhibitors	One meta-analysis included 3 randomized trials with 1,657 patients and three independent cohorts of 358 patients[77,78]	Worse OS[77]	n.d.
Adjuvant therapy	n.d.	n.d.	n.d.

DFS, disease-free survival; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; n.d., not described; NAFLD, non-alcoholic fatty liver disease; OS, overall survival; PFS, progression-free survival.

meta-analyses concluded that patients with NAFLD-related HCC had better overall and disease-free survival after hepatic resection than patients with HCC of other etiologies.[66,67] However, serious perioperative complications were significantly more common among patients with NAFLD-related HCC (33.3%) than among those with HBV-related HCC (15.7%).[87] Two studies also suggested higher perioperative complications and mortality among patients with NAFLD-related HCC than among those with HCC of other etiologies.[88,89] Therefore, although hepatic resection may be associated with good overall and disease-free survival of patients with NAFLD-related HCC in the long term, such patients should be carefully evaluated preoperatively to check for cardiovascular complications or metabolic diseases and to reduce perioperative complications and mortality.

The indications for local ablation of HCC are stricter than those for hepatic resection, but the requirements for liver function are relatively low (Child-Pugh A or B). A retrospective analysis based on the USA's Surveillance, Epidemiology, and End Results database showed that the overall survival rate after radiofrequency ablation was similar for patients with NAFLD-related HCC as for patients with HCC of other etiologies.[68] Another multicenter retrospective cohort in France found patients with NAFLD-related HCC were significantly older, more obese and had more components of metabolic syndrome. However, there were no differences in morbidity, tumor recurrence and overall survival among patients with NAFLD-related HCC vs other aetiologies.[69] Therefore, radiofrequency ablation has achieved similar long-term oncological outcomes in NAFLD-related HCC compared to other etiologies. However, more studies are needed to confirm these findings.

Liver transplantation

In 2013, NASH was the second main cause of inclusion in the liver transplant waiting list, after HCV infection.[90,91] Compared to the USA's situation,[90,92] HCC prevalence may be higher among European patients who receive liver transplants because of NASH, and the overall survival and transplant survival among these patients are similar to those among patients who receive liver transplants for other reasons.[91] NASH has been identified as an independent risk factor for early death after liver transplantation.[93]

Diabetes compromises the prognosis of liver transplantation patients, and diabetes combined with obesity further degrades it, especially in the presence of HCC.[91,94] Therefore, obese HCC patients are at significantly higher risk of perioperative life-threatening complications related to liver transplantation. Patients with NAFLD-related HCC are generally older and obese, and they have cardiovascular and cerebrovascular problems, which complicate liver transplantation and make such patients less likely to receive the transplant. In one study of 1,208 liver transplant recipients, the overall survival rate was lower for patients with NAFLD-related HCC than for those with HCC of other etiologies.[68] Three retrospective studies found that overall survival after liver transplantation was similar between patients with

NAFLD-related HCC and patients with HCC of other etiologies.[90,91,95] A meta-analysis of nine studies involving 717 patients with NASH and 3,520 patients without NASH found no differences in their overall survival at 1, 3, or 5 years after liver transplantation.[70] That meta-analysis concluded that NASH patients are at lower risk of transplant failure than non-NASH patients but at higher risk of post-transplant death from cardiovascular complications or septicemia. The higher incidence of postoperative complications in NASH patients may reflect erythrocyte hyperaggregation and hyperfibrinogen due to metabolic syndrome, which may create a prethrombotic state and predispose the patient to thromboembolism and atherosclerotic thrombotic events.[96]

In conclusion, the most frequent causes of death after liver transplantation in patients with NAFLD-related HCC are tumor recurrence, extrahepatic metastasis, infection, as well as cardiovascular and cerebrovascular complications. Nevertheless, these patients show similar long-term post-transplant survival as patients with HCC of other etiologies. Improving our understanding and management of metabolic risk factors may reduce perioperative risks associated with liver transplantation in patients with NAFLD-related HCC. As NAFLD prevalence increases worldwide, so too does the number of steatosis allografts. Such grafts show worse function and shorter time to failure,[97] and effective tools to quantify the extent of steatosis are needed.

TACE and radiotherapy

TACE is the standard treatment for intermediate stage HCC according to European and USA guidelines.[58,59,62] In the Chinese HCC guidelines, TACE can be used for patients in stages Ib to IIIb.[60] A retrospective study found no difference in time to disease progression, overall survival, or complications after TACE between 30 patients with NASH-related HCC and 190 patients with HCC without NASH.[71] A small retrospective study found that body mass index >25 kg/m^2 was associated with lower rate of tumor control and greater risk of progression after TACE.[98]

Although European and USA guidelines on HCC mention radiotherapy, they do not explicitly recommend it at any stage of the disease.[58,59,62] The Chinese guidelines, in contrast, recommend radiotherapy for stages IIIa and IIIb.[60] Although evidence seems to be growing that external radiation therapy can benefit patients with HCC,[99,100] data are lacking on NAFLD-related HCC. A retrospective study found no difference in overall survival or radiation injury between 87 patients with NAFLD-related HCC or 62 with HBV-related HCC after yttrium-90 radioembolization.[72] Larger studies are needed in order to draw reliable conclusions about the efficacy and safety of TACE or radiotherapy for NAFLD-related HCC.

Systemic therapy

Systemic treatments for HCC include mainly molecularly targeted drugs and immune checkpoint inhibitors (ICIs).[41,101,102] HCC guidelines recommend these therapies for patients with advanced HCC whose Eastern Cooperative Oncology Group (ECOG) score is 0-1 and whose liver function is Child-Pugh grade A or B.[58–62]

Many phase III clinical trials of molecularly targeted agents as first- or second-line therapies against advanced HCC have been reported,[102,103] but patients in these trials have not been stratified by NAFLD or NASH status. An international multicenter cohort study showed that sorafenib treatment was associated with similar overall survival (p=0.57) and adverse events between 183 patients with NAFLD-related HCC and 5,018 patients with HCC of other etiologies.[73] Another retrospective study also found that sorafenib was associated with similar median overall survival between 37 patients with NAFLD-related HCC (23.4 months) and 143 patients with other types of HCC (27.0 months) (p=0.17).[74]

Lenvatinib is a standard targeted therapy for advanced HCC.[104] A multicenter retrospective study from Japan found that median progression-free survival was longer among 103 patients with NAFLD- or NASH-related HCC than among 427 patients with viral- or alcohol-related HCC (9.3 vs. 7.5 months, p=0.012).[75] Nevertheless, median overall survival was similar between the two groups (20.5 vs. 16.9 months, p=0.057), which was confirmed in multivariate analysis. Another retrospective study from Japan found better outcomes for patients with alcohol- or NASH-related HCC (n=22) than for patients with HBV- or HCV-related HCC (n=45) in terms of objective response rate (59.1% vs. 46.7%), median progression-free survival (13.7 vs. 6.6 months, p<0.01), and median overall survival ("not reached" vs. 15.9 months, p<0.01).[105] In an international multicenter retrospective study of 1,232 patients with advanced HCC, those who also had NASH showed significantly higher overall and progression-free survival than patients with HCV or HBV infection or other etiologies after first-line treatment with lenvatinib.[76] A retrospective study in the USA showed 12-month progression-free survival rates of 64.9% for 233 patients with total advanced HCC after first-line lenvatinib therapy, compared to 43.0% for the subset of 32 patients who also had NASH.[106,107] The corresponding 12-month overall survival rates were 72.6% and 66.0%. More studies are needed to confirm the efficacy of molecularly targeted drugs against NAFLD- or NASH-related HCC.

A number of recent prospective and retrospective studies have reported the safety and efficacy of ICIs alone or in combination with such molecularly targeted agents as first- or second-line treatments against advanced HCC.[102,103,108] However, these studies did not perform subgroup analyses based on NAFLD or NASH status. Recently, a meta-analysis[105] of the randomized controlled trials CheckMate 459,[109] IMbrave150,[110] and KEYNOTE-240[111] found that ICI treatment was effective against virus-related HCC but ineffective against HCC unrelated to viral infection. Consistently, three studies found significantly better overall survival after ICI therapy among patients with HCC unrelated to NAFLD than among those with NAFLD-related HCC.[77,78] In animal studies, ICI treatment failed to slow tumor progression in a mouse model of NAFLD-related HCC,[77] while it did slow the progression of HCC in non-NASH mice.[112] Therefore, current ICI therapies may not benefit patients with NAFLD-related HCC, which should be explored in future studies.

The combination of molecularly targeted drugs and ICI is associated with higher objective response rate and longer overall survival for patients with advanced HCC than either treatment alone.[103,108,110] Compared to patients with HCC of other etiologies, those with NAFLD-related HCC may have better overall survival after lenvatinib treatment but worse overall survival after ICI treatment (Table 2). Future studies should investigate the efficacy of lenvatinib plus ICI against NAFLD-related HCC.

Adjuvant therapy

Hepatic resection, liver transplantation, and ablation are the curative treatment options for HCC, but the postoperative recurrence rate can exceed 50%.[58–62] European and USA HCC guidelines do not recommend any adjuvant therapy,[58,59,62] whereas Chinese and South Korean HCC guidelines recommend TACE and adoptive immunotherapy.[60,61] Given the

growing evidence for ICI efficacy against advanced HCC, several ongoing phase III clinical trials are exploring the efficacy of adjuvant ICI monotherapy or combination therapy in patients at high risk of recurrence. For example, the Imbrave-050 trial will compare recurrence-free survival after adjuvant atezolizumab plus bevacizumab or rigorous monitoring.[113] The CHECKMATE-9DX trial will compare recurrence-free survival after adjuvant nivolumab or placebo.[114] The EMERALD-2 trial will compare recurrence-free survival after adjuvant treatment with durvalumab alone, devarumab combined with bevacizumab, or placebo.[115] Patients at high risk of recurrence will be included in all three trials. We look forward to the results of these trials to provide guidance about treatment options after surgery. In addition, these trials should allow subgroup analysis based on HCC etiology, providing options for the adjuvant treatment of NAFLD-related HCC.

Future prospects

With the spread of metabolic syndrome around the world, NAFLD has become the main cause of chronic liver disease worldwide, and it will soon become the main cause of HCC. Clinical characteristics typical of metabolic syndrome, such as old age, obesity, type 2 diabetes, or cardiovascular complications may increase the risk of NAFLD-related HCC. NAFLD can directly progress to HCC without fibrosis or cirrhosis, and since patients are not routinely screened for NAFLD, HCC is frequently diagnosed at an advanced stage, resulting in worse long-term survival. Third, metabolic syndrome concomitant with HCC may limit therapeutic options, such as eliminating the possibility of liver transplantation or increasing risk of cardiovascular complications after surgery. Finally, although many studies have examined the metabolomics and lipidomics of NAFLD and NASH,[28] specific molecular characteristics and diagnostic markers remain elusive.

Principles behind the diagnosis and treatment of NAFLD-related HCC are similar to those for HCC of other etiologies. Primary prevention is key. Lifestyle changes and drugs such as metformin, statins, and aspirin have been suggested as primary preventive strategies.[116] Secondary prevention will become more effective as drugs to treat NAFLD become available.[117] Attention should also be paid to tertiary prevention in the form of NAFLD prevention as well as early detection and timely, individualized treatment of NAFLD-related HCC.

If NAFLD-related HCC can be detected at an early stage, more patients will have the opportunity to receive curative treatment that improves long-term outcomes. Screening for HCC is the most important step to improve secondary prevention, but only if patients at high risk are identified. At present, HCC guidelines[58–62] include patients with cirrhosis as the focus group for monitoring. NAFLD guidelines recommend routine screening only for NAFLD or NASH patients with advanced liver fibrosis or cirrhosis.[48–50] However, in the absence of cirrhosis, NAFLD or NASH is the primary cause of HCC, so even NAFLD or NASH patients without cirrhosis should be monitored as well. One of the greatest clinical challenges in NAFLD screening is determining whether patients with pre-cirrhotic NAFLD are at sufficiently high risk of developing HCC to justify screening for it. Establishing a model to predict risk of HCC in the presence of NAFLD may allow differentiated patient management that could greatly reduce medical costs.[118–121] For example, a scoring system developed in Taiwan can stratify the general population, identifying patients at high risk of HCC and thereby reducing healthcare costs.[122] Other risk prediction models based on non-invasive clinical characteristics can accurately predict the risk of HCC in HBV-infected patients.[123,124]

Individualized treatment is also important. Not all treatments are suitable for all patients with NAFLD-related HCC, so comorbidities of NAFLD patients should be taken into account. Certain biological markers may help guide the choice of treatment for patients with NAFLD-related HCC. For example, markers could identify which patients would benefit most from molecularly targeted drugs and ICI therapy, reducing ineffective treatment costs and unnecessary risk of complications. For example, a multicenter retrospective study found that levels of C-reactive protein and alpha-fetoprotein could accurately predict overall survival and tumor response to ICI therapy in patients with advanced HCC.[125]

The above problems and challenges in the prevention, screening, diagnosis, and treatment of NAFLD/NASH provide a direction for basic and clinical research. Continuous research and clinical efforts can help improve diagnosis, treatment, and management of NAFLD-related HCC in the near future.

Conclusions

As the prevalence of NAFLD/NASH and NAFLD-related HCC increases worldwide, more attention and research need to focus on these patients. Currently, there is no treatment strategy specific for NAFLD-related HCC. Thus, prevention is a top priority, which can involve public health measures and efforts to improve NAFLD screening tools, establish models for predicting HCC among patients with NAFLD, and induce lifestyle changes that reduce metabolic risk factors. Advanced tumor stage, old age, obesity, and comorbidities limit the use of some HCC therapies, such as hepatectomy and transplantation. Because NAFLD patients are at greater risk of perioperative complications, careful preoperative evaluation is required. The use of local ablation, radiotherapy, and TACE in NAFLD-related HCC has not been well investigated, and more studies are needed to evaluate these strategies. The efficacy of different therapies can depend on HCC etiology; for example, ICI appears to work better against HBV- or HCV-related HCC than against NAFLD-related HCC. However, this and related findings need to be verified carefully in light of the substantial number of cases of NAFLD and NASH that go undiagnosed, such that the HCC in such patients is misattributed to other etiologies. Finally, etiological stratification and/or efficacy prediction using biomarkers may significantly improve patient outcomes. Raising awareness of the burden of NAFLD and implementing screening programs are the main goals pursued by health authorities around the world, with the common objective of improving the prognosis of patients with NAFLD-related HCC.

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Conflict of interest

JHZ has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2020. The other authors have no conflict of interests related to this publication.

Author contributions

Conception of the study (JHZ), acquirement and analyzation of the data, drafting and revision of the manuscript, and approving the final version to be published (All Authors).

Data sharing statement

All data used in this study can be obtained from the cited literature.

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