

Hepatocellular Carcinoma Due to Nonalcoholic Fatty Liver Disease: Current Concepts and Future Challenges

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Abstract: Obesity has been labeled as the global pandemic of the 21st century, resulting from a sedentary lifestyle and caloric excess. Nonalcoholic fatty liver disease (NAFLD), characterized by excessive hepatic steatosis, is strongly associated with obesity and metabolic syndrome and is estimated to be present in one-quarter of the world population, making it the most common cause of the chronic liver disease (CLD). NAFLD spectrum varies from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis. The burden of NAFLD has been predicted to increase in the coming decades resulting in increased rates of decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver-related deaths. In the current review, we describe the pathophysiology of NAFLD and NASH, risk factors associated with disease progression, related complications, and mortality. Later, we have discussed the changing epidemiology of HCC, with NAFLD emerging as the most common cause of CLD and HCC. We have also addressed the risk factors of HCC development in the NAFLD population (including demographic, metabolic, genetic, dietary, and lifestyle factors), presentation of NAFLD-associated HCC, its prognosis, and the issue of HCC development in non-cirrhotic NAFLD. Lastly, the problems related to HCC screening in the NAFLD population, the remaining challenges, and future directions, especially the need to identify the high-risk individuals, will be discussed. We will conclude the review by summarizing the clinical evidence for treating fibrosis and preventing HCC in those at risk with NAFLD-associated HCC.

Keywords: nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, hepatocellular carcinoma, metabolic syndrome, HCC screening

Introduction

The World Health Organization estimates that 39% of adults are overweight, while 13% are obese.¹ The burden of obesity and associated comorbidities is expected to rise in the coming decades, especially since 40 million children were estimated to be overweight or obese in 2018.^{1,2} Obesity is a known risk factor for cardiovascular diseases.^{3,4} It is closely associated with metabolic complications, including diabetes mellitus (DM), hyperlipidemia (HLD), and nonalcoholic fatty liver disease (NAFLD).⁵ High body mass index (BMI) is associated with an increased risk of different types of cancers, including liver and colon cancer.^{6,7} More frightening is the fact that obesity doubles the mortality risk in patients with liver cancer.⁸

NAFLD is the most common cause of chronic liver disease (CLD). It is characterized by hepatic steatosis (HS) either by imaging or histology without secondary causes of hepatic fat accumulation, such as excessive alcohol consumption (daily ≥ 30 g for men and ≥ 20 g for women), medications, or other chronic liver diseases.^{9,10} NAFLD includes two pathologically distinct conditions: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFL is

defined as the presence of $\geq 5\%$ HS without evidence of hepatocellular injury in the form of hepatocyte ballooning. NASH is characterized by steatosis with inflammation and hepatocyte ballooning with or without liver fibrosis.¹¹

Recently, it has been recommended to rename NAFLD as Metabolic dysfunction-associated fatty liver disease (MAFLD). This new definition has been proposed to better encapsulate the spectrum of fatty liver disease. MAFLD diagnosis is based on hepatic steatosis (based on histological, imaging, or blood biomarker) and one of the following three conditions: type 2 diabetes mellitus, overweight/obesity, or metabolic dysregulation.¹² However, this manuscript will be limited to the prior definition of NAFLD rather than the entire umbrella of MAFLD disease.

NAFLD is often labeled as the liver manifestation of metabolic syndrome and is strongly associated with obesity, type 2 diabetes mellitus (T2DM), HLD, and hypertension (HTN).¹³ There has been a significant rise in NAFLD prevalence in the last two decades. This trend mirrors a similar uptrend in the prevalence of obesity and diabetes and is thought to result from the sedentary lifestyle and changing dietary patterns.^{13,14} Insulin resistance is an essential component in the underlying pathophysiology of NAFLD. Expectedly, the prevalence of NAFLD has increased by three folds in patients with metabolic syndrome.^{14,15} Globally, the prevalence of NAFLD is estimated to be 25.24% (95% CI: 22.10–28.65), with the highest prevalence in the Middle East and South America and the lowest in Africa.¹⁴ A recent meta-analysis has put the burden of NAFLD may be even higher in Asia, with a prevalence of 30%.¹⁶ Modelling studies have indicated that the burden of NAFLD will continue to rise in the future.^{17,18} As the growing population of NAFLD patients ages, they will develop further complications associated with the disease. This will likely result in higher rates of decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver-related deaths.¹⁷

Pathophysiology and Disease Progression in NAFLD

The original “two-hit” hypothesis proposed to explain the pathophysiology of steatohepatitis was perhaps an oversimplification of the process.¹⁹ It stated that steatosis was the first hit, which sensitized the liver, followed by the “second hit” of oxidative stress leading to necro-inflammation resulting in NASH.¹⁹ However, it is now believed that multiple factors are involved in fatty liver disease pathogenesis. A range of environmental factors, including but not limited to diet, lifestyle, insulin resistance, and dysbiosis of gut microbiota acting in a genetically or epigenetically susceptible host, modify the responses to caloric excess.^{20,21} Insulin resistance and hyperinsulinemia are central in this pathogenesis, leading to fatty acid accumulation. This accumulation may result in lipotoxicity and inflammation, causing cell damage and subsequent activation of progenitor cells resulting in fibrosis and disease progression.^{2,22}

Not all patients with NAFLD are at an equal risk of developing complications. One study reported that 2.4–12.8% of patients with NAFLD would experience disease progression or liver-related mortality ranging over three to seven years follow-up.²³ It is thus of paramount importance to identify patients who are at higher risk of developing these complications. Both NAFL and NASH can progress to advanced liver fibrosis.^{24–27} In one meta-analysis of 411 patients with biopsy-proven NAFL or NASH, 43% had stable disease, one-third had fibrosis progression, and 22% had disease improvement. The rate of fibrosis progression in NASH patients was double that of the patients with NAFL.²⁵ Currently, it is not clear which NAFLD patients are likely to progress and develop advanced liver disease. However, patients presenting with lobular inflammation or hepatic fibrosis at the time of diagnosis are at higher risk of disease progression than those presenting with steatosis alone.²⁴ Increasing age and uncontrolled metabolic risk factors are also associated with NAFLD disease progression.²⁴

McPherson et al studied 108 patients (81 with NASH and 27 with NAFL) using paired liver biopsies. They found out that there was no difference in the proportion of patients exhibiting fibrosis progression between the two groups.²⁷ A recent meta-analysis demonstrated that among NAFLD patients, the stage of liver fibrosis is a strong predictor of all-cause mortality and morbidity. Compared with no fibrosis, incremental rise in fibrosis stages was associated with a five to twelve-fold increased risk of death and liver-related events, including liver failure, HCC and, need for transplantation.²⁸ This meta-analysis did not suggest any differential risk between NAFL and NASH patients, as the risk of mortality and morbidity associated with increasing fibrosis stage appeared similar in both the groups.²⁸

However, this topic remains debatable as the differential diagnosis of NAFLD and NASH is a well-recognized clinical practice controversy.²⁹ It is possible that some NASH patients may be wrongly labeled as non-NASH patients, as liver biopsy captures the snapshot of the clinical spectrum of NAFLD patients at only one point in time. Also, patients with advanced fibrosis may have lost some active NASH features when, in fact, NASH was the original causative factor of fibrosis.²⁸

Our understanding of risk factors that promote fibrosis progression in NAFLD patients is still evolving. The presence of metabolic traits, such as DM, HTN, HLD, and obesity, have been associated with the risk of progression to cirrhosis³⁰ and mortality.³¹ DM confers the most significant risk of fibrosis progression.^{30,32} Regardless of the driving mechanisms, fibrosis in NAFLD patients is associated with future disease progression. The degree of fibrosis is associated with increased liver-specific and all-cause mortality, independent of any other histopathological feature.^{33–37}

HCC and NAFLD

Changing Epidemiology of HCC

Liver cancer is the fifth most common diagnosed cancer and the fourth leading cause of worldwide cancer deaths in 2018. Hepatocellular carcinoma (HCC) is the most common primary liver cancer comprising of 75%–85% of cases.^{38,39} There were 841,000 new cases reported in 2018, and it accounted for 782,000 deaths annually.³⁸ Liver cancer has a male predominance with a mortality rate two to three times higher in men than women.^{38,40,41} When assessing the underlying etiology of liver disease in patients with HCC, women were more likely to have NASH cirrhosis compared to men. Women also tend to present more often with non-cirrhotic HCC than men and have less advanced disease at presentation with greater overall survival.⁴² HCC remains the second leading cause of cancer-related deaths in men. Globally, incident cases of liver cancer increased by 114.0% from 471,000 in 1990 to 1,007,800 in 2016. The overall age-standardized incidence rate increased by an average of 0.34% (95% CI 0.22%–0.45%) per year in this period.⁴³ There is a considerable variation in the prevalence of HCC across the globe due to the difference in causative etiologies. A higher prevalence of HCC was observed in China, South East Asia, and sub-Saharan Africa, mirroring the prevalence of chronic hepatitis B virus infection in these regions. On the other hand, Japan, Italy, and France have a high prevalence of HCC because of the high prevalence of hepatitis C virus (HCV) infection.⁴⁴ According to the global HCC BRIDGE study between 2005 and 2012, the most common risk factor for HCC was hepatitis C virus in North America, Europe, and Japan, while hepatitis B virus (HBV) accounted for the majority of cases in China, South Korea, and Taiwan.⁴⁵

In recent years, there has been a change in the epidemiology of HCC. Recent innovations in antiviral therapies and successful implementation of vaccination have led to better control of HBV and HCV, in turn leading to a drop in incidence of HCC associated with these viruses in some regions around the world as highlighted in the Global Burden of Disease study; however, the study also noted an unfavorable overall uptrend in the incidence of HCC, including in countries with a high socio-demographic index like the Netherlands, the UK, and the USA.⁴³

In the last decade, growing evidence has supported a trend toward NASH overtaking viral hepatitis as the leading cause of HCC in western countries.^{46–50} NASH is the second leading etiology of HCC leading to liver transplant in the US between 2002 and 2012,⁴² and the most rapidly growing indication of liver transplant in patients with HCC.^{46,47} NASH-related HCC increased from 8.3% in 2002 to 10.3% in 2007 and further rose to 13.5% in 2012. In the same periods, transplantation for HCC due to NASH increased fourfolds.⁴⁶ NAFLD/NASH was reported to be the most common underlying etiologic risk factor (59%) for HCC development, followed by DM and HCV in another study.⁴⁸ Recently, a study of 13,648 Medicare patients with HCC reported that while the overall incidence of HCC is increasing, mortality rates are declining. NAFLD remains the most important cause and an independent predictor of HCC in this patient cohort.⁴⁹ Younossi et al corroborated similar findings in a study in which adult liver transplant candidates were included between 2002 and 2016. The proportion of NASH-related HCC cases increased 7.7-fold from 2.1% to 16.2%, and the prevalence of HCC in liver transplant (LT) candidates with NASH increased by 11.8-fold.⁴⁷ Similar findings of an increase in the proportion of NASH related liver transplant and decline in HCV-related patients requiring transplant have been reported by Goldberg et al and in the analysis from the national Organ Procurement and Transplant Network (OPTN).^{50,51}

Incidence of HCC in NAFLD

As previously discussed, the incidence and prevalence of NAFLD are increasing worldwide. In the largest meta-analysis of 8.5 million NAFLD patients, the annual incidence of HCC in NAFLD patients was 0.44 per 1000 person-years,¹⁴ much less than the incidence of HCC in chronic HBV infection.⁵² In the same meta-analysis, the incidence rate for HCC in NASH patients was significant at 5.29 cases per 1000 person-years.¹⁴ Ascha et al compared the incidence of HCC

development in cirrhotic patients secondary to HCV or NASH. They noted that 12.8% of NASH cirrhotic and 20.3% of HCV-cirrhotic patients developed HCC over a median follow-up of 3.2 years.⁵³ Yearly cumulative incidence of HCC was found to be 2.6% in patients with NASH-cirrhosis, compared with 4.0% in patients with HCV cirrhosis.⁵³ Although the incidence of HCC development is lower in NASH patients, the overall burden of NAFLD and NASH patients would suggest that the absolute number of patients developing NAFLD-related HCC will continue to increase in the future.

Kanwal et al reported that the incidence of HCC in NAFLD patients was 0.21/1000 patient-years (PY), with patients having cirrhosis at the highest risk of 10.6/1000 PY. However, 20% of patients with NAFLD who developed HCC had no evidence of cirrhosis.⁵⁴ A large cross-sectional study from Europe recently showed that patients with NASH are 60% more likely to develop HCC than patients without NASH after adjusting for other associated factors.⁵⁵ In Asian patients with biopsy-proven NAFLD, liver-specific mortality was 2.34/1000 PY, and HCC incidence was 4.17/1000 PY. Liver fibrosis was the most significant predictor of liver-related but not overall mortality.⁵⁶

Overall, the incidence and prevalence of NAFLD are increasing, and in the last three decades, NAFLD and alcohol-related liver disease are the two liver diseases with a growing prevalence. This is synchronous with the increasing rates of obesity and T2DM.⁵⁷ These rising rates of obesity, DM, and metabolic syndrome contribute to ever-increasing numbers of NAFLD-related HCC.⁵⁸ Although the relative risk of HCC associated with obesity, DM, and metabolic syndrome is not as high as the risk associated with HBV or HCV, the higher prevalence of these conditions account for higher population attributable fractions (PAF), with 36.6% for obesity and DM versus 22.4% for HCV and 6.3% for HBV.^{59,60} Table 1 summarizes incidence, trend and risk factors of HCC among NAFLD/NASH patients in few selected studies.

HCC in Cryptogenic Cirrhosis

It is also important to mention that previously classified cryptogenic cirrhosis cases are now more and more recognized as “Burnt-out” NASH or advanced stage of NASH.²⁶ Hence, the incidence of NAFLD-related HCC tends to be underquoted previously either because of misdiagnosis as cryptogenic cirrhosis or metabolic syndrome remaining under quantified in some regions of the world.⁶¹ A majority of patients with cryptogenic cirrhosis share many similarities with NASH, where both groups were strongly associated with DM and obesity.^{62–65} It has been reported that likely more than half of the patients with cryptogenic cirrhosis had prior histological or clinical features associated with NAFLD.⁶² Also, an increase of visceral fat area in cryptogenic HCC patients and the negative correlation with liver–spleen density ratio measurements also support the idea that cryptogenic cirrhosis is burnt-out NAFLD in which visceral fat remains but liver fat is depleted.⁶³ Further clarification of this diagnosis is needed in the future to estimate the true incidence of HCC in patients with NAFLD.

HCC in Non-Cirrhotic NAFLD

Cirrhosis remains the most important cause for the development of HCC, but in NAFLD patients, HCC can develop even in the absence of cirrhosis. Several studies have shown that up to 50% of patients with NAFLD-related HCC had no clinical or histological evidence of cirrhosis.^{66–72} A multicenter prospective study from Italy showed that 50% of NAFLD-related HCC patients had no evidence of cirrhosis. After adjusting for confounders, the survival rate of NAFLD-related HCC patients was similar to HCV-related HCC patients.⁶⁶ Ertle et al reported that among 162 patients with HCC, patients with NAFLD/NASH-related HCC exhibited a higher prevalence of metabolic features, and 41% had no features of cirrhosis.⁶⁷ Similarly, another study found out that NAFLD risk factors are present in most patients with HCC in the non-cirrhotic liver.⁷³ Alexander et al described the association of hepatic steatosis with the development of HCC in non-cirrhotic liver.⁷⁴ The presence of NAFLD and components of metabolic syndrome, particularly obesity and DM, have been independently associated with HCC development and together contribute to the risk of HCC in the non-cirrhotic liver.^{75–77} Recently, Tobair et al have shown that among patients with non-cirrhotic NAFLD, male gender, alcohol consumption, and high FIB-4 index were risk factors for HCC development.⁷⁸ Elevated ALT along with increasing age have been identified as independent risk factors for HCC development among NAFLD patients.⁷⁹ Non-cirrhotic NAFLD-related HCC patients are more likely to present with advanced HCC falling outside the Milan criteria but have better overall survival as compared to cirrhotic patients developing HCC.⁸⁰

Table I Incidence, Trend, and Risk Factors for HCC in NAFLD

Study Author Year	Study Type	Population	Study Duration or Follow-Up in Years	Cumulative Incidence	Risk Factors and Other Findings
Cho et al, 2011 ¹⁸⁰	Retrospective cohort	329 patients with non-B non-C, non-alcohol, or specific cause-related HCC	2001–2010	NR	Increased proportion of NAFLD related HCC increased from 3.8% to 12.2%
Dyson et al, 2014 ¹²⁸	Retrospective cohort	632 patients with HCC	2000–2010	NR	The proportion of NAFLD HCC 21.5% (136/632) in 2010. 10 fold increase in NAFLD HCC over 10 years
Wong et al, 2014 ⁴⁶	Retrospective cohort	UNOS registry; 61,868 adults with LT including 10,061 with HCC	2002–2012	NR	Increase in % of NASH related HCC 8.3% in 2002 versus 10.3% in 2007 versus 13.5% in 2012
Younossi et al, 2015 ¹²⁷	Retrospective cohort	SEER registries, 4929 HCC cases 14,937 controls	2004–2009	NR	The proportion of NAFLDHCC: 14.1%; 9% annual increase of NAFLDHCC;
Park et al, 2015 ⁴⁵	Retrospective cohort	BRIDGE, 14 countries, 18,031 HCC patients	2005–2012	NR	The proportion of NASHHCC: North America 12%, Europe 10%, China 5%, South Korea 6%, Japan 2%
Beste et al, 2015 ¹⁸¹	Retrospective cohort	129,998 cirrhosis, 21,326 HCC	2001–2013	NR	Incidence of NAFLDHCC increased from 2.63 to 5.14 per 100, 000
Younossi et al, 2019 ⁴⁷	Retrospective cohort	158,347 adult LT candidates 26,121 HCC	2002–2017	NR	The proportion of NASH in HCC increased 7.7-fold from 2.1% to 16.2%
Hashimoto et al, 2009 ¹⁸²	Prospective Cohort	137 NASH with advanced fibrosis	1990–2007	5-year cumulative incidence of HCC was 7.6%	RF: Older age, AST level AST, low grade of histological activity, and advanced fibrosis stage. 5-year survival rate was 82.8%
Yatsuji et al, 2009 ¹⁸³	Prospective cohort	68 patients with cirrhotic NASH 69 patients with HCV Cirrhosis	1990–2006	5-year HCC rate was 11.3% for NASH	the 5-year survival rates were 75.2%
Ascha et al, 2010 ⁵³	Prospective cohort	195 NASH cirrhosis 315 HCV cirrhosis	2003–2007 3.2 yrs. follow up	2.6% yearly CI	12.8% of NASH cirrhosis developed HCC RF: Older age and alcohol consumption
Kawamura et al, 2012 ⁸⁵	Retrospective cohort	6508 patients with NAFLD	1997–2010 Median follow-up Yrs.	Cumulative rates of NAFLDHCC were 0.02% (year 4), 0.19% (year 8), 0.51% (year 12)	RF: AST level ≥ 40 , platelet count ≤ 150 , age ≥ 60 years and diabetes at baseline.

(Continued)

Table 1 (Continued).

Study Author Year	Study Type	Population	Study Duration or Follow-Up in Years	Cumulative Incidence	Risk Factors and Other Findings
Amarapurkar et al 2013 ¹⁸⁴	Retrospective cohort	585 patients with liver cirrhosis NASH-related cirrhosis 7%, cryptogenic cirrhosis 17.8%	Cumulative follow-up 6.8 + 1.2 years	The annual rate of cirrhotic NASHHCC: 0.46%	The annual rate of cryptogenic cirrhosis HCC: 0.6%
Kodama et al, 2013 ¹⁸⁵	Retrospective cohort	72 patients with NASH cirrhosis and 85 with ALD cirrhosis	1990–2010	5 yrs. CI 10.5% in NASH-cirrhosis	RF: older age, higher γ -GTP level, and higher Child-Pugh score
Younossi et al, 2016 ¹⁴	Meta-analysis	86 studies with population of 8,515,431	1989–2015	NAFLD-HCC incidence 0.44 per 1000 person-years	The global prevalence of NAFLD: 25.24%
Vilar-Gomez et al, 2018 ³⁵	Retrospective cohort	458 NAFLD patients, bridging fibrosis/compensated cirrhosis	1995–2016 mean follow-up time of 5.5 years	1 yr CI. 0.2 F3 1.8 CPT A5 4.7 CPT A6	RF: Older age, male sex, diabetes, current smoking, (All cohort) Moderate alcohol consumption, current smoking (Cirrhosis cohort) 10 years accumulated NAFLDHCC rate: 9%
Marot et al, 2016 ¹⁸⁶	Retrospective cohort	752 patients with cirrhosis (78 NAFLD, 145 HCV, 529 ALD)	1995–2014	Annual risks of NAFLDHCC: 3.1%	10-year cumulative incidence rate: 23.7%
Bhala et al, 2011 ¹⁸⁷	Prospective/Retrospective cohort	247 NAFLD patients (118 F3, 129 F4)	mean follow up of 7.1 yrs.	2.4% of NAFLD patients developed HCC	No risk factors identified
Lee et al 2017 ⁷⁹	Retrospective cohort	18,080 noncirrhotic NAFLD	6.3 years	1 year (0.18) 5 years (1.03) 10 years (2.73)	RF: Older age High ALT
Fuji et al 2022 ⁵⁶	Retrospective cohort	1398 patient with biopsy-confirmed NAFLD	Median follow-up period 4.6 years 8874 person-years	HCC incidence 4.17/1000 person-years (95% CI 3.02–5.75).	Liver-specific mortality 2.34/1000 person-years overall mortality 5.34/1000 person-years
Pinyopornpanish et al 2021 ⁸⁴	Retrospective cohort	392,800 adult patients with NAFLD. 367,690 non-cirrhotic NAFLD 25,110 cirrhotic NAFLD	Median follow up 5 years 2015 to 2020	HCC in non-cirrhotic NAFLD 4.6/10,000 persons HCC in cirrhotic NAFLD 374.4/10,000 persons	RF for HCC in non-cirrhotic NAFLD Age > 65 DM ever had elevated ALT Male gender Smoking

(Continued)

Table 1 (Continued).

Study Author Year	Study Type	Population	Study Duration or Follow-Up in Years	Cumulative Incidence	Risk Factors and Other Findings
Alexander et al 2019 ¹⁵⁴	Matched-cohort study	136,703 patients with NAFLD/NASH	Median follow up of 3.3 years	Incidence of NAFLD-HCC 0.3 per 1000 person-years,	Hazard ratio for HCC among NAFLD patients was 3.51 DM at baseline strongest independent predictor of HCC
Kanwal et al 2018 ⁵⁴	Retrospective cohort	296,707 NAFLD patients with matched controls	2004–2015 Mean follow up of 9 years	0.21/1000 PY	490 NAFLD patients developed HCC during a mean follow up of 9 years HR for HCC among NAFLD patients: 7.62 RF: Cirrhosis, Older Hispanics
Sanyal et al, 2006 ¹⁸⁸	Prospective cohort	152 NASH cirrhosis	10 years	10 patients developed HCC over 10 years	No risk factors identified

Abbreviations: NR, Not reported; RF, Risk factors.

Overall, non-cirrhotic NAFLD patients have 2.5-fold higher risk of developing HCC than other etiologies of CLD without cirrhosis.⁸¹ However, the overall risk of HCC development in non-cirrhotic NAFLD is not well quantified but is thought to be less than the 1.5% per year threshold for the efficacy of HCC surveillance (>0.25 life-years gained).⁵⁴ Therefore, systematic HCC screening may not be prudent and is currently not recommended by the American Association for the study of liver disease (AASLD) and American gastroenterological Association (AGA) for HCC surveillance in non-cirrhotic NAFLD patients.^{82,83} Recently, one large study from the US has shown that prevalence of HCC in non-cirrhotic NAFLD is 4.6/10,000 persons and 374.4/10,000 among cirrhotic NAFLD patients. Age > 65 years, presence of DM, smoking, male gender, and even one time elevated ALT were the risk factors identified for HCC development in non-cirrhotic NAFLD patients. The presence of all these five factors increased the prevalence to 45.5/10,000 persons.⁸⁴

In the absence of well-defined risk scoring systems for HCC development in non-cirrhotic NAFLD patients, it may be useful to consider surveillance for HCC in those at the highest possible risk, such as older male patients with alcohol use history, elevated ALT levels, diabetes, or advanced fibrosis as determined by non-invasive methods. However, this remains a controversial topic.

Overview of Risk Factors

The strongest risk factor for the development of HCC is the presence of liver cirrhosis, as more than two-thirds of HCC cases develop in patients with cirrhosis. The incidence rate is 25-fold higher in NAFLD patients with advanced fibrosis than patients without significant fibrosis.⁸⁵ However, certain other demographic, metabolic, and genetic factors have been associated with the development of HCC in NAFLD. Here, we will briefly describe those risk factors.

Demographic Risk Factor

Increasing age and male gender are associated with the development of HCC in NASH patients with cirrhosis.^{35,53,79,85,86} Ascha et al examined a cohort of NASH cirrhosis patients for the development of HCC. They found out that older age was associated with the development of HCC in multivariate regression analysis while the male gender was associated with HCC in univariate analysis.⁵³ These findings were also confirmed by Corey et al in a case-control study showing that older age, male gender, and non-Hispanic ethnicity were risk factors associated with HCC development in NASH cirrhosis patients.⁸⁶ Vilar et al³⁵ also found that in patients with NASH-related bridging fibrosis or cirrhosis, older age

and male gender are independent risk factors for the development of HCC. Lee et al noticed that the 10-year cumulative HCC incidence was highest in older (age >55 years) patients with ALT elevation,⁷⁹ while Kawamura showed that elderly NAFLD patients with DM, elevated serum AST, and thrombocytopenia are at the highest risk of HCC development.⁸⁵ Male patients with NASH appear to be at higher risk of developing HCC,⁷⁰ and several mechanisms have been proposed to explain this difference. Estrogen has been associated with HCC suppression in females via inhibiting the JAK1-STAT6 signaling pathway.⁸⁷ Sex-specific differences in exposure to HCC risk factors may also contribute to the higher risk of HCC among men. Men are more likely to be infected with hepatitis B and C viruses, smoke more, consume more alcohol, and have increased liver iron stores compared to women.⁸⁸ Lastly, androgens have been linked with upregulation of inflammation in men with elevated cytokine levels, particularly relevant in HCC related to HBV.⁸⁹

Ethnicity also appears to play a role in NAFLD-related HCC. Hispanics are more likely than non-Hispanics to develop HCC^{90,91} and have an increased risk of NAFLD development.¹⁴ US-born Hispanics have a higher incidence of HCC development than Hispanics born outside the US, while the reverse is true for Asians, suggesting that socio-economic, environmental, and cultural differences may play a more substantial role than genetics.⁹²

Metabolic Risk Factors

Metabolic syndrome, obesity, and DM are linked with NAFLD development. They have also been associated with the development of HCC independently. Obesity has been linked with the development of multiple cancers and an increased risk of mortality overall.^{6,93} For HCC specifically, Nair et al studied patients who underwent liver transplants and demonstrated that obesity was an independent predictor for HCC in patients with alcohol-related cirrhosis and cryptogenic cirrhosis.⁹⁴ In a meta-analysis of 11 cohort studies, Larsen et al demonstrated that the relative risks of liver cancer were 1.17 for overweight and 1.89 for obese compared with normal-weight persons.⁹⁵ While elevated BMI is an independent risk factor, visceral or central adiposity specifically is associated with increased risk of HCC.⁹⁶ Visceral adiposity is a risk factor for HCC recurrence after curative treatment in patients with suspected NASH.⁹⁷ It has been demonstrated that intramuscular fat deposition, sarcopenia, and visceral adiposity rather than BMI alone are independent risk factors for a poor prognosis in HCC patients. The proportion of these body composition components is higher in obese and underweight patients than normal-weight patients. Sarcopenia and intramuscular fat deposition contribute to muscle weakness resulting in reduced activities associated with daily living. Also, they are associated with insulin resistance, vitamin D deficiency, and increased inflammatory cytokine levels, which may explain the increased risk of HCC.⁹⁸

The prevalence of metabolic syndrome, as defined by the US National Cholesterol Education Program Adult Treatment Panel III criteria (complete definition in Table 2),⁹⁹ is associated very strongly with NAFLD development and has also been linked with HCC development. In the Surveillance, Epidemiology, and End Results (SEER)-Medicare database study, which studied HCC cases between 1993 and 2005, metabolic syndrome was significantly associated with

Table 2 National Cholesterol Education Program Adult Treatment Panel III Definition for Metabolic Syndrome (2001)

	Three or More of the Following Risk Factors
Fasting plasma glucose	>5.6 mmol/L (100 mg/dL)
Blood pressure	>130/≥85 mm Hg
Triglycerides	≥1.7 mmol/L (150 mg/dL)
High-density lipoprotein cholesterol	Men: <1.03 mmol/L (40 mg/dL) Women: <1.29 mmol/L (50 mg/dL)
Obesity	Men: waist circumference >102 cm Women: waist circumference >88 cm

Notes: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486–2497.

the increased risk of HCC and intrahepatic cholangiocarcinoma.¹⁰⁰ Also, the presence of each additional metabolic trait (diabetes, hypertension, dyslipidemia, and obesity) in NAFLD patients increases the risk of HCC, with DM conferring the greatest risk.³⁰ Metabolic disorders contributed more to the burden of HCC in this population as a risk factor than any other factors, including smoking, alcohol, and viral hepatitis.¹⁰¹ Chen et al has shown in a nationwide cohort that while metabolic syndrome alone without NAFLD does not increase the risk of HCC, it significantly increases the risk of hepatocarcinogenesis in patients with NAFLD.¹⁰²

The evidence linking DM with the development of HCC is robust.^{103–107} Raff et al showed that DM increases the risk of HCC in NAFLD and alcohol-related liver disease patients.¹⁰³ Two separate meta-analyses have provided evidence that DM is associated with increased risk of HCC and HCC mortality.^{104,107} This association is independent of geographic location, alcohol consumption, history of cirrhosis, or infections with hepatitis B or C virus. Also, duration of DM, level of glycemic control, use of sulfonylureas, or insulin treatment possibly in combination increases the risk of HCC, while metformin has a protective effect on HCC development.^{104,108} Yang et al demonstrated similar results that DM is associated with increased risk of HCC in NAFLD-related cirrhosis patients.¹⁰⁶

Genetic Risk Factors

Host genetic polymorphisms are involved in HCC pathogenesis and may serve as risk factors and predictive biomarkers.¹⁰⁹ At least three common genetic variants in the patatin-like phospholipase domain-containing protein 3 (PNPLA3), transmembrane 6 superfamily member 2 (TM6SF2), and membrane-bound O-acyltransferase domain-containing 7 (MBOAT7) genes have been robustly linked to NAFLD in the population. The study of these genes' role highlights novel pathways in the development of NAFLD and their possible role in HCC development.¹¹⁰

The rs738409 C > G variant in the PNPLA3 gene, encoding an I148M mutation, is independently associated with NAFLD and is also associated with fibrosis progression and HCC development.^{111–115} Initially, the variant allele *PNPLA3* (rs738409; I148M) was associated with increased hepatic fat levels and hepatic inflammation and was more prevalent among Hispanics.¹¹¹ Later, it was shown that carriage of the PNPLA3 polymorphism is also associated with a greater risk of progressive steatohepatitis, fibrosis, and HCC.¹¹² This association is independent of potential confounders, including age, gender, BMI, presence of DM, advanced fibrosis, or cirrhosis.¹¹² Two separate meta-analyses have shown that PNPLA3 is associated with an increased risk of advanced fibrosis and is an independent risk factor for HCC among patients with nonalcoholic steatohepatitis or alcohol-related cirrhosis.^{113,114}

The rs58542926 C > T variant in the TM6SF2 gene, encoding an E167K mutation, is associated with hepatic steatosis and an increased risk of liver fibrosis.^{116,117} Its role in HCC development, however, remains uncertain.¹¹⁸ The rs641738 C > T variant of the MBOAT7 gene has been shown to increase the risk of hepatic steatosis and progressive liver disease in NAFLD patients.¹¹⁹ It is also associated with an increased risk of HCC in non-cirrhotic patients with NAFLD.¹²⁰ A genome-wide study of histologically proven NAFLD patients from Japan found a polymorphism in the *DYSF* gene to be associated with HCC in addition to the known PNPLA3 polymorphism.¹²¹

It is important to emphasize that the above studies were cross-sectional in design, thus carrying their known limitations. Given that NAFLD has a polygenic inheritance pattern, identifying a single genetic mutation predictive of HCC development is challenging. The data on the impact of selected single nucleotide polymorphisms (SNPs) on HCC occurrence is lacking, and the findings need to be validated in prospective cohorts before they can be incorporated in clinical and biochemical parameters to identify patients at the highest risk of HCC development who may benefit from surveillance.^{109,110}

Alcohol and Smoking

Although significant alcohol intake is excluded from the definition of NAFLD, it has been shown that any level of alcohol intake is associated with a higher risk of HCC development in NASH patients compared to patients who have never consumed alcohol.⁵³ Recently, a longitudinal study has shown that moderate alcohol consumption among compensated NASH-cirrhotic patients may exacerbate liver disease progression and increase the risk of hepatic decompensation, HCC, and death.³⁵ Smoking has also been linked with the development of HCC in general,¹²² and has been shown to increase the risk of HCC development by two folds in one study.³⁵ Based on these findings, NAFLD patients, especially those with advanced fibrosis, should be counseled for smoking cessation and advised against alcohol consumption.

Presentation of NAFLD-Related HCC

Patients with NAFLD-related HCC are older at presentation than patients with non-NAFLD-related HCC patients and are more likely to be men.¹⁰ NAFLD-related HCC patients have been shown to have more extrahepatic comorbidities but have a lower prevalence of cirrhosis, with only 66% of the HCC patients have underlying cirrhosis.^{10,66,123} Patients with NAFLD-related HCC have less severe liver dysfunction at the time of diagnosis, more often had the presence of metabolic syndrome, and had a lower model for end-stage liver disease scores.^{123,124} Compared to HCV-related HCC patients, NAFLD-related HCC patients tend to be diagnosed with smaller-sized tumors, but there is no difference in terms of the total number of lesions or the status of microvascular invasion or lymph node involvement.^{53,124} The size of the NAFLD-HCC tumor is inversely related to the extent of cirrhosis as determined by the Child-Pugh score.¹²⁵ It has also been shown that NAFLD patients have slower tumor growth rate as compared to viral-related HCC.¹²⁵ Trabecular carcinoma is the most common histopathological type of HCC in NAFLD patients.¹²⁶

Prognosis of NAFLD-Related HCC

The data on the prognosis and survival of NAFLD-related HCC patients is conflicting. NAFLD-related HCC patients are diagnosed at more advanced stages due to less systematic surveillance and therefore may not be good candidates for all available treatment options.¹⁰ It has been shown that despite retained liver function, patients with NASH-related HCC had reduced overall survival^{123,127} and advanced tumor stage.¹²⁷ However, the opposite trend has been reported in other studies showing that the survival rate of NAFLD-related HCC patients is at least the same as of HCV-HCC patients.^{66,126} Reddy et al showed improved survival in NASH-related HCC patients with recurrence rates the same as other causes.¹²⁴ Despite NASH-related HCC patients being older at the time of presentation and having advanced disease, similar survival may be attributed to incidental presentation and lower cirrhosis prevalence.¹²⁸ NAFLD-related HCC patients undergoing surgical resection have increased post-resection morbidity and 30-day mortality than HCV and HBV-related HCC patients.^{129,130} However, overall survival is comparable between the NAFLD-related HCC and Hepatitis virus-related HCC, with the NAFLD-related HCC group having better disease-free survival.^{69,126,127} A recent meta-analysis has also demonstrated that patients with NAFLD-related HCC have better disease-free and overall survival after liver resection than non-NAFLD-related HCC.¹³² When all forms of curative therapies were considered, overall survival was similar between the two groups, but disease-free survival favored the NAFLD-related HCC group.¹³² However, in cases of advanced HCC, one study showed that NAFLD-related HCC patients have reduced overall survival when treated with anti-PD1 (programmed death-1) or anti-PDL1 (programmed death ligand-1) agents as compared to HBV or HCV-related HCC. This reduced responsiveness of HCC to immunotherapy in NASH patients might be attributable to aberrant T cell activation resulting in tissue damage and impaired immune surveillance.¹³³ However, the evidence on this topic is evolving rapidly, and further studies are needed to confirm or refute these observations.

NAFLD-Related HCC and Liver Transplant

NASH is the fastest growing indication for liver transplant in patients with HCC.^{46,47} Patients undergoing liver transplantation with NAFLD-related indications tend to fare the same as other conditions. In a meta-analysis, patients with NASH who underwent liver transplants had similar 1, 3, and 5 years survival rates as patients without NASH. However, patients with NASH were more likely to die from cardiovascular complications or sepsis.¹³⁴ Specifically for NASH-related HCC patients, Sadler et al demonstrated that overall survival at 1, 3, and 5 years and tumor recurrence was the same for NASH-related HCC and non-NASH-related HCC patients, and NASH status appeared to have a protective effect for tumor recurrence among patients with tumors beyond Milan criteria.¹³⁵

Post liver transplant, the incidence of recurrent NAFLD is 59%, 57%, 82% at 1, 3, and 5 years follow-up, similar to de novo NAFLD incidence. However, the incidence of recurrent NASH is significantly higher than de novo NASH; 53%, 57.4%, and 38% for recurrent NASH vs 1 3%, 16%, and 17%, for de novo NASH at 1, 3, and 5 years post liver transplant.¹³⁶ Post-transplant, high BMI, hyperlipidemia, and alcohol abuse history are predictors of hepatic steatosis development.^{136,137} Hepatic steatosis, though extremely common after liver transplantation, does not seem to have an

adverse effect on post liver transplant outcomes,¹³⁸ but biopsy-proven NASH post liver transplant is a significant risk factor for lower long-term survival.¹³⁹

Issue of Surveillance

Current American and European guidelines do not recommend separate surveillance guidelines for non-cirrhotic NAFLD-related HCC. However, there is considerable concern that some level of surveillance is needed for non-cirrhotic NAFLD-related HCC.¹⁴⁰ As noted previously, patients with non-cirrhotic NAFLD-related HCC are more likely to be older, picked up at an advanced stage, have an incidental presentation, and have a higher prevalence of metabolic syndrome and cardiovascular diseases. Also, almost one-third of the patients with NAFLD-related HCC have no underlying cirrhosis.^{66,128} Given the ever-increasing incidence of NAFLD, the burden of NAFLD-related HCC will continue to increase in the future, highlighting the need to develop predictive biomarkers to identify specific high-risk subgroups. The most important issue is the non-invasive diagnosis of patients with advanced fibrosis, as fibrosis is the most important factor in NAFLD patients associated with adverse outcomes. Several serum biomarkers have shown good accuracy to identify patients with advanced fibrosis, who needs close followup and surveillance for the development of cirrhosis and HCC.¹⁰ NAFLD fibrosis score (NFS), Hepamet Fibrosis Score (HFS), and FIB-4 outperform other scores in the identification of fibrosis and prediction of long-term outcomes including mortality.^{141,142} NFS and FIB-4 are the best at predicting long-term liver-related events, while NFS is the best predictor of HCC.¹⁴¹ FIB-4 ≥ 2.67 is a strong predictor of both all-cause mortality and adverse liver-related outcomes, including progression to NASH, cirrhosis, end-stage liver disease, and transplantation.¹⁴³ The Hepamet fibrosis score provides greater advantage in selecting NAFLD patients who should undergo liver biopsy.¹⁴²

Patients with NAFLD-related cirrhosis are less likely to undergo HCC surveillance resulting in HCC being detected at a more advanced stage.^{66,128} Ultrasonography – the recommended surveillance modality – is operator-dependent and is challenging in centrally overweight patients with heterogeneous fatty liver.¹⁴⁴ It has been shown that sensitivity of ultrasound (US) for HCC detection is significantly worse for obese patients, patients with NASH and advanced cirrhosis (Child C).^{145,146} Overall sensitivity of US for HCC detection is 82% compared to cross-sectional imaging, but it is reduced in obese patients (BMI ≥ 30 kg/m²) to 76% versus 86% for non-obese patients and in NASH patients to 59% versus 84% for non-NASH patients.¹⁴⁶

Despite these limitations, guidelines have recommended using the US abdomen every six months with or without AFP.^{9,10} However, it has been recommended that the adequacy of US should be documented in assessing the liver parenchyma for mass lesions. When the adequacy of US is sub-optimal, computed tomography or magnetic resonance imaging with or without AFP should be used for future surveillance every six months.⁸² It has been shown that in select subgroup of cirrhosis patients who are at high risk of developing HCC (annual HCC risk $>3\%$), MRI-based HCC screening is cost-effective and can increase early tumor detection.¹⁴⁷

For patients with cirrhosis, different models are available to predict the risk of HCC. The Toronto HCC risk index is a validated scoring system to predict the 10-year risk of HCC in cirrhotic patients based on commonly available parameters such as age, sex, underlying etiology, and platelets.¹⁴⁸ GALD and BALAD-2 models have shown good value for diagnosing HCC and predicting patient survival, respectively.¹⁴⁹ However, they are not specific for NAFLD-related HCC patients. Ioannou et al have recently developed a simple model to estimate HCC risk in NAFLD cirrhosis patients. The model includes age, gender, DM, BMI, platelets, albumin, and AST to ALT ratio and exhibits an area under the receiver operating characteristic curve (AUROC) of 0.75. This risk-based screening was shown to have a net benefit over the standard approach.¹⁵⁰ For NAFLD patients, validated HCC risk prediction models are needed to identify the patients at high risk who would benefit the most from surveillance.¹⁵¹

In practice, we agree with the approach suggested in the “AGA Clinical Practice Update on Screening and Surveillance for Hepatocellular Carcinoma in Patients with NAFLD” of using two non-invasive tests to assess advanced liver cirrhosis and fibrosis. Patients having unequivocal evidence of cirrhosis or advanced fibrosis (FIB-4 > 3.25 , or transient elastography score >16.1 kPa or >5 kPa for magnetic resonance elastography) should be included in regular HCC surveillance.⁸² Patients with no or low-grade fibrosis (F0-F2) should be followed up with assessment of the fibrosis stage every 1–3 years. Although patients with F3 fibrosis have shown to have an increased risk of HCC compared to

patients with stage F0 to F2 fibrosis,¹⁵² no recommendations can be made about the induction of such patients in regular HCC surveillance. However, we suggest that patients with F3 fibrosis who have additional risk factors for HCC development (older age, male gender, diabetes, any degree of alcohol intake) should be closely monitored.¹⁵³

For evaluation of NAFLD after liver transplant, the patients are screened with hepatic imaging by post-transplant protocol. Patients with steatosis but no elevation of their serum transaminases are followed with standard protocol imaging. However, if liver enzymes are increased, either transient elastography (TE) or magnetic resonance elastography (MRE) to determine if patients have fibrosis. Patients without fibrosis can be followed with yearly TE to ensure no disease progression. If F3 fibrosis is noted, they are screened for HCC every six months with imaging. Lesions noted on imaging are further characterized via cross-sectional imaging and survey by standard protocol.

Prevention of NAFLD-Related HCC

The presence of cirrhosis among NAFLD patients is the most significant risk factor for HCC development. In addition, DM has been linked with the risk of HCC among NAFLD patients.¹⁵⁴ Apart from being linked with the development and progression of NAFLD, DM and obesity are independently associated with the development of HCC.^{7,155} Lifestyle and dietary interventions targeting the development of obesity, DM, and metabolic syndrome or their reversal on a population-based level would be a cost-effective way to reduce the HCC risk.³⁸ The interplay of different pathophysiological states of hepatic steatosis from NAFLD to NASH to cirrhosis leading to HCC development, as well factors associated with disease progression and prevention are summarized in Figure 1.^{2,10,22}

Physical activity has also been shown to reduce the incidence of HCC by 36% in one study,¹⁵⁶ with the level of reduction correlating with the level of physical activity.^{156,157}

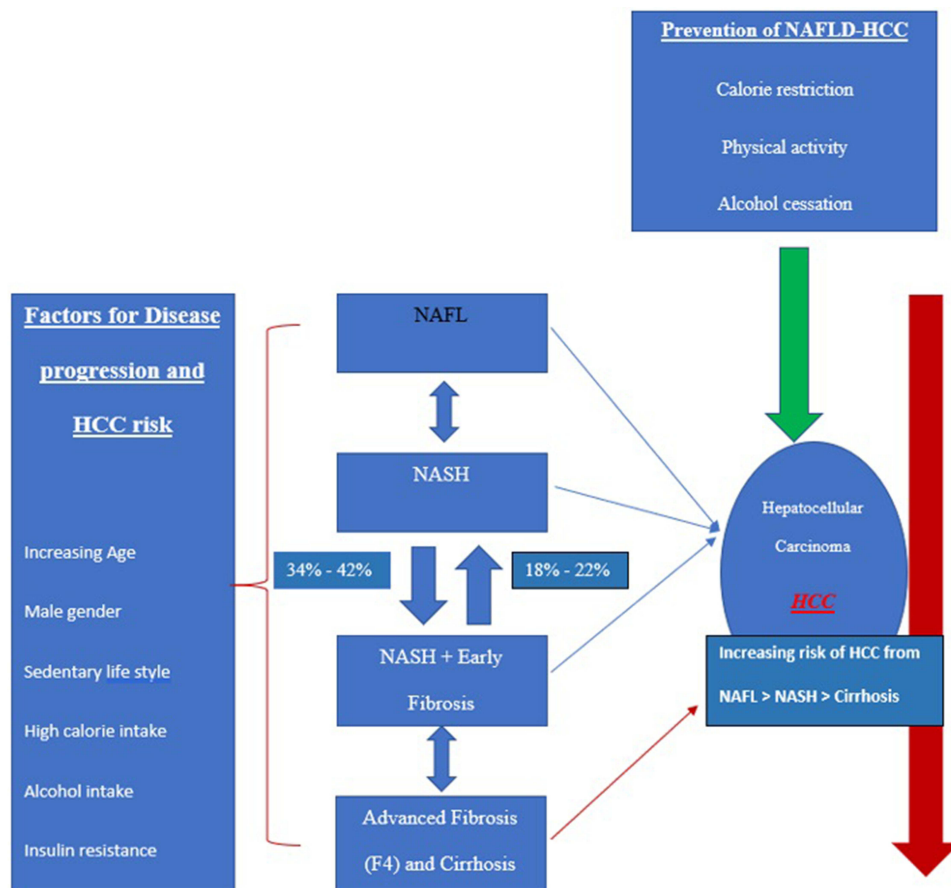


Figure 1 Pathophysiological states of NAFLD and HCC along with risk factors for disease progression and HCC prevention.^{2,10,23}

Daily consumption of fruits and vegetables is associated with decreased cancer risk.¹⁵⁸ A meta-analysis noted that increased intake of vegetables, but not fruits, was associated with a lower risk for HCC. Every 100 g/day increase in vegetable intake decreased the risk of HCC by 8%.¹⁵⁹ Among different dietary patterns, close adherence to the Mediterranean diet appears most protective against HCC.¹⁶⁰ The beneficial effect of the Mediterranean diet and exercise seems to extend beyond the potential impact of weight loss and should be recommended to all patients with NAFLD/NASH.¹⁶¹

Alcohol cessation has also been shown to reduce HCC development risk by 6–7% a year.¹⁶² Among beverages, coffee consumption has been shown to reduce the risk of HCC. In one population-based prospective cohort study, people who drank 2–3 cups per day of coffee had a 38% reduction in the risk for HCC and a 46% reduction in risk of death from chronic liver disease than those who did not take coffee.¹⁶³ A meta-analysis also confirmed that the risk of HCC is reduced by 40% for any coffee consumption.¹⁶⁴

In addition to dietary and lifestyle interventions, the use of pharmacological therapy, such as statins and metformin, for the prevention of HCC appears to be interesting. Multiple studies have shown the protective effect of metformin against HCC development.^{79,165,166} A meta-analysis of 19 studies involving 550,882 diabetic subjects showed that metformin use reduced liver cancer risk by 48%. This association was independent of hepatitis B/C virus infection status, cirrhosis, obesity, behavioral factors, and time-related bias.¹⁶⁵ The protective effect of metformin seems independent of the hypoglycemic effect since other hypoglycemic agents like sulfonylureas and exogenous insulin have been linked with increased risk of HCC development.^{167,168} Angiotensin-converting enzyme inhibitors (ACEIs) but not angiotensin receptor blockers (ARBs) have also been shown to decrease the risk of cirrhotic complications and HCC development, with greater benefit noted in CKD patients.¹⁶⁹

For statins, dose-dependent reduction in incident cirrhosis and HCC has been demonstrated in both HCV and HBV infected patients.^{170,171} Atorvastatin and Fluvastatin seem to have the highest protective role among statins class.^{170,172}

Anti-fibrotic therapies acting to halt and possibly reverse fibrosis progression in NAFLD patients are at various stages of development and, hopefully, will prevent the development of HCC when used in practice. Selonsertib, an ASK1 inhibitor, was shown in a Phase 2 trial to reduce liver fibrosis in patients with nonalcoholic steatohepatitis and stage 2–3 fibrosis,¹⁷³ but failed to meet the primary efficacy endpoint of improvement in fibrosis stage in NASH and bridging fibrosis or compensated cirrhosis in two separate Phase III randomized trials.¹⁷⁴ Cenicriviroc, a dual inhibitor of fibrosis-promoting CCR2/CCR5, showed improvement in fibrosis among NASH patients with no worsening of steatohepatitis in a phase 2 study.¹⁷⁵ Currently, a Phase 3, multicenter, randomized, clinical trial of subjects with NASH and stage F2 or F3 fibrosis is undergoing to evaluate the efficacy and safety of Cenicriviroc (AURORA, NCT03028740).¹⁷⁶

Another drug Elafibranor, a PPAR α/δ agonist, showed to halt fibrosis progression in non-cirrhotic NASH patients in a phase 2 trial.¹⁷⁷ However, recently, in phase III trial RESOLVE-IT, elafibranor failed to meet its primary (NASH resolution) and secondary endpoints (improvement of fibrosis stage) (NCT02704403). Obeticholic acid (OCA), a nuclear Farnesoid X receptor (FXR) activator, has been shown to ameliorate NASH and improve fibrosis in the REGENERATE trial.¹⁷⁸ However, pruritus is a significant side effect of the drug affecting clinical compliance, and long-term health effects of obeticholic acid are still for debate.¹⁷⁹

The development of effective anti-fibrotic therapy is the need of the hour for NAFLD patients, as the severity of liver fibrosis is directly related to liver-associated morbidity and mortality. While it is thought that decreasing the presence of fibrosis and NASH may reduce the risk of developing HCC, none of the emerging therapies have shown a reduction in the incidence of HCC in NAFLD patients.

Conclusion

NAFLD is the most common cause of chronic liver disease, and the burden of NAFLD-associated liver disease is expected to continue to worsen in the future. NAFLD-related cirrhosis and HCC share the same risk factors, including DM, obesity, and metabolic syndrome. The incidence of HCC in NAFLD-related cirrhosis is estimated to be between 1% and 3% per year, exceeding the threshold of >1.5% per year, justifying regular HCC surveillance in this population.⁸³ The need for HCC surveillance in non-cirrhotic NAFLD is not cost-effective currently, and more evidence is needed on

this topic from more extensive prospective studies. Non-cirrhotic NAFLD patients have a threefold increased risk of HCC development compared to other causes of liver disease,⁸¹ however, the overall incidence remains low and undefined (2.7% at 10 years for non-cirrhotic NAFLD vs 15% at 10 years in NAFLD-related cirrhosis).¹⁴⁰ While the current guidelines suggest against HCC surveillance in non-cirrhotic NAFLD patients, those with advanced fibrosis or cirrhosis suggested by non-invasive markers may warrant consideration for surveillance. Currently, the role of genetic risk factors and concurrent comorbid conditions is not well incorporated into surveillance guidelines. The development of predictive biomarker models and risk scores to identify the high-risk population remain an unmet clinical need. Clinical guidelines should consider this, and a risk score should be proposed based on genetic risk factors and comorbid conditions to identify the highest risk patients for HCC development in non-cirrhotic NAFLD.

Abbreviations

NAFLD, Nonalcoholic fatty liver disease; CLD, Chronic liver disease; NASH, Nonalcoholic steatohepatitis; HCC, Hepatocellular carcinoma; DM, Diabetes mellitus; HLD, Hyperlipidemia; BMI, Body mass index; HS, Hepatic steatosis; HTN, Hypertension; HCV, Hepatitis C virus; HBV, Hepatitis B virus; US, Ultrasound.

Disclosure

Dr David Victor is a member of advisory board in Eisai and Exelixis, outside the submitted work. The authors report no other conflicts of interest in this work.

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