Review

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Epidemiology of non-alcoholic fatty liver disease and hepatocellular carcinoma

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Summary

The prevalence of hepatocellular carcinoma (HCC) is increasing worldwide, whereas that of most other cancers is decreasing. Non-alcoholic fatty liver disease (NAFLD), which has increased with the epidemics of obesity and type 2 diabetes, increases the risk of HCC. Interestingly, NAFLD-associated HCC can develop in patients with or without cirrhosis. A lack of awareness about NAFLD-related HCC has led to delays in diagnosis. Therefore, a large number of patients with HCC are diagnosed with advanced-stage HCC with low 5-year survival. In this context, increasing awareness of NAFLD and NAFLD-related HCC may lead to earlier diagnosis and more effective interventions.

Keywords: cirrhosis; non-cirrhosis; natural history; awareness; surveillance

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Introduction

Since their discoveries, hepatitis B (HBV) and hepatitis C (HCV) viruses have been recognised as the most common aetiologies of hepatocellular carcinoma (HCC).[1] However, in the mid-1980s, vaccination for the prevention of HBV and testing for HCV in blood products were introduced, leading to public health efforts to reduce the burden of HBV and HCV infections.[2,3] Furthermore, development of highly effective suppressive therapy for HBV and curative treatment for HCV with direct-acting antiviral agents, have reduced the numbers of patients with chronic viral hepatitis, potentially reducing long-term complications of liver disease, including the burden of HCC.[2,3] In fact, the most recent data from the Global Burden of Disease project have indicated that the incidence, mortality, and disability-adjusted life years related to virus-associated hepatitis and HCC are decreasing.[2] In contrast, alcohol-related liver disease (ALD) and its associated complications remain an important cause of cirrhosis and HCC. In the United States, ALD is currently the most common indication for liver transplantation and an important cause of HCC and liver-related mortality.[4]

Another important cause of cirrhosis and HCC is non-alcoholic fatty liver disease (NAFLD). In fact, parallel to the recent advances in viral hepatitis, the world has been experiencing an epidemic of obesity and type 2 diabetes which are important risk factors for NAFLD and its progressive form, non-alcoholic steatohepatitis (NASH).[2] It important to remember that NAFLD and ALD share similar histopathological features and are both driven by the ingestion of certain foods and/or drinks. In fact, both NAFLD and ALD cause hepatic steatosis that can progress to steatohepatitis, cirrhosis and HCC.[5,6] On the other hand, diagnoses of NAFLD and NASH require exclusion of excessive alcohol use.[7] Currently, it is estimated that 25% to 30% of the adult population is thought to be living with NAFLD, while more than 50% of individuals with type 2 diabetes and 90% of the morbidly obese have NAFLD.[8,9] Additionally, it is estimated that approximately 1.5% to 6% of the general population have underlying NASH.[9–11] Furthermore, 10–15% of patients with NAFLD are believed to have hepatic fibrosis which is an important predictor of adverse long-term outcomes.[9–13] Risk factors for NAFLD are metabolic in nature and include obesity, insulin resistance, type 2 diabetes, hypertension, and dyslipidaemia.[9,10,13–16] Male sex and older age are also risk factors for NAFLD.[17,18]

In addition to increased mortality, NAFLD is also associated with a significant burden related to patient-reported and economic outcomes.[19–22] Persons with NAFLD report lower physical functioning and higher levels of fatigue and depression or anxiety compared to persons without NAFLD. The economic burden of NAFLD has been estimated to be enormous.[19–22] Although NAFLD is associated with metabolic risk factors, up to 40% of patients with NAFLD may not be obese but can still be considered metabolically unhealthy.[8,23–25]

Recently, it has become increasingly clear that NAFLD is rapidly becoming the most common cause of chronic liver disease and cirrhosis.[2,26] In addition, NASH is the second-most common indication for liver transplantation in the United States.[27,28] Although complications of cirrhosis are common indications

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for liver transplantation among patients with NASH, HCC has become a leading indication.[27] In addition to the data from the United States, this is reflected in the global burden of HCC. In fact, although the incidence rates for most cancers are decreasing, the incidence of liver cancer is increasing worldwide. In this context, liver cancer is presently the sixth-most common cancer worldwide and the second-most common cause of cancer-related death; HCC accounts for 75%–85% of all liver cancers.[3,29] As such, NAFLD-related HCC is considered a major contributor to HCC worldwide.[30,31] A recent study predicted that the age-standardised incidence rates per 100,000 person-years for primary liver cancer would increase for men and women by the year 2030 in most countries, with the main driver of the increase being NAFLD and/or NASH.[3] Another study reported that the prevalence of NASH-related HCC increased by 68% from 2010 through 2015.[31] Yet another study of data from the Scientific Registry of Transplant Recipients for the years 2002–2016, found that the prevalence of NAFLD- and/or NASH-related HCC was increasing.[32] Researchers found that among 158,347 adult liver transplant candidates, the proportion of HCC associated with HCV infection and ALD remained stable, the proportion associated with HBV infection decreased, and the proportion associated with NASH increased almost 8-fold.[32] A similar trend was noted in Europe where researchers analysed data from the European Liver Transplant Registry and found that the number and proportion of liver transplants performed for NASH increased from 1.2% in 2002 to 8.4% in 2016. Furthermore, HCC was more common in patients with NASH than other liver diseases.[33]

Incidence of HCC in patients with NASH, with or without cirrhosis

The association of HCC with NAFLD has been well described.[34–38] However, it is important to recognise that cirrhosis increases the risk of HCC in patients with NASH, as it does in patients with other types of liver disease. On the other hand, NAFLD patients without cirrhosis are also at risk, albeit lower, of HCC.[35–39] Among US Medicare patients, NAFLD was associated with 19.2% of HCC cases (32.07% in inpatientsand 20.22% outpatients), whereas HCV infection was associated with only 9.75% of HCC cases.[40] Between 2005 and 2014, the rate of HCC among Medicare recipients increased from 46.3 per 100,000 to 62.8 per 100,000 (average annual percentage change, 3.4%; p <0.001). The rate of NAFLD-associated HCC increased from 9.32 per 100,000 to 13.61 per 100,000, whereas the rate of HCV-associated HCC increased from 6.18 per 100,000 to 16.54 per 100,000 (p <0.001). In comparison to patients with HBV-related HCC, patients with NAFLD-associated HCC had higher mortality (odds ratio 1.87; p <0.001).[40,41]

Evidence from non-invasive tests indicate that the presence of advanced fibrosis, in addition to cirrhosis, is associated with an increased risk of HCC. Moderate liver stiffness, determined by transient elastography, has been shown to be a marker of significant fibrosis and is independently associated with the development of HCC in patients with NAFLD.[35] The annual incident rate for HCC in patients with moderate liver stiffness is 0.2 HCC cases per 100 person-years.[24,35] It is important to note that the annual incidence of HCC associated with NAFLD in patients with cirrhosis has been reported to range from 1% to 3%, with a general incidence rate estimated to be >1.5%. However, in patients with NAFLD-associated HCC without cirrhosis, the reported annual incident rates have been reported at approximately 0.08 cases per 1,000 person-years.[42–44]

Key points

- NAFLD/NASH liver diseases are becoming the leading cause for HCC.
- NAFLD-related HCC can develop in those with and without cirrhosis.
- The presence of type 2 diabetes increases the risk of HCC 2-fold and risk of death from HCC 1.5-fold.
- The presence of metabolic syndrome along with type 2 diabetes increases the risk of HCC 5-fold.
- Obesity (BMI >30 kg/m^2) doubles the risk of HCC, while a BMI >35 kg/m^2 quadruples the risk of HCC.
- Non-obese persons with metabolic comorbidities are at risk of NAFLD and NAFLD-related HCC.
- Waist circumference as a surrogate for visceral obesity is an important measure to consider in addition to BMI when assessing risk of HCC.
- NAFLD-related HCC tumours are large and can be hypervascular.
- There is low disease awareness about NAFLD and NAFLD-related HCC which leads to diagnostic delays and contributes to late-stage diagnosis of HCC with high mortality.
- Continued education of health care providers and public health programmes about NAFLD, its risk factors, associated outcomes (including HCC), diagnosis, and preventative measures are urgently needed.

Other risk factors for HCC in patients with NAFLD

In addition to the presence of cirrhosis, other factors are associated with higher risk for HCC.[23,24,45–49] The most important risk factors for HCC include the presence of diabetes and insulin resistance, obesity, older age, and male sex.[24,45–49] In the United States, ethnicity has been associated with the development of HCC; Mexican-Americans have been found to be at higher risk.[24] In addition, less physically active individuals, with more metabolic components, are also at increased risk.[23,24] Type 2 diabetes is an independent risk factor for HCC, increasing the risk of developing HCC 2-fold and increasing the risk of death from HCC 1.5-fold.[48] Similarly, the presence of metabolic syndrome along with type 2 diabetes increases the risk of HCC 5-fold.[23] As such, the increasing number of metabolic components present increases the risk of adverse long-term outcomes, including mortality.[23,50]

Obesity also affects the risk of HCC. The presence of obesity (BMI >30 kg/m^2) doubles the risk of HCC, whereas among those with a BMI >35 kg/m^2, the risk of HCC is increased 4-fold.[50] It is important to note that the presence of metabolic abnormalities in a non-overweight or obese person with NAFLD has been linked with progression of NAFLD to cirrhosis and liver cancer, as well as to increased mortality.[23] For those with obesity, it is important to understand the role of central or visceral adiposity. For example, waist circumference as an anthropometric measure of visceral obesity has been associated with an increase in all-cause mortality even among individuals who are not obese or overweight.[50] This observation indicates the importance of evaluating the presence of visceral obesity and the risk for obesity-related HCC. In this context, it will be important to not only consider BMI but also waist circumference when determining risk of HCC among persons with metabolic liver diseases such as NAFLD. It is important to remember that features of the metabolic syndrome are shared risk factors associated with elevated HCC risk, not only among patients with NAFLD but also among those with ALD and other liver diseases.[51,52]

Progression of NAFLD-associated HCC

HCC is a lethal cancer – the average time from diagnosis to death is less than 2.5 years and only about 10% of patients survive for 5 years.[53,54] Data from the Surveillance, Epidemiology, and End Results registry with linkage to Medicare files indicated that from 2004 through 2009, the number of NAFLD-associated cases of HCC increased at an annual rate of 9%.[32] Additionally, patients with NAFLD-associated HCC were older, had a shorter survival time, had more heart disease, and were more likely to die from liver cancer than patients with other types of HCC (all p <0.0001). A diagnosis of NAFLD increased 1-year mortality 1.2-fold, especially among patients who were older and from lower-income strata.[32] A study of more than 10 million Medicare recipients determined the prevalence of NAFLD to be 5.7%, with almost 30% of patients with NAFLD found to have cirrhosis.[54] The calculated cumulative risks of NAFLD progressing to cirrhosis, and of compensated cirrhosis progressing to decompensated cirrhosis were 39% and 45% over 8 years of follow-up, respectively. Independent predictors of progression included cardiovascular disease (CVD), renal impairment, dyslipidaemia, and diabetes. The cumulative risk for HCC was 76.2% in patients with NAFLD.[54]

Studies conducted outside the United States have reported similar rates of progression. An analysis of a large patient database in Germany reported a cumulative incidence rate of end-stage liver disease (decompensated cirrhosis, liver transplant, or HCC) of 13.5% at 2 years and 16.7% at 5 years in patients with NAFLD and compensated cirrhosis.[55] In a study from Japan, the most common malignancy among patients with NAFLD or NASH was HCC; the incidence of HCC in patients with advanced or severe fibrosis (F3/F4) ranged from 10.5% to 20.0%. Among patients with NASH, mortality from HCC was 40.0% over 2.7 years.[56]

Pathophysiology of HCC in patients with NAFLD or NASH

Development of fibrosis and then cirrhosis can increase the risk of HCC. However, in patients with NAFLD, metabolic disorders such as type 2 diabetes or insulin resistance affect the risk of HCC, regardless of the presence of cirrhosis.[57–73] (Fig. 1) The pathway to carcinogenesis might involve the release of inflammatory cytokines, such as tumour necrosis factor-α (TNF), interleukin 6 (IL6), leptin, and resistin, along with decreased amounts of adiponectin. Increased secretion of TNF and reduced levels of adiponectin lead to insulin resistance and increased exposure of hepatocytes to free fatty acids. Insulin resistance inhibits oxidation of fatty acids, leading to increased intracellular fatty acids, which cause oxidative damage to DNA by stimulating microsomal peroxidases that induce genetic mutations. The mutagen 4-hydroxy-2-nonenal (4-HNE) is believed to contribute to hepatocarcinogenesis and has been associated with a

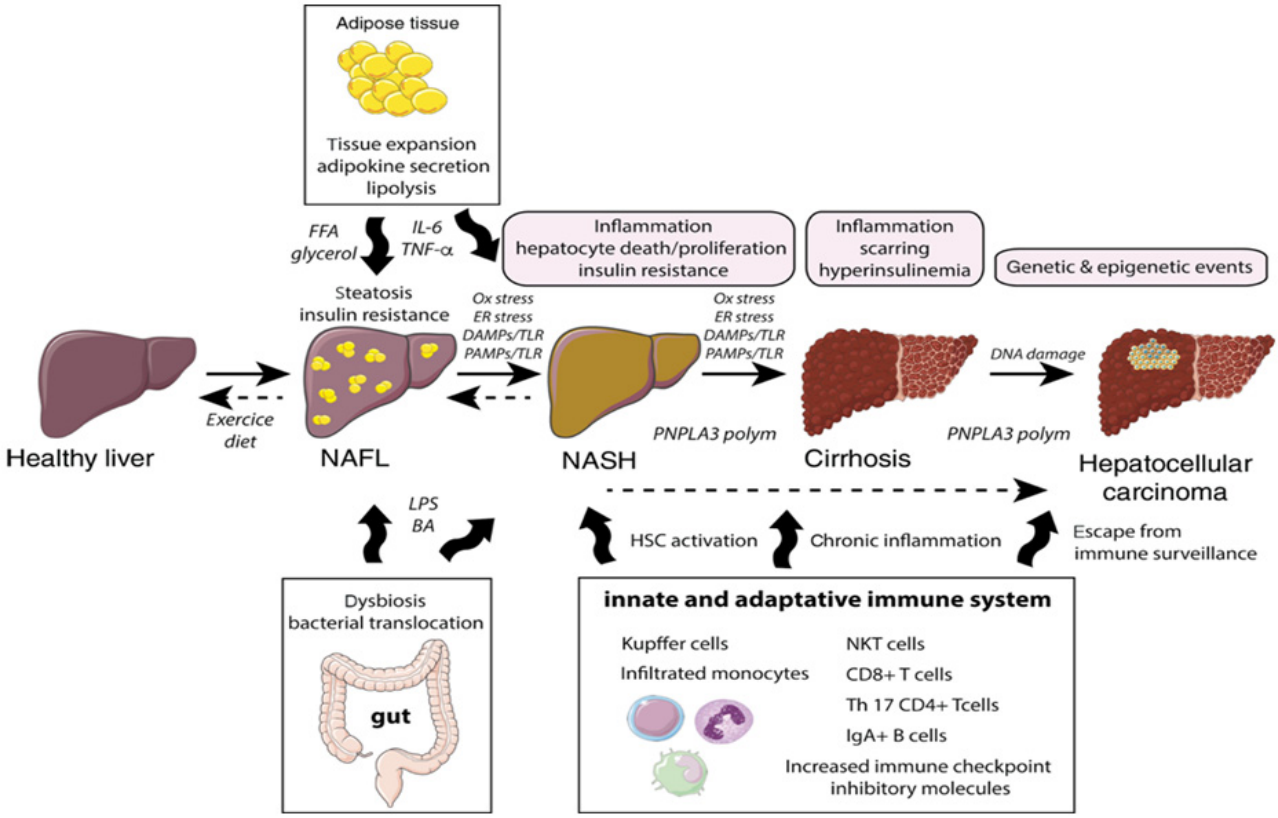

Fig. 1. Diagram of the pathophysiology of NAFLD-related hepatocellular carcinoma. NAFLD, non-alcoholic fatty liver disease. Figure reproduced with permission from DeGruyer publishing. The figure is from Lequoy M, Gigante E, Couty JP, Desbois-Mouthon C. Hepatocellular carcinoma in the context of non-alcoholic steatohepatitis (NASH): recent advances in the pathogenic mechanisms. Horm Mol Biol Clin Investig. 2020 Feb 29;41(1):/j/hmbci.2020.41.issue-1/hmbci-2019-0044/hmbci-2019-0044.xml. doi: 10.1515/hmbci-2019-0044. PMID: 32112699.

mutation at codon 249 in the *TP53* gene. In addition, insulin resistance and hyperinsulinemia cause release of insulin-like growth factor 1 and insulin receptor substrate 1, which regulate cell proliferation and inhibition of apoptosis and might contribute to the development of HCC.[57–73]

It is also important to remember that HCCs are often hypervascular, including arterialisation and sinusoidal capillarisation.[73–75] This state of increased angiogenesis is thought to result from imbalances in the vascular endothelial growth factor (VEGF), fibroblast growth factors, platelet-derived growth factors (PDGFs), angiopoietins, hepatocyte growth factor, endoglin (CD105) as well as the inhibitors of angiostatin, endostatin, thrombospondin-1, and others.[73–76]

It is important to note that obesity is a proinflammatory state. In this context, inflammation alters a pathway regulated by signal transducer and activator of transcription 3 (STAT3) to contribute to HCC initiation, progression, metastasis, and immune suppression.[77] Detection of the phosphorylated form of STAT3 in hepatocytes and hepatic stellate cells correlated with the severe histologic features of NASH, including lobular inflammation, ballooning inflammation, and an advanced stage of fibrosis.[78] These hypervascularity and pro-inflammatory states promote tumour growth and progression of HCC which may involve the entire liver or predominantly one lobe of the liver. Although there may be a predominance of HCC in the right lobe of the liver in patients with NASH, more data are needed to confirm this assertion.

Outcomes in patients with NAFLD and HCC

Patients with NAFLD have poor outcomes when they develop HCC, due to the aggressive behaviour of these tumours and shortcomings in the clinical management of these patients.[79–81] Another factor that affects outcome is lack of HCC surveillance among patients with NAFLD.[82–85] A significantly higher percentage of patients with NAFLD-associated HCC did not receive HCC surveillance in the 3 years before their HCC diagnosis compared to patients with alcohol- or HCV-associated HCC.[32] As a result, a smaller proportion of patients with NAFLD-associated HCC received HCC-specific treatment compared to patients with HCV-associated HCC.[32]

Furthermore, only 40% of HCC cases are found via surveillance while most are found incidentally when these tumours are no longer amenable to curative treatment.[86] In fact, patients with NAFLD-associated HCC most likely present with larger, single, undifferentiated tumours, which are usually beyond the Milan criteria for liver transplantation.[32,80–85]

Awareness of NAFLD as an important liver disease is relatively low among healthcare practitioners.[82–85] This could lead to lower rates of assessment for both the presence and complications of liver disease, including lower rates of screening for HCC, leading to delays in diagnosis and more advanced HCCs. Another potential contributor to delayed diagnosis is the heterogeneity of patients with NAFLD at risk of HCC. As noted previously, HCC can develop in patients with NAFLD who do not have cirrhosis.[36,37,72,80,81,87–90] Since most HCC guidelines recommend surveillance for patients with cirrhosis, diagnosing HCC before symptoms develop is difficult.[43,89] On the other hand, recommending universal screening for all patients with NAFLD is not currently cost effective. In fact, the rate of HCC in patients with NAFLD without cirrhosis is 0.21/1,000 person-years, which is lower than the threshold for screening, so screening is not recommended at this time.[91,92]

It is possible that learning more about HCC risk in patients without cirrhosis could lead to development of algorithms to identify those at higher risk for HCC. For example, patients with NAFLD with multiple risk factors (older obese men with diabetes and hypertension) might be considered for a targeted surveillance programme.[36,37,72,80,81,86–92] Large, prospective studies are needed to identify risk factors and develop appropriate surveillance protocols. Non-invasive tests are also needed to identify patients at high risk of HCC, as patients with NAFLD and evidence of advanced fibrosis might also be considered for HCC screening.[93–100]

Ultrasound is the most cost effective and widely available diagnostic modality. It should be considered as the first line of a diagnostic evaluation, when there is a good acoustic window (obesity is a major obstacle to obtaining a good acoustic window) with well trained, experienced technicians available.[94–99] Additionally, non-invasive tests such as the fibrosis 4 (FIB-4) scoring system can be used to identify patients at high risk of cirrhosis.[94,95,100,101] The FIB-4 score is derived from age and laboratory measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count; it is easily calculated using an online tool (https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis). A FIB-4 score >2.67 is the recommended cut-off for screening – scores above this cut-off value are associated with an increased risk of HCC not only in patients with cirrhosis but also in patients without a diagnosis of cirrhosis.[94,95]

However, FIB-4 scores >1.3 might be used by non-specialty clinicians to identify patients for referral to specialty care, where additional technologies to assess liver stiffness or serum fibrosis tests will be available.[101] The NAFLD fibrosis score (NFS) is calculated based on age, platelets, AST to ALT ratio, albumin levels, BMI, and fasting glucose level. Scores of 1.455 or less exclude advanced fibrosis and scores greater than 0.675 identify patients with advanced fibrosis with high accuracy.[99]

The enhanced liver fibrosis (ELF) score (an extracellular matrix marker set consisting of tissue inhibitor of metalloproteinases 1, amino-terminal propeptide of type III procollagen, and hyaluronic acid) is a relatively new test that has shown good predictive value in ruling in advanced fibrosis, but its predictive power to rule out advanced fibrosis is weaker.[100] However, when the ELF score is combined with another non-invasive test scores, such as the FIB-4 score, the positive and negative predictive power of the ELF test is excellent.[102] Further discussion of other non-invasive tests is beyond the scope of this article, but we refer the reader to the guidelines mentioned above for a complete discussion and an algorithm for application.[90,93]

Treatment

Given the aforementioned factors and challenges, with low awareness of NAFLD in clinical practice, most patients with HCC related to NAFLD present without a previous diagnosis of either NAFLD or NASH. As such, treatment options are, in many cases, limited.[98] However, if NAFLD or NASH is diagnosed before the onset of advanced fibrosis, treatment can be geared towards the prevention of advanced fibrosis. Although no medications have been approved for reversal of fibrosis in patients with NASH, several treatment regimens have shown promise. These include obeticholic acid and metabolic drugs, such as semaglutide and other similar drugs.[103–105]

Until effective treatments for NASH are approved, diet and exercise are important lifestyle modifications which improve hepatic fibrosis and potentially long-term outcomes in patients with NASH. In this context, a Mediterranean-style diet is most frequently recommended, with the goal of decreasing body weight by 5% to 10%. Diet can be accompanied by 150 minutes of moderate exercise.[106] Although lifestyle changes may impact fibrosis, the impact on long-term outcomes is not currently available.[92,107]

In addition, bariatric surgery can be an effective and successful intervention in very obese patients who meet surgical criteria.[108] Nevertheless, for patients with cirrhosis, careful consideration must be given to weighing the risks and benefits of bariatric surgery, especially as studies have demonstrated that those with cirrhosis may experience significant complications post-surgery.[109,110]

Other preventive HCC treatments should include counselling for the cessation of smoking and reducing alcohol consumption, when appropriate, as well as management of hypercholesteremia and type 2 diabetes and obesity, if present.[111,112] In fact, some treatment of risk factors for NASH may provide potential benefit for HCC. In this context, statin use has been associated with reduced progression of HCC and increased survival times in patients with diabetes and advanced HCC.[113,114] Despite these data, it is too early to provide a universal recommendation for the use of statins in the treatment of HCC. Nevertheless, statins should be continued to reduce CVD events in patients with NAFLD at high risk of CVD, as treatment with atorvastatin has been shown to reduce CVD events in patients with NAFLD.[113,114]

Another commonly used medication for patients with NAFLD is metformin for the treatment of associated type 2 diabetes. In this context, metformin has been noted to downregulate the expression of several lipogenic enzymes and *de novo* lipogenesis, which could contribute to a reduction in the risk of HCC.[115,116] In addition to metformin, the incidence of HCC was reported to be decreased among patients taking thiazolidinedione for type 2 diabetes, whereas patients taking alpha-glucosidase inhibitors appeared to have an increased risk of HCC while sulfonylureas or meglitinides had no effects.[117] Although the mechanism is not entirely clear, pioglitazone is a PPAR-γ agonist and helps to regulate glucose, lipid metabolism, and inflammation by restoring insulin sensitivity in adipose tissue, hepatocytes, and muscle cells. In patients with NASH, pioglitazone seems to improve steatosis, inflammation, and the stage of fibrosis.[118] However, given the potential side effects of weight gain and bone loss in women, as well as not being indicated in those with left ventricular heart failure, the risks and benefits need to be considered carefully prior to widespread use.[90,118] Finally, glucagon-like peptide-1 receptor agonists (liraglutide and semaglutide) can lower glucose levels by increasing insulin secretion, reducing glucagon concentration, suppressing appetite (resulting in weight loss), and increasing sensitivity to insulin in hepatocytes and adipocytes. In a large trial of liraglutide in patients with NASH, significant improvement in hepatic inflammation was noted compared to placebo.[105] More recently, semaglutide has been shown to be effective in improving steatohepatitis but not hepatic fibrosis.[119] Given the high prevalence of diabetes among individuals with NAFLD or NASH, this information could help physicians select anti-diabetic agents which may improve

Table 1. Treatment options for those with NASH-related HCC.*

Treatment category and criteria	Name	Survival benefit
Curative • Single liver nodule less than 2 cm • Barcelona Clinic Liver Cancer (BCLC) stage 0 • Early stage HCC (BCLC stage A) who have a single nodule less than 5 cm or 3 or fewer nodules less than 3 cm. • Transplant candidacy is determined primarily by the Milan Criteria: a single tumour less than 5 cm in diameter, or up to 3 tumours not larger than 3 cm in diameter, confined to the liver	1. Liver transplantation 2. Radiofrequency ablation 3. Surgical resection	1. Five years or greater (above references) 2. 34% alive at 5 years with better survival associated with Child-Pugh A, albumin–bilirubin score 1, single-nodule tumour sized <2 cm, and alpha-fetoprotein <20 ng/ml. 3. 7.2% alive at 10 years with better survival for those with better hepatic function, a wider surgical margin and the absence of satellite lesions at the time of the resection.[120]
Palliative • Interventional Radiology • Tyrosine kinase inhibitors medications	1. Transarterial chemoembolization-TACE 2. Sorafenib, an oral multikinase inhibitor that inhibits tumour cell progression and angiogenesis (Other medications and for those who progress on sorafenib include: lenvatinib (not used in the United States), regorafenib (not used in the United States), and nivolumab (in the United States nivolumab is only allowed to be administered in combination with ipilumamab after progression on sorafenib) Medications that can be used as first line therapy rather than Sorafenib include lenvatinib (not approved in the United States) and atezolizumab plus bevacizumab (approved for use in the United States and only for those without prior systemic treatment)	1. Approximately 13.4 months; however dependent on stage of disease ex. BCLC stage C or greater.[108] 2. Approximately 3 months but dependent on macroscopic vascular invasion, high alpha fetoprotein, and high neutrophil-to-leukocyte at start of treatment.[110] 3. The newer medication may extend life several more months than sorafenib.[123]

HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis.
* These are general to HCC treatment and survival may be affected by liver disease aetiology.

NASH outcomes, including HCC. Nevertheless, further studies are needed to confirm the long-term benefits of these agents.

It is important to remember that once HCC develops, other treatment options must be considered. For patients with early-stage HCC, there are several potentially curative treatment options, including radiofrequency ablation, surgical resection, and liver transplantation. In this context, liver transplantation is associated with the longest survival time (median 5 years)[120–122] (Table 1). Given that HCC is usually detected at a relatively late stage, most patients are not candidates for liver transplantation but may be eligible for palliative therapies including interventional radiology procedures such as transarterial chemoembolisation.[123,124]

Finally, systemic treatment for HCC has become an option for those with advanced disease. In this context, advanced HCC is treated with tyrosine kinase inhibitors such as sorafenib, lenvatinib, and regorafenib which target the known HCC pathways.[125–130] The most commonly used treatment is sorafenib, an oral multi-kinase inhibitor that inhibits tumour cell progression and angiogenesis by blocking the VEGF/PDGF pathways and the STAT3 pathway. Currently, sorafenib appears to confer a survival benefit of almost 3 months compared to placebo (sorafenib *vs.* placebo [10.7 *vs.* 7.9 months; hazard ratio 0.69; 95% CI 0.55–0.87; p <0.001]) which was validated in a study conducted in the Asia-Pacific region. The prognostic factors shown to play a role in poorer survival included: macroscopic vascular invasion, high alpha-fetoprotein, and high neutrophil-to-leukocyte ratio, while predictors of better survival included no extrahepatic spread, having HCV compared to other liver diseases and a low neutrophil-to-leukocyte ratio.[127] However, the benefits and risks of sorafenib in patients with NAFLD/NASH are incompletely understood, especially as this population tends to be older and more likely to have comorbidities which limit the use of sorafenib. Therefore, more studies are needed that focus on the use of sorafenib in those with NAFLD/NASH, especially given the concurrent limitation of assessing liver function in those with NAFLD/NASH.[130] Until recently only a few other medications had been approved for the treatment of non-resectable HCC, especially if one progresses on sorafenib. These medications included lenvatinib which has been shown to be non-inferior to sorafenib as a first-line therapy; regorafenib which is a globally approved treatment option for patients who progress on sorafenib, as well as nivolumab in combination with ipilumamab which is the only approved post-sorafenib option in the United States.[131–134] However, a new combination consisting of atezolizumab plus bevacizumab led to better overall and progression-free survival outcomes than sorafenib in a recent phase III trial.[135] As a result, in May of 2020, the FDA approved atezolizumab plus bevacizumab for use in non-resectable HCC among patients who have not received prior systemic treatment.[135] Interestingly, none of these medications were directly studied for their effects on NAFLD/NASH-related HCC, so further studies are warranted to determine the effect of these medications on NAFLD-related HCC and survival.

As noted, liver transplantation, which has the highest odds of increasing survival, presents many challenges for patients with NASH-associated HCC. Since many patients with NASH have obesity and other related comorbidities, these patients are at an increased risk of death while awaiting a liver.[136–141] Furthermore, these patients can develop fatty liver or steatohepatitis when they receive a transplanted liver which can potentially impact their post-transplant course.[136–141]

Conclusion

The prevalence of HCC is increasing exponentially due to worldwide increases in obesity and type 2 diabetes, and therefore NASH. In fact, the prevalence of NASH and ALD is increasing and they could soon replace viral hepatitis-associated HCC as the top indication for liver transplant. However, NASH-associated HCC is usually detected late in its course when only palliative treatment is available. Therefore, efforts must focus not only on prevention of NAFLD and NASH, but also on increasing awareness of NAFLD, so that treatment and timely referral to specialty care can be accomplished and this trend can be reversed.

Abbreviations

ALD, alcohol-related liver disease; CVD, cardiovascular disease; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PDGF, platelet-derived growth factor; STAT3, signal transducer and activator of transcription 3; TNF, tumour necrosis factor-α; VEGF, vascular endothelial growth factor.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

ZMY, manuscript development, writing and editing; LH, manuscript development, writing and editing.

Supplementary data

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