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REVIEW ARTICLE

Hepatocellular carcinoma and non-alcoholic fatty liver disease

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Abstract
Nonalcoholic fatty liver disease (NAFLD) is considered the most common liver disorder worldwide, affecting 25.2% of the general population. In fact, NAFLD is among the most common etiologies for hepatocellular carcinoma (HCC). The burden of NAFLD is primarily driven by the epidemic of obesity and type 2 diabetes which are expected to worsen throughout the world. In this context, the burden of NAFLD and associated HCC and cirrhosis are also expected to increase. Despite its growing disease burden, diagnostic tools and treatment modalities remain very limited. This conundrum of increasing prevalence and limited treatment options will be reflected as increasing number of NAFLD-related cirrhosis and HCC cases. This article reviews the most updated information about NAFLD-related HCC and provides some insight into strategies that must be considered to reduce its potential disease burden.

Keywords Non-alcoholic fatty liver disease · Non-alcoholic steatohepatitis · Cirrhosis · Hepatocellular carcinoma · Hepatitis C virus · Hepatitis B virus

Abbreviations

DM	Diabetes mellitus
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PNPLA3	Patatin-like phospholipase domain containing 3
SNPs	Single-nucleotide polymorphisms
TM6SF2	Transmembrane 6 superfamily member 2

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of metabolic fatty liver disorders, the hallmark of which is excessive fat deposition in the hepatic parenchyma [1–3]. The pathologic spectrum of NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), advanced fibrosis and cirrhosis which increases the risk of progression to end stage liver disease [4, 5]. Furthermore, it is now recognized that cryptogenic cirrhosis is most likely burnt-out NASH [6]. Although simple steatosis is recognized as a relatively benign liver disease with limited risk of progression, NASH is clearly associated with a progressive course of disease where approximately 20% of patients could potentially develop cirrhosis or its complications [7, 8].

The development of cirrhosis is associated with a significantly increased risk of hepatocellular carcinoma (HCC), with the annual incidence of HCC arising from cirrhosis ranging from 2 to 5% [9, 10]. Although historically, chronic viral hepatitis B (HBV) or C (HCV) have been responsible for the majority of HCC cases, the advent of highly effective treatment for HBV and HCV is expected to change this trajectory. On the other hand, the prevalence of NAFLD and NASH is increasing with very limited effective treatment options. This is leading to increasing numbers of NAFLD or NASH-related HCC [11–15]. A recent study from the United States revealed that among patients with HCC, NAFLD was the most common underlying etiology in the Medicare database [16].

In fact, worldwide, approximately 2 billion adults are obese or overweight [17, 18] and an estimated 415 million people have diabetes worldwide, which together are playing

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a significant role in the rise of NAFLD, especially in the USA and Western countries [19–21]. Additionally, type 2 diabetes has become a daunting epidemic in the Asia Pacific region, with some experts estimating a 150% increase in diabetes rate between 2000 and 2035, emphasizing the increasing burden of the disease to that region of the world [22, 23]. The prevalence of NAFLD in the obese and diabetics can be over 50%. Furthermore, the global prevalence of NAFLD in the general population is about 25.2% with the highest prevalence rates (over 30%) reported from the Middle East and South America [17, 18]. However, due to its high population and changing lifestyle habits, Asia is likely to have the highest number of patients with diabetes and metabolic syndrome, the conditions that boost the incident NAFLD cases [24]. In this context, a recent meta-analysis revealed that the prevalence of NAFLD in Asia is 30%, regardless of the diagnostic method [25].

Other studies, which used steady-state prevalence models, reported higher prevalences of NAFLD with predictions that 64 million people in the US and 52 million people in Germany, France, Italy and the UK have NAFLD [17, 18]. In a separate modeling study, it was forecasted that cases of NAFLD are to increase from 83 million cases in 2015 to 101 million by 2030, and NASH cases will increase from 1.5 to 2.7 million by 2030 [17, 26]. It should be noted that the definition of obesity is not uniform across the globe and individuals in the Asia–Pacific region tend to have a lower BMI than the rest of the world. In this part of the world, recent studies have also demonstrated a growing problem with both obese NAFLD as well as lean NAFLD and lean NASH. Interestingly, a study from Bangladesh reported that among patients with NAFLD, 25% of the study population was non-obese and the prevalence of NASH in the non-obese patients was as high as 53% [27].

Although the prevalence of NASH in the general population is not available, it is estimated to be 1.5% and 6.5% [15, 17, 28]. Although NAFLD and NASH both have ≥ 5% hepatic steatosis, the inflammation with hepatocyte injury which is present in NASH seems to be a surrogate of a more progressive form of liver disease. This point is important as it is the presence of fibrosis that is independently associated with mortality in those with NAFLD/NASH [2, 29–32]. On the other hand, the progression of fibrosis in NASH is non-linear. In fact, it has been suggested that periods of fibrosis progression in NASH may be followed by periods of regression. The exact factors promoting progression or regression in NASH are not known. Nevertheless, on an average about 15–20% of patients with NASH can experience a progressive course leading to cirrhosis [33].

As noted previously, the exact factors responsible for progression in NASH are not known. Nevertheless, disease progression in NASH can be influenced by both biological and genetic mechanisms which include chronic hyperinsulinemia, dysbiosis of gut microbiota (which includes activation of the toll-like receptor 4), elevated levels in the deoxycholic bile acid, and polymorphisms in the genes patatin-like phospholipase domain-containing 3 (PNPLA3) and transmembrane 6 superfamily member 2 (TM6SF2). The exact interaction of these factors in determining the course of NASH is not known.

As previously noted, fibrosis stage determines prognosis in NASH. Although liver biopsy is the current gold standard of staging fibrosis, it has major limitations. In this context, a number of non-invasive tests such as NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4), AST to platelet ratio index (APRI) have been developed to risk stratify NASH patients at risk for advanced fibrosis [34–36]. These non-invasive tests are easy to use as they are compiled from routine laboratory tests and clinical measurements. In addition to the risk of advanced fibrosis, these patients are also at risk for HCC. In this context, the GALAD score which is comprised of gender, age, lens culinaris agglutinin-reactive α-fetoprotein, α-fetoprotein, and des-γ-carboxyprothrombin was developed to determine the likelihood for an individual patient with cirrhosis to have HCC [37]. Having these non-invasive tests to risk stratify patients with NASH and advanced fibrosis or even HCC may help clinician decide when a patient may need to be sent for further diagnostic work-up without presenting patients with undue risk.

The pathogenesis of NAFLD and NAFLD-related HCC

Hepatic steatosis is caused by the accumulation of fat in hepatocytes through various mechanisms. One mechanism is related to increased free fatty acid supply to liver cells, either due to increased dietary fat or by increased lipolysis in the adipose tissue [38]. This increased influx of lipid particles into the liver cells results in increased de novo hepatic lipogenesis, decreased free fatty acid oxidation, and decreased very low-density lipoprotein secretion, all leading to accumulation of fat in the liver [39].

In patients with NAFLD, the main type of lipid stored in the hepatocytes are triglycerides. On the other hand, in some patients with NAFLD, accumulation of free fatty acids in the hepatocytes, especially in the mitochondria, can lead to the formation of reactive oxygen radicals which can mediate hepatocyte injury, leading to NASH and fibrosis [40]. Furthermore, insulin resistance and hyperinsulinemia, typically seen in patients with NAFLD, can lead to increased hepatic lipogenesis, followed by impaired suppression of increased lipolysis in adipose tissue, resulting in an increased influx of free fatty acid to the liver, making hepatocytes more susceptible to various other insults, such as oxidative stress from reactive oxygen radicals, activation of transforming

growth factor beta (TGF-beta), dysregulated and increased hepatocyte apoptosis, stellate cell activation, and dysregulation of adipocytokines [38, 41]. These pathogenic processes which result in hepatocyte injury fall under the "multiple-hit hypothesis" in which multiple hits to a fatty liver are required to cause progressive liver disease.

As this process continues, inflammatory pathways and stellate cells are activated leading to hepatic fibrosis and in some patients, cirrhosis. Furthermore, cirrhosis can predispose some of these patients with NASH to hepatocellular carcinoma (HCC). Although HCC in NAFLD primarily arises in patients with underlying cirrhosis, some patients with NAFLD or NASH can develop HCC in the absence of cirrhosis. The exact pathogenesis of HCC in NAFLD has not been fully described but both obesity and diabetes seem to play a critical role. In this context, secretion of pro-inflammatory cytokines like TNF-alpha and interleukin-6 may lead to the activation of the signal transducer and the activator of transcription 3, both of which are potentially involved in tumor pathogenesis [42]. On the other hand, in some patients, changes in the gut microbiota may cause production of reactive oxygen species, which in turn leads to DNA damage and increased risk of cancer development in NASH [43]. Finally, as described below, there is a genetic predisposition to cancer in some patients, especially in those who carry PNPLA3 rs378409 allele in a homozygote way [44].

The incidence of NAFLD-related HCC

Worldwide, primary liver cancer is the seventh most common form of newly diagnosed cancer, and the third leading cause of cancer related death. [45, 46]. Although viral hepatitis remains responsible for an estimated 60–85% of HCC cases worldwide, NAFLD/NASH-related HCC is increasingly becoming an important cause of HCC. By some estimates, NAFLD/NASH may be responsible for 30-40% of HCC cases worldwide [47].

Although the exact incidence rates for HCC are not available for many countries in the world, one meta-analysis suggests that the global annual incidence of HCC in persons with NAFLD is estimated to be 0.44 per 1000 person-years, while for those with NASH, the incidence of HCC is higher at 5.29 per 1000 person years most likely due to the inflammatory state in those with NASH which promotes fibrosis and disease progression [18]. In another study using data from the Surveillance, Epidemiology, and End Results database, investigators determined that there was a 9% annual increase in the number of HCC cases attributed to NAFLD covering a 6-year period of time from 2004 to 2009. These investigators and others have also found that persons with NAFLD-related HCC incur a shorter survival time after diagnosis which may be related to NAFLD-related HCC being diagnosed at a more advanced stage as compared to other liver disease such as viral hepatitis. Also, NAFLD-related HCC seems to occur as a large solitary mass that is moderately to well differentiated which makes them suboptimal candidates for curative resection or liver transplantation [7, 48–51].

Although the risk of HCC is higher in NASH-related cirrhosis, there is also evidence that HCC can occur in the absence of cirrhosis in NAFLD and NASH [52]. In fact, according to one study, only 35.5% of NAFLD related HCC cases occurred in patients who had bridging fibrosis or cirrhosis on biopsy [7]. To compare with other liver diseases, patients with NAFLD are five times more likely than patients with HCV to develop HCC in the absence of cirrhosis [50, 53]. However, there is some evidence in regards to the interaction of hepatitis B virus (HBV) with NAFLD and liver disease outcomes. In fact, the presence of fatty liver in those with chronic hepatitis B (CHB) patients has been reported to contribute to HBsAg seroclearance. Additionally, some authors have reported an association between hepatic steatosis and HBV with development of advanced liver fibrosis and/or HCC. In contrast, other authors have failed to confirm these findings [54–59]. Therefore, further study is warranted before a determination can be made about the interaction of NAFLD, CHB and liver outcomes [4, 15, 16].

Risk factors for NAFLD-related HCC

There are a number of important risk factors that can potentially promote HCC in patients with NASH. In one population-based cohort study, the incidence of primary liver cancer was increased fourfold in patients with clinical diabetes and this risk was independent of other factors (i.e. alcoholism, cirrhosis and hepatitis) [60]. Other studies have suggested that a combination of both T2DM and obesity doubles the risk for HCC [50, 61, 62]. The mechanisms involved in this increased risk related to diabetes is not well understood, but it has been postulated that years of hyperinsulinemia and elevated levels of proinsulin and split products of proinsulin interact with liver cells which stimulate mitogenesis or carcinogenesis [60].

Similar to other studies of HCC, men have been noted to have an increased incidence of NASH-related HCC [63, 64]. A number of genetic factors have also been implicated. In this context, a range of single-nucleotide polymorphisms (SNPs) have been linked with the presence of NAFLD and the risk of disease progression to advanced fibrosis [33, 65]. Patatin-like phospholipase domain containing 3 (PNPLA3) and transmembrane 6 superfamily member 2 (TM6SF2) have been strongly associated with the severity of steatosis [66]. PNPLA3 polymorphism is believed to impair mobilization

of triglycerides from hepatic lipid droplets, and TM6SF2 variant is thought to impair the trafficking of pre-VLDL particles. PNPLA3 polymorphisms are noted to not only lead to increased risk for steatohepatitis and fibrosis, but also to a threefold increased risk of HCC. Risk is independent of age, gender, body mass index (BMI), type 2 diabetes mellitus (T2DM), and presence of fibrosis or cirrhosis [67].

Prognosis of NAFLD-associated HCC

Prognosis of NAFLD-related HCC seems to be worse than other liver diseases. A recent prospective comparative observational study of patients with NAFLD-related HCC and HCV-related HCC found that patients with NAFLD-associated disease incurred a shorter survival than patients with HCV-related disease [13]. This is likely due to late detection with higher tumor burden with NAFLD-related HCC. When matched for tumor stage, there was no difference in survival between the groups suggesting that it was not NAFLD itself that worsened the prognosis, but the tumor burden which could have been related to timely and appropriate screening [50, 68].

Currently, the American Association for the Study of Liver Diseases (AASLD) recommends that all patients with cirrhosis should undergo HCC surveillance with abdominal US every 4–6 months [67, 69]. Unfortunately, surveillance is less likely to detect early HCC in patients with NAFLD. This may be related to a number of reasons one of which is the failure of ultrasound to detect small HCC in patients with visceral obesity. Added to this, occurrence of HCC in the absence of cirrhosis will not target these individuals for screening [67]. A recent study which looked at the cost-effectiveness of screening all patients with NASH without cirrhosis concluded that this strategy is not currently cost-effective [70].

Treatment options

As with all cases of HCC, NAFLD-associated HCC staging is based on liver function, performance status, along with tumor number, size and spread [67]. The choice of treatment is highly driven by the stage of HCC, the hepatic function of the host, and the presence of other co-morbidities as well as available expertise. In terms of staging, although there are numerous staging algorithms available, Barcelona Clinic Liver Cancer (BCLC) staging is one of the most commonly used systems. Given the fact that NAFLD-associated disease is typically diagnosed at later stages, treatment options are typically limited. In the case that NAFLD-associated HCC is detected at an early stage, local ablation, transarterial chemoembolization (TACE), resection and transplantation are potential treatment options [47, 67]. Previous studies have reported that liver transplantation is associated with a 75% 5-year survival rate in early-stage HCC [47]. Recent data from the United States revealed that the number of patients with NAFLD-associated HCC who underwent a transplant increased by fourfold, making it the fastest growing indication for liver transplantation [17, 71]. However, given the disease burden at the time of diagnosis, the vast majority of NAFLD-associated HCC patients are treated with supportive care.

Therefore, the focus of treatment in patients with NAFLD will be to decrease their risk of progression to fibrosis, cirrhosis or HCC. Given the large metabolic syndrome component of the disease, controlling diabetes, hypertension and hyperlipidemia are paramount. More specifically, a recent meta-analysis concluded that incidence of HCC was reduced by 50% when metformin was used for diabetes treatment but was increased with sulfonylurea or insulin, and unchanged with glitazones [72, 73]. In another large study, investigators determined that the use of liraglutide and sitagliptin with metformin (but not insulin or glargine) significantly reduced body weight, intrahepatic lipids, and visceral adipose tissue in addition to improving glycemic control [74]. Statins, through antiproliferative, proapoptotic, anti-angiogenic, and immunomodulatory effects, may reduce HCC as well. Another meta-analysis found, that with the use of statins, the risk of HCC was reduced by 37% after adjusting for all other confounders. Further reduction in other risks may complement and lead to a reduction in the rate of HCC [75, 76].

Summary

In conclusion, the incidence of NAFLD-associated HCC is on the rise. As we continue to implement highly effective treatments for HBV- and HCV-related liver disease, NAFLD is rapidly becoming an important cause of HCC in the world. However, NAFLD-associated HCC carries a poor prognosis given that few patients with NASH-HCC are candidates for curative treatment such as liver transplantation since most patients have large tumors or significant comorbidities which preclude curative interventions. Therefore, the most optimal strategy is prevention of HCC. Thus, preventative interventions should focus on risk mitigation through the management of obesity, diabetes and hyperlipidemia and early detection in patients at high risk for HCC such as those with advanced fibrosis. Future research is needed to develop tests that can better detect the early stages of disease as well as a cost-effective non-invasive test that can reliably predict development of HCC in NASH. These tests can become a part of clinical guidelines to help clinicians more appropriately manage NAFLD/NASH patients who are at high risk for HCC.

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Compliance with ethical standards

Conflict of interest Zobair M. Younossi has received research funds or served as consultant to Gilead Sciences, Intercept, NovoNordisk, BMS, Abbvie, BMS, Terns and Viking. Pegah Golabi, Logan Rhea and Linda Henry have no conflict of interest to disclose.

References

1. Younossi ZM, Loomba R, Anstee QM, Rinella ME, Bugianesi E, Marchesini G, et al. Diagnostic modalities for non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and associated fibrosis. Hepatology. 2017. https://doi.org/10.1002/hep.29721
2. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–357. https://doi.org/10.1002/hep.29367
3. Golabi P, Otgonsuren M, de Avila L, Sayiner M, Rafiq N, Younossi ZM. Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD). Medicine 2018;97:e0214. https://doi.org/10.1097/MD.0000000000010214
4. Younossi ZM, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology 2011;53:1874–1882. https://doi.org/10.1002/hep.24268
5. Younossi ZM, Stepanova M, Rafiq N, Henry L, Loomba R, Makhlouf H, et al. Nonalcoholic steatofibrosis independently predicts mortality in nonalcoholic fatty liver disease. Hepatol Commun 2017;1:421–428. https://doi.org/10.1002/hep4.1054
6. Younossi Z, Stepanova M, Sanyal AJ, Harrison SA, Ratziu V, Abdelmalek MF, et al. The conundrum of cryptogenic cirrhosis: adverse outcomes without treatment options. J Hepatol 2018;69:1365–1370. https://doi.org/10.1016/j.jhep.2018.08.013
7. Paradis V, Zalinski S, Chelbi E, Guedj N, Degos F, Vilgrain V, et al. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. Hepatology 2009;49:851–859. https://doi.org/10.1002/hep.22734
8. Golabi P, Sayiner M, Fazel Y, Koenig A, Henry L, Younossi ZM. Current complications and challenges in nonalcoholic steatohepatitis screening and diagnosis. Expert Rev Gastroenterol Hepatol 2016;10:63–71. https://doi.org/10.1586/17474124.2016.1099433
9. Younossi Z, Henry L. Contribution of alcoholic and nonalcoholic fatty liver disease to the burden of liver-related morbidity and mortality. Gastroenterology 2016;150:1778–1785. http://dx.doi.org/10.1053/j.gastro.2016.03.005
10. Kim D, Li AA, Perumpail BJ, Gadiparthi C, Kim W, Cholankeril G, et al. Changing trends in etiology-based and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. Hepatology 2019. https://doi.org/10.1002/hep.30161
11. Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. J Clin Oncol 2016;34:1787–1794. https://doi.org/10.1200/JCO.2015.64.7412
12. Altekruse SF, Devesa SS, Dickie LA, McGlynn KA, Kleiner DE. Histological classification of liver and intrahepatic bile duct cancers in SEER registries. J Registry Manag 2011;38:201–205. https://www.ncbi.nlm.nih.gov/pubmed/23270094. Accessed 25 Oct 2019
13. Golabi P, Fazel S, Otgonsuren M, Sayiner M, Locklear CT, Younossi ZM. Mortality assessment of patients with hepatocellular carcinoma according to underlying disease and treatment modalities. Medicine 2017;96:e5904. https://doi.org/10.1097/MD.0000000000005904
14. Sayiner M, Golabi P, Younossi ZM. Disease burden of hepatocellular carcinoma: a global perspective. Dig Dis Sci 2019. https://doi.org/10.1007/s10620-019-05537-2
15. Sayiner M, Younossi ZM. Identifying patients at risk from nonalcoholic fatty liver-related hepatocellular carcinomas. Hepat Oncol 2016;3:101–103. https://doi.org/10.2217/hep-2016-0002
16. Hester D, Golabi P, Paik J, Younossi I, Mishra A, Younossi ZM. Among medicare patients with hepatocellular carcinoma, non-alcoholic fatty liver disease is the most common etiology and cause of mortality. J Clin Gastroenterol 2019. https://doi.org/10.1097/MCG.0000000000001172
17. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019;70:151–171. https://doi.org/10.1016/j.jhep.2018.09.014
18. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84. https://doi.org/10.1002/hep.28431
19. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11–20. https://doi.org/10.1038/nrgastro.2017.109
20. Kim D, Touros A, Kim WR. Nonalcoholic fatty liver disease and metabolic syndrome. Clin Liver Dis 2018;22:133–140. https://doi.org/10.1016/j.cld.2017.08.010
21. Ogurtsova K, da Rocha-Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 2017;128:40–50. https://doi.org/10.1016/j.diabres.2017.03.024
22. Nanditha A, Ma RCW, Ramachandran A, Snehalatha C, Chan JCN, Chia KS, et al. Diabetes in Asia and the Pacific: implications for the global epidemic. Diabetes Care 2016;39:472–485. https://doi.org/10.2337/dc15-1536
23. Unnikrishnan R, Pradeepa R, Joshi SR, Mohan V. Type 2 diabetes: demystifying the global epidemic. Diabetes 2017;66:1432–1442. https://doi.org/10.2337/db16-0766
24. Wong VWS, Chu WCW, Wong GLH, Chan RSM, Chim AML, Ong A, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. Gut 2012;61:409–415. https://doi.org/10.1136/gutjnl-2011-300342
25. Li J, Zou B, Yeo YH, Feng Y, Xie X, Lee DH, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2019;4:389–398 https://doi.org/10.1016/S2468-1253(19)30039-1
26. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018;67:123–133. https://doi.org/10.1002/hep.29466
27. Alam S, Gupta UD, Alam M, Kabir J, Chowdhury ZR, Alam AKMK. Clinical, anthropometric, biochemical, and histological characteristics of nonobese nonalcoholic fatty liver disease patients of Bangladesh. Indian J Gastroenterol 2014;33:452–457. https://doi.org/10.1007/s12664-014-0488-5

28. Lazo M, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, et al. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988–1994. Am J Epidemiol 2013;178:38–45. https://doi.org/10.1093/aje/kws448
29. Hagström H, Nasr P, Ekstedt M, Hammar U, Stål P, Hultcrantz R, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017;67:1265–1273. https://doi.org/10.1016/j.jhep.2017.07.027
30. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389–397.e10. https://doi.org/10.1053/j.gastro.2015.04.043
31. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology 2017;65:1557–1565. http://dx.doi.org/10.1002/hep.29085
32. Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547–1554. https://doi.org/10.1002/hep.27368
33. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13:643–654.e1–9. https://doi.org/10.1016/j.cgh.2014.04.014 **(quiz e39–40)**
34. Alkhouri N, McCullough AJ. Noninvasive diagnosis of NASH and liver fibrosis within the spectrum of NAFLD. Gastroenterol Hepatol 2012;8:661–668. https://www.ncbi.nlm.nih.gov/pubmed/24683373. Accessed 25 Oct 2019
35. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA 2015;313:2263–2273. https://doi.org/10.1001/jama.2015.5370
36. Atay K, Canbakan B, Alan O, Koroglu E, Hatemi I, Kepil N et al. Evaluation of non-invasive diagnostic methods as indicators of fibrosis in patients with nonalcoholic fatty liver disease. Biomed Res 2017. http://www.biomedres.info/biomedical-research/evaluation-of-noninvasive-diagnostic-methods-as-indicators-of-fibrosis-in-patients-with-nonalcoholic-fatty-liver-disease.html. Accessed 25 Oct 2019
37. Johnson PJ, Pirrie SJ, Cox TF, Berhane S, Teng M, Palmer D, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev 2014;23:144–153. https://doi.org/10.1158/1055-9965.EPI-13-0870
38. Fabbrini E, Mohammed BS, Magkos F, Korenblat KM, Patterson BW, Klein S. Alterations in adipose tissue and hepatic lipid kinetics in obese men and women with nonalcoholic fatty liver disease. Gastroenterology 2008;134:424–431. https://doi.org/10.1053/j.gastro.2007.11.038
39. Perla FM, Prelati M, Lavorato M, Visicchio D, Anania C. The role of lipid and lipoprotein metabolism in non-alcoholic fatty liver disease. Children 2017. https://doi.org/10.3390/children4060046
40. Nassir F, Ibdah JA. Role of mitochondria in nonalcoholic fatty liver disease. Int J Mol Sci 2014;15:8713–42. https://doi.org/10.3390/ijms15058713
41. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism 2016;65:1038–1048. https://doi.org/10.1016/j.metabol.2015.12.012
42. Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer. Eur J Cancer 2005;41:2502–2512. https://doi.org/10.1016/j.ejca.2005.08.016
43. Dongiovanni P, Romeo S, Valenti L. Hepatocellular carcinoma in nonalcoholic fatty liver: role of environmental and genetic factors. World J Gastroenterol 2014;20:12945–12955. https://doi.org/10.3748/wjg.v20.i36.12945
44. Krawczyk M, Stokes CS, Romeo S, Lammert F. HCC and liver disease risks in homozygous PNPLA3 p.I148M carriers approach monogenic inheritance. J Hepatol 2015. https://doi.org/10.1016/j.jhep.2014.10.048
45. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol 2013. https://doi.org/10.1097/MCG.0b013e3182872f29
46. Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, Kohler B, et al. Cancer incidence in five continents: inclusion criteria, highlights from volume X and the global status of cancer registration. Int J Cancer 2015;137:2060–2071. https://doi.org/10.1002/ijc.29670
47. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118–1127. https://doi.org/10.1056/NEJMra1001683
48. Singal AG, Manjunath H, Yopp AC, Beg MS, Marrero JA, Gopal P, et al. The effect of PNPLA3 on fibrosis progression and development of hepatocellular carcinoma: a meta-analysis. Am J Gastroenterol 2014;109:325–334. https://doi.org/10.1038/ajg.2013.476
49. Younossi ZM, Otgonsuren M, Henry L, Venkatesan C, Mishra A, Erario M, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology 2015;62:1723–1730. https://doi.org/10.1002/hep.28123
50. Piscaglia F, Svegliati-Baroni G, Barchetti A, Pecorelli A, Marinelli S, Tiribelli C, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. Hepatology 2016;63:827–838. https://doi.org/10.1002/hep.28368
51. Giannini EG, Marabotto E, Savarino V, Trevisani F, di Nolfo MA, Del Poggio P, et al. Hepatocellular carcinoma in patients with cryptogenic cirrhosis. Clin Gastroenterol Hepatol 2009;7:580–585. https://doi.org/10.1016/j.cgh.2009.01.001
52. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol 2018. https://doi.org/10.1016/j.cgh.2018.05.057
53. Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2016;14:124–131.e1. https://doi.org/10.1016/j.cgh.2015.07.019
54. Chen YC, Sheen IS, Chu CM, Liaw YF. Prognosis following spontaneous HBsAg seroclearance in chronic hepatitis B patients with or without concurrent infection. Gastroenterology 2002;123:1084–1089. https://doi.org/10.1053/gast.2002.36026
55. Chu CM, Lin DY, Liaw YF. Clinical and virological characteristics post HBsAg seroclearance in hepatitis B virus carriers with hepatic steatosis versus those without. Dig Dis Sci 2013;58:275–281. https://doi.org/10.1007/s10620-012-2343-9
56. Seto WK. Chronic hepatitis B and metabolic risk factors: a call for rigorous longitudinal studies. World J Gastroenterol 2019;25:282–286. https://doi.org/10.3748/wjg.v25.i3.282
57. Yilmaz B, Koklu S, Buyukbayram H, Yalçin K, Korkmaz U, Posul E, et al. Chronic hepatitis B associated with hepatic steatosis, insulin resistance, necroinflammation and fibrosis. Afr Health Sci 2015;15:714–718. https://doi.org/10.4314/ahs.v15i3.3

58. Charatcharoenwitthaya P, Pongpaibul A, Kaosombatwattana U, Bhanthumkomol P, Bandidniyamanon W, Pausawasdi N, et al. The prevalence of steatohepatitis in chronic hepatitis B patients and its impact on disease severity and treatment response. Liver Int 2017;37:542–551 https://doi.org/10.1111/liv.13271.
59. Wang CC, Kao JH. Hepatitis B virus infection and decreased risk of nonalcoholic fatty liver disease: a cohort study. Hepatology 2017. https://doi.org/10.1002/hep.29252
60. Adami HO, Chow WH, Nyrén O, Berne C, Linet MS, Ekbom A, et al. Excess risk of primary liver cancer in patients with diabetes mellitus. J Natl Cancer Inst 1996;88:1472–1477. https://doi.org/10.1093/jnci/88.20.1472
61. Nair S, Mason A, Eason J, Loss G, Perrillo RP. Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? Hepatology 2002;36:150–155. https://doi.org/10.1053/jhep.2002.33713
62. Lagiou P, Kuper H, Stuver SO, Tzonou A, Trichopoulos D, Adami HO. Role of diabetes mellitus in the etiology of hepatocellular carcinoma. J Natl Cancer Inst 2000;92:1096–1099. https://doi.org/10.1093/jnci/92.13.1096
63. Yasui K, Hashimoto E, Komorizono Y, Koike K, Arii S, Imai Y, et al. Characteristics of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011;9:428–433 https://doi.org/10.1016/j.cgh.2011.01.023 **(quiz e50)**
64. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90. https://doi.org/10.3322/caac.20107
65. Anstee QM, Day CP. The genetics of nonalcoholic fatty liver disease: spotlight on PNPLA3 and TM6SF2. Semin Liver Dis 2015;35:270–290. https://doi.org/10.1055/s-0035-1562947
66. Liu Y-L, Reeves HL, Burt AD, Tiniakos D, McPherson S, Leathart JBS, et al. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. Nat Commun 2014;5:4309. https://doi.org/10.1038/ncomms5309
67. Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. Nat Rev Gastroenterol Hepatol 2019. https://doi.org/10.1038/s41575-019-0145-7
68. Than NN, Ghazanfar A, Hodson J, Tehami N, Coldham C, Mergental H, et al. Comparing clinical presentations, treatments and outcomes of hepatocellular carcinoma due to hepatitis C and non-alcoholic fatty liver disease. QJM 2017;110:73–81. https://doi.org/10.1093/qjmed/hcw151
69. European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–943. https://doi.org/10.1016/j.jhep.2011.12.001
70. Reig M, Gambato M, Man NK, Roberts JP, Victor D, Orci LA, et al. Should patients With NAFLD/NASH Be surveyed for HCC? Transplantation 2019;103:39–44. https://doi.org/10.1097/TP.0000000000002361
71. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the US. Hepatology 2014;59:2188–2195. https://doi.org/10.1002/hep.26986
72. Chen H-P, Shieh J-J, Chang C-C, Chen T-T, Lin J-T, Wu M-S, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. Gut 2013;62:606–615. https://doi.org/10.1136/gutjnl-2011-301708
73. Zhang H, Gao C, Fang L, Zhao H-C, Yao S-K. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients: a meta-analysis. Scand J Gastroenterol 2013;48:78–87. https://doi.org/10.3109/00365521.2012.719926
74. Yan J, Yao B, Kuang H, Yang X, Huang Q, Hong T, et al. Liraglutide, sitagliptin, and insulin glargine added to metformin: the effect on body weight and intrahepatic lipid in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease. Hepatology 2019;69:2414–2426. https://doi.org/10.1002/hep.30320
75. Marengo A, Rosso C, Bugianesi E. Liver cancer: connections with obesity, fatty liver, and cirrhosis. Annu Rev Med 2016;67:103–117. https://doi.org/10.1146/annurev-med-090514-013832
76. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. Gastroenterology 2013;144:323–332. https://doi.org/10.1053/j.gastro.2012.10.005