Curr Hepatology Rep (2017) 16:374–381
https://doi.org/10.1007/s11901-017-0376-4

FATTY LIVER DISEASE (S HARRISON AND J GEORGE, SECTION EDITORS)

Managing HCC in NAFLD

Darren Hiu-Sun Foog[1] · **Deborah Kwok**[1] · **Becky Ching-Yeung Yu**[1] · **Vincent Wai-Sun Wong**[1,2]

Published online: 19 October 2017

Abstract
Purpose of Review We aim to review the epidemiology, risk factors, diagnosis, and treatment of hepatocellular carcinoma (HCC) in patients with non-alcoholic fatty liver disease (NAFLD).
Recent Findings NAFLD-HCC is increasingly common in Western countries and has become the third leading cause of HCC in the USA. While cirrhosis is the most important risk factor for NAFLD-HCC, one third of such patients are non-cirrhotic. Few cases of NAFLD-HCC are identified by screening, resulting in delayed presentation. Liver resection, transplantation, and local ablative therapy are curative treatments for HCC. Although medical and surgical complications are more common after surgery for NAFLD-HCC because of obesity, the long-term outcome is similar to that for other causes of HCC.
Summary NAFLD-HCC is expected to become a major cause of morbidity and mortality. Better understanding of the risk factors of NAFLD-HCC and development of prediction tools will help select patients for screening and improve outcomes.

Keywords Fatty liver · Non-alcoholic steatohepatitis · Cirrhosis · Hepatocellular carcinoma · Liver resection · Liver transplantation

This article is part of the Topical Collection on *Fatty Liver Disease*

✉ Vincent Wai-Sun Wong
wongv@cuhk.edu.hk

[1] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, 9/F, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, Hong Kong

[2] State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Shatin, Hong Kong

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, affecting 25% of the global adult population [1••, 2]. The active form of NAFLD, i.e., non-alcoholic steatohepatitis (NASH), is associated with faster fibrosis progression, but some patients with simple steatosis or non-alcoholic fatty liver may still have disease progression [3•]. In the past decade, NAFLD/NASH has rapidly become a major cause of hepatocellular carcinoma (HCC) and end-stage liver disease in Western countries [4••, 5••]. However, because previous studies on HCC included mainly patients with chronic viral hepatitis or alcoholic liver disease, data on NAFLD-related HCC remain scarce. In this article, we review the epidemiology, risk factors and clinical characteristics of NAFLD-HCC. Special emphasis is given to the issue of non-cirrhotic HCC, which occurs in a significant proportion of patients with NAFLD- HCC, and how this may affect HCC surveillance. While there are limited data on the treatment of NAFLD-HCC, we highlight challenges of applying treatment to obese patients.

Epidemiology

HCC is the third leading cause of cancer death worldwide and also accounts for 70–80% of the total liver cancer burden [6]. The majority of the cause of HCC is viral infection, namely by hepatitis C in the US and hepatitis B globally [7]. However, recently, statistics reveal NAFLD as an emerging cause of HCC, particularly in the developed world (Fig. 1). According to the Surveillance, Epidemiology and End Results registries, NAFLD-HCC has shown a 9% annual increase from 2004 to 2009 in the USA [4••]. In another hospital cohort of 162 HCC patients in Germany, 22% were due to NASH and 14% were cryptogenic, the latter probably largely

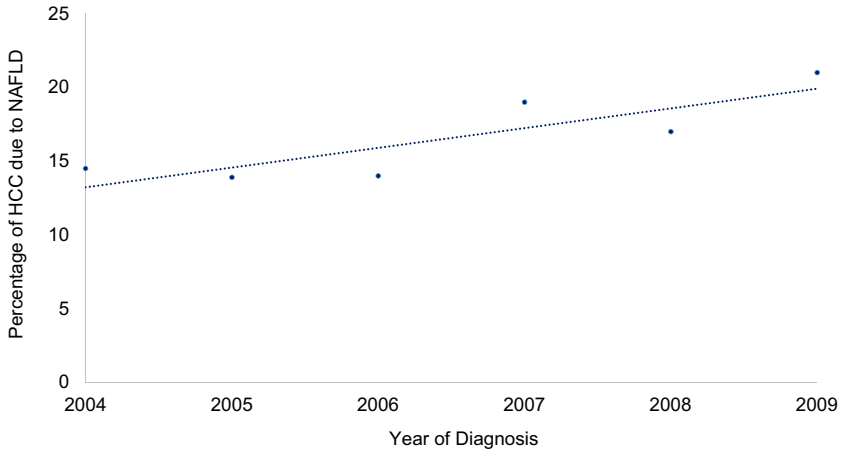

Fig. 1 Percentage of HCC due to NAFLD in the USA from 2004 to 2009 [Data source from the Surveillance, Epidemiology and End Results (SEER) registries [4••]]

due to burnt-out NASH [8]. The recent increase in NAFLD-HCC may be attributed to an expanding population with metabolic disorder and increased awareness and screening for HCC. Furthermore, the development of effective treatment for chronic viral hepatitis has likely resulted in a relative increase in the proportion of HCC due to NASH.

In terms of ethnicity, the highest incidences of HCC occur among Asians and Pacific Islanders, followed by Hispanics, American Indians, with the lowest occurrence among white people [9]. However, in the USA, 76% of the patients with NAFLD-HCC were whites [4••]. Similarly, longitudinal NAFLD cohorts from Asia report very low incidence of HCC in the range of 0.25–0.65% in 5 years [10, 11•, 12]. Yet, a longer follow-up period is needed for the study of liver outcomes. Besides, since NAFLD takes decades to progress and childhood obesity is a recent phenomenon in the developing world, major changes in global epidemiology is expected in the future [13]. Studies from Japan and Korea have already reported increasing proportion of HCC attributable to NAFLD [14, 15].

In addition, current statistics may underestimate how NAFLD contributes to the development of HCC. Cryptogenic cirrhosis may account for up to 30–40% of all HCC cases [6], and thus, the role of NAFLD may be understated. In addition, NAFLD may act synergistically with other metabolic factors such as obesity and type 2 diabetes in promoting HCC. For instance, metabolic diseases and hepatic steatosis are associated with increased risk of cirrhosis and HCC in patients with chronic hepatitis B [16, 17].

Risk Factors

Demographic Factors

Like in other liver diseases, the incidence of NAFLD-HCC increases with age (Table 1). In a retrospective cohort study of 6508 NAFLD patients from Japan, patients older than 60 years had more than 4 times the risk of developing HCC than younger individuals [10]. In most studies, patients with NAFLD-HCC are older than those with other causes of HCC, suggesting that NAFLD/NASH progresses more slowly than other liver diseases [4••, 18, 19].

HCC is well known to occur more commonly in male patients [20]. The same holds true for NAFLD-HCC as well, though the male/female ratio varies widely from 1.6 to 11 across studies [4••, 21].

Lifestyle Factors

NAFLD is strongly associated with metabolic syndrome [22•]. In the USA, obesity and diabetes account for 37% of the population-attributable fraction of HCC, an effect even stronger than that of viral hepatitis [23]. Patients with obesity and diabetes are more likely to develop advanced fibrosis and NAFLD-HCC [10, 24, 25•]. High body mass index (BMI) is also associated with HCC development in patients with cryptogenic cirrhosis, a condition believed to be largely due to burnt-out NASH [26]. At the population level, obesity increases the risk of HCC in men and women irrespective of the underlying liver disease [27, 28].

Furthermore, smoking has been linked to liver fibrosis and HCC [29, 30]. Although the observation is subject to recall bias and reverse causation, all NAFLD patients should quit smoking because of numerous other health benefits. On the other hand, studies on the effect of modest to moderate alcohol

Table 1 Modifiable and unmodifiable risk factors of NAFLD-related HCC

Modifiable factors	Unmodifiable factors
- Obesity	- Age
- Diabetes	- Male gender
- Fibrosis stage	- Genetics
- Smoking (?)	- Family history

consumption on NAFLD severity and outcomes have yielded conflicting results [31].

Disease Severity

Although NAFLD-HCC can develop in a non-cirrhotic liver, cirrhosis remains the most important risk factor for HCC development in NAFLD patients. The incidence of HCC exceeds 1–2% per year in patients with advanced fibrosis or cirrhosis [18, 19, 32]. Fibrosis stage is also associated with liver-related mortality in a dose-dependent manner [33•]. On the other hand, whether the other histological features of NASH such as hepatocyte ballooning and lobular inflammation are predictive of HCC is a matter of debate. In several longitudinal studies, the association between NASH and mortality became insignificant after adjusting for fibrosis stage [34, 35].

Genetics

A number of gene variants have been shown to be associated with NAFLD in candidate-gene and genome-wide association studies. The most robust finding has been with the patatin-like phospholipase domain-containing 3 (*PNPLA3*) gene. It is associated with not only NAFLD but also its histological severity [36, 37]. The rs738409 variant is a loss-of-function mutation (I148M), resulting in reduced triacylglycerol hydrolysis in hepatocytes and reduced secretion of very low-density lipoprotein [38]. It also results in a fibrogenic phenotype of hepatic stellate cells [39]. In human studies, the at-risk genotype is more commonly found in patients with NAFLD-HCC [21, 40].

The transmembrane 6 superfamily 2 (*TM6SF2*) gene variant (rs58542926, E167K) not only occurs at a low frequency in the population but also increases the risk of NAFLD [41, 42]. It affects the lipidation of very low-density lipoprotein [43]. It may also increase the risk of fibrosis, but data on NAFLD-HCC are limited [44].

Non-cirrhotic HCC

A number of small case series suggest that 30–50% of patients with NAFLD-HCC occur in a non-cirrhotic liver [8, 45]. Subsequently, a large cohort of 1500 HCC patients from US Veterans hospitals confirmed that a third of NAFLD-related and idiopathic HCCs might be non-cirrhotic based on histology, clinical features, and non-invasive tests of fibrosis [46•]. While the observation may be partly due to selection bias, the natural history of NAFLD and shared pathophysiology of NASH and HCC may also explain the high proportion of non-cirrhotic HCC in NAFLD patients (Table 2).

Clinical Characteristics

Data on the clinical characteristics of NAFLD-HCC are scarce. Because NAFLD is the hepatic manifestation of metabolic syndrome, the majority of patients with NAFLD-HCC have diabetes and hypertension [47••, 48]. Delayed diagnosis is common for NAFLD-HCC [47••, 49]. Unlike patients with chronic viral hepatitis, NAFLD patients seldom undergo regular ultrasound surveillance. When a patient presents with symptoms such as right upper quadrant pain and jaundice, the cancer is usually at an advanced stage. As a result, such patients are less likely to receive curative HCC treatment. In an Italian cohort, Piscaglia and colleagues found that patients with NAFLD-HCC had shorter overall survival than those with hepatitis C-related HCC (HCV-HCC) (27.2 vs. 34.4 months), and the difference persisted after propensity score matching (30.2 vs. 36.9 months) [47••]. However, there was no significant difference in liver-related mortality between the two causes of HCC, and the difference was instead driven by cardiovascular mortality. Late diagnosis may be due to the absence of risk factors such as cirrhosis. Patients with NAFLD-HCC may also have lower alpha-fetoprotein levels, thus failing to trigger a diagnostic workup [48]. Even when abdominal ultrasonography is performed for screening or diagnostic purposes, its performance is suboptimal in obese patients [47••]. Furthermore, owing to cardiovascular risk and comorbidities as well as the requirement of larger liver grafts because of body size, patients with NAFLD-HCC are less likely to receive liver transplantation [48]. Together with more advanced cancer staging, this further limits treatment options for patients with NAFLD-HCC. Future research should be directed to identifying patients with NAFLD who require surveillance so that they can be treated earlier and have a better prognosis.

As for tumor characteristics, a higher percentage of NAFLD-HCC patients have a larger, infiltrative tumor [47••]. This is largely due to delayed diagnosis, similar to what is observed for patients with other liver diseases who do not have regular surveillance [50].

Screening

Current guidelines recommend cirrhotic patients undergo 6-month abdominal ultrasonography and/or alpha-fetoprotein (AFP) testing for HCC screening regardless of etiologies [51, 52]. Abdominal ultrasonography is frequently used because of its non-invasive nature, low cost, and high availability. However, it may not be a sensitive tool for NAFLD patients who are often obese [53]. While computed tomography and magnetic resonance imaging would achieve a higher diagnostic accuracy, the radiation exposure (computed tomography), cost, and availability limit their role as routine screening tools. The HCC biomarker AFP is also

Table 2 Potential causes of a high proportion of NAFLD-related HCC arising from non-cirrhotic livers

Selection bias	Since some patients with burnt-out NASH are classified as having cryptogenic cirrhosis, not counting them as having NAFLD-HCC would reduce the proportion of cirrhotic patients.
Natural history	In general, NAFLD patients have a slower rate of fibrosis progression than those with other liver diseases such as chronic viral hepatitis. As a result, cirrhosis is less common among NAFLD patients. Given the huge population of non-cirrhotic NAFLD patients, there would also be many cases of non-cirrhotic HCC.
Mechanistic link	Proinflammatory and metabolic pathways are involved in the pathophysiology of both NASH and HCC. Metabolic conditions may promote faster hepatocarcinogenesis before cirrhosis sets in. This phenomenon is observed in not only NASH but also other chronic liver diseases.

often used. Nevertheless, AFP is normal in up to 30% of HCC patients, and limited data suggest that AFP may even be less sensitive for NAFLD-HCC [45, 47••]. Des-γ-carboxy prothrombin (DCP) is another HCC biomarker commonly used in Japan together with AFP to improve the sensitivity for HCC detection, but a significant proportion of patients with NAFLD-HCC also have normal DCP [45]. Further studies are required to define the optimal screening method.

Recent studies indicate that NAFLD-HCC can arise from cirrhotic and non-cirrhotic livers (see above), thereby raising the question whether there is a need for surveillance on non-cirrhotic population. Given the huge number of NAFLD patients, mass screening for all would not be feasible. Studies should better define HCC risk factors in the non-cirrhotic population, and it would be helpful to develop prediction scores as in the case of chronic hepatitis B [54].

Diagnosis

The diagnosis of HCC in a NAFLD patient is no different from patients with other liver diseases. Dynamic cross-sectional imaging using four-phase computed tomography or magnetic resonance imaging with contrast is the preferred diagnostic test [51, 52]. Early arterial enhancement and portal venous washout reflect the difference in blood supply for HCC (predominantly hepatic artery) and the adjacent liver parenchyma (predominantly portal vein) and can be used to distinguish HCC from other liver lesions. Whether these tests perform differently for NAFLD-HCC is currently unclear. However, because NAFLD patients have a higher BMI, contrast-enhanced ultrasonography is expected to have inferior performance and cannot be recommended. In case a diagnosis cannot be made through imaging studies, targeted biopsy of the liver lesion may be considered.

Treatment

Treatment options are limited for patients with decompensated liver disease even if the tumor is small. Therefore, most HCC staging systems incorporate both tumor factors and liver function in guiding treatment. The Barcelona Clinic Liver Cancer (BCLC) system is one of the most commonly used systems [51, 52]. For stage A (early stage), curative treatments such as liver resection, liver transplantation, and local ablative therapy may be performed. Transarterial chemoembolization (TACE) for stage B (intermediate stage), sorafenib for stage C (advanced stage), and supportive treatment for stage D (terminal stage) are recommended. At the moment, most studies on liver resection and transplantation for NAFLD-HCC have been retrospective. Furthermore, most studies on local ablative therapy, TACE, and sorafenib treatment did not specifically examine patients with NAFLD-HCC.

Surgical Treatment

Liver resection is only suitable for 15–30% patients with single nodules smaller than 5 cm, good liver function, and no portal hypertension (Child-Pugh class A) [51, 52]. Several studies have shown that patients with NAFLD-HCC have similar or even better resection outcomes compared with those with HCV-HCC [55, 56]. In a multicenter Italian study, patients with metabolic syndrome-related HCC had better 5-year overall survival (65.6 vs. 61.4%), better recurrence free survival (37.0 vs. 27.5%), and lower recurrence rate (44.6 vs. 65.2%) than those with HCV-HCC after liver resection [57]. Nevertheless, advanced fibrosis and necroinflammatory activity are associated with a higher risk of major complications after liver resection in patients with metabolic syndrome-related HCC, which calls for better peri-operative management [58].

Liver transplantation not only removes HCC but also grants a healthy liver to the patient. It is however limited by the supply of organs. Currently, transplantation listing is based on the model for end-stage liver disease (MELD) score in many countries, and there is considerable difference in the policy of whether patients with HCC should have priority over patients with chronic liver failure.

Because of late presentation and high cardiovascular risk, few patients with NAFLD-HCC can receive liver

transplantation [48, 59]. On the other hand, NAFLD patients who receive liver transplantation have similar survival as patients with chronic hepatitis C and alcoholic liver cirrhosis [48, 60]. In a 10-year follow-up study, NAFLD-HCC patients may even have higher disease-free survival than HCV-HCC patients (85 vs. 65%), indicating less aggressive HCC [61]. Moreover, patients with morbid obesity have a lower graft and overall survival than those with a lower BMI [62]. It is important to note that while obese patients suffer from more surgical complications, they are also at risk of cardiovascular events and infection following surgery. When feasibility of treatment, treatment choice, response, and complications are all taken into account, patients with NAFLD-HCC have a lower overall survival than those with other etiologies [59].

Local Ablative Therapy

Local ablative therapy can be performed percutaneously, laparoscopically, or during open surgery under image guidance to destroy tumors for patients who cannot tolerate liver resection. Radiofrequency ablation (RFA) produces a necrotic area up to 4 cm and is the preferred option. Because of heterogeneity in study populations, the comparative effectiveness of RFA and liver resection remains uncertain [63]. For lesions smaller than 3 cm, RFA may achieve a similar overall survival, though the local recurrence rate appears slightly increased. In some series, RFA is more often performed than liver resection or transplantation [48]. Obesity adds minor technical difficulties to RFA, as obese HCC patients require more sessions of RFA. However, HCC patients with or without obesity have similar rates of major complications and overall survival [64].

Percutaneous ethanol injection rarely achieves complete tumor necrosis when the tumor is larger than 3 cm, and it is less effective than RFA in eliminating microscopic satellite lesions. Nonetheless, it still has a role when RFA cannot be performed because of close proximity to major blood vessels or the diaphragm. Other techniques such as microwave ablation and high-intensity focused ultrasound are increasingly available; data on their performance on NAFLD-HCC are eagerly awaited.

Transarterial Chemoembolization

TACE is not curative but has been shown to improve survival and is reasonably well tolerated. It is therefore suggested for patients with intermediate stage HCC not amenable to RFA. It involves delivering chemotherapy to the tumor through cannulation and occluding its feeding artery with embolizing agents, ideally sustaining a high concentration of chemotherapy in the tumor leading to necrosis. There is a variety of antineoplastic and embolizing agents but there lacks a standardized protocol for TACE [63]. Patients with advanced cirrhosis and poor liver function are not suitable for TACE, as embolization may lead to liver failure and possibly death.

In one study, a larger proportion of NAFLD-HCC patients were treated with TACE (41 vs. 28%) compared to HCV-HCC patients probably due to late presentation [48]. Recognized post-TACE complications include postembolization fever, nausea and vomiting, abdominal pain, and infection. Occasionally life-threatening complications including acute hepatic decompensation and acute kidney injury may develop. In NAFLD-HCC patients, a large tumor diameter and a high bilirubin level are predictive of liver decompensation [65]. Additionally, NAFLD patients may have concomitant diabetic nephropathy or other causes of chronic kidney disease placing them at higher risk for contrast induced nephropathy.

Systemic Therapy and Supportive Care

Sorafenib is a multikinase inhibitor that has antitumor activity through antiproliferative, antiangiogenic, and proapoptotic effects [66]. It is the first-line systemic treatment for advanced HCC. Again, because of late diagnosis, more NAFLD-HCC patients receive sorafenib than HCV-HCC patients [59]. HCC patients with impaired liver function (ALBI grade > 1, Child-Pugh B) may have a poorer outcome and be better managed with supportive treatment. Studies on the effects of combined therapy of TACE and sorafenib produced mixed results [67]. Regorafenib, recently approved by the FDA in April 2017, may improve survival of HCC patients who do not respond to sorafenib [68]. The use of sorafenib in patients undergoing dialysis has not been studied. Patients with chronic kidney failure from diabetes mellitus should be treated with caution.

Supportive treatment is reserved for patients who can no longer tolerate other HCC treatment. It focuses on the management of pain, ascites, edema, and hepatic encephalopathy.

Prevention

Since HCC almost never develops in patients without liver disease, NAFLD-HCC would not occur if we can prevent NAFLD in the first place. Healthy diet and regular exercise can effectively prevent NAFLD. Even in NAFLD patients, a reduction of 10% or more of the body weight can reverse NAFLD/NASH in the majority of cases and even improve fibrosis [69, 70•]. Observational data and animal experiments also show that exercise can prevent HCC development [71].

Although there is no registered pharmacological treatment for NASH at present, four drugs have entered phase

3 development and may be available for clinical use in the near future. Among them, obeticholic acid, selonsertib, and cenicriviroc were shown to improve fibrosis in phase 2 studies [72•]. While fibrosis is the most important predictor of liver-related outcomes in NAFLD patients, long-term studies will be required to determine the clinical benefits of these new agents [33•].

Among existing agents, metformin and statin have been shown to reduce HCC in diabetic patients and patients with chronic viral hepatitis [73, 74]. Because such data were largely derived from observational studies, it is possible that the perceived benefits are due to selection bias, with metformin and statin less often used in patients with advanced liver disease. Nonetheless, the bottom line is that the safety of these agents in patients with chronic liver disease is well proven, and their metabolic and cardiovascular benefits are beyond doubt.

Conclusions

With the global epidemic of obesity and NAFLD, NAFLD-HCC is expected to become a major cause of morbidity and mortality. Because of the large number of patients and the issue of non-cirrhotic HCC, many patients with NAFLD-HCC are not detected by screening and thus present at an advanced stage, rendering curative treatment impossible. While medical and surgical complications are more common after liver resection or transplantation for NAFLD-HCC patients, the long-term outcome is comparable to that in patients with other liver diseases. Therefore, further studies on NAFLD-HCC risk prediction are worthwhile and will inform practice. Lifestyle modification remains the cornerstone for the prevention and treatment of NAFLD/NASH. A number of pharmacological agents for NASH are under evaluation, and long-term studies will determine their impact on NAFLD-HCC.

Funding Information Vincent Wai-Sun Wong is supported by the General Research Fund (Project ref. 14108916) from the Hong Kong SAR Government to conduct NAFLD research.

Compliance with Ethical Standards

Conflict of Interest Vincent Wong has served as a consultant or advisory board member for AbbVie, Allergan, Gilead Sciences, Janssen, Perspectum Diagnostics, and Pfizer and received lecture fees from Bristol-Myers Squibb, Echosens, Gilead Sciences, and Merck. Darren Hiu-Sun Foog, Deborah Kwok, and Becky Ching-Yeung Yu each declare no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• 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. **This is an important meta-analysis on the epidemiology of NAFLD across different continents.**
2. Wong VW, Chu WC, Wong GL, Chan RS, Chim AM, 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;61:409–15.
3.• 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;13:643–54. e641–649; quiz e639–640. **This systematic review reports the rate of fibrosis progression and highlights that patients with non-alcoholic fatty liver may also progress over time, albeit at a slower rate.**
4.•• 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;62:1723–30. **This study shows that NAFLD is an increasingly common cause of HCC in USA.**
5.•• Goldberg D, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology. 2017;152:1090–9. e1091.**This study shows that NAFLD is an increasingly important indication for liver transplantation.**
6. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology. 2012;142:1264–73. e1261
7. Chan SL, Wong VW, Qin S, Chan HL. Infection and cancer: the case of hepatitis B. J Clin Oncol. 2016;34:83–90.
8. Ertle J, Dechene A, Sowa JP, Penndorf V, Herzer K, Kaiser G, et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. Int J Cancer. 2011;128:2436–43.
9. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol. 2009;27:1485–91.
10. Kawamura Y, Arase Y, Ikeda K, Seko Y, Imai N, Hosaka T, et al. Large-scale long-term follow-up study of Japanese patients with non-alcoholic fatty liver disease for the onset of hepatocellular carcinoma. Am J Gastroenterol. 2012;107:253–61.
11. Wong VW, Wong GL, Yeung JC, Fung CY, Chan JK, Chang ZH, et al. Long-term clinical outcomes after fatty liver screening in patients undergoing coronary angiogram: a prospective cohort study. Hepatology. 2016;63:754–63.
12.• Leung JC, Loong TC, Wei JL, Wong GL, Chan AW, Choi PC, et al. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. Hepatology. 2017;65:54–64. **This histological cohort provides outcome data on Asian NAFLD patients.**
13. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol. 2017;67:862–73.

14. Cho EJ, Kwack MS, Jang ES, You SJ, Lee JH, Kim YJ, et al. Relative etiological role of prior hepatitis B virus infection and nonalcoholic fatty liver disease in the development of non-B non-C hepatocellular carcinoma in a hepatitis B-endemic area. Digestion. 2011;84(Suppl 1):17–22.
15. Tateishi R, Okanoue T, Fujiwara N, Okita K, Kiyosawa K, Omata M, et al. Clinical characteristics, treatment, and prognosis of non-B, non-C hepatocellular carcinoma: a large retrospective multicenter cohort study. J Gastroenterol. 2015;50:350–60.
16. Wong GL, Wong VW, Choi PC, Chan AW, Chim AM, Yiu KK, et al. Metabolic syndrome increases the risk of liver cirrhosis in chronic hepatitis B. Gut. 2009;58:111–7.
17. Chan AW, Wong GL, Chan HY, Tong JH, YH Y, Choi PC, et al. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. J Gastroenterol Hepatol. 2017;32:667–76.
18. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology. 2010;51:1972–8.
19. Bhala N, Angulo P, van der Poorten D, Lee E, Hui JM, Saracco G, et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. Hepatology. 2011;54:1208–16.
20. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007;132:2557–76.
21. Liu YL, Patman GL, Leathart JB, Piguet AC, Burt AD, Dufour JF, et al. Carriage of the PNPLA3 rs738409 C>G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol. 2014;61:75–81.
22.• Wong VW, Wong GL, Yeung DK, Lau TK, Chan CK, Chim AM, et al. Incidence of non-alcoholic fatty liver disease in Hong Kong: a population study with paired proton-magnetic resonance spectroscopy. J Hepatol. 2015;62:182–9. **This study uses the sensitive method of proton-magnetic resonance spectroscopy to study the incidence and risk factors of NAFLD.**
23. Welzel TM, Graubard BI, Quraishi S, Zeuzem S, Davila JA, El-Serag HB, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. Am J Gastroenterol. 2013;108:1314–21.
24. Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. J Hepatol. 2005;42:132–8.
25.• Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut. 2016;65:1359–68. **This study reports a high prevalence of advanced fibrosis among diabetic patients.**
26. 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
27. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348:1625–38.
28. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology. 2010;51:1820–32.
29. Zein CO, Unalp A, Colvin R, Liu YC, McCullough AJ, Nonalcoholic Steatohepatitis Clinical Research N. Smoking and severity of hepatic fibrosis in nonalcoholic fatty liver disease. J Hepatol. 2011;54:753–9.
30. Koh WP, Robien K, Wang R, Govindarajan S, Yuan JM, Yu MC. Smoking as an independent risk factor for hepatocellular carcinoma: the Singapore Chinese Health Study. Br J Cancer. 2011;105:1430–5.
31. Ajmera VH, Terrault NA, Harrison SA. Is moderate alcohol use in nonalcoholic fatty liver disease good or bad? A critical review. Hepatology. 2017;65:2090–9.
32. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin Gastroenterol Hepatol. 2012;10:1342–59. e1342
33.• 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;65:1557–65. **This study, among others, highlights the important role of fibrosis in determining the prognosis of NAFLD patients.**
34. 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;149:389–97. e310
35. Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal 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;61:1547–54.
36. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology. 2011;53:1883–94.
37. Shen J, Wong GL, Chan HL, Chan HY, Yeung DK, Chan RS, et al. PNPLA3 gene polymorphism accounts for fatty liver in community subjects without metabolic syndrome. Aliment Pharmacol Ther. 2014;39:532–9.
38. Pirazzi C, Adiels M, Burza MA, Mancina RM, Levin M, Stahlman M, et al. Patatin-like phospholipase domain-containing 3 (PNPLA3) I148M (rs738409) affects hepatic VLDL secretion in humans and in vitro. J Hepatol. 2012;57:1276–82.
39. Bruschi FV, Claudel T, Tardelli M, Caligiuri A, Stulnig TM, Marra F, et al. The PNPLA3 I148M variant modulates the fibrogenic phenotype of human hepatic stellate cells. Hepatology. 2017;65:1875–90.
40. Seko Y, Sumida Y, Tanaka S, Mori K, Taketani H, Ishiba H, et al. Development of hepatocellular carcinoma in Japanese patients with biopsy-proven non-alcoholic fatty liver disease: association between PNPLA3 genotype and hepatocarcinogenesis/fibrosis progression. Hepatol Res. 2017;47:1083–92
41. Pirola CJ, Sookoian S. The dual and opposite role of the TM6SF2-rs58542926 variant in protecting against cardiovascular disease and conferring risk for nonalcoholic fatty liver: a meta-analysis. Hepatology. 2015;62:1742–56.
42. Wong VW, Wong GL, Tse CH, Chan HL. Prevalence of the TM6SF2 variant and non-alcoholic fatty liver disease in Chinese. J Hepatol. 2014;61:708–9.
43. Smagris E, Gilyard S, BasuRay S, Cohen JC, Hobbs HH. Inactivation of Tm6sf2, a gene defective in fatty liver disease, impairs lipidation but not secretion of very low density lipoproteins. J Biol Chem. 2016;291:10659–76.
44. Dongiovanni P, Petta S, Maglio C, Fracanzani AL, Pipitone R, Mozzi E, et al. Transmembrane 6 superfamily member 2 gene variant disentangles nonalcoholic steatohepatitis from cardiovascular disease. Hepatology. 2015;61:506–14.
45. 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;9:428–33. quiz e450
46.• 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;14:124–31. e121.**This study suggests that NAFLD-HCC commonly arises from a non-cirrhotic liver.**

47.•• 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;63:827–38. **This prospective cohort illustrates that NAFLD-HCC is often diagnosed late, rendering curative treatment less feasible.**

48. 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.

49. Pereira K, Salsamendi J, Casillas J. The global nonalcoholic fatty liver disease epidemic: what a radiologist needs to know. J Clin Imaging Sci. 2015;5:32.

50. CY W, Hsu YC, Ho HJ, Chen YJ, Lee TY, Lin JT. Association between ultrasonography screening and mortality in patients with hepatocellular carcinoma: a nationwide cohort study. Gut. 2016;65:693–701.

51. 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;56:908–43.

52. Heimbach J, Kulik LM, Finn R, Sirlin CB, Abecassis M, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2017. https://doi.org/10.1002/hep.29086.

53. Machado MV, Cortez-Pinto H. Non-invasive diagnosis of non-alcoholic fatty liver disease. A critical appraisal. J Hepatol. 2013;58:1007–19.

54. Wong VW, Janssen HL. Can we use HCC risk scores to individualize surveillance in chronic hepatitis B infection? J Hepatol. 2015;63:722–32.

55. Wakai T, Shirai Y, Sakata J, Korita PV, Ajioka Y, Hatakeyama K. Surgical outcomes for hepatocellular carcinoma in nonalcoholic fatty liver disease. J Gastrointest Surg. 2011;15:1450–8.

56. Reddy SK, Steel JL, Chen HW, DeMateo DJ, Cardinal J, Behari J, et al. Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. Hepatology. 2012;55:1809–19.

57. Vigano L, Conci S, Cescon M, Fava C, Capelli P, D'Errico A, et al. Liver resection for hepatocellular carcinoma in patients with metabolic syndrome: a multicenter matched analysis with HCV-related HCC. J Hepatol. 2015;63:93–101.

58. Cauchy F, Zalinski S, Dokmak S, Fuks D, Farges O, Castera L, et al. Surgical treatment of hepatocellular carcinoma associated with the metabolic syndrome. Br J Surg. 2013;100:113–21.

59. Weinmann A, Alt Y, Koch S, Nelles C, Duber C, Lang H, et al. Treatment and survival of non-alcoholic steatohepatitis associated hepatocellular carcinoma. BMC Cancer. 2015;15:210.

60. Wong RJ, Chou C, Bonham CA, Concepcion W, Esquivel CO, Ahmed A. Improved survival outcomes in patients with non-alcoholic steatohepatitis and alcoholic liver disease following liver transplantation: an analysis of 2002-2012 United Network for Organ Sharing data. Clin Transpl. 2014;28:713–21.

61. Hernandez-Alejandro R, Croome KP, Drage M, Sela N, Parfitt J, Chandok N, et al. A comparison of survival and pathologic features of non-alcoholic steatohepatitis and hepatitis C virus patients with hepatocellular carcinoma. World J Gastroenterol. 2012;18:4145–9.

62. Conzen KD, Vachharajani N, Collins KM, Anderson CD, Lin Y, Wellen JR, et al. Morbid obesity in liver transplant recipients adversely affects longterm graft and patient survival in a single-institution analysis. HPB (Oxford). 2015;17:251–7.

63. Raza A, Sood GK. Hepatocellular carcinoma review: current treatment, and evidence-based medicine. World J Gastroenterol. 2014;20:4115–27.

64. Ohki T, Tateishi R, Shiina S, Sato T, Masuzaki R, Yoshida H, et al. Obesity did not diminish the efficacy of percutaneous ablation for hepatocellular carcinoma. Liver Int. 2007;27:360–7.

65. Siriwardana RC, Niriella MA, Dassanayake AS, Liyanage CA, Upasena A, Sirigampala C, et al. Factors affecting post-embolization fever and liver failure after trans-arterial chemo-embolization in a cohort without background infective hepatitis—a prospective analysis. BMC Gastroenterol. 2015;15:96.

66. Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther. 2008;7:3129–40.

67. Lin S, Hoffmann K, Schemmer P. Treatment of hepatocellular carcinoma: a systematic review. Liver Cancer. 2012;1:144–58.

68. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389:56–66.

69. Wong VW, Chan RS, Wong GL, Cheung BH, Chu WC, Yeung DK, et al. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. J Hepatol. 2013;59:536–42.

70.• Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of non-alcoholic steatohepatitis. Gastroenterology. 2015;149:367–78. e365; quiz e314-365. **This prospective cohort study highlights that weight loss can not only improve NASH but also reverse fibrosis.**

71. Piguet AC, Saran U, Simillion C, Keller I, Terracciano L, Reeves HL, et al. Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of steatosis. J Hepatol. 2015;62:1296–303.

72.• Wong VW, Chitturi S, Wong GL, Yu J, Chan HL, Farrell GC. Pathogenesis and novel treatment options for non-alcoholic steatohepatitis. Lancet Gastroenterol Hepatol. 2016;1:56–67. **This is a recent review on drug development for NASH.**

73. Chen HP, Shieh JJ, Chang CC, Chen TT, Lin JT, MS W, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. Gut. 2013;62:606–15.

74. Hsiang JC, Wong GL, Tse YK, Wong VW, Yip TC, Chan HL. Statin and the risk of hepatocellular carcinoma and death in a hospital-based hepatitis B-infected population: a propensity score landmark analysis. J Hepatol. 2015;63:1190–7.