INTRODUCTION

In a recent review pooling data from 86 studies including 8.5 million subjects from 22 countries, the global estimated prevalence of non-alcoholic fatty liver disease (NAFLD) is 25.24%, with a peak prevalence in the Middle East and Latin America, and the disease increases with age. Thus, NAFLD is the most prevalent liver disease worldwide. Moreover 51.34% of patients are obese, and 22.51% have diabetes. This short review will focus on the risk factors of the progression of NAFLD to advanced fibrosis and HCC.

THE PROGRESSION OF LIVER FIBROSIS IN NON-ALCOHOLIC FATTY LIVER DISEASE

NAFLD is a slowly progressive disease, which does not lead to end-stage liver disease in most cases. It is difficult to estimate the rate of progression of NAFLD to severe fibrosis because of the high risk of selection bias when liver biopsies are performed in these patients, as well as the different criteria defining NAFLD in different cohorts. NAFLD may progress to non-alcoholic steatohepatitis (NASH), which poses a significant risk of progression to hepatic cirrhosis, diabetes, hepatocellular carcinoma, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, obesity.
and non-hepatic complications and mortality. The average progression of liver fibrosis in NASH patients is 0.09% (95% CI: 0.06-0.12),\(^1\) with an incidence of severe fibrosis of approximately 68 per 1000 person-years.

In a more recent systematic review and meta-analysis reporting fibrosis stage-specific mortality from five NAFLD cohort studies,\(^5\) patients were at increasing risk of both liver-related and all-cause mortality as the stages of fibrosis increased. The estimated all-cause mortality rate ratio was 1.58 (in patients with stage 1 fibrosis) increasing to 2.52, 3.48 and 6.40 for stages 2, 3 and 4 fibrosis respectively. The increase was more dramatic in the liver-related mortality ratio, which sky-rocketed from 1.41 in patients with stage 1 fibrosis to 9.57, 16.69 and 42.30 in patients with stages 2, 3 and 4 fibrosis respectively.\(^4\) Thus, fibrosis stage determines liver-related mortality, and its impact increases exponentially with progression to more severe lesions. It is clear that with the current epidemic of the metabolic syndrome, and the ageing of the affected population the global clinical and financial burden of NAFLD is bound to be staggering in the decades to come.

2.1 | Risk factors of progression

The risk factors for the progression of NAFLD to liver fibrosis are not fully understood. Although age has been associated with increasingly severe liver fibrosis in NASH patients, this is probably related to accumulating metabolic alterations occurring in the elderly with a long duration of liver disease. In a cross-sectional study in 432 patients, 26.8% with NASH and 17.4% with moderate to severe liver fibrosis, the independent predictors of moderate to severe fibrosis were male sex, Caucasian ethnicity, type 2 diabetes and increased liver enzymes, but not age.\(^5\) The increased risk of fibrosis affects not only men, but also postmenopausal women and those who have undergone premature menopause.\(^6\) Time from menopause is also directly associated with an increased likelihood of more severe liver fibrosis, after several adjustments (OR for each 5-year unit = 1.2, 95% CI 1.1-1.3, \(P = .002\)).\(^6\) Ethnicity is also associated with NASH and fibrosis. However, although Hispanic ethnicity may predispose to NASH,\(^7\) it is unclear whether this is also associated with increased progression of liver disease,\(^8\) which has been suggested in Caucasians.\(^5\) The differences among ethnic groups may be partly explained by genetic polymorphisms, most importantly an isoleucine to methionine protein variant at position 148 of the patatin-like phospholipase domain-containing 3 (PNPLA3) factor, a protein expressed in the liver and involved in lipid metabolism.\(^9\) PNPLA3 variants are associated with the progression of liver fibrosis and cirrhosis independent from liver inflammation and NASH.\(^10\) Another rarer polymorphism that occurs in TM6SF2 has also been shown to be associated with advanced liver fibrosis and cirrhosis independent from age, BMI, diabetes and PNPLA3 genotype.\(^11\)

Higher rates of fibrosis progression are observed in patients who are obese, or with type 2 diabetes.\(^2,3,12,13\) In an important, well-designed prospective study in 52 patients with histologically proven NAFLD, who systematically underwent a biopsy after 36 months,\(^2\) fibrosis progressed in 14 (27%), was stable in 25 (48%) and regressed in 13 (25%). It is important to note that these authors identified a decrease in BMI and waist circumference as independent predictors of stable liver disease activity and fibrosis.\(^2\) Clinical and laboratory factors associated with the progression of fibrosis were also critically assessed in a meta-analysis of seven studies with paired biopsies.\(^14\) Interestingly, this analysis found that the presence of arterial hypertension and low aspartate to alanine aminotransferase ratio at baseline liver biopsy were associated with the progression of fibrosis, but not age, ethnicity or diabetes. Higher grades of steatosis also seemed also to be more likely to lead to disease progression, but this was only based on two studies, where, oddly, the baseline severity of necroinflammation was not predictive of fibrosis progression. The authors correctly emphasized the heterogeneity among studies, and the difficulty of firmly establishing the independent factors of fibrosis progression in NAFLD patients, where several confounders, especially related to lifestyle, may play a role.

2.2 | Weight reduction has a beneficial role

Reduction in body weight has been identified as a major predictor of stability or improvement in liver lesions, including the stage of fibrosis.\(^15-17\) This has also been reported in patients undergoing bariatric surgery to manage obesity,\(^18\) although in these cases the mechanisms leading to improved liver lesions may also involve changes in intestinal hormone secretion.

A large prospective study analysed the effects of lifestyle changes to reduce body weight in 293 patients with histologically proven NASH, followed for 1 year.\(^17\) Paired liver biopsies were collected at the beginning and end of the observation period in 261 patients. Improvement or even the resolution of NASH was more frequent in those who lost weight. In particular, NASH resolved in 90% of the patients who lost ≥10% of their weight and fibrosis regressed in 45%. However, a subsequent multicentre cross-sectional study of 1058 biopsy-proven NAFLD patients, emphasized the...
importance of distinguishing obesity from metabolic status. A metabolically healthy status was defined in that study by the absence of diabetes, low HDL, hypertriglyceridemia and arterial hypertension. The number of altered metabolic factors determined the risk of NASH and significant fibrosis. Interestingly, the latter was more frequently observed in the presence of adverse metabolic conditions in both obese and non-obese patients. Patients who were not obese but metabolically unhealthy more often had significant liver fibrosis than healthy obese patients (31.7% vs 11.4%, \( P < .0001 \)). The authors mentioned that metabolically healthy obese patients are not entirely healthy and emphasized that the greatest impact on NASH and liver fibrosis is determined by a metabolically unhealthy status, which should be the real focus of patient counselling.

### 3 | PROGRESSION TO HCC

NAFLD may progress to hepatocellular carcinoma (HCC). According to a large, recent meta-analysis, the incidence of HCC among persons with simple NAFLD is very low, that is, 0.44 per 1000 person-years (range, 0.29-0.66), which is much less than that commonly reported for chronic hepatitis B or C. In patients with NASH, on the other hand, the annual HCC incidence rate increases by more than 10-fold, that is, 5.29 per 1000 person years (95% CI: 0.75-37.56), which is remarkable but still less than that reported for other chronic liver disorders. These incidence rates should be considered in relation to two major epidemiological observations which have a significant public health impact. Firstly, the global prevalence of NAFLD is higher than that of any other chronic liver disorder such as chronic viral hepatitis B or C. Secondly, the disease burden of HCC in NAFLD/NASH patients is increasing. In an analysis of the Scientific Registry of Transplant Recipients, including patients on the liver transplantation waiting list in the US between 2002 and 2016, the proportion of patients with NASH and HCC increased 7.7-fold (from 2.1% to 16.2%, \( P < .0001 \)). The prevalence of HCC with NASH on the same list increased 11.8-fold during the same period, showing it to be the fastest growth of all causes of liver disease listed for liver transplantation in the US, followed by chronic hepatitis B (6.0-fold), alcohol-related liver disease (3.4-fold) and chronic hepatitis C (2.3-fold). Global estimates confirm this tendency. A recent modelling study assessing the future burden associated with NAFLD in China, France, Germany, Italy, Japan, Spain, United Kingdom and the US suggested that even if obesity and type 2 diabetes level off in the next few years, the prevalence of NASH could continue to increase with the long-term sequelae, including HCC, doubling until 2030, due to the ageing (and increase) in the world population.

#### 3.1 | Risk factors of HCC

The risk factors of HCC in patients with NAFLD/NASH are only partly known. Although advanced liver fibrosis frequently precedes HCC, like in other chronic liver disorders, a significant proportion of HCCs occur in non-cirrhotic livers. Although early studies included patients who underwent surgical resection, liver transplantation or were recruited in tertiary referral centres, creating a potential referral bias, recent studies with large databases have confirmed this observation. One important retrospective cohort study performed in patients with HCC diagnosed from 2005 to 2010 in the US Veterans Health Administration investigated the risk factors for the development of HCC in the absence of cirrhosis. Medical records of 1500 patients were reviewed and 194 of them had no evidence of cirrhosis. A greater proportion of patients with HCC without cirrhosis had metabolic syndrome, NAFLD or had no risk factors of chronic liver disease compared to those with cirrhosis. Patients with NAFLD and HCC had a more than 5-fold higher risk of having HCC without cirrhosis, than those with hepatitis C virus (HCV)-associated HCC, for example. Similarly, patients with HCC and the metabolic syndrome had an unadjusted OR of 5.0 (95% CI 3.1-7.8) to have HCC without cirrhosis. Overall, 34.6% of patients with NAFLD and HCC had no evidence of cirrhosis, compared to 8.9% in patients with HCV, 7.7% in those with hepatitis B virus (HBV), and 11.1% in those with alcohol-related liver disease. The lack of cirrhosis in a significant proportion of NAFLD patients has been extensively confirmed and may occur in about 30%-50% of patients. The evidence was particularly convincing in a multicentre observational prospective study performed in Italy, which not only confirmed that ~50% of patients with NASH and HCC were non-cirrhotic, but that less than half of them had been identified during routine screening programmes, raising the troublesome issue of how to identify curative HCC. It is important to note that HCC in NAFLD patients were larger at diagnosis and more frequently presented with an infiltrative pattern. Despite this, after careful patient propensity score matching, the survival rates of NAFLD HCC were similar to those observed in patients with HCV infection. Nevertheless, the authors emphasize the importance of identifying patients with NAFLD without cirrhosis who could benefit from surveillance, and respond to curative therapies.

Several additional studies have assessed the risk factors associated with the development of HCC in NAFLD/NASH which may be relevant to design targeted screening strategies. The features associated with the metabolic syndrome besides age and male sex, such as diabetes, arterial hypertension and increased BMI, are strongly and frequently among the independent risk factors. One study assessed whether obesity is an independent factor of HCC in patients with advanced cirrhosis undergoing liver transplantation. In the 19 271 patients included in the study with an incidence of HCC of 3.4% (n = 659), obesity was an independent factor for HCC in patients with advanced cirrhosis undergoing liver transplantation. In the 19 271 patients included in the study with an incidence of HCC of 3.4% (n = 659), obesity was an independent factor for HCC in patients with advanced cirrhosis undergoing liver transplantation. In the 19 271 patients included in the study with an incidence of HCC of 3.4% (n = 659), obesity was an independent factor for HCC in patients with advanced cirrhosis undergoing liver transplantation. In the 19 271 patients included in the study with an incidence of HCC of 3.4% (n = 659), obesity was an independent factor for HCC in patients with advanced cirrhosis undergoing liver transplantation. In the 19 271 patients included in the study with an incidence of HCC of 3.4% (n = 659), obesity was an independent factor for HCC in patients with advanced cirrhosis undergoing liver transplantation. In the 19 271 patients included in the study with an incidence of HCC of 3.4% (n = 659), obesity was an independent factor for HCC in patients with advanced cirrhosis undergoing liver transplantation. In the 19 271 patients included in the study with an incidence of HCC of 3.4% (n = 659), obesity was an independent factor for HCC in patients with advanced cirrhosis undergoing liver transplantation. In the 19 271 patients included in the study with an incidence of HCC of 3.4% (n = 659), obesity was an independent factor for HCC in patients with advanced cirrhosis undergoing liver transplantation.
associated with an increased risk of HCC (HR = 4.2, 95% CI = 1.2-14.2, \( P = .02 \)), together with age (each decade increasing by an HR of 1.8) and decreased serum albumin (HR = 2.1, 95% CI = 1.5-2.9, \( P < .01 \)), while BMI and arterial hypertension were not. These results were validated in an analysis of liver transplantation registrants with NASH, where diabetes was still found to be an independent predictor of HCC (HR = 1.3, 95% CI = 1.0-1.7, \( P = .03 \)).

A study performed in Taiwan in 23 820 persons followed for 14 years analysed the association between obesity, diabetes and HCC, depending on the presence or absence of HBV or HCV infection,\(^3\) based on a link with the national tumour registry. Obesity was independently associated with an increased risk of HCC (RR 4.13; 95% CI, 1.38-12.4) in anti-HCV positive patients, but not in those with HBV. Importantly, persons without HCV or HBV had a two-fold increased risk of HCC after controlling for other metabolic factors (RR, 2.36; 95% CI, 0.91-6.17). Diabetes was associated with HCC irrespective of the presence or absence of HBV and HCV.

3.2 | Physical activity has a beneficial effect

Because the metabolic syndrome has a confirmed, negative impact on the risk of HCC, one could hypothesize that the level of physical activity should have a beneficial effect. Indeed, this association was first reported in a mouse model characterized by the spontaneous development of NASH and HCC.\(^3\) Mice fed standard chow were randomized to an exercise (motorized treadmill) or sedentary routine for 32 weeks. At the end of the observation period, the exercising mice had fewer, smaller liver tumours, although no effect was identified on steatosis or NASH. Exercise resulted into increased phosphorylation of AMPK and its substrate raptor, leading to decreased mTOR activity. These experimental observations have been elegantly confirmed by recent data in humans. A landmark multinational cohort study (the European Prospective Investigation into Cancer and Nutrition Cohort, the EPIC Study) assessed the impact of vigorous physical activity on different types of liver cancer in more than 470 000 persons followed for a median of 14.9 months.\(^3\) The multivariate-adjusted HR for HCC was 0.55 (95% CI 0.38-0.80) in active compared to inactive participants. Waist circumference and BMI explained respectively ~40% and 30% of the association. Vigorous physical activity for at least 2 h/wk was also found to be beneficial to the risk of HCC (HR 0.50, 95% CI 0.33-0.76) compared to no vigorous activity, after taking into consideration potential confounders. Interestingly, the presence and level of physical activity was not correlated to the risk of other liver cancers, such as intrahepatic bile duct cancers or non-gallbladder extrahepatic bile duct cancers.

Similarly, treatment of diabetes can reduce the risk of HCC. Indeed, this has been shown in several studies, especially in Asia. A nationwide study performed in Taiwan analysed 47 820 diabetic patients.\(^3\) Independent factors associated with the risk of HCC were HCV, HBV, insulin use, cirrhosis and metformin use. In particular, each additional year of metformin use reduced the risk of HCC by about 7% in diabetic patients. Another study in 19 349 newly diagnosed diabetic patients and 77 396 control persons without diabetes recruited from the same Taiwan National Health Insurance Research Database showed a clear dose-dependent reduction in the risk of HCC in diabetics taking metformin. The risk reduction was greater than that in patients taking thiazolidinediones (51% vs 44% reduction).\(^3\) Interestingly, statins also seem to protect from HCC. A nested case-control study from Korea in patients with newly diagnosed diabetes reported an adjusted OR of 0.36 (95% CI 0.22-0.60) in statin users vs non-users. Risk reduction was accentuated with an increase of cumulative defined daily doses.\(^3\)

3.3 | The role of genetics

Finally, genetics seems to play a role in the risk of HCC in NAFLD patients. The association of PNPLA3 variants and severe liver lesions has been confirmed in several studies. Heterogeneity at rs738409 has also been associated with the risk of HCC in patients with NAFLD.\(^3\) Variant frequencies were significantly different between 100 NAFLD-HCC cases (CC = 28, CG = 43, GG = 29) and 275 NAFLD-controls (CC = 125, CG = 117, GG = 33). After adjustment for age, gender, diabetes, BMI and cirrhosis, each copy of the rs738409 G variant led to an additive risk for HCC with an OR of 2.26. The risk of HCC among GG homozygotes was five-fold vs wild type CC. These important results suggest that genetic variants could help stratify at risk patients in whom strict surveillance for HCC could be beneficial, independent of the presence of cirrhosis.\(^4\) More data and prospective studies are clearly needed to further confirm this hypothesis.

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CONFLICT OF INTEREST

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ORCID

Francesco Negro https://orcid.org/0000-0003-4046-4806

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease – metaanalytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73-84.
2. Wong VW, Wong GL, Choi PC, et al. Disease progression of nonalcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut. 2010;59:969-974.
3. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol. 2015;62:1148-1155.
4. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology. 2017;65:1557-1565.
5. Hossain N, Afendy A, Stepanova M, et al. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009;7:1224-1229.

6. Klar J, Yang JD, Abdelmalik MF, et al. A longer duration of estrogen deficiency increases fibrosis risk among postmenopausal women with nonalcoholic fatty liver disease. Hepatology. 2016;64:85-91.

7. Younossi ZM, Stepanova M, Negro F, et al. Non-alcoholic fatty liver disease in lean individuals in the United States. Medicine. 2012;91:319-327.

8. Bambha K, Belt P, Abraham M, et al. Ethnicity and nonalcoholic fatty liver disease. Hepatology. 2012;55:769-780.

9. Valentí L, Al-Serri A, Daly AK, et al. Homozgyosity for the patatin-like phospholipase-3/adiponutrin 148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. Hepatology. 2010;51:1209-1217.

10. Pelusi S, Cespiati A, Rametta R, et al. Prevalence and risk factors of significant fibrosis in patients with nonalcoholic fatty liver without steatohepatitis. Clin Gastroenterol Hepatol. 2019;17(11):2310-2319. e6.

11. Liu Y-L, Reeves HL, Burt AD, et al. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. Nat Commun. 2014;5:4309.

12. 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;42:132-138.

13. Pais R, Charlotte F, Fedchuk L, et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatol. 2013;59:550-556.

14. 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.e1-9.

15. Cho JY, Chung TH, Lim KM, Park HJ, Jang JM. The impact of weight changes on nonalcoholic fatty liver disease in adult men with normal weight. Korean J Fam Med. 2014;35:243-250.

16. You DM, Volk CG, Philo L, Partridge BJ. Weight loss outcomes after liver biopsy in patients with nonalcoholic fatty liver disease. Dig Liver Dis. 2014;46:1136-1137.

17. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology. 2015;149(67-78):e5.

18. de Freitas AC, Campos AC, Coelho JC. The impact of bariatric surgery on nonalcoholic fatty liver disease. Curr Opin Clin Nutr Metab Care. 2008;11:267-274.

19. Ampuero J, Aller R, Gallego-Durán R, et al. The effects of metabolic status on non-alcoholic fatty liver disease-related outcomes, beyond the presence of obesity. Aliment Pharmacol Ther. 2018;48:1260-1270.

20. Younossi S, Stepanova M, Ong JP, et al. Non-alcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol. 2019;17:748-755.

21. Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. J Hepatol. 2018;69:896-904.

22. Bralet M-P, Régaimeau J-M, Pineau P, et al. Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. Hepatology. 2000;32:200-204.

23. Paradis V, Zaliński S, Chelbi E, et al. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. Hepatology. 2009;49:851-859.

24. Yeh MM, Daniel HD, Torbenson M. Hepatitis C-associated hepatocellular carcinomas in non-cirrhotic livers. Mod Pathol. 2010;23:276-283.

25. Smoot RL, Nogorney DM, Chandan VS, et al. Resection of hepatocellular carcinoma in patients without cirrhosis. Br J Surg. 2011;98:697-703.

26. Ertle J, Dechêne A, Sowa J-P, et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. Int J Cancer. 2011;128:2436-2443.

27. Mittal S, El-Serag HB, Sada YH, 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(1):124-131.e1.

28. Yasui K, Hashimoto E, Komorizono Y, et al. Characteristics of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2011;9:428-433.

29. Reddy SK, Steel JL, Chen H-W, et al. Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. Hepatology. 2012;55:1809-1819.

30. Sanyal A, Poklepovic A, Moyneur E, Barghout V. Population-based risk factors and resource utilization for HCC: US perspective. Curr Med Res Opin. 2010;26:2183-2191.

31. Piscaglia F, Svegliati-Baroni G, Barchetti A, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. Hepatology. 2016;63:827-838.

32. 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.

33. Yang JD, Ahmed F, Mara KC, et al. Diabetes is associated with increased risk of hepatocellular carcinoma in cirrhosis patients with nonalcoholic fatty liver disease. Hepatology. 2019. [Epub ahead of print].

34. Chen C, Yang H, Yang W, et al. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. Gastroenterology. 2008;135:111-121.

35. Piguet A-C, Saran U, Simillion C, et al. Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of steatosis. J Hepatol. 2015;62:1296-1303.

36. Baumeister SE, Schlesinger S, Aleksandrova K, et al. Association between physical activity and risk of hepatobiliary cancers: a multinational cohort study. J Hepatol. 2019;70:885-892.

37. Chen H-P, Shieh J-J, Chang C-C, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. Gut. 2013;62:606-615.

38. Kim G, Jang SY, Nam CM, Kang ES. Statin use and the risk of hepatocellular carcinoma. J Hepatol. 2012;57:1832-1837.

39. Liu YL, Patman GL, Leathart JB, et al. Carriage of the PNPLA3 I148M polymorphism influences fibrosis in patients with nonalcoholic fatty liver disease. J Hepatol. 2012;55:1809-1819.

40. Goossens N, Singal AG, King LY, et al. Cost-effectiveness of risk score-stratified hepatocellular carcinoma screening in patients with cirrhosis. Clin Transl Gastroenterol. 2017;8:e101.

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