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Review paper

Hepatocellular carcinoma in patients with non-alcoholic steatohepatitis – epidemiology, risk factors, clinical implications and treatment

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Abstract

In recent years, rapid growth of incidence of metabolic syndrome, obesity and diabetes has been noted worldwide. Concurrent non-alcoholic steatohepatitis (NASH) has become a dominant factor of hepatic cirrhosis and hepatocellular carcinoma (HCC). The most important risk factors of transition from NASH to HCC are the degree of liver fibrosis, diabetes, obesity, age and male gender. Body mass index (BMI) reduction and increase of physical activity limit the risk of occurrence of HCC. Also, treatment of diabetes with metformin and application of statins have potential anticancer effects. Patients with HCC due to NASH should be treated in line with BCLC staging. Distant results of HCC therapy in the course of non-alcoholic fatty liver disease (NAFLD) are similar to the results of cancer of different aetiologies. However, patients with the metabolic syndrome are at high perioperative risk, and thus require accurate preparation, especially cardiological, in order to avoid that risk.

Key words: NAFLD, HCC, NASH.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver occurring worldwide. In 2015 it was the fourth cancer in the world in terms of mortality, and sixth in terms of prevalence. The number of new cases in 2015 increased by 75% in comparison to 1990. The greatest rate of prevalence concerns Asian countries and sub-Saharan region of Africa. The essential etiological factor of HCC development is post-inflammatory cirrhosis induced by viral hepatitis (B or C), HBV or HCV, as well as alcoholic cirrhosis, and any hepatic cirrhosis, regardless of its aetiology [1-3]. In recent years, rapid growth of incidence of metabolic syndrome, obesity and diabetes has been noted worldwide. The majority of authors claim that concurrent non-alcoholic steatohepatitis is becoming a dominant factor of hepatic cirrhosis and HCC [4, 5]. Growing frequency of occurrence, global range, and multimorbidity concomitant with the mentioned pathologies are becoming a true challenge both for practitioners dealing with diagnosis and treatment of HCC, as well as for public health employees in general [6].

Epidemiology

Non-alcoholic fatty liver disease (NAFLD) affects one fourth of the world population. There are various concomitant diseases and pathological states: obesity in 51%, type 2 diabetes in 41%, hyperlipidaemia in 69%, hypertension in 39%, and in 42% of cases all components of the metabolic syndrome [7, 8]. Non-alcoholic steatohepatitis (NASH), a more active and severe form of non-alcoholic fatty liver, affects 1.5% to 6.5% of the general population, which accounts for ca. 10-20% of patients with NAFLD. In papers based on liver biopsy results, transition from NAFLD to NASH was confirmed far more frequently, in as many as 59% of cases [5]. NASH is characterized with a typical histopathological image: ballooning degeneration and

inflammation in the hepatocytes, which causes progressing fibrosis and hepatic cirrhosis and hepatocellular carcinoma [5-8]. It is estimated that the mortality caused by liver diseases and general mortality in patients with NAFLD is, respectively, 0.77 and 11.7 per 1000 person-years, while analogical indicators in the case of patients with NASH are considerably higher, respectively 15.44 and 25.56 per 1000 person-years [8]. The main cause of death of patients with NAFLD/NASH is cardiovascular disease (48%); the second, non-liver solid malignant tumours – gastric cancer, pancreatic cancer, bowel cancer, ovarian cancer, lung cancer, breast cancer (22%); and the third, hepatic complications – hepatic cirrhosis and HCC (10%) [5, 9]. It was found that patients with NAFLD incur a 64% higher risk of coronary heart disease, heart attack, stroke and coronary heart disease. Death risk due to heart diseases varies from 1.55 to 1.85 and is considerably higher in comparison to patients with chronic hepatitis C [5, 10-14]. The relation between NAFLD and atherosclerosis, which is the cause of cardiovascular disease (CVD), seems logical. Dyslipidaemia with a high level of triglycerides and decreased level of HDL in combination with insulin resistance in patients with NAFLD accelerates the onset of atherosclerosis [15].

Addressed in numerous papers [5, 6, 16-18], as mentioned above, the unspecified percentage of transition from NAFLD to NASH, slow progression of NASH to hepatic cirrhosis, gravity and significance of global epidemic of obesity and metabolic syndrome undervalued by the majority of doctors, and the consequences stemming from it, all add up to a situation where 38-45% of cases of hepatic cirrhosis in the course of NAFLD are diagnosed only at the stage of advanced liver failure [5, 19]. Moreover, the cases of liver cancers originating from NASH are diagnosed later and are more advanced than hepatocellular carcinomas of different aetiologies [5, 15]. Numerous authors also claim that a large percentage, perhaps even 30-75%, of so-called cryptogenic cirrhosis (CC) may in reality be a form of hepatic cirrhosis induced by NAFLD [5, 20, 21]. It has serious prognostic implications, as the affinity of this kind of cirrhosis to HCC is markedly higher in comparison to cirrhosis of different aetiologies [5, 22, 23].

In the group of patients with hepatic cirrhosis in the course of NASH, hepatocellular carcinoma is becoming the most common cause of death, not only because of cancer itself, but also because of the age of the patients and numerous concomitant diseases [5, 24, 25]. Numerous authors have noted an increase in occurrences of HCC in the course of NAFLD. In the UK in the years 2000-2010 the percentage of cancers induced by NASH increased from 21.5% to 34.8%. In the USA between 2004 and 2009 the annual growth of NASH involvement in the emergence of HCC was 9%. In Asia the percentage of nonviral cases of HCC in the years 1991-2010 increased from 10% to 24.1% [5, 26, 27]. Cumulative annual frequency of HCC incidence in patients with cirrhosis on the background of NAFLD ranges from 2.4% to 12.8%, while the annual risk of transition from NASH to liver cancer is estimated at 0.3% [24, 28, 29]. A permanent increase of the HCC percentage is also observed, reaching 37% of cases, emerged in the course of NASH without concomitant hepatic cirrhosis [24, 29, 30].

Hepatocellular carcinoma risk factors

According to the majority of authors, the most important risk factors of transition from NASH to HCC are: the degree of progression of liver fibrosis, diabetes and insulin resistance, as well as obesity, age and male gender [24, 29]. Diabetes is an independent factor, doubling the risk of HCC, and death risk due to hepatocellular carcinoma in the course of diabetes rises by 1.56 [31-33]. Similarly, obesity is a significant HCC risk factor. Patients with HCC in the course of NASH had higher body mass index (BMI) (27 kg/m^2) than patients with HCC with induced HCV (24 kg/m^2). With BMI greater than 30 kg/m^2 the risk of cancer almost doubles, and with BMI greater than 35 kg/m^2 it increases almost fourfold [24, 29, 31]. The connection of hepatocellular carcinoma with metabolic syndrome, diabetes, obesity and hypercholesterolemia is highly visible. Among patients with HCC in the course of NAFLD, patients with diabetes and obesity prevail. In the group of patients with metabolic syndrome and diabetes, the risk of HCC is five times greater in comparison to patients without these pathologies [31]. Renal failure coexisting frequently with metabolic syndrome is the cause of an increasing number simultaneous liver-kidney transplantations [16]. Not all patients presenting symptoms of metabolic syndrome, such as diabetes, dyslipidaemia or fatty liver disease (FLD), are fat. It affects 10% to 20% of the white population with BMI less than 25 kg/m^2, where liver fibrosis greater than F2 is diagnosed in ca. 27% of cases. The progression of liver disease in slim patients with metabolic obesity may also lead to hepatic cirrhosis and liver cancer [31]. The aforementioned cryptogenic cirrhosis, in comparison to alcoholic cirrhosis and post-inflammatory cirrhosis, coexists far more frequently with: diabetes (in 56% in comparison to, respectively, 17% and 11%), obesity (in 50% in comparison to, respectively, 17% and 14%), and fatty liver disease (FLD), exceeding 20% (in 61% in comparison to, respectively, 17% and 19%) [24, 31]. This suggests that cryptogenic

cirrhosis (CC) in a large percentage is an advanced form of cirrhosis on the background of NAFLD. It has been shown that CC in patients with obesity may be complicated by HCC in 27% of cases [5, 22-24, 31]. In terms of demography and threats stemming from it, numerous studies, included those conducted in Japan, indicated advanced age of the patients with HCC in the course of NASH in comparison to the age of patients with cancer induced with HCV. These regularities concerned both women and men [31, 34]. Among patients with hepatocellular carcinoma males prevail, but such a statistically significant correlation has not been proved in the HCC group in the course of NASH [24, 35]. Among other risk factors in the development of HCC in NAFLD, the increase of intrahepatic iron content and alcohol intake are mentioned. An increased iron concentration in hepatocytes was measured in patients with liver cancer in the course of NASH in comparison to patients with only uncomplicated hepatic steatosis [24, 29]. Chronic alcohol consumption increases the risk of transition from NASH to HCC more than threefold [24, 36].

The mentioned risk factors influencing the increase of oncogenesis in patients with NAFLD gave the basis for numerous studies on investigating its pathomechanisms. The transition from dysplasia to cancer may be induced by numerous carcinogenic mechanisms. Numerous paths and multi-factorial pathogenic mechanisms such as inflammation, cirrhosis, diabetes and insulin resistance, lipid metabolism disorders, intestinal dysbiosis and genetic disorders in the form of polymorphisms play a role, according to many authors, in the development of HCC [24, 29, 31, 37-39].

Following the guidelines of AASLD (the American Association for the Study of Liver Diseases) for patients with hepatic cirrhosis, including those in the course of NASH, they should all be screened for HCC. Ultrasound of the liver every 6 months, together with the evaluation of AFP, is therefore compulsory [40]. It does not (yet?) concern patients with NAFLD/NASH without hepatic cirrhosis. Diagnosing a growing number of HCC cases, reaching even 50%, caused by NAFLD without cirrhosis, and later cancer diagnoses, in comparison to other HCC aetiologies, resulting in delaying the treatment, necessitate the performance of research concerning the rationale behind and the cost efficiency of screening tests in this group of patients [24, 41-44].

Prevention

The proven negative influence of metabolic syndrome, increasing the risk of cancer transition in patients with NASH, paved the way for, initially intuitive, later proven, behaviours, and various therapies potentially helping in cancer prevention. It has been demonstrated that intensive physical exercise decreases the risk of HCC [44, 45]. The treatment of diabetes with metformin reduces the risk of cancer by 7% annually. Similarly, therapy with statins prevents carcinogenesis [46, 47]. BMI reduced through dietary change or bariatric surgery reduces the incidence of diabetes, as well as the risk of HCC occurrence, by decreasing the degree of liver fibrosis [48-50]. In contrast to alcohol, the intake of more than 2 cups of coffee daily decreases the risk of liver cancer by 27% [50, 51]. Papers discuss potentially preventive measure of other medications such as branched-chain amino acids (BCAAs), interferon, non-steroidal anti-inflammatory drugs (NSAIDs) (aspirin) and anticoagulants [50].

Treatment

There is a lack of reports on special methods of HCC treatment dedicated to patients with NAFLD [15, 24]. Patients should be treated in line with BCLC staging [52]. According to Bruix [53], an expert in therapies used in HCC, only patients with a single lump not larger than 5 cm, no feature of decompensated liver fibrosis – ascites, jaundice and portal hypertension, and the number of thrombocytes exceeding 100,000/mm^3 – should be qualified as candidates for liver resection surgery. What follows, only patients in whom resection cannot be performed due to liver failure, and who fulfil the Milan criteria (one lump smaller than 5 cm, alternatively up to 3 lumps, each smaller than 3 cm, with no evidence of vascular invasion), should become eligible for liver transplantation (LTx). Thermal tumour ablation is currently the most frequently used strategy in surgical treatment of HCC. Limitations of the application are the patient's liver failure and unfavourable position of the lesion. In patients with multiple foci of the neoplasm, without extrahepatic spread, transarterial chemoembolization (TACE) is used. Sorafenib, regorafenib and immunomodulators extend the survival of patients in advanced cases of HCC, not eligible for the abovementioned therapies [53]. The basic aim of surgical treatment is radical resection of the tumour and preventing recurrence. The 5-year survival is 60% from the time of resection, with low, lower than 3%, perioperative mortality. Frequent cancer recurrences, reaching 70% in the course of 5 years, pose a major problem [54, 55]. Long-term results of thermal tumour ablation 2 cm in size are comparable to the results of liver resection surgery [54, 55]. After transplantation, due to HCC in patients meeting the Milan criteria, cancer recurrences occur in 10% to 15% of cases.

After broadening eligibility criteria, in larger lumps, they occur far more often [55, 56]. In order to improve the results of liver transplantation, many centres adopted various auxiliary criteria, including α-fetoprotein (AFP) concentration in serum, which turned out to be helpful in determining the risk of recurrence, and therefore in the assessment of prognosis. According to many authors, exclusion criteria for supplementation of the Milan criteria with AFP concentration in serum allow for the exclusion of patients with an aggressive form of cancer, resulting in a high degree of recurrences. The level of 1000 ng/ml was adopted as the boundary AFP concentration, above which the risk of recurrence is very high. However, some centres indicate the level of 400 ng/ml [56]. NASH is currently the second indication for liver transplantation in the USA in terms of frequency [57]. Kidney failure, frequently concomitant with metabolic syndrome and diabetes in patients with uncontrolled cirrhosis in the course of NASH, caused an increase of simultaneous kidney liver transplantations. Their percentage increased from 2003 to 2011 in the USA from 6.3% to 19.2% respectively [15]. Moreover, NASH is an increasingly frequent indicator for LTx due to HCC, but it results in numerous clinical implications [55]. Patients with NASH and confirmed liver cancer directed for surgical treatment are usually elderly people, with concomitant diseases, with less developed liver failure and usually larger lumps in comparison to patients with HCC of different aetiologies. Late cancer diagnoses are the results of lack of screening tests in patients with NAFLD, where no cirrhosis was observed yet, as well as difficulties with ultrasound scanning of small focal changes in fatty liver. The period of cancer diagnosis therefore gets extended, which delays the decision to treat the patient. After qualifying the patient for LTx, the waiting time for the surgical treatment of patients with cancer in the course of NAFLD is longer than in patients with hepatic cirrhosis of different aetiologies, taking into account the lower MELD indicator, showing a lower degree of liver failure in these patients. This results in an increased number of cancellations on the waiting list for LTx caused by, in the first place, cancer development exceeding the Milan criteria, and secondly mortality caused by concomitant diseases. An additional factor preventing transplantation is the fact of portal vein thrombosis, occurring more often than in other types of cirrhosis, reaching 10.1%, in patients with NAFLD [15, 24, 58-61]. For these reasons, the majority of patients with HCC in the course of NAFLD have liver resection procedures, and only a small fraction of patients are eligible for LTx [24, 30]. Three- and 5-year survival of patients with NAFLD from the time of LTx does not significantly differ from the results of liver transplantation from other reasons [15, 59, 62-64]. The fact remains that in the first two years from the time of LTx, the main causes of death are IVD, sepsis, and severe obesity [15, 59, 63]. The 5-year survival of the recipient from the time of LTx without obesity in comparison to patients with BMI > 40 kg/m^2 is 78.8% and 51.3% respectively. 50% of patients with BMI higher than 35 and diabetes die within 1 year from the time of LTx. Some patients with severe obesity cannot, taking into account the high death risk, be qualified for liver transplantation [15, 59, 63]. The mentioned risk factors necessitate a thorough cardiology analysis of patients with NAFLD eligible for surgical treatment. Performing coronary angiography with the use of catheters and coronary artery stenting is recommended, because 70% of cardiac complications occurring in the perioperative period are the cause of 50% of deaths from the time of LTx [15, 59]. Due to numerous risk factors, eligibility of patients with liver cancer in the course of NAFLD for surgical treatment becomes a true challenge for the medical team, which by necessity needs to be interdisciplinary.

Disclosure

The authors declare no conflict of interest.

References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.
2. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132: 2557-2576.
3. Akinyemiju T, Abera S, Ahmed M, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. JAMA Oncol 2017; 3: 1683-1691.
4. Michelotti GA, Machado MV, Diehl AM. NAFLD, NASH and liver cancer. Nat Rev Gastroenterol Hepatol 2013; 10: 656-665.
5. Huang TD, Behary J, Zekry A. Non-alcoholic fatty liver disease (NAFLD): a review of epidemiology, risk factors, diagnosis and management. Intern Med J 2019. Available from https://doi: 10.1111/imj.14709
6. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology 2016; 64: 1577-1586.
7. Castera L, Friedrich-Rust M, Loomba R, et al. Assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology 2019; 156: 1264-1281.
8. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Metaanalytic assessment of prevalence, incidence and outcomes. Hepatology 2016; 64: 73-84.
9. Nasr P, Ignatova S, Kechagias S, et al. Natural history of nonalcoholic fatty liver disease: A prospective follow-up study with serial biopsies. Hepatol Commun 2017; 2: 199-210.

10. Stepanova M, Rafiq N, Makhlouf H, et al. Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). Dig Dis Sci 2013; 58: 3017-3023.
11. Musso G, Gambino R, Cassader M, et al. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med 2011; 43: 617-649.
12. Targher G, Arcaro G. Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. Atherosclerosis 2007; 191: 235-240.
13. Targher G, Marra F, Marchesini G. Increased risk of cardiovascular disease in non-alcoholic fatty liver disease: causal effect or epiphenomenon? Diabetologia 2008; 51: 1947-1953.
14. Lindenmeyer CC, McCollough, A. The natural history of nonalcoholic fatty liver disease – an evolving view. Clin Liver Dis 2018; 22: 11-21.
15. Mikolasevic I, Filipec-Kanizaj T, Milic S, et al. Nonalcoholic fatty liver disease and liver transplantation – Where do we stand? World J Gastroenterol 2018; 24: 1491-1506.
16. Cai J, Zhang XJ, Li H. Progress and challenges in the prevention and control of nonalcoholic fatty liver disease. Med Res Rev 2019; 39: 328-338.
17. Patel PJ, Banh X, Horsfall LU, et al. Underappreciation of non-alcoholic fatty liver disease by primary care clinicians: limited awareness of surrogate markers of fibrosis. Intern Med J 2018; 48: 144-151.
18. Van Asten M, Verhaegh P, Koek G, et al. The increasing burden of NAFLD fibrosis in the general population: time to bridge the gap between hepatologist and primary care. Hepatology 2017; 65: 1078.
19. Pais R, Barritt AS, Calmus Y, et al. NAFLD and liver transplantation: Current burden and expected challenges. J Hepatol 2016; 65: 1245-1257.
20. Caldwell SH, Oelsner DH, Iezzoni JC, et al. Cryptogenic cirrhosis: Clinical characterization and risk factors for underlying disease. Hepatology 1999; 29: 664-669.
21. Van der Porter D, Samer CF, Ramezani-Moghadam M, et al. Hepatic fat loss in advanced nonalcoholic steatohepatitis: are alterations in serum adiponectin the cause? Hepatology 2013; 57: 2180-2188.
22. Yoshioka Y, Hashimoto A, Yatsuji, et al. Nonalcoholic steatohepatitis: cirrhosis, hepatocellular, and burnt-out NASH. Gastroenterol 2004; 39: 1215-1218.
23. Ratziu V, Bonyhay l, Di Martino V, et al. Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis. Hepatology 2002; 35: 1485-1493.
24. Cholankerii G, Patel R, Khurana S, et al. Hepatocellular carcinoma in non-alcoholic steatohepatitis: Current knowledge and implications for management. WJH 2017; 9: 533-543.
25. Akuta N, KawamuraY, Arase Y, et al. Hepatocellular carcinoma is the most common liver-related complication in patients with histopathologically-confirmed NAFLD in Japan. BMC Gastroenterol 2018; 18: 165.
26. Wong SW, Ting YW, Chan WK. Epidemiology of non-alcoholic fatty liver disease-related hepatocellular carcinoma and its implications. JGH Open 2018; 2: 235-241.
27. Dyson J, Jaques B, Chattopadyhay D, et al. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. J Hepatol 2014; 60: 110-117.
28. 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: 1342-1359.
29. Zoller H, Tilg H. Nonalcoholic fatty liver disease and hepatocellular carcinoma. Metabolism 2016; 65: 1151-1160.
30. Bengtsson B, Stal P, Wahlin S, et al. Characteristics and outcome of hepatocellular carcinoma in patients with NAFLD without cirrhosis. Liver Int 2019; 39: 1098-1108.
31. Berkan-Kawinska A, Piekarska A. Hepatocellular carcinoma in non-alcohol fatty liver disease – changing trends and specific challenges. Curr Med Res Opin 2020; 36: 235-243.
32. Wang C, Wang X, Gong G, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systemic review and meta-analysis of cohort studies. Int J Cancer 2012; 130: 1639-1648.
33. Chettouh H, Lequoy M, Fartoux L, et al. Hyperinsulinemia and insulin signalling in the pathogenesis and the clinical course of hepatocellular carcinoma. Liver Int 2015; 35: 2203-2217.
34. Yatsuj S, Hashimoto E, Tobari M, et al. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic Hepatitis C. J Gastroenterol Hepatol 2009; 24: 248-254.
35. 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.
36. Tobari M, Hashimoto E, Taniai M, et al. The characteristics and risk factors of hepatocellular carcinoma in nonalhololic fatty liver disease without cirrhosis. J Gastroenterol Hepatol 2019. Available from https://doi: 10.1111/jgh.14867
37. Takakura K, Oikawa T, Nakano M, et al. Recent insights into the multiple pathways driving non-alcoholic steatohepatitis derive hepatocellular carcinoma. Front Oncol 2019; 9: 762.
38. Desterke C, Chiappini F. Lipid related genes altered in NASH connect inflammation in liver pathogenesis progression to HCC: a canonical pathway. Int J Mol Sci 2019; 20: 5594.
39. Brandi G, De Lorenzo S, Candela M, et al. Microbiota, NASH, HCC and potential role of probiotics. Carcinogenesis 2017; 38: 231-240.
40. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018; 68: 723-750.
41. Mittal S, Sada YH, El-Serag HB, et al. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. Clin Gastroenterol Hepatol 2015; 13: 594-601.
42. Noureddin M, Rinella ME. Nonalcoholic fatty liver disease, diabetes, obesity, and hepatocellular carcinoma. Clin Liver Dis 2015; 19: 361-379.
43. Margini C, Dufour JF. The story of HCC in NAFLD: from epidemiology, across pathogenesis, to prevention and treatment. Liver Int 2016; 36: 317-324.
44. Negro F. Natural history of NASH and HCC. Liver Int 2020; 40: 72-76.
45. 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.
46. Chen HP, Shieh JJ, Chang CC, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. Gut 2013; 62: 606-615.
47. Kim G, Jang SY, Nam CM, et al. Statin use and the risk of hepatocellular carcinoma in patients at high risk: A nationwide nested case-control study. J Hepatol 2018; 68: 476-484.
48. Kwak M, Mehaffey JH, Hawkins RB, et al. Bariatric surgery is associated with reduction in non-alcoholic steatohepatitis and hepatocellular carcinoma: A propensity matched analysis. Am J Surg 2020; 19: 504-507.

49. Yang Y, Zhang D, Feng N, et al. Increased intake of vegetables, but not fruit, reduces risk for hepatocellular carcinoma: a meta-analysis. Gastroenterology 2014; 147: 1031-1042.
50. Fujiwara N, Friedman SL, Goossens N, et al. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol 2018; 68: 526-549.
51. Kennedy OJ, Roderick P, Buchanan R, et al. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. BMJ Open 2017; 7: 013739.
52. Kikuchi L, Oliveira CP, Alvares-da-Silva MR, et al. Hepatocellular carcinoma management in nonalcoholic fatty liver disease patients: applicability of the BCLC staging system. Am J Clin Oncol 2016; 39: 428-432.
53. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018; 391: 1301-1314.
54. Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019; 380: 1450-1462.
55. Nahon P, Vibert E, Nault JC, et al. Optimizing curative management of hepatocellular carcinoma. Liver Int 2020; 40: 109-115.
56. Kim B, Kahn J, Terrault NA. Liver transplantation as therapy for hepatocellular carcinoma. Liver Int 2020; 40: 116-121.
57. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology 2014; 59: 2188-2195.
58. Muthiah MD, Sanyal AJ. Current management of non-alcoholic steatohepatitis. Liver Int 2020; 40: 89-95.
59. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia 2016; 59: 1121-1140.
60. Young K, Aguilar M, Gish R, et al. Lower rates of receiving model for end-stage liver disease exception and longer time to transplant among nonalcoholic steatohepatitis hepatocellular carcinoma. Liver Transpl 2016; 22: 1356-1366.
61. Tsochatzis E, Coilly A, Nadalin S, et al. International liver transplantation consensus statement on end-stage liver disease due to nonalcoholic steatohepatitis and liver transplantation. Transplantation 2019; 103: 45-56.
62. Castello B, Aquilera V, Blazquez MT, et al. Post-transplantation outcome in non-alcoholic steatohepatitis cirrhosis: Comparison with alcoholic cirrhosis. Ann Hepatol 2019; 18: 855-861.
63. Conzen KD, Vachharajani N, Collins KM, et al. Morbid obesity in liver transplant recipients adversely affects long term graft and patient survival in a single-institution analysis. HPB (Oxford) 2015; 17: 251-257.
64. Chitturi S, Wong VW, Chan WK, et al. The Asia-Pacific Working Party on non-alcoholic fatty liver disease guidelines 2017 – Part 2: Management and special groups. J Gastroenterol Hepatol 2018; 33: 86-98.