Editorial Commentary

Metabolic dysfunction-associated fatty liver disease and hepatocellular carcinoma: present and future

Feng Gao[1], Gang Chen[2,3,4], Christopher D. Byrne[5], Giovanni Targher[6,7], Tan To Cheung[8], Ming-Hua Zheng[9,10,11]

[1]Department of Gastroenterology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [2]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [3]Key Laboratory of Diagnosis and Treatment of Severe Hepato-Pancreatic Diseases of Zhejiang Province, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [4]Hepatobiliary Pancreatic Tumor Bioengineering Cross International Joint Laboratory of Zhejiang Province, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [5]Southampton National Institute for Health and Care Research, Biomedical Research Centre, University Hospital Southampton and University of Southampton, Southampton General Hospital, Southampton, UK; [6]Department of Medicine, University of Verona, Verona, Italy; [7]IRCCS Sacro Cuore-Don Calabria Hospital, Negrar di Valpolicella, Italy; [8]Department of Surgery, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China; [9]MAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [10]Institute of Hepatology, Wenzhou Medical University, Wenzhou, China; [11]Key Laboratory of Diagnosis and Treatment for the Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China

Correspondence to: Ming-Hua Zheng, MD, PhD. MAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, No. 2 Fuxue Lane, Wenzhou 325000, China; Institute of Hepatology, Wenzhou Medical University, Wenzhou, China; Key Laboratory of Diagnosis and Treatment for the Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China. Email: zhengmh@wmu.edu.cn.

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Metabolic dysfunction-associated fatty liver disease (MAFLD), previously termed non-alcoholic fatty liver disease, is one of the most common causes of chronic liver disease, affecting around 30% of the world's adults (1). MAFLD encompasses a spectrum of liver conditions, ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), which can progress to cirrhosis and hepatocellular carcinoma (HCC) (2,3). HCC has become the third leading cause of cancer-related mortality worldwide (4). Most patients with HCC have a background of chronic liver disease due to hepatitis B and hepatitis C virus (HCV), alcohol abuse, or MAFLD. With the advent of highly effective pharmacotherapies for viral hepatitis and the increasing prevalence of obesity worldwide, MAFLD is becoming the fastest growing cause of cirrhosis and HCC. Recent data from the Italy (using the ITA.LI.CA database) showed that MAFLD was diagnosed in most patients with HCC (almost 70%), and it is predicted that MAFLD will explain nearly all the causes of HCC in Italy in the next decade (5). Studies from other countries have also shown a rapid increase in the percentage of patients with HCC attributed to MAFLD over the past two decades, and it is anticipated that MAFLD-related HCC will soon be the leading indication for liver transplantation (4,6).

The analysis from the ITA.LI.CA database suggested that around 90% of MAFLD-related HCC may develop in patients with advanced fibrosis or cirrhosis, thus highlighting the pathogenic role of liver fibrosis in cancer development (5). Previous studies have also observed that HCC incidence increased with fibrosis stage (4). Although

liver biopsy represents the 'gold standard' method for staging liver fibrosis, it is an invasive diagnostic procedure with some associated acute risks. The use of non-invasive tests has been suggested for screening of liver fibrosis (7). In addition, a two-step approach using blood-based fibrosis tests [e.g., fibrosis index-4 (FIB-4)] followed by vibration-controlled transient elastography (VCTE) has been proposed to accurately identify advanced fibrosis in MAFLD patients. Studies have reported that increased non-invasive liver fibrosis scores, including FIB-4, were associated with a substantially increased risk of HCC (8).

Why is it that MAFLD/MASH is so important in the etiology and pathogenesis of HCC? Although HCC primarily arises in patients with advanced fibrosis and cirrhosis, there is evidence that MASH may increase the risk of HCC even in the absence of advanced fibrosis/cirrhosis (5). According to some studies, about 15–50% of HCC cases arise in MASH patients without cirrhosis (9). These patients do not have an indication for routine HCC surveillance based on the current guidelines (10). Therefore, early recognition of HCC in non-cirrhotic MASH patients is currently a major challenge. Risk factors for HCC include older age, obesity, type 2 diabetes, and genetic susceptibility [e.g., the patatin-like phospholipase domain-containing protein-3 (*PNPLA3*) and the transmembrane 6 superfamily member 2 protein (*TM6SF2*) genetic variants] (11). As such, these factors occurring independently of liver fibrosis, may be important in the pathogenesis of HCC (9). At present, the precise pathogenesis of HCC in MAFLD is not fully understood, but it seems phenotypically different from HCC occurring in people with HCV-related cirrhosis or other chronic liver diseases. Several factors have been proposed that might explain this discordance in MAFLD, including insulin resistance, the DNA damage response, increased oxidative stress, abnormal immune responses and changes in gut microbiota (11).

Compared to HCC occurring as a result of other etiologies, a lower proportion of patients with HCC are identified by surveillance strategies in MAFLD (5). This may be related to several reasons, one of which is the failure of liver ultrasound to detect small HCC in people with MAFLD because of the presence of increased subcutaneous fat and greater liver fat accumulation. Additionally, while there is general agreement about the application of surveillance programs in patients with MAFLD-related cirrhosis, there is currently no consensus regarding HCC surveillance in non-cirrhotic patients. Current guidelines recommend ultrasound surveillance every six months for patients with advanced fibrosis and cirrhosis (10). However, surveillance with ultrasound of a very large population with non-cirrhotic MAFLD is not feasible and would be hugely costly.

Future research is needed to develop a cost-effective test that can better stratify the risk of HCC in patients with non-cirrhotic MAFLD and identify subgroups of patients who may benefit from HCC surveillance. Recently, an international consortium has developed a new blood-based risk score (i.e., the LiverRisk score) using six simple laboratory variables (circulating levels of aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl-transferase, glucose, total cholesterol, and platelet count) together with age and sex. This new blood-based risk score was validated against VCTE-assessed liver stiffness and was shown to efficiently predict HCC in the general population (12). However, an assessment of the cost-effectiveness of this score is needed.

The prognosis of MAFLD-related HCC is controversial. The analysis from the ITA.LI.CA database reported that the median overall survival was significantly lower in patients with non-MAFLD HCC than in those with MAFLD-related HCC, and the protective effect of MAFLD on the liver-related survival was independent of the HCC stage and treatment type (5). However, other studies reported that after adjusting for possible confounding factors (including the tumor stage), no significant difference in survival was detected between patients with MAFLD-related HCC and those with non-MAFLD HCC (13).

At present, there are no approved drugs for MAFLD/MASH. However, some treatments, such as liraglutide, semaglutide and pioglitazone that have proved effective in NASH, are licensed for treating type 2 diabetes that may be present as a feature of MAFLD. Preventative interventions should focus on risk mitigation through managing obesity, type 2 diabetes, and dyslipidemia and early detection in patients at high risk for HCC, such as those with advanced fibrosis/cirrhosis. Patients with early HCC are more likely to be eligible for curative treatments such as ablation, surgical resection, or liver transplantation. However, patients with MAFLD-related HCC are more likely to be diagnosed at later stages, with larger tumors, and have more frequent extrahepatic metastases (11). These characteristics will limit treatment strategies, influencing the prognosis. Moreover, in combination with advanced age and comorbidities associated with MASH, such as type 2 diabetes, cardiovascular disease and chronic kidney disease, curative procedures need careful consideration (11,14,15).

In conclusion, future studies are needed in non-cirrhotic

MAFLD to recognize patients at high risk of HCC and to better understand the pathogenesis of HCC in this patient group. A better understanding of the pathogenesis in patients with non-cirrhotic MAFLD at high HCC risk and earlier detection of HCC will likely lead to more effective treatment approaches and better clinical outcomes.

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Footnote

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