Editorial Commentary

An ever-increasing metabolic dysfunction-associated fatty liver disease-related hepatocellular carcinoma: what are problems and countermeasures?

Shigeo Shimose^, Tsubasa Tsutsumi^, Dan Nakano^, Tomoya Sano^, Keisuke Amano^, Takumi Kawaguchi^

Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan

Correspondence to: Takumi Kawaguchi, MD, PhD. Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan. Email: takumi@med.kurume-u.ac.jp.

Comment on: Vitale A, Svegliati-Baroni G, Ortolani A, *et al.* Epidemiological trends and trajectories of MAFLD-associated hepatocellular carcinoma 2002-2033: the ITA.LI.CA database. Gut 2023;72:141-52.

Keywords: Hepatoma; hepatic steatosis; metabolic syndrome; viral hepatitis; lenvatinib (LEN)

Submitted Oct 19, 2023. Accepted for publication Oct 30, 2023. Published online Nov 09, 2023

doi: 10.21037/hbsn-23-538

View this article at: https://dx.doi.org/10.21037/hbsn-23-538

Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths worldwide (1). HCC has been classified into viral or non-viral HCC according to the etiology and the incidence of viral HCC is decreasing. In contrast, the incidence of non-viral HCC is increasing and fatty liver is becoming a major etiology for the HCC. In 2020, a new concept of fatty liver disease, metabolic dysfunction-associated fatty liver disease (MAFLD), was proposed by the International Expert Panel consisting of 32 specialists from 22 countries (2,3). Now, MAFLD is considered an independent major etiology for HCC like hepatitis B virus (HBV) and hepatitis C virus (HCV) (4).

Recently, Vitale *et al.* assessed the epidemiological trajectories of MAFLD-related HCC in recent and future using the Italian Cancer Liver ITA.LI.CA database (1). They found that MAFLD was diagnosed in 68.4% of patients with HCC. The proportion of MAFLD significantly increased over time. Then, in approximately 6 years, MAFLD will be the primary cause of incident HCC in Italy. They also pointed out an important issue: patients with MAFLD-related HCC frequently had large tumors and extrahepatic metastases due to a lack of an effective screening system (1).

A feature of MAFLD is the inclusion criteria of metabolic disorders. MAFLD is diagnosed when fatty liver is coexistent with obesity, type 2 diabetes, or two or more metabolic disorders. Since these metabolic disorders are risk factors for various life-threatening events, MAFLD is considered useful for enclosing patients at high risk (2). In fact, MAFLD can predict the progression of atherosclerotic cardiovascular risk and other various extrahepatic diseases (5). Moreover, MAFLD can capture patients at high risk of hepatic fibrosis as well as HCC (3,4).

Vitale *et al.* described that MAFLD-related HCC accounted for approximately 70% of Italian patients with HCC. One epoch-making finding of this study was that the MALFD would overtake HCV as the cause of HCC within a few years (1). Enomoto *et al.* previously investigated the transition in the etiologies of HCC by a nationwide survey of Japan (6). The study demonstrated a decreasing trend in the incidence of viral HCC and an increasing trend due to fatty liver disease and alcoholic liver disease (6). In addition, Myers *et al.* reported the prevalence of MAFLD-related HCC increased from 21% in 1990–1994 to 68% in 2010–2014 from the Geneva Cancer Registry data (7). Since no medication is approved for MAFLD, the incidence of

^ ORCID: Shigeo Shimose, 0000-0003-2068-8386; Tsubasa Tsutsumi, 0000-0001-6571-9874; Dan Nakano, 0000-0001-6098-1224; Tomoya Sano, 0000-0002-3229-3149; Keisuke Amano, 0000-0003-2017-7973; Takumi Kawaguchi, 0000-0002-7064-4325.

MAFLD-related HCC is thought to further increase in the future.

Vitale *et al.* also described that patients with MAFLD-related HCC had a better survival period than patients with non-MAFLD HCC. However, the median survival time was still less than 3 years in patients with MAFLD-related HCC (1). MAFLD-related HCC showed a larger tumor size and was associated with a higher prevalence of extrahepatic metastases than non-MAFLD-related HCC (1). Similarly, a meta-analysis showed that non-alcoholic fatty liver disease (NAFLD)-related HCC had a larger tumor size than HCV-related HCC (8). Noteworthy, only 32.8% of patients with NAFLD-associated HCC underwent surveillance for HCC before cancer diagnosis (8). The problem to be solved is the development of a surveillance system for early diagnosis of HCC in patients with MAFLD.

A unique feature of the MAFLD definition is that a diagnosis of MAFLD can be made irrespective of the diagnosis of any other liver disease, including viral hepatitis (4). This allows clinicians to investigate the interaction between viral hepatitis and MAFLD. The impact of the MAFLD on HCC development has been reported in chronic HBV-infected patients. Huang *et al.* reported that MAFLD increased the risk of long-term mortality/transplantation and liver-related events in 408 HBV-infected patients with antiviral therapy (9). Thirty-five patients (8.6%) experienced 43 liver-related events, among which 32 events were HCC. However, steatosis and HBV activity are known to be inversely correlated (9). HBV-infected patients with concurrent steatosis tended to have lower viral activity, including lower serum HBV DNA levels and higher rates of hepatitis B surface antigen seroclearance. Therefore, the influence of co-existing fatty liver in HBV-infected patients remained controversial. Although MAFLD and chronic hepatitis B (CHB) are well-established etiologies for HCC, whether concurrent MAFLD and HBV lead to a higher risk of HCC development than HBV alone is inconclusive.

The presence of fatty liver has also been reported to increase the risk of HCC even in patients with HCV eradication (10). A Japanese multicenter cohort study of 2,055 patients who underwent HCV eradication found that obesity was associated with a higher risk of HCC (11). MAFLD is a combination of risk factors for HCC, including fatty liver, obesity, diabetes mellitus, and metabolic syndrome (2). However, no study investigated the direct impact of MAFLD on the occurrence of HCC in HCV-infected and post-treated patients.

Patients with non-viral HCC are frequently diagnosed at an intermediate or advanced stage of HCC (12), and many patients with HCC undergo systemic therapies. At present, various systemic therapies have been developed for patients with unresectable HCC (u-HCC), such as molecular-targeted agents, and immune checkpoint inhibitors (ICIs) (12). Therefore, it is crucial to explore biomarkers to benefit from systemic drug therapy and stratification of the therapeutic effects of systemic therapy in patients with u-HCC. Pfister *et al.* reported an interesting insight that ICI treatment is insufficiently effective against nonalcoholic steatohepatitis (NASH)-related HCC (13). Therefore, it is important to identify the factors responsible for systemic therapies in patients with NASH-related HCC.

Lenvatinib (LEN), a molecular-targeted agent, has shown efficacy in the treatment of u-HCC and improves the prognosis of patients with u-HCC (12). In terms of LEN treatment, Rimini *et al.* reported that overall survival was longer in patients with NASH-related HCC compared with those with non-NASH HCC (14). Moreover, MAFLD is reported as an independent predictive factor for improved overall survival in patients with u-HCC treated with LEN (12). Thus, MAFLD-related HCC patients may benefit from treatment with LEN. However, in terms of treatment with ICIs, there are few reports on stratified treatment effects of MAFLD in the real world. Moreover, taking into consume amounts of alcohol intake and stigmatization, a new definition for fatty liver disease "metabolic dysfunction-associated steatotic liver disease (MASLD)" was proposed by the NAFLD Nomenclature consensus group (15). Similar to MAFLD, MASLD is diagnosed by inclusion criteria of metabolic dysfunction. However, different from MAFLD, MASLD excludes patients with moderate and heavy alcohol consumption. No study yet reported epidemiological trajectories of MASLD-related HCC in recent and future.

In summary, there is no doubt that MAFLD-related HCC will continue to further increase (*Figure 1*). Along with the development of new therapeutic agents for MAFLD, future research should be focused on (I) the efficient surveillance system for MAFLD-related HCC, (II) the effects of MAFLD on hepatocarcinogenesis in HBV/HCV-infected patients, and (III) highly effective systemic therapy for MAFLD-related HCC.

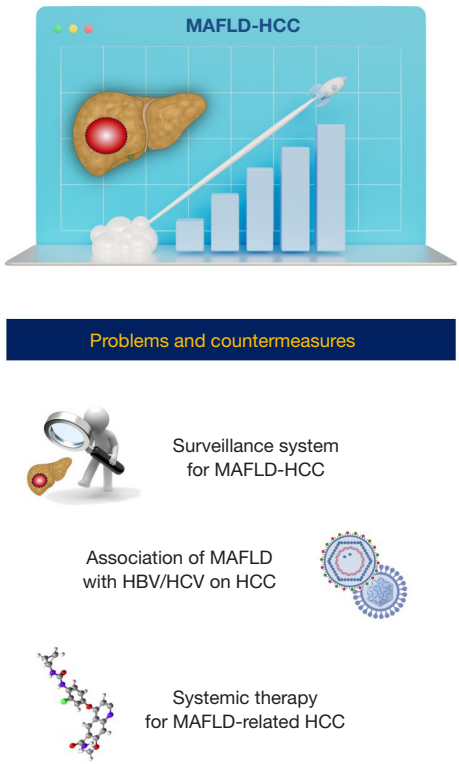

Figure 1 A scheme for an ever-increasing MAFLD related HCC and its problems and countermeasures. MAFLD, metabolic dysfunction-associated fatty liver disease; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

Acknowledgments

Funding: This editorial was supported by AMED (Grant No. JP23fk0210090).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-538/coif). T.K. received lecture fees from Eisai Co., Ltd., Janssen Pharmaceutical K.K., Taisho Pharmaceutical Co., Ltd., Kowa Company, Ltd., Otsuka Pharmaceutical Co., Ltd., ASKA Pharmaceutical Co., Ltd., AbbVie GK., and EA Pharma Co., Ltd. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work and in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Vitale A, Svegliati-Baroni G, Ortolani A, et al. Epidemiological trends and trajectories of MAFLD-associated hepatocellular carcinoma 2002-2033: the ITA.LI.CA database. Gut 2023;72:141-52.
2. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73:202-9.
3. Kawaguchi T, Tsutsumi T, Nakano D, et al. MAFLD: Renovation of clinical practice and disease awareness of fatty liver. Hepatol Res 2022;52:422-32.
4. Kawaguchi T, Tsutsumi T, Nakano D, et al. MAFLD enhances clinical practice for liver disease in the Asia-Pacific region. Clin Mol Hepatol 2022;28:150-63.
5. Tsutsumi T, Eslam M, Kawaguchi T, et al. MAFLD better predicts the progression of atherosclerotic cardiovascular risk than NAFLD: Generalized estimating equation approach. Hepatol Res 2021;51:1115-28.
6. Enomoto H, Ueno Y, Hiasa Y, et al. The transition in the etiologies of hepatocellular carcinoma-complicated liver cirrhosis in a nationwide survey of Japan. J Gastroenterol 2021;56:158-67.
7. Myers S, Neyroud-Caspar I, Spahr L, et al. NAFLD and MAFLD as emerging causes of HCC: A populational study. JHEP Rep 2021;3:100231.
8. Tan DJH, Ng CH, Lin SY, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. Lancet Oncol 2022;23:521-30.
9. Huang SC, Liu CJ. Chronic hepatitis B with concurrent

metabolic dysfunction-associated fatty liver disease: Challenges and perspectives. Clin Mol Hepatol 2023;29:320-31.
10. Tada T, Nishimura T, Matono T, et al. Association of liver stiffness and steatosis with hepatocellular carcinoma development in patients with hepatitis C virus infection who received direct-acting antiviral therapy and achieved sustained virological response. Hepatol Res 2021;51:860-9.
11. Minami T, Tateishi R, Fujiwara N, et al. Impact of Obesity and Heavy Alcohol Consumption on Hepatocellular Carcinoma Development after HCV Eradication with Antivirals. Liver Cancer 2021;10:309-19.
12. Shimose S, Hiraoka A, Casadei-Gardini A, et al. The beneficial impact of metabolic dysfunction-associated fatty liver disease on lenvatinib treatment in patients with non-viral hepatocellular carcinoma. Hepatol Res 2023;53:104-15.
13. Pfister D, Núñez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021;592:450-6.
14. Rimini M, Kudo M, Tada T, et al. Nonalcoholic steatohepatitis in hepatocarcinoma: new insights about its prognostic role in patients treated with lenvatinib. ESMO Open 2021;6:100330.
15. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Ann Hepatol 2023;29:101133.

Cite this article as: Shimose S, Tsutsumi T, Nakano D, Sano T, Amano K, Kawaguchi T. An ever-increasing metabolic dysfunction-associated fatty liver disease-related hepatocellular carcinoma: what are problems and countermeasures? HepatoBiliary Surg Nutr 2023;12(6):941-944. doi: 10.21037/hbsn-23-538