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## T-cell therapy for HBV-HCC

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## Editorial

# Metabolic dysfunction-associated fatty liver disease is a ubiquitous latent cofactor in viral- and alcoholic-related hepatocellular carcinoma: Editorial on "Global prevalence of metabolic dysfunction-associated fatty liver disease-related hepatocellular carcinoma: A systematic review and meta-analysis"

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An international expert panel proposed a new definition of fatty liver disease: metabolic dysfunction-associated fatty liver disease (MAFLD).[1] The major difference from nonalcoholic fatty liver disease (NAFLD) is that MAFLD does not require a history of alcohol intake or other causes of liver disease. The proposed change in terminology from NAFLD to MAFLD is not simply an acronym change; in particular, the MAFLD definition is characterized as picking up all fatty livers with metabolic dysfunction, and it is thought to be possible to examine the association with other causes of liver disease that could not be examined with NAFLD.[2-5]

In this issue, Crane et al.[6] investigated the global total prevalence of MAFLD in the hepatocellular carcinoma (HCC) cohort (total-MAFLD). They divided MAFLD into sole liver disease (single-MAFLD) or concurrent liver disease in which MAFLD is a contributing factor (mixed-MAFLD). A meta-analysis of 22 studies found that the prevalence of HCC due to total-MAFLD and single-MAFLD was 48.7% and 12.4%, respectively. In mixed-MAFLD, they also revealed that the prevalence of MAFLD observed in HCC due to hepatitis B virus, hepatitis C virus, or alcohol-related liver disease was 40.0%, 54.1%, and 64.3%, respectively. HCC in the mixed-MAFLD group had a significantly higher likelihood of cirrhosis and a lower likelihood of metastasis compared to that in the single-MAFLD group, and a higher platelet count and lower likelihood of macrovascular invasion compared to that in the non-MAFLD group. Taking advantage of MAFLD, the authors disclosed a high preva-

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lence of MAFLD in viral- or alcohol-related HCC. They also revealed the characteristics of HCC in patients with mixed-MAFLD by comparing them to patients with single-MAFLD or non-MAFLD.

The rate of MAFLD-related HCC is rising worldwide.[7] The rate of HCC from whole NAFLD patients is estimated to be 0.01–0.13%/year, whereas that of HCC from NAFLD-derived cirrhosis increases to 0.3–4.7%.[8] The development of liver fibrosis is a prognostic factor for patients with fatty liver. Yamamura et al.[9] investigated the difference in screening ability for liver fibrosis in MAFLD compared to NAFLD. They reported that MAFLD has a sensitivity of 93.9% and can better identify patients with advanced liver fibrosis than NAFLD, which has a sensitivity of 73.0%. In other words, MAFLD is more useful than NAFLD for capturing patients with fibrosis. However, the degree of fibrosis is different among patients with MAFLD. Wang et al. validated four non-invasive serum fibrosis tests to predict long-term risks of clinical outcomes in MAFLD patients using two cohorts. They reported that a high Hepascore or FIB-4 index was useful in predicting liver-related death, decompensation, and HCC.[10] This means that the incidence of HCC is higher in patients with advanced liver fibrosis in MAFLD compared to those without advanced liver fibrosis. Consequently, the risk of HCC in MAFLD patients should be assessed based on the degree of liver fibrosis.

The liver is a central organ to regulate various metabolisms including protein synthesis and sarcopenia is frequently seen in patients with chronic liver disease.[11] The muscle is not only a locomotory organ but also an endocrine organ to regulates energy metabolism. Therefore, sarcopenia is also a risk factor for various metabolic dysfunctions including obesity and type 2 diabetes mellitus. Accordingly, the prevalence of sarcopenia is high in patients with MAFLD. Previous studies used population-based large databases and found that the proportion of sarcopenic subjects was 9.90–19.42% among individuals with MAFLD.[12] These studies also found that sarcopenic subjects with MAFLD had a higher risk of significant hepatic fibrosis than non-sarcopenic subjects with MAFLD. Since hepatic fibrosis is a potent risk factor for HCC, sarcopenia is an additive risk factor for HCC in patients with MAFLD. This study by Crane et al.[6] demonstrated that MAFLD is a common etiology for HCC; however, they did not evaluate an association between sarcopenia and HCC. Therefore, it cannot be denied the possibility that sarcopenia is a confounding factor in the association between MAFLD and HCC. Particularly, sarcopenia is a feature of non-obese MAFLD[13] and should be evaluated in future studies.

In MAFLD criteria, alcohol consumption above the NAFLD threshold can also be investigated in a stepwise way, depending on the amount of alcohol consumption. This advantage allows us to examine the interactions between alcoholic liver disease and MASLD. In this study by Crane et al.[6], the prevalence of HCC due to alcohol-related liver disease in mixed-MAFLD was as high as 64.3%. However, the amount of alcohol intake was not evaluated. Light (1.0–9.9 g/day) or moderate (10.0–29.9 g/day for men; 10.0–19.9 g/day for women) alcohol consumption is commonly observed in patients with NAFLD, and approximately two-thirds of fatty liver patients are light drinkers.[14] Chang et al.[15] investigated the relationship between alcohol consumption and liver fibrosis and reported that moderate alcohol consumption was an independent factor for the worsening of fibrosis. Kawamura et al.[16] also evaluated the effect of drinking on the incidence of HCC in almost ten thousand Japanese patients with steatohepatitis without viral hepatitis. They stratified according to daily amount of alcohol intake and observed that the incidence of HCC increased with increasing levels of ethanol consumption. In addition, in a multivariate analysis, they reported that ethanol consumption of ≥40 g/day was an independent risk factor for HCC.[16] As alcohol consumption affects metabolic dysfunction and liver fibrosis even in small amounts, the relationship between MAFLD and the onset of HCC should include the amount of alcohol consumed.

Recently, immune checkpoint inhibitors have emerged as the primary treatment for advanced HCC.[17] First, the effectiveness of combination therapy with atezolizumab plus bevacizumab was proven in May 2020 (IMbrave150).[18] Second, the effectiveness of combination therapy with tremeli-

**Abbreviations:**
MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma


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mumab plus durvalumab was proven in August 2022 (HIMALAYA).[19] These combination therapies were shown to have extended patients' survival compared to the sorafenib group in randomized controlled trials; however, the therapeutic effect in MAFLD patients is unknown. Previously, we investigated the impact of MAFLD on the efficacy of lenvatinib.[20] In our previous study, the overall survival rate was significantly higher in the MAFLD group than in the non-MAFLD group. Although the study by Crane et al.[6] shows an association between MAFLD and the onset of HCC, it remains unclear whether MAFLD has a significant effect on the treatment response of HCC. Future studies on the effect of MAFLD on the treatment response of HCC may provide clinically useful information.

In conclusion, by positive diagnostic criteria of MAFLD, Crane et al.[6] disclosed that MAFLD widely affects HCC not only as a sole etiology but more so as a co-factor in the mixed-etiology of HCC, such as viral- or alcohol-related HCC. This study had limited information on hepatic fibrosis, sarcopenia, the amount of alcohol intake, and the treatment response to ICIs. However, the benefit of systematically ascertaining metabolic dysfunction along with fatty liver uncovered a new pathogenesis of HCC that had not been elucidated before. MAFLD may be of great significance in elucidating the pathogenesis of HCC.

### Authors' contributions

All authors were responsible for the interpretation of data, the drafting, and the critical revision of the manuscript for important intellectual content.

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### Conflicts of Interest

Takumi Kawaguchi received lecture fees from ASKA Pharmaceutical Co., Ltd., Taisho Pharmaceutical Co., Ltd., Kowa Company, Ltd., AbbVie GK., Eisai Co., Ltd., Novo Nordisk Pharma Ltd., Janssen Pharmaceutical K.K., Otsuka Pharmaceutical Co., Ltd., EA Pharma Co., Ltd. The other author has no conflicts of interest.

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