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Letter to the Editor

Metabolic Phenotypes: Drivers of Health Outcomes in Fatty Liver Diseases

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Dear Editor,

Nonalcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD) are the leading causes of chronic liver disease worldwide, representing major contributing factors of cirrhosis and hepatocellular carcinoma (HCC) and highlighting the major public health importance of these conditions.[1,2] NAFLD and AFLD share common biological mechanisms and may eventually coexist in the same person.[3] Accumulating evidence indicates no safe threshold for alcohol consumption in NAFLD patients. Alcohol use is a significant risk factor for the progression of liver disease in individuals with NAFLD, eventually impacting mortality in those with metabolic syndrome.[4] On the other hand, among patients with AFLD, metabolic syndrome, and obesity may hasten the progression of liver disease and increase the incidence and mortality from HCC. Indeed, the synergistic effect between alcohol consumption and metabolic syndrome on the progression of fatty liver disease has been demonstrated.[5]

Using the acronym NAFLD as an umbrella term has been recognized as a problematic issue in the field of hepatology. The dilemma is primarily caused by the notable heterogeneity of the patients included in that classification and the absence of positive NAFLD criteria, making it challenging to categorize individuals with metabolic changes and alcohol consumption above the established threshold for NAFLD. It also impedes the recognition of dual etiology for liver disease in individuals with moderate or excessive alcohol consumption and metabolic disturbances. Thus, the NAFLD nomenclature has recently been revised, and a new acronym, MAFLD (metabolic dysfunction-associated fatty liver disease), has been proposed to better characterize the disease.[6] The absence of an alcohol intake limit is the most notable change between the MAFLD diagnostic criteria and the previously used criteria for NAFLD. Therefore, NAFLD patients with metabolic dysfunction and those with AFLD and metabolic dysfunction contributing to the disease process should all be included in this fatty liver disease spectrum (Fig. 1). Patients with MAFLD should be at increased risk of hepatic and extrahepatic events, including cardiovascular disease (CVD), chronic kidney disease (CKD), and extrahepatic cancers. In fact, cirrhosis is the leading specific cause of death in patients with NAFLD, followed by CVD and extrahepatic diseases, indicating the multisystem involvement in the disease.[7]

In a study published in this issue, Fan *et al*.[8] used data from the UK Biobank Resource to investigate the impact of different metabolic phenotypes on the risk of incident liver-related events (cirrhosis, liver transplantation, and liver cancer) and extrahepatic conditions, such as CVD, CKD, and extrahepatic malignancies in individuals with NAFLD or AFLD. Fatty liver disease, as defined by a fatty liver index ≥60, was classified as NAFLD for 103,248 people who drank less than 20 g/day for women and 30 g/day for men and AFLD for 43,974 persons who drank more than those amounts. Metabolic dysfunction was defined by the presence of one of the following conditions: type 2 diabetes mellitus, hypertension, or dyslipidemia. The patients were followed for a median period of 8.2 years. They found that NAFLD and AFLD were significantly associated with an increased risk of health outcomes, which were modified differently by metabolic phenotypes. Interestingly, the metabolically obese normal-weight cohort had a higher risk of liver-related complications than the metabolically obese overweight group. This finding was supported by data from a longitudinal study demonstrating that lean patients with NAFLD had an increased risk of the development of cirrhosis, hepatic decompensation, liver failure, or HCC compared with NAFLD patients with a higher body mass index, independent of baseline liver fibrosis stage.[9] Sarcopenia characterized by a progressive loss of skeletal muscle mass and function may cause metabolic disorders and deteriorate fatty liver disease in the lean body habitus. Many recent studies have explored the relationship between sarcopenia and fatty liver disease. A recent longitudinal study found a link between sarcopenia and an increased risk of all-cause mortality in the presence and absence of NAFLD.[10] However, further research is required to determine for the causes of poor outcomes in NAFLD and AFLD with metabolically obese normal-weight.

This population-based study by Fan *et al*.[8] also demonstrated that metabolic dysfunction enhanced the risks of CVDs, CKDs, and cancers in overweight/obese people with NALFD or AFLD compared with individuals free of fatty liver

Abbreviations: AFLD, alcoholic fatty liver disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease.

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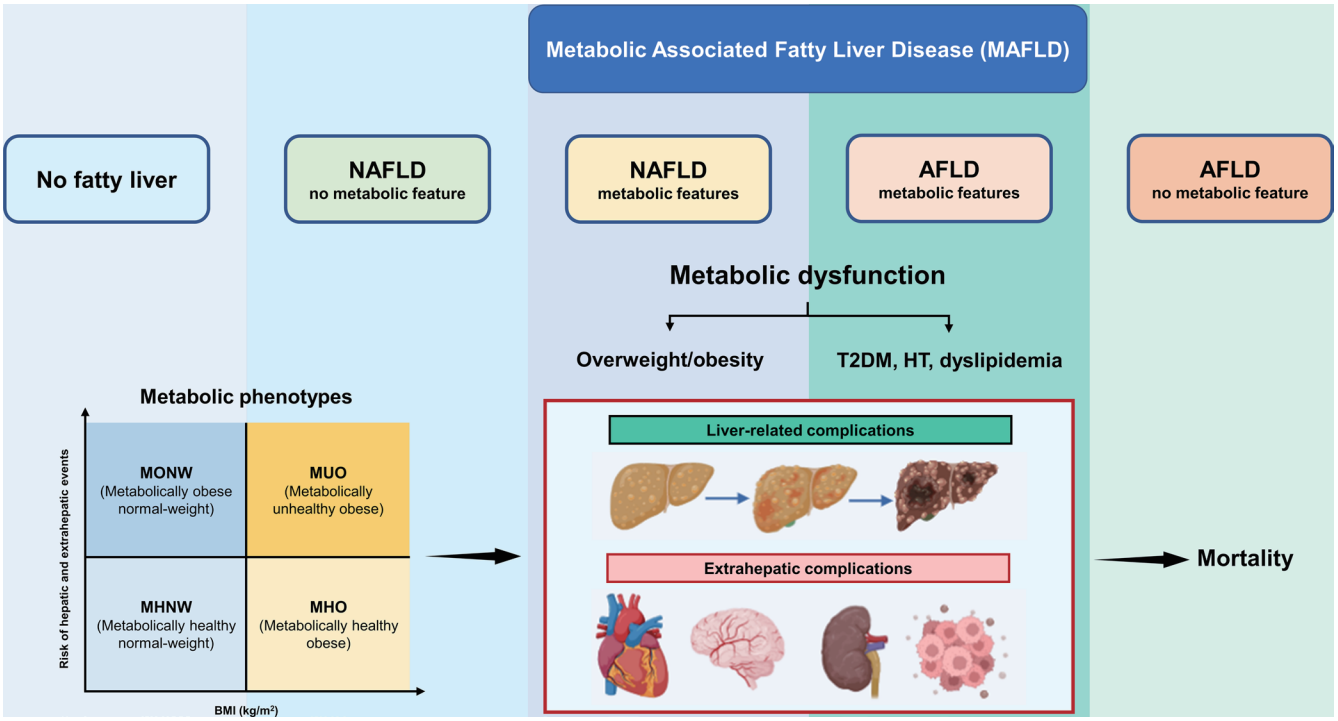

Fig. 1. Metabolic phenotypes as drivers of health outcomes in patients with fatty liver diseases. AFLD, alcoholic fatty liver disease; DM, diabetes mellitus, HT, hypertension; MAFLD, metabolic associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease.

and with phenotype of metabolically healthy normal-weight. This finding highlights the synergistic effect of obesity and metabolic dysfunction on the development of extrahepatic diseases in patients with fatty liver disease, regardless of alcohol consumption. Together, the findings by Fan *et al*.[8] provide further support for the idea that NAFLD and AFLD are components of a broader multisystem disease that include different amounts of alcohol intake and metabolic phenotypes. The findings have raised many questions, so further studies are warranted to determine the effect of metabolic phenotypes on fatal outcomes in fatty liver disease and to develop prognostic tools for a more accurate evaluation of individual risk for adverse outcomes.

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Conflict of interest

PC has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2013, the author has no other conflict of interests related to this publication.

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