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EDITORIAL COMMENT

New Insights Into the Relation Between Metabolic Dysfunction Associated Fatty Liver Disease and Cardiovascular Disease*

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In 2020, a new concept of fatty liver, metabolic dysfunction-associated fatty liver disease (MAFLD), was proposed.[1] This disorder is defined as fatty liver coexisting with obesity, type 2 diabetes, or 2 or more metabolic abnormalities. Metabolic abnormalities are risk factors not only for the progression of fatty liver disease, but also for atherosclerosis, so clinicians should be aware that cardiovascular death is among the unfavorable outcomes. A study using the Japanese medical insurance claims database (JMDC Claims Database) reported that the incidence of cardiovascular disease (CVD) was increased among both MALFD and nonalcoholic fatty liver disease (NAFLD) groups of participants with hypertriglyceridemia and diabetes mellitus.[2] In addition, a meta-analysis of 10 articles showed that the MAFLD group had a 1.57-fold higher risk of death from CVD than the non-MAFLD group.[3] Furthermore, a study in the U.S. Third National Health and Nutrition Examination Survey (NHANES III) showed that mortality resulting from CVD in NAFLD without metabolic abnormalities was similar to that in patients without fatty liver.[4]

In this issue of *JACC: Asia*, Ohno et al[5] use the aforementioned JMDC Claims Database to analyze two new perspectives. The first is the setting of atrial fibrillation (AF) and heart failure (HF) as outcomes in addition to the association between MAFLD and CVDs. The prevalence of AF and HF is increasing worldwide, as well as in Asia, with the aging of the population; elucidation of the risk factors for AF and HF is an important public health issue. Another perspective included a comparison of the risk of fatty liver without metabolic disorders, metabolic disorders without fatty liver, and MAFLD, whereas most previous studies compared the impact of NAFLD and MAFLD on CVD. In particular, metabolic disorders, which in this study consisted of diabetes, metabolic syndrome, and obesity, are typical risk factors for CVD by themselves. Accordingly, it should be clarified to what extent the risk of CVD is increased when fatty liver is combined with metabolic disorders. In this study, a total of 3,279,918 individuals aged 40 to 74 years were followed up for approximately 3 years, and 62,746 HF events and 15,408 AF events were recorded. Compared with the group without fatty liver or metabolic disorders, the HRs for HF and AF were all above 1.5 in the MAFLD group, compared with approximately 1.1 to 1.2 in both the metabolic disorders and fatty liver groups. This study suggests that MAFLD is associated with an increased risk of developing HF and AF, thus implying clinical importance of this new liver disease concept, which is a valuable finding and has rarely been reported before.

However, the definition of metabolic disorders may underestimate the CVD risk. Metabolic disorders in this study were defined as diabetes mellitus, overweight status (body mass index [BMI] $\geq$23 kg/m^2), or metabolic syndrome (defined by the Japanese criteria). However, a large cohort study of Japanese populations showed that the CVD risk for metabolic syndrome is mainly determined by the number of associated risk factors (hypertension, lipid abnormalities, and glucose intolerance) both in obese and nonobese individuals, and there was no increased CVD risk in the obese group with no associated risk factors.[6] Furthermore, a BMI of 23 kg/m^2

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is not an adequate cutoff point for an increased health risk in the Japanese population,[7] and it may be problematic to equate risk in these patients with risk in patients with diabetes. This is a continuing issue that should always be kept in mind when conducting similar analyses in Asian populations in the future. Another problem of this study is that it used medical claims information from Japanese companies; there are no data for people aged 75 years and older, when the insurance system automatically shifts to a public senior citizen insurance system in Japan. From this age group, the incidence and prevalence of both HF and AF increase rather rapidly; further follow-up studies in adults aged 75 years and older are therefore needed. In addition, the medical insurance database in Japan is derived from data used to determine the price of payment under the health insurance for all system; thus, as Ohno et al[5] note, there are some doubts about the accuracy of the diagnostic criteria. In addition, a longer follow-up period will be necessary.

The introduction of the concept of MAFLD has made it easier to validate risk in community epidemiologic and database studies. For the assessment of fatty liver in MAFLD, liver tissue histologic examinations are not included in the diagnostic criteria. Furthermore, in the absence of imaging studies such as ultrasonography, indices such as the fatty liver index (FLI), which is calculated by BMI, abdominal circumference, and blood biochemical test results, can be used for diagnosis, as applied in the study by Ohno et al.[5] The FLI is being introduced in community-based epidemiologic studies and has been shown to predict the development of diabetes and hypertension.[8,9] Successful use of the FLI may enable inexpensive international collaborative studies, such as those among Asian countries. Conversely, because the formula for calculating the FLI includes items used in the definition of metabolic abnormalities of MAFLD, such as BMI and triglycerides, the pathologic significance of MAFLD defined by the FLI may differ from that of MAFLD defined on the basis of fatty liver diagnosed by imaging or histologic examination; the differences related to diagnostic method should be examined from now on.

The conventional meaning of the term NAFLD tended to focus on alcohol ingestion, thus making it difficult to understand the pathophysiology of fatty liver disease. In addition, alcohol intake is difficult to estimate objectively, and the presence of metabolic disorders is fundamentally important for an individual's prognosis, regardless of the cause of fatty liver. If MAFLD showed an additive risk for CVD on the presence of metabolic disorders, as observed in the present study,[5] then biologic mechanisms that contribute to this increased risk should be elucidated. For example, Hirano et al[10] noted that small dense low-density lipoprotein cholesterol, the most powerful predictor of CVD among lipid biomarkers, is specifically elevated in patients with MAFLD, independent of triglycerides and visceral fat accumulation.

In any case, there is currently a lack of basic knowledge about MAFLD regarding the molecular basis of the pathogenesis and ways of application in risk stratification for CVD, liver disease, and cancer. Therefore, improving disease awareness and clarifying acceptable methods for drug development and biomarker discovery are key issues. However, MAFLD is a disease concept suitable for large-scale epidemiologic collaborations, and future epidemiologic studies are expected to provide significant insights into its pathogenesis.

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REFERENCES

1. 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;73:202–222.

2. Yoneda M, Yamamoto T, Honda Y, et al. Risk of cardiovascular disease in patients with fatty liver disease as defined from the metabolic dysfunction associated fatty liver disease or nonalcoholic fatty liver disease point of view: a retrospective nationwide claims database study in Japan. *J Gastroenterol*. 2021;56:1022–1032.

3. Wen W, Li H, Wang C, et al. Metabolic dysfunction associated fatty liver disease and cardiovascular disease: a meta-analysis. *Front Endocrinol (Lausanne)*. 2022;13:934225.

4. Huang Q, Zou X, Wen X, Zhou X, Ji L. NAFLD or MAFLD: which has closer association with all-cause and cause-specific mortality?-Results from NHANES III. *Front Med (Lausanne)*. 2021;8:693507.

5. Ohno R, Kaneko H, Suzuki Y, et al. Association of metabolic dysfunction-associated fatty liver disease with risk of HF and AF. *JACC Asia*. 2023;3(6):908–921.

6. Iso H, Cui R, Takamoto I, et al. Risk classification for metabolic syndrome and the incidence of cardiovascular disease in Japan with low prevalence

of obesity: a pooled analysis of 10 prospective cohort studies. *J Am Heart Assoc*. 2021;10:e020760.

7. Hozawa A, Hirata T, Yatsuya H, et al. Association between body mass index and all-cause death in Japanese population: pooled individual participant data analysis of 13 cohort studies. *J Epidemiol*. 2019;29:457–463.

8. Hirata A, Sugiyama D, Kuwabara K, et al. Fatty liver index predicts incident diabetes in a Japanese general population with and without impaired fasting glucose. *Hepatol Res*. 2018;48:708–716.

9. Wu D, Hirata A, Hirata T, et al. Fatty liver index predicts the development of hypertension in a Japanese general population with and without dysglycemia. *Hypertens Res*. 2023;46:879–886.

10. Hirano T, Satoh N, Ito Y. specific increase in small dense low-density lipoprotein-cholesterol levels beyond triglycerides in patients with diabetes: implications for cardiovascular risk of MAFLD. *J Atheroscler Thromb*. Published online July 11, 2023. https://doi.org/10.5551/jat.64271

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