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Editorial

Clinical impact of five cardiometabolic risk factors in metabolic dysfunction-associated steatotic liver disease (MASLD): Insights into regional and ethnic differences

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Steatotic liver disease (SLD) serves as an overarching term encompassing various chronic liver conditions characterized by hepatic steatosis, highlighting the pivotal role of cardiometabolic risk factors in previous non-alcoholic fatty liver disease (NAFLD).[1] Unlike NAFLD, which primarily relies on exclusionary diagnostic criteria, SLD acknowledges liver diseases stemming from alcohol consumption and viral infections as concurrent pathologies. SLD terminology allows liver disease caused by alcohol and viruses to be considered a concomitant disease and is presented to enable the more holistic management of patients with SLD.[2]

Recently, Iwaki et al. employed the Clinical Outcome Non-alcoholic Fatty Liver Disease (CLIONE) cohort, an Asian biopsy-proven metabolic dysfunction-associated steatotic liver disease (MASLD) cohort, and reported that 99% of existing patients with NAFLD could satisfy the new MASLD definition criteria.[3] The CLIONE cohort was established by the Japan Study Group of NAFLD (JSG-NAFLD) at 11 centers across Japan for the following purposes: 1) to clarify the prevalence, natural history, and prognosis of Japanese patients with MASLD; 2) for noninvasive diagnosis of MASLD or severe fibrosis; and 3) to develop pharmacological treatments for MASLD. All CLIONE data were compiled and analyzed using the REDCap database.[4] Iwaki et al.[3] underscore the clinical significance of assessing metabolic risk factors in individuals with MASLD and emphasize the importance of resuming and reinforcing the management of these factors. Although existing research consistently demonstrates that cardiometabolic risk factors elevate liver-related mortality and overall mortality in individuals with SLD, the emerging era of MASLD warrants further inquiry into additional considerations.

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Importantly, there remains a paucity of data on whether MASLD can exacerbate the incidence of fatal cardiovascular events or mortality in response to cardiometabolic risk factors. This gap in knowledge underscores the need for targeted investigations to elucidate the potential impact of MASLD on cardiovascular outcomes in the context of metabolic risk factors. Addressing this gap is crucial for enhancing our understanding of the comprehensive health implications of MASLD and informing more effective management strategies for affected individuals.[5] In a recent nation-wide large-scale study using 9.77 million Korean health check-up records, individuals with MASLD showed higher rates of cardiovascular events and cardiovascular mortality compared to their non-MASLD counterparts and control subjects.[6] Similarly, another study using data from 28,000 individuals who underwent magnetic resonance imaging-estimated proton density fat fraction within the UK Biobank revealed that patients with MASLD experienced a higher number of cardiovascular events than those experienced by non-MASLD subjects.[7] However, metabolic dysfunction independently increased the incidence of non-fatal cardiovascular events, regardless of the presence of fatty liver. Interestingly, within the population with metabolic dysfunction, no significant difference in stroke incidence was observed between patients who have SLD (=MASLD) and those who do not have SLD, with rates remaining at 1.3 and 1.4%, respectively. Similarly, the incidence of ischemic heart disease did not show a significant difference and was 7.0 and 6.1% for MASLD and non-SLD with metabolic dysfunction, respectively.[7] A recent analysis of US National Health and Nutrition Examination Survey data also revealed that patients with MASLD exhibited higher overall mortality and cardiovascular mortality than normal controls. However, after adjusting for cardiometabolic risk factors, MASLD itself did not emerge as an independent risk factor for cardiovascular or overall mortality.[8] MASLD is closely associated with cardiovascular events and demonstrates a bidirectional relationship with components of the metabolic syndrome. However, additional evidence is required to establish whether MASLD increases cardiovascular mortality or fatal events even independently after adjusting cardiometabolic risk factors.

Another unresolved issue regarding cardiometabolic risk factors in the MASLD era is the size of the effect of cardiometabolic risk factors and whether the cutoff value for each risk factor should vary depending on region and race. As mentioned earlier, the impact and magnitude of cardiovascular mortality in patients with MASLD differed slightly in the data presented in the West and the East. Additionally, the magnitude of the impact on liver cancer occurrence differed between the CLIONE and Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) cohorts. The all-cause mortality of patients with F3 metabolic dysfunction-associated steatohepatitis in the NASH CRN and CLIONE cohorts was similar (0.89 vs. 0.82, respectively).[9] However, in the NASH CRN cohort, the annual hepatocellular carcinoma incidence rate in patients with F3 MASLD was 0.34%, whereas in the CLIONE cohort, this rate was 1.42%.[4] Liver-related mortality was relatively higher in the CLIONE cohort than in the NASH CRN cohort, implying a high level of extrahepatic mortality (cardiovascular or extrahepatic malignancy) in the CRN cohort.

Finally, Iwaki et al.[3] offered valuable insights into the significance of cardiometabolic risk factors in patients with MASLD. In patients with MASLD, individuals with cardiometabolic risk factors exhibited more severe histological severity and higher mortality rates compared to individuals with cryptogenic SLD. However, in this cohort, no clear dose-dependent pattern was observed based on specific combinations of cardiometabolic risk factors. Using data from the UK biobank, Fan et al.[7] showed variations in the impact of glucose and lipid metabolic parameters on cardiovascular events. Moreover, the scientific rationale underlying the selection of five cardiometabolic parameters and their respective cutoffs warrants further clarification.[10] For instance, evidence highlights the importance of C-reactive protein as a prognostic factor in MASLD subjects.[11]

In the future, additional scientific evidence will be essential for determining the selection and optimal cutoffs of the five cardiometabolic risk factors included in MASLD diagnosis. Moreover, we are also waiting on the impact size of each cardiometabolic risk factor, along with individualized cutoffs by region and race depending on regional racial differences. Fu-

Abbreviations:

SLD, steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; CLIONE, Clinical Outcome Nonalcoholic Fatty Liver Disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NASH CRN, Nonalcoholic Steatohepatitis Clinical Research Network

ture investigations should explore the long-term impact of hard outcomes based on the number and type of cardiometabolic risk factors, facilitating risk classification and tailored interventions.

Authors' contribution

JHO drafted the manuscript. DWJ reviewed and finalized the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.

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