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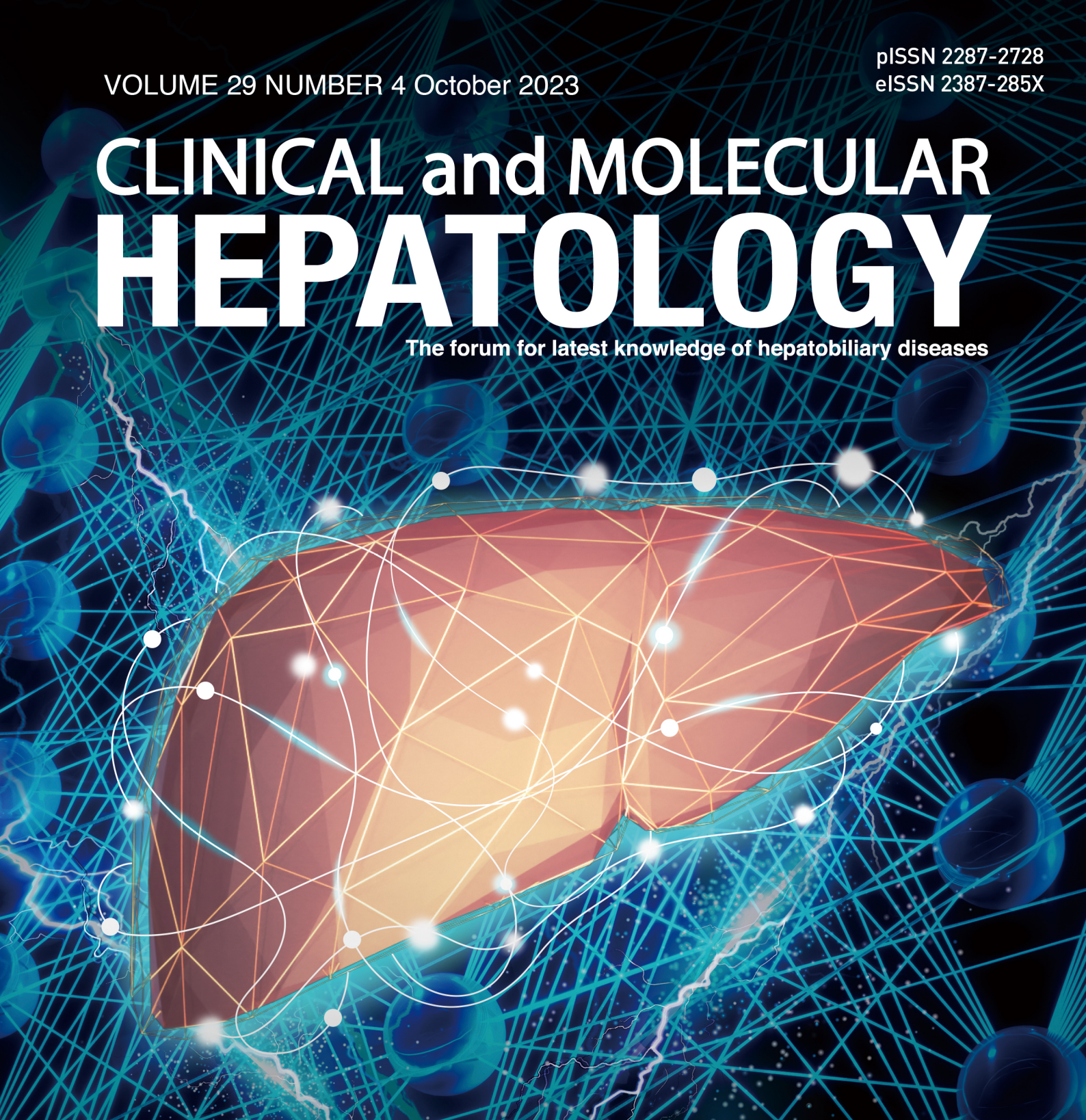

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Editorial

Adding to the confusion in more than just the name

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See Article on Page 831

The year 2020 witnessed a paradigm shift in the way we conceptualised and thought about the fatty liver disease which is responsible for a majority of the cases we see in routine clinical practice. For the past 40 years, "non-alcoholic fatty liver disease (NAFLD)", a term coined to define a histological lesion, was used to describe a disease entity that was clearly common and rising in prevalence in parallel with that of diabetes and overweight/obesity. Despite decades of discomfort with the term, NAFLD told clinicians and patients what the disease is not, instead of what the disease is, and was associated with the stigma linked to the term "alcohol". Inertia, as is common in many areas of medicine, persisted. All this changed with two landmark papers by an international panel that proposed a new term, "metabolic (dysfunction) associated fatty liver disease" or metabolic dysfunction-associated fatty liver disease (MAFLD), and its new definition.[1,2]

What is not as well appreciated by the field is that the papers were a proposal firstly of a term that reflected accumulated knowledge on disease pathogenesis, and secondly and perhaps more importantly, it proposed a set of criteria on exactly what constituted the disease. The papers were published to wide acclaim (and some discontent) as a conceptual advance in the field, and were there for all clinicians to examine for its clinical utility at the bedside and for clinical research. As fatty liver disease due to metabolic dysregulation impacts the life-course, paediatric criteria were also proposed.[3] Subsequent years have seen more than 4,000 citations for the two sentinel papers, over 7,000 publications using the MAFLD terminology and definition, and widespread acceptance in clinical practice guidelines including the first by the Asian Pacific Association for the Study of Liver (APASL),[4] the Middle East and North Africa,[5] the Chinese Society of Hepatology,[6] and many other national societies as well as patient organisations.[7] From the perspective of clinical research, MAFLD and its definition demonstrated clinical utility, increased disease awareness, and importantly, identified patients who are most at risk of hepatic and extrahepatic outcomes as compared to NAFLD.[8-11] Another aspect that was not appreciated at inception was that MAFLD neatly stratified patients into three distinct groups (those with diabetes,

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those with overweight/obesity, and those with MAFLD but a healthy weight), each with its own distinct patient profile in cross-sectional studies, and different disease trajectories and outcomes.[11] Such stratification has allowed clinicians to prognosticate, and will enable tailored treatments based on phenotype in the future.

In the current issue, Kim and colleagues[12] undertake an appraisal of the terminology and definition of another term, "metabolic dysfunction associated-steatotic liver disease (MASLD)". Clearly, removal of any reference to alcohol in the proposed name is welcome and long overdue, as is acceptance of metabolic dysregulation as a core tenant and prerequisite for disease diagnosis. The fact that the proposal of MASLD has come after four decades highlights the inertia of societies and the importance of innovation and renewal from the grass roots in all scientific disciplines.

While the authors have undertaken an appraisal from both a hepatology and endocrinology perspective, as they imply, MASLD is a proposal with many unresolved questions. First and foremost, as suggested by others in the field and patient groups, the term "fatty liver", when used to describe a liver with fat, is not stigmatising.[13,14] Moreover, as circulated on social media and from first-hand experience, clinicians know from every day experience that when a patient is told they have MASLD, the first question asked is "what does steatotic liver disease mean," to which the answer invariably is that you have a "fatty liver".

Be that as it may, Kim and colleagues highlight that there are concerns with the MASLD definition, as well as several persisting misconceptions about the definition of MAFLD. It is stated that MAFLD fails to incorporate alcohol consumption into its diagnostic criteria. The simple answer to this often repeated statement, as highlighted in the original papers, is that MAFLD defines a particular form of liver disease due to systemic metabolic dysregulation; the disease (MAFLD) has nothing to do with whether or not a patient drinks alcohol, or for that matter, if the patient has concomitant viral hepatitis or not. For example, if a patient has hepatitis C, it does not mean that the patient cannot also have a second liver disease, such as hepatitis B. Only by defining what disease one is, can we decide if a patient also has disease two. MASLD fails to meet this basic tenant for disease diagnosis, which should encompass all patients with the disease. Using the MASLD terminology, if you meet the MASLD criteria and have "significant" alcohol consumption you have a different disease - MetALD. MetALD is not a separate disease but the coexistence of two concomitant diseases in the same person. By the MASLD logic, if a patient has hepatitis B infection or hepatitis C infection with MASLD, the patient should be given a separate disease name, as this is common in many parts of the world. MAFLD deftly avoids this issue by precisely defining what MAFLD is (similar to how we define what hepatitis C or B is) and stating that "patients who meet the criteria to diagnose MAFLD and who also have one of these concomitant conditions should be defined as having dual (or more) aetiology fatty liver disease".[2] In the example with a metabolic risk factor and hepatitis C, the steatotic liver disease (SLD) terminology reverts back to "combination aetiology", exactly as proposed in the MAFLD definition. Identifying alcohol as a "special case" does not meet scientific scrutiny; as Kim and colleagues suggest, "the exact threshold for alcohol consumption that may lead to liver damage remains unclear. Although some studies have proposed protective effects of mild alcohol consumption others have indicated no safe level of alcohol consumption especially among individuals with MASLD. Furthermore, the extent of metabolic dysfunction and the amount of alcohol consumption may vary over time among individuals".[12] With these very real caveats, would it not be more consistent and logical to define each liver disease a person has on its own merits rather than adding a new disease term with an arbitrary definition? Even in those with alcohol consumption of >60 grams per day, it is a fallacy to consider that metabolic dysfunction will not contribute to their disease trajectory. In real life, liver disease outcomes are a combination of all the liver insults, however minor or major, and arbitrary categorisation simply muddies the water, something that MAFLD cannot be accused of.

Another common misconception is that of "oversight" of steatohepatitis. To be clear, MAFLD is a set of criteria for clinical diagnosis, while steatohepatitis is a histological diagnosis. The histological features of the disease (steatosis, steatohepatitis, and fibrosis) are what they are, and MAFLD in no way

Abbreviations:

NAFLD, nonalcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; APASL, Asian Pacific Association for the Study of Liver; MASLD, metabolic dysfunction associated steatotic liver disease; SLD, steatotic liver disease; HDL, high density lipoprotein; ALD, alcohol-related liver disease

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detracts from the histological disease activity (metabolic steatohepatitis) and/or fibrosis stage as reported in the original papers.[1,2]

The salient subcategories of SLD are illustrated in Figure 1[12]; MASLD is diagnosed if one of the listed cardiometabolic risk factors are present in a person with hepatic steatosis. This would mean that a person with hypertension and hepatic steatosis has MASLD, or for that matter, steatosis and a low high density lipoprotein (HDL), with no clear evidence that these individuals have any adverse liver-related outcomes; for HDL and diastolic BP, their link to insulin resistance and steatosis is weak. A problem with the MASLD definition is that it tries to be "all things to all people," which is a problem inherent in consensus (rather than data-driven) approaches. MASLD is exactly as per the previous NAFLD definition, a heterogenous collection of diseases. Indeed, studies have suggested that MASLD and NAFLD are almost identical. In contrast, for MAFLD, several population-based studies have indicated that the three risk groups have varying initial presentations, different disease trajectories, and different hepatic and extrahepatic outcomes and in all cases, outcomes worse than those with NAFLD only, highlighting the clinical utility of the definition.[8-11] As the critique suggests, over 90% of Koreans (and for that matter, people in most affluent countries) with SLD have at least one cardiometabolic risk factor. This "may lead to potential over-classification of MASLD and MetALD but under-classification of pure alcohol-related liver disease (ARLD), cryptogenic SLD, and SLD with specific aetiology".[12] Unlike the MAFLD criteria, which has a clear definition for MAFLD cirrhosis, the lack of a definition or a statement on MASLD-related cirrhosis also "continues to puzzle".[12]

Kim and colleagues[12] should be congratulated on their critique of MASLD. Given the various concerns, while MASLD is an advance on NAFLD, in many aspects it adds to confusion rather than representing a bold, innovative and rigorous attempt to redefine the field of fatty liver disease.

Conflicts of Interest

The author has no conflicts to disclose but there might be perceived conflicts as stated in ICJME form.

Advisory board of NovoNordisk, Gilead, Roche, Abbvie, Astra zenica, Boehringer-ingelheim.

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