CRediT authorship contribution statement

Kenneth Cusi: Writing – original draft, Writing – review & editing. **Zobair Younossi:** Writing – original draft, Writing – review & editing. **Michael Roden:** Writing – original draft, Writing – review & editing.

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Reply to: "From NAFLD to MASLD: Promise and pitfalls of a new definition'

To the Editor:

From the beginning of this process, EASL, AASLD, and ALEH have been united in advancing the field for patients with steatotic liver disease [1]. We recognize that the journey to consensus has been challenging and, as one might expect from a consensus process addressing a topic with numerous divergent opinions, not all individual perspectives and arguments can be accommodated. Guided by a steering committee comprised of 35 international experts, including Cusi, Younossi, and Roden, and supported by a Delphi panel of 234 individuals, the initiative has garnered endorsement from over 70 societies globally. This was a thoughtfully considered exercise lasting over 3 years, reflecting extensive due diligence, and is now actively being implemented across the world.

The core objective of this endeavour was to establish a framework for understanding the spectrum of steatotic liver diseases, encompassing alcohol-related liver disease, in an affirmative and non-stigmatizing manner. Moreover, a key consideration in developing this new nomenclature was to provide a platform that could accommodate new findings and be adapted in the future. In that regard we agree and look forward to new studies that will inform and shape the field in years to come.

In their letter [2], the authors suggest that due to the requirement for a cardiometabolic risk factor (CMRF), the metabolic dysfunction-associated steatotic liver disease (MASLD) diagnosis is subtly different and requires validation in different populations. This comment is surprising as there is almost complete overlap between MASLD and non-alcoholic fatty liver disease (NAFLD), a fact indeed acknowledged by the authors. Data from population-based studies, biomarker consortia, biopsy proven cohorts and incident NAFLD confirm that MASLD, as currently defined, overlaps almost entirely with NAFLD. This consideration was paramount in the discussions about a change in definition to ensure that the prior literature remained valid and relevant. The requirement for at least one CMRF was a topic of much debate with a range of views on whether none, one, two or even more factors be required. A pragmatic view was taken that only one factor should be required to superimpose as much as possible with the previous NAFLD population.

Thus, we find ourselves in disagreement with the reservations the authors express concerning the requirement of a CMRF in the context of hepatic steatosis to make a diagnosis of MASLD. These criteria are not merely meant to act as a surrogate for insulin resistance, rather, they are important comorbidities associated with hepatic steatosis as well as steatohepatitis, fibrosis progression and cardiovascular outcomes. The authors approach the subject positing insulin resistance as the pivotal factor in explaining MASLD. While insulin resistance is undeniably significant both as a cause and consequence of steatotic liver disease, it may not be evident with routine testing. Moreover, Cusi et al. argue that only 50% of individuals who are overweight have insulin resistance, suggesting significant discordance – this was one of the reasons for allowing other established cardiometabolic risk factors that were not all directly restricted to insulin resistance to support the diagnosis.

We acknowledged that there may be individuals with hepatic steatosis who are clinically suspected of having MASLD yet fail to meet any of the cardiometabolic criteria. Hence, there is a caveat in the manuscript noting that these individuals may have possible MASLD as noted in the following excerpt - *'If there is uncertainty and the clinician strongly suspects metabolic dysfunction despite the absence of CMRF, then the term possible MASLD can be considered pending additional testing.'* Moreover, such patients are unlikely to have advanced disease and can be reassessed at a future time. Thus, the proposition of an "early MASLD" group does not seem clinically pertinent, given the minimal liver-related risk in this demographic. It also overlooks the possibility of other, as yet undefined, causes of steatosis.

Maintaining the alcohol thresholds for defining MASLD and providing an affirmative diagnostic framework emphasizing the importance of CRMF are valuable with respect to the current literature and implementation. This consensus-driven approach offers a high-level framework and we agree that fostering research for validation in various contexts is imperative.

Regional liver societies are unified in their support for the nomenclature as it has been presented - the framework is clear, and the path forward entails refinements based on validations and emerging

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EASL, AASLD and ALEH stand united to advance the field of steatotic liver disease

literature. Additionally, it outlines a clear connection to clinical care pathways which emphasize the importance of cardiometabolic risk factors in disease incidence and progression. This new nomenclature thereby serves as a catalyst to propel the field forward, fostering the development of improved biomarkers, new treatments and ultimately better care for patients.

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Authors' contributions

All authors contributed equally.

Declaration of Competing Interest

Norah A. Terrault consults for Moderna. She received institutional grants from GSK, Genentech-Roche, Helio Health, Gilead, and Durect. She has other interests in CCO and Simply Speaking. Aleksander Krag has served as speaker for Novo Nordisk, Norgine, Siemens and Nordic Bioscience and participated in advisory boards for Norgine, Siemens, Resalis Therapeutics, Boehringer Ingelheim and Novo Nordisk, all outside the submitted work. Research support; Norgine, Siemens, Nordic Bioscience, Astra, Echosense. Consulting Takeda, Resalis Therapeutics, Zealand Pharma, Novo Nordisk, Boehringer Ingelheim. Board member and co-founder Evido. Phillip Newsome consults, advises, is on the speakers' bureau, and received grants from Novo Nordisk. He consults and advises Boehringer Ingelheim, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Intercept, Madrigal, Pfizer, Poxel, and Sun Pharma. He is on the speakers' bureau for AiCME. Mary E. Rinella consults for Boehringer Ingelheim, CytoDyn, GlaxoSmithKline, Intercept, Madrigal, NGM Bio, and Sonic Incytes. Graciela Castro Narro has nothing to disclose.

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Correspondence: "A multisociety Delphi consensus statement on new fatty liver disease nomenclature"

Dear Editor,

Steatotic liver disease (SLD) has been proposed by Rinella *et al.* as the new overarching term to encompass various aetiologies of steatosis, including metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD and increased alcohol intake (MetALD), alcohol-associated liver disease (ALD), specific aetiology SLD, and cryptogenic SLD [1]. However, unlike metabolic dysfunction-associated fatty liver disease (MAFLD) suggested by Eslam *et al.* in 2020, blood biomarkers and scores were not explicitly outlined as one of the methods for identifying hepatic steatosis [2]. These biomarkers or scores, such as the fatty liver index, are deemed appropriate for extensive epidemiological studies to detect hepatic steatosis in adults [2]. Indeed, the European clinical practice guidelines state that validated biomarkers and scores are acceptable substitutes for diagnosing fatty liver when imaging methods are unavailable or impractical, such as in big epidemiological surveys [3].

With increasing clinical and public health burdens from SLD, a population-based study is currently being conducted to determine its prevalence in Malaysia [4]. Biomarkers and scores are very useful here because imaging is neither financially nor logistically feasible in the nationwide survey [4]. Thus, biomarkers and scores can be important for low- and middle-income countries like Malaysia, where the availability and cost of imaging affect feasibility [3]. Besides that, their use in primary care can increase awareness and early diagnosis of SLD, which is essential for secondary disease prevention. Furthermore, the fibrosis-4 (FIB-4) score can be used to screen for more severe SLD.[5] Those with less severe SLD can be managed in the primary care setting. In contrast, referrals for further evaluations are necessary for individuals with high or intermediate scores [5].

With a better understanding of the pathophysiology and epidemiology of SLD, it is clear that multi-disciplinary collaborative efforts are vital to managing the complex disease [1,2,5]. Public health-wise, determining the national prevalence of SLD is essential to gauge the issue's magnitude [4] accurately. The information can raise SLD priority in health agenda setting at the national level, catalyze evidence-based policymaking to prevent and manage SLD, and incorporate SLD into the broader noncommunicable disease prevention and control initiatives due to shared common risk factors [4,5]. Public health practitioners play a crucial role in raising awareness and knowledge of various stakeholders on SLD, with healthcare professionals in primary care and the general population being the key target groups [5]. In this sense, accepting and including readily available biomarkers and scores for identifying hepatic steatosis is essential and should be considered in future updates of the nomenclature or guidelines on the disease.