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EDITORIAL

From NAFLD to MASLD: what does it mean?

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1. Introduction

In 1980, Ludwig and colleagues [1] described a disease, unnamed since then, called nonalcoholic steatohepatitis (NASH) which was characterized by liver steatosis, hepatocyte injury, liver inflammation, and fibrosis. Subsequently, the term nonalcoholic fatty liver disease (NAFLD) was introduced to encompass the histological spectrum of steatosis to steatohepatitis [2]. NAFLD is characterized by fat accumulation exceeding 5% within the liver, i.e. steatosis, and necessitates the exclusion of secondary causes of fatty liver including alcoholic liver disease (ALD) [3] (Figure 1).

The rapidly escalating global prevalence of NAFLD coupled with advancements in our comprehension of disease's pathophysiology paved the way for a shift from a diagnosis of exclusion to a positive diagnosis delineated by specific criteria. In 2020, an international consortium of experts proposed the term metabolic dysfunction-associated fatty liver disease (MAFLD) as a replacement for NAFLD [4]. According to these criteria, individuals exhibiting hepatic steatosis, based on histological, imaging or blood biomarkers evidence, and fulfilling criteria for obesity or type 2 diabetes mellitus (T2DM) or having evidence of metabolic disturbance determined by the presence of two other metabolic abnormalities, were classified as having MAFLD (Figures 1 and 2). Importantly, the diagnosis of MAFLD does not require the exclusion of significant alcohol intake and other causes of steatosis [4] (Figure 1). Within the framework of the MAFLD definition, the term 'non-alcoholic' was considered insufficient in capturing the contemporary understanding of the disease and was subsequently replaced, whereas the terminology 'fatty' persisted. However, this latter term may carry connotations of stigma for certain patients. In order to address these and other challenges, a modified Delphi process was conducted in June 2023 [5], led by the American Association for the Study of Liver Diseases and the European Association for the Study of Liver in collaboration with the Asociación Latinoamericana para el Estudio del Hígado. This process also engaged prestigious academic professionals worldwide, along with regulatory agencies and patient advocacy organizations, culminating in a consensus and the proposal of a new definition and nomenclature. More precisely, the term 'non-alcoholic' was removed and the term 'fatty' was replaced with 'steatotic.' Subsequently, the disease was renamed to metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD encompasses patients with steatosis, evaluated by histological (biopsy) or imaging findings, and at least one of the five cardiometabolic risk factors (CMRFs) (Figure 1). Similarly, the metabolic dysfunction-associated steatohepatitis (MASH) supplanted the NASH. MASH can progress to bridging fibrosis, cirrhosis, and hepatocellular carcinoma (Figure 3). Additionally, the term MetALD was introduced to encompass patients with MASLD and increased alcohol intake (20–50/30–60 grams for females/males per day) [5] (Figure 1). According to the latest published data by two studies that applied the new nomenclature, the prevalence of MASLD in general population was 28.9% [8] and 47.2% [9] in US and Korean individuals, respectively. Of note, the prevalence of MetALD was 1.6% [8] and 6.4% [9] in the aforementioned populations, respectively.

2. What does that transition mean?

The redefinition from NAFLD to MASLD underscores the need for the diagnosis to be based on affirmative rather than exclusionary criteria and emphasizes the role of metabolic disturbances. The change in nomenclature has some important benefits. First, MASLD will no longer addressed as the hepatic manifestation of metabolic syndrome refereed solely to hepatologists, but it will require a multidisciplinary approach involving specialists from various realms, including hepatology, endocrinology, and cardiovascular medicine, dietitians, and ideally primary care physicians. In this context, the unmet need for the use of noninvasive methods (i.e. serum markers of liver fibrosis and elastography) to identify patients with potentially evolving MASH and need for referral to hepatologists becomes even more essential. Furthermore, it is believed by a large consensus that the new definition will enhance awareness of the disease by harmonizing the diagnostic criteria to those of well-recognized phenotypic characteristics of T2DM and cardiovascular disease (CVD) in which patients are way more familiar to comprehend. To this end, He et al. showed that the new MASLD criteria are better suited to

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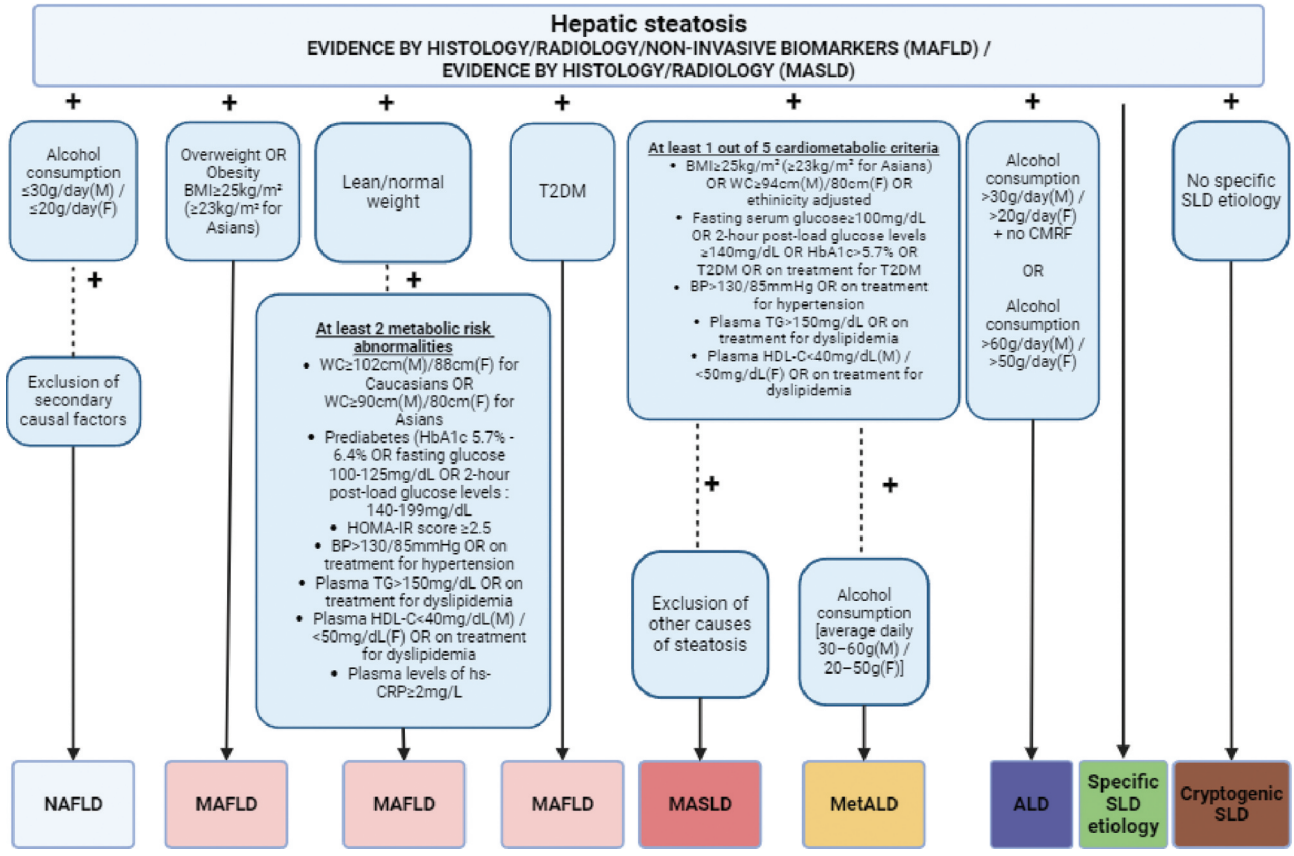

Figure 1. Definitions of nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated alcoholic liver disease (MetALD), specific etiology steatotic liver disease (SLD), and cryptogenic SLD.

Abbreviations: ALD, alcoholic liver disease; BMI, body mass index; BP, blood pressure; CMRF, cardiometabolic risk factor; F, females; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; M, males; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction- and alcohol-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; SLD, steatotic liver disease; TG, triglycerides; WC, waist circumference.

identify patients at risk for T2DM [10], while other authors demonstrated that MASLD can better define lean patients with steatosis than MAFLD criteria in a cohort of well-characterized NAFLD patients [11]. Those findings were confirmed by Ramirez-Mejia et al. who showed that new nomenclature encompasses a higher proportion of patients compared to MAFLD approach and that was mainly attributed to the capture of lean individuals [12]. This is of importance given that almost 20% of all patients with NAFLD are lean [13], and recent meta-analyses showed that those patients had increased risk of overall and CVD-related mortality compared to their non-lean counterparts [14,15]. An additional positive aspect of the new nomenclature is the preservation of existing data generated during the past three decades, since 98% of the currently existing cohorts of NAFLD patients would fulfil the new MASLD criteria [5], while it seems that the design of interventional studies would not be affected. As far as now, it seems that there is no difference respective to mortality rate, hepatic and extrahepatic-related outcomes as well as predictive biomarkers when comparing NAFLD and MASLD cases [16]. Lastly, one more benefit of the new nomenclature is the recognition of MetALD as a distinct entity. Although preliminary data exist so far, a recent meta-analysis of five studies with nearly 10 million individuals showed that MetALD was associated with worse outcomes compared to MASLD, predominantly attributed to the increased CVD- and cancer-related mortality [17]. However, it is of major importance to precisely categorize patients into the MASLD, MetALD, or ALD category (Figure 1).

3. Challenges and limitations

We should point out that the primary metabolic dysfunction driving MASLD is insulin resistance (IR). However, not all CMRFs have the same impact on predicting IR since high-density lipoprotein cholesterol and diastolic blood pressure are slightly associated with IR [5]. Furthermore, steatosis and IR can exist in the absence of any of the five CMRFs, especially in younger individuals. Along this line, a patient with hepatic steatosis and no significant alcohol consumption was classified as NAFLD, while under the light of renaming and no evident CMRF will be labeled as cryptogenic steatotic liver disease (SLD). On the contrary, following MAFLD definition, the use of Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and levels of high-sensitive C-reactive protein are also applied as criteria of classification, although their use is limited in everyday clinical practice. In fact, a misclassification as 'cryptogenic SLD' could pose clinical implications as it may hinder patient monitoring and diminishing the focus on lifestyle modifications aimed at

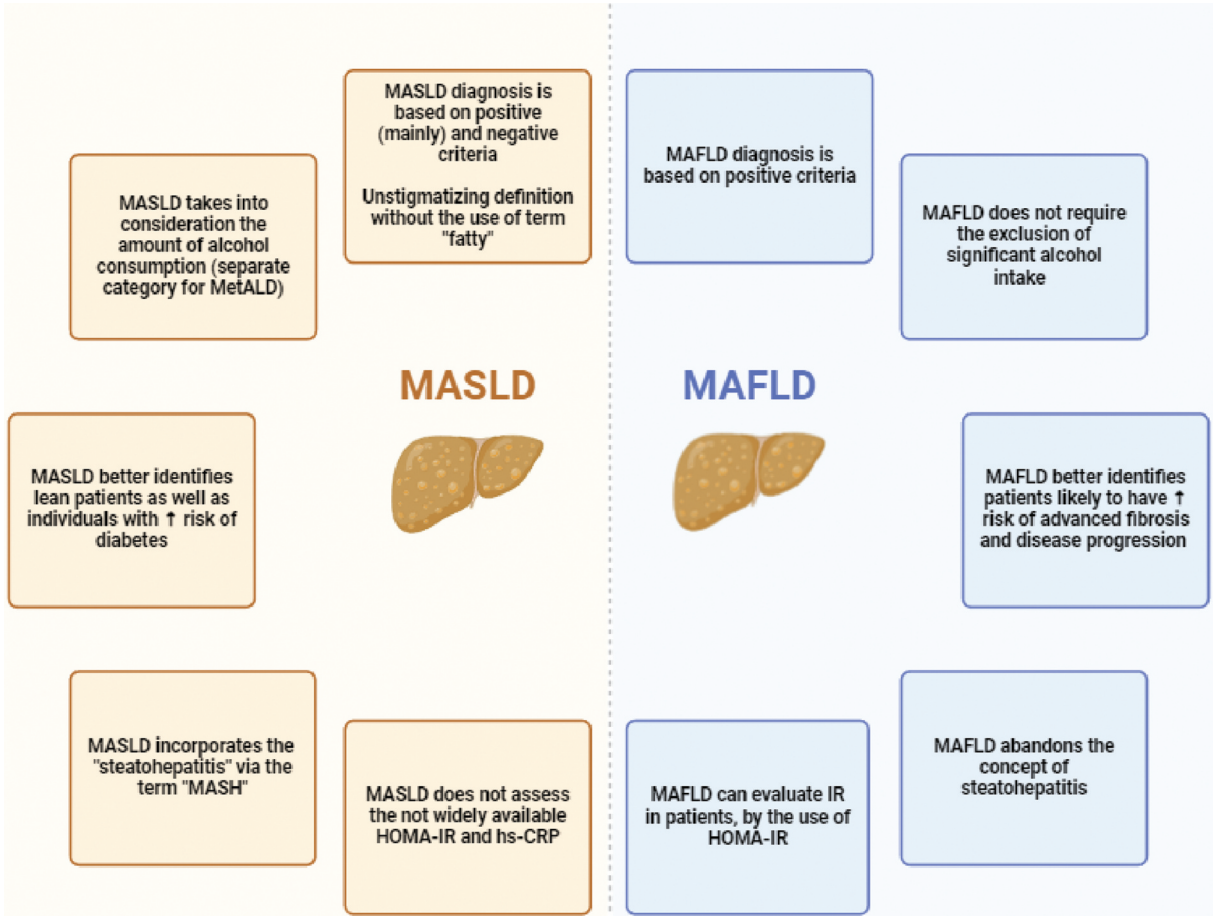

Figure 2. Comparison of the main characteristics and advantages of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated fatty liver disease (MAFLD).

Abbreviations: CMRF, cardiometabolic risk factor; DILI, drug-induced liver injury; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; hs-CRP, high-sensitive C-reactive protein; IR, insulin resistance; MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction- and alcohol-associated steatotic liver disease.

preventing liver disease progression, CVD-related outcomes, and extrahepatic complications. Instead of that, it has been proposed that these patients could be classified as 'early' or 'possible' MASLD [18]. Nonetheless, those patients are highly unlikely to have advanced liver disease and can be monitored and reassessed in the future; alternatively, IR tests such as HOMA-IR or glucose tolerance tests, possibly on individual basis, would be helpful in this setting.

Noteworthy, despite the higher engagement of lean patients under MASLD definition, the term 'steatotic,' which is largely unfamiliar to most patients, can actually decrease disease awareness and patients' empowerment [19], while three independent studies [12,20,21] have shown that MAFLD can better identify patients at higher risk for advanced fibrosis and progressive liver disease than MASLD. This underscores a significant concern on whether the underlying objective of the new nomenclature should focus on the diagnosis of more patients or on the identification of those at higher risk for adverse outcomes. However, more solid ground is needed since we believe that over time, we will be able to optimize the use of relatively limited healthcare resources and prioritize early intervention for those most likely to benefit from it. Moreover, the enrollment of patients' populations in the future studies shall be based on the specific scientific question that needs to be addressed.

A point of major importance is that establishing a diagnosis of MASLD does not negate the need to examine to rule out other causes of SLD especially in children in whom genetic defects can predispose to developing MASLD [22]. Along this line, patients carrying a gain or a loss of function of specific variants such as PNPLA3, TM6SF2, and HSD17B13 are predisposed to develop MASLD and are not regarded as a separate category. This is because, these variations act as modifiers for both MASLD and ALD, rather than direct causative factors, unlike rare genetic variants associated with monogenic diseases.

4. Conclusion

NAFLD has been renamed to MASLD, emphasizing the key metabolic factors of obesity, IR, endothelial dysfunction, and dyslipidemia. We are in line with the consensus group that the new nomenclature (MASLD) is an affirmative and non-stigmatizing appellation that could facilitate enhanced risk assessment and early intervention, thus resulting in better patient outcomes. The new definition is also expected to

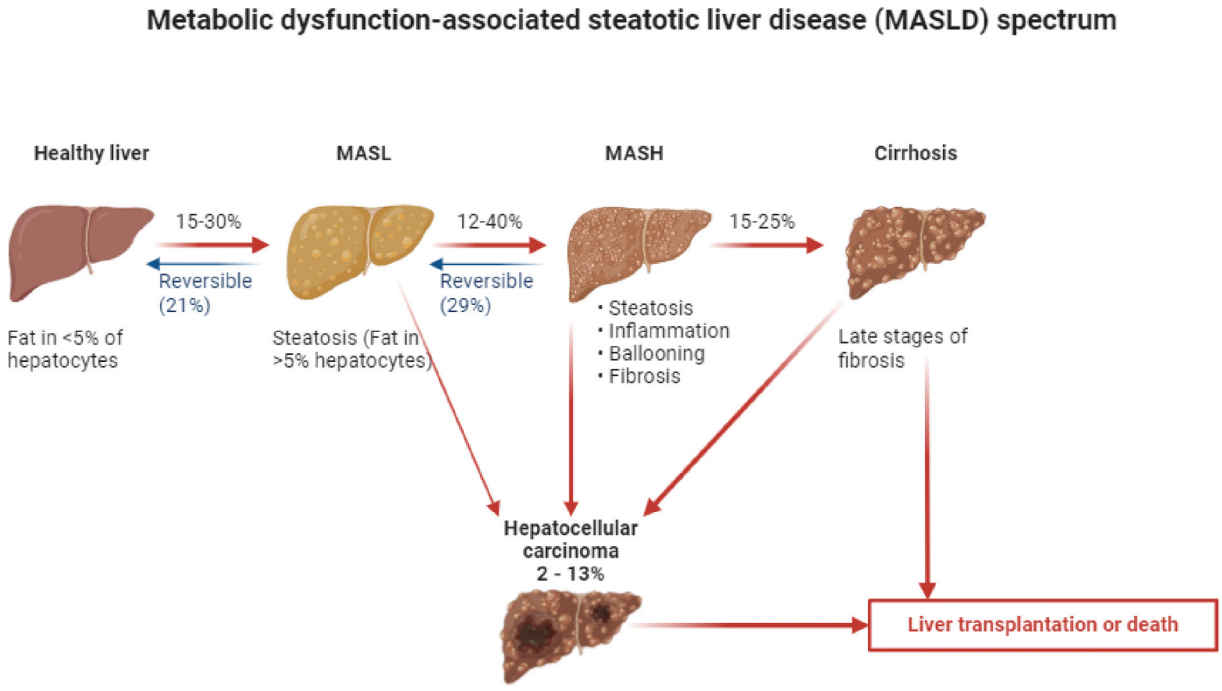

Figure 3. Natural history of metabolic dysfunction-associated steatotic liver disease (MASLD) [6,7].

Abbreviations: HCC, hepatocellular carcinoma; MASL, metabolic dysfunction-associated steatotic liver; MASH, metabolic dysfunction-associated steatohepatitis.

increase awareness of the disease and via that increased recruitment for therapeutic interventional clinical trials. In line with that, different subgroups of MASLD may be generated based on the presence of CMRFs, which can lead to subtrials with different endpoints. The establishment of a new separate nomenclature for MASLD and significant alcohol intake known as MetALD represents an opportunity to generate new knowledge for this common group of patients regarding its prevalence and characteristics in order to better clarify the impact of alcohol in SLD, thus laying the foundations for a holistic approach of these patients. In light of the new nomenclature, new clinical trials specifically designed for MetALD and ALD are also needed. Envisioning the future of personalized medicine, the concept of sub-categorizing a MASLD patient according to the presence of CMRFs, although at a nascent stage since now, may hold the key for disease stratification and management, optimally tailored on an individualized basis [23]. In conclusion, we believe that the decision to adopt the MASLD definition signifies a step in the correct direction. As members of the scientific community, we believe that we shall rely on the plethora of data generated in the past under NAFLD nomenclature and look forward to the advancements related to more effective and personalized treatment of MASLD in the years to come.

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Declaration of interest

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