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**From** **metabolic dysfunction-associated fatty liver disease to metabolic dysfunction-associated steatotic liver disease: Controversy and consensus**

Chen L. From MAFLD to MASLD

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**Abstract**

The newly released nomenclature of metabolic dysfunction-associated steatotic liver disease (MASLD) in the 2023 European Association for the Study of the Liver Congress has raised great clinical concerns. This marks the second instance of significant renaming of non-alcoholic fatty liver disease since the introduction of metabolic dysfunction-associated fatty liver disease (MAFLD) in 2020. The nomenclature and definitions of MASLD and MAFLD exhibit significant disparities as well as substantial consensus. The disparities regarding the framework of nomenclature, the definitions, the clinical management, and the impact on the clinical outcomes between MASLD and MAFLD were comprehensively compared in this editorial. Additionally, the consensus reached by the MASLD and MAFLD definitions also emphasizes positive diagnosis rather than negative diagnosis within the framework of establishing a diagnostic approach. Furthermore, they acknowledged the pivotal role of metabolic dysfunction in the pathogenesis of MAFLD or MASLD and the positive role of increasing the awareness of the disease in public. Fortunately, the non-invasive tests remains effective in the MASLD and MAFLD era. Elucidating these disparities would contribute to a more comprehensive comprehension of the nature of steatotic liver disease and enhance clinical practice. Thus, more efforts are required to reach more consensus about these important topics.

**Key Words:** Non-alcoholic fatty liver disease; Metabolic dysfunction-associated fatty liver disease; Metabolic dysfunction-associated steatotic liver disease; Nomenclature; Metabolic risk factors

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**Core Tip:** The nomenclature for non-alcoholic fatty liver disease has undergone name changes twice in a span of three years. However, there exist significant disparities and some consensus between the transition from metabolic dysfunction-associated fatty liver disease to metabolic dysfunction-associated steatotic liver disease. Clarifying these discrepancies would greatly benefit clinical practice and trials.

**INTRODUCTION**

With the escalating prevalence of obesity and type 2 diabetes mellitus (T2DM) in the general population, fatty liver disease has become a predominant etiology of chronic liver disease worldwide[1,2]. Non-alcoholic fatty liver disease (NAFLD), first named by Jurgen Ludwig in 1986, was defined as hepatic steatosis affecting at least 5% of hepatocytes without any other causes of liver injury[3]. NAFLD encompasses a histological spectrum of disorders ranging from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) and can progress to liver cirrhosis or hepatocellular carcinoma[4]. Due to its exclusionary diagnostic criteria, the term NAFLD has encountered significant challenges in both diagnosis and treatment, particularly when patients with NAFLD present with concurrent alcohol consumption or viral hepatitis. In 2020, a novel nomenclature of “metabolic dysfunction-associated fatty liver disease (MAFLD)” was proposed by a panel of international experts from 22 countries to address these concerns.

The MAFLD framework emphasizes the importance of metabolic dysfunction, as demonstrated by the revised definitions of overweight/obesity, T2DM, or the presence of at least two metabolic risk abnormalities, regardless of the underlying etiologies and comorbidities such as alcohol consumption and viral hepatitis[5]. However, the revised definition of MAFLD, which encompasses alcoholism and acknowledges the coexistence of multiple etiologies, raises concerns regarding its impact on the natural history and therapeutic development of the condition, as well as the potential stigmatization associated with the term “fatty”. Recently, three large pan-national liver associations, including the American Association for the Study of Liver Disease, European Association for the Study of the Liver, and Latin American Association for the Study of the Liver, proposed a novel nomenclature for steatotic liver disease (SLD) and metabolic dysfunction-associated SLD (MASLD) through a modified Delphi process. In this novel nomenclature, the umbrella term, SLD, is classified into two distinct subcategories based on the presence and absence of a cardiometabolic risk factor (CMRF). Furthermore, the subcategory of CMRF is further classified into MASLD and MetALD depending on the alcohol consumption. MASLD is defined as the presence of hepatic steatosis in conjunction with at least one CMRF and no other discernible cause[6]. Within a span of merely 3 years, two distinct nomenclatures were successively proposed. The magnitude of the controversy surrounding these nomenclatures remains substantial, with societies yet to reach a consensus. Therefore, elucidating the disparities and similarities between MASLD and MAFLD is imperative.

**THE CONTROVERSY BETWEEN MASLD AND MAFLD**

***The disparity in the framework of nomenclature between MASLD and MAFLD***

MASLD is a branched term under the overarching term of SLD, which encompasses a broad spectrum of causes contributing to hepatic steatosis. The term MASLD, which excludes alcoholic consumption and other concomitant etiologies, is parallel with MetALD, alcoholic liver disease (ALD), other specific etiology SLD, and cryptogenic SLD. From this perspective, MASLD can be regarded as a negative diagnosis. MASLD focuses on the intricate relationship between hepatic fat deposition and metabolic dysfunction while excluding the effects of alcohol. While MAFLD is a positive diagnosis regardless of alcohol consumption or other concomitant liver diseases. MAFLD is a single overarching term encompassing the primary and secondary fatty liver disease as long as it meets the criteria of metabolic dysfunction. Nevertheless, the MAFLD leads to more heterogeneity in the disease spectrum compared to MASLD. Given the global popularity of alcohol consumption, the coexistence of NAFLD and alcohol consumption poses challenges for diagnosing NAFLD; this issue can be readily resolved by adopting the term MAFLD. However, alcohol consumption interacts with components of the metabolic syndrome to exert synergistic or supra-additive effects on the development and progression of liver disease, further complicating the natural history of MAFLD[7]. The introduction of the term MetALD provides a framework to study the natural history of such a distinct subcategory that has both alcohol consumption and metabolic dysfunction.

***The disparity in the definitions of MASLD and MAFLD***

Regarding the identification of steatosis, the MASLD criteria recommend confirmation through either imaging or histological methods. While the MAFLD criteria confirm steatosis by histological methods, or non-invasive tests (NITs) based on imaging approach or blood biomarkers. Moreover, the MAFLD criteria enumerate the NITs including ultrasound, vibration-controlled transient elastography, computed tomography or magnetic resonance imaging (MRI), MRI–derived proton density fat fraction, and fatty liver index. From this perspective, the MAFLD criteria provide more options for the identification of steatosis.

One of the most prominent distinctions between MASLD and MAFLD is the identification of metabolic risk factors, which intend to identify patients likely to have insulin resistance as the main cause of hepatic steatosis. According to the MAFLD criteria, two out of seven metabolic risk factors must be met for patients without T2DM or obesity as outlined below: waist circumference ≥ 102/88 cm in Caucasian men and women or ≥ 90/80 cm in Asian men and women; blood pressure ≥ 130/85 mmHg; plasma triglycerides ≥ 1.70 mmol/L; plasma high density lipoprotein-cholesterol < 1.0 mmol/L for men and < 50 mg/dL < 1.3 mmol/L for women; prediabetes (fasting glucose levels 5.6 to 6.9 mmol/L, or 2-h postload glucose levels 7.8–11.0 mmol or HbA1c 5.7% to 6.4%); homeostasis model assessment-insulin resistance (HOMA-IR) score ≥ 2.5; and plasma high-sensitivity C-reactive protein (hs-CRP) level > 2 mg/L. The MASLD criteria necessitate the fulfillment of at least one out of the five cardiometabolic risk factors, which are similar to those outlined in the MAFLD criteria, except HOMA-IR and hs-CRP levels. As HOMA-IR and hs-CRP levels are not universally measured in all clinical settings, the MASLD criteria are more accessible and intuitive than the MAFLD criteria. A recent study has demonstrated that the MASLD criteria outperforms the MAFLD criteria in identifying fatty liver disease among lean patients, despite the absence of hs-CRP data[6]. However, which criterion is superior in identifying metabolic dysfunction and insulin resistance remains unclear.

***The difference in the management of steatohepatitis***

The MAFLD definition abandons the dichotomous stratification into steatohepatitis and non-steatohepatitis, which was established during the NAFLD era. The dichotomous classification of steatohepatitis and non-steatohepatitis may fail to capture the complete spectrum of disease response to alterations in underlying metabolic dysfunctions or pharmacological interventions[5]. The MAFLD definition places greater emphasis on the degree of activity and stage of fibrosis, rather than being entangled in the presence or absence of steatohepatitis. These changes inevitably exerted a significant impact on clinical trials, particularly in terms of endpoint selection, as the current objective of drug development is to achieve the resolution of NASH without any deterioration in liver fibrosis[8]. However, the definition of MASLD emphasizes that the presence of steatohepatitis carries prognostic implications and should remain an important distinction. Consequently, retaining the term “steatohepatitis” is imperative in both clinical practice and trial endpoints. Moreover, the MASLD definition suggests replacing the term NASH with metabolic dysfunction-associated steatohepatitis (MASH), which may reduce the confusion in clinical practice and trials[6]. The MASLD definition also permitted the integration of MASH with additional assessment of fibrosis severity.

***The difference in the impact on clinical outcomes***

The divergent framework of nomenclature and definition between MASLD and MAFLD implies the likelihood of disparate impact on clinical outcomes. Due to the heterogeneous nature of MAFLD, MAFLD has a more detrimental impact on clinical outcomes compared to MASLD. Based on the Third National Health and Nutrition Examination Survey (NHANES III), studies have demonstrated that MAFLD is associated with an elevated risk of all-cause and cardiovascular mortality, whereas NAFLD alone does not increase the risk of all-cause mortality[9]. MAFLD criteria identified a significant group of individuals with more comorbidities and worse prognosis compared with those with NAFLD only[10]. However, another study demonstrated no observed differences in cumulative all-cause and cause-specific mortality between MAFLD and NAFLD after adjusting for alcohol-associated liver disease[11].

A recent NHANES III study demonstrated that both the MAFLD-only and MASLD/MAFLD overlap subgroups exhibited significantly higher all-cause mortality, as opposed to the MASLD-only subgroup. With regard to cause-specific mortality, MAFLD was significantly associated with an increased risk for cardiovascular disease -related and diabetes-related mortalities, whereas MASLD was independently related to a higher risk of diabetes-related mortality[12]. Another study based on NHANES III also failed to demonstrate the association between MASLD and all-cause mortality after adjustment for demographic and other factors such as body mass index and hepatitis B and C viral infections. On the contrary, MetALD and ALD were significantly associated with all-cause mortality[13].

***The difference in stigmatization of nomenclature***

The renaming is partly motivated by the stigmatization associated with terms such as “fatty” and “nonalcoholic.” During the Delphi process, the terms “nonalcoholic” and “fatty” were deemed to be stigmatizing by 61% and 66% of panelists, respectively[6]. However, the vote percentage does not surpass the priori threshold of ≥ 67%, thus failing to achieve a consensus. Perceptions of stigma differ widely across different languages and cultures. In certain Indian languages, the term “fatty” is associated with robust health and would be considered a compliment. There is no justification for stigmatizing “non-alcoholic” fatty liver disease, as it is not “alcoholic”[14]. Depending on the regions and cultural contexts, the transition from “fatty” to “steatosis” may be either ambiguous or unattainable. Additionally, the term “steatosis” can be overly medicalized, which may confuse the patients[15]. Interestingly, a recent survey in Mexico revealed that 69.5% of participants expressed that incorporating the term “alcohol” in the disease nomenclature carries a stigmatizing connotation and advocated for its exclusion. In contrast, 85.6% of participants indicated that they do not perceive the inclusion of “fatty” as stigmatizing and preferred retaining it to enhance effective communication regarding the disease[16]. Some experts argued that the change from NAFLD to MASLD and destigmatization is driven by political correctness rather than scientific rationale[14]. To date, the Asian Pacific Association for the Study of the Liver still advocates MAFLD and does not endorse MASLD, highlighting the ongoing controversy among various associations.

**THE CONSENSUS BETWEEN MASLD AND MAFLD**

***The consensus on positive diagnosis and metabolic dysfunction***

Both MASLD and MAFLD definitions adapt positive criteria and abandon the exclusive criterion of “non-alcoholic.” Once hepatic steatosis is identified, either by histopathology or by imaging method, the diagnosis of steatotic liver disease or fatty liver disease is established. Both MASLD and MAFLD acknowledge metabolic dysfunction as the primary driver of disease progression. Moreover, metabolic dysfunction independently contributes to cardiometabolic outcomes. The complex interplay of metabolic, inflammatory, and vascular mechanisms exacerbates systemic atherogenesis; thereby, promoting the development and progression of cardiovascular diseases[17].

***The consensus on increasing the awareness of the disease***

The previous term NAFLD, which has been in use for four decades, is an exclusive criterion that implies no association with alcoholic consumption and overlooks the role of metabolic dysfunction in its pathogenesis. The term MASLD or MAFLD conveys an intuitive message to patients regarding the etiology, facilitating their comprehension of pathophysiology and treatment. The wide spread of novel nomenclature will enhance public awareness about metabolic dysfunction as an etiology for liver disease.

***The consensus on the effectiveness of NITs***

The changes in nomenclature raise a concern regarding the continued effectiveness of the NITs established in previous decades, which were based on extensive epidemiological data. The worries about the potential negative impact of changes in diagnostic criteria for biomarkers is warranted. Fortunately, the extensively validated NITs still can be applied under novel criteria. A recent liver biopsy-based study demonstrated that the Index of NASH (ION) exhibited superior discriminatory ability for detecting the presence of MASLD, while the aspartate aminotransferase to platelet ratio index and fibrosis-4 score effectively differentiated severe fibrosis stages[18].

**UNRESOLVED QUESTIONS**

The novel MASLD nomenclature also raises new questions. Firstly, in some patients, the hepatic steatosis vanishes while progressing to cirrhosis. The absence of steatosis prompts the question of whether such patients should be diagnosed with cryptogenic SLD or MASLD-cirrhosis[19]. Secondly, should the patients who drink more than 350/420 g/wk and fulfill one out of five CMRFs be diagnosed with MetALD, or should they be diagnosed with ALD? Conversely, should the patients who intake alcohol below 350/420 g weekly and without CMRFs be diagnosed as ALD, or should they be diagnosed with MetALD? Thirdly, patients with coexisting fatty liver and hepatitis B should be diagnosed as MASLD or other specific etiology SLD?

**CONCLUSION**

The term NAFLD has been proposed for nearly four decades; however, with time, it no longer adequately encompasses the pathophysiology of fatty liver disease, necessitating a change in its nomenclature. Indeed, the modification of a well-established or entrenched term poses great challenges. Within more than just 3 years, two distinct nomenclatures, namely MAFLD and MASLD, have been proposed sequentially. The novel nomenclatures not only modify the framework and operational definitions but also provide fresh insights into the pathophysiology and treatment strategies. More importantly, the renaming has significantly enhanced public awareness. Nevertheless, the substantial disparities between MAFLD and MASLD imply controversies among various professional associations, thereby may confuse physicians and patients. More research and debates are needed to reach a consensus in the future.

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