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"What's in a name?" – The implications of change in nomenclature for fatty liver disease from NAFLD to MAFLD to MASLD

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Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide [1]. The global prevalence of NAFLD is 30% and is increasing. NAFLD is also the leading cause of liver-related morbidity and mortality (1). Ludwig *et al*. first reported the term "non-alcoholic steatohepatitis (NASH)" in 1980 [2]. They reported a liver condition mimicking alcoholic hepatitis that can progress to cirrhosis in persons who did not consume a significant amount of alcohol. Over the next two decades, it became increasingly clear that a large group of patients with cirrhosis previously labelled as "cryptogenic" (cause unknown) shared some common features. These patients did not have typical causes of cirrhosis like a history of chronic unsafe alcohol use, chronic viral hepatitis, autoimmune hepatitis, hemochromatosis or Wilson's disease. Instead, they tended to have a higher body mass index (BMI), diabetes, hypertension, high triglycerides (hypertriglyceridemia), low HDL or a family history of these conditions. Therefore, in 2007, Farrell *et al*., in the Asian-Pacific Working Party for NAFLD, proposed the operational definition of NAFLD [3]. NAFLD was defined as the accumulation of hepatic fat (>% 5 of hepatocytes), as evidenced by radiologic or histologic examination, in the absence of a coexisting aetiology of chronic liver disease or secondary cause of steatosis (including significant alcohol consumption, use of steatotic drugs or inherited or acquired metabolic states). Although this definition has been unchallenged for nearly two decades, recently, there have been calls for change in the nomenclature and the categorization of steatotic liver disease (SLD).

The recent two recommendations to replace NAFLD are metabolic dysfunction-associated fatty liver disease (MAFLD – pronunciation: Ma-fuld) and metabolic dysfunction-associated steatotic liver disease (MASLD – pronunciation: Ma-zuld) [4-6]. These proposed nomenclature changes embrace the central role of metabolic dysfunction in the patho-physiology of hepatic steatosis.

While cardiovascular disease is the leading cause of mortality in patients with SLD, those with more severe liver fibrosis are at increased risk of liver-related mortality, with the risk growing exponentially with the fibrosis

stage [7]. This leading article will critically analyze the proposed new MASLD nomenclature and its potential benefits, pitfalls, and implications for clinical practice and research.

NAFLD is an umbrella term covering a spectrum of diseases ranging from simple non-alcoholic fatty liver (NAFL) (i.e. fat deposition with no or mild inflammation, but no fibrosis) to NASH (i.e. fat deposition with inflammation and hepatocellular injury, with or without fibrosis) to cirrhosis [8]. Whereas NAFL is the most common disease manifestation, a more progressive disease course, NASH is present in 10-20% of affected individuals. NASH furthermore progresses in a substantial number of patients towards liver cirrhosis and hepatocellular carcinoma [8].

The pathophysiology of NAFLD is complex and heterogeneous, involving lipotoxicity, hepatic immune disturbances, gut dysbiosis, and commonly hepatic and systemic insulin resistance, defining this disorder as a prototypic systemic metabolic disorder [8]. Most NAFLD subjects are likely to have one or more features of metabolic syndrome (MetS) associated with insulin resistance, such as obesity, type 2 diabetes mellitus (T2DM), hypertension and atherogenic dyslipidemia [9]. Not surprisingly, many affected patients have other disease manifestations, and indeed, cardiovascular disease, chronic kidney disease, and extrahepatic malignancies are all contributing substantially to patient outcomes [10].

There has been some dissatisfaction with the terminology "non-alcoholic" in NAFLD, which overemphasizes "alcohol" and underemphasizes the root cause of SLD, namely, the predisposing metabolic risk factors. The term "non-alcoholic" used by the early researchers was derived from superficial similarities in the histopathological findings of these patients compared to those with alcohol-related liver disease due to the lack of knowledge about the pathophysiological basis of MASLD at that time.

The proposed terms MAFLD and MASLD have more in common than not and are more appropriate for the SLD associated with MetS. Both MAFLD and MASLD definition change was understandably driven, at least in part, by a need for a "positive" diagnosis rather than a "negative" one, i.e. by the exclusion of excessive alcohol use and any other chronic liver disease. In both MAFLD and MASLD, there is a removal of the need for the exclusion of concurrent liver disease to entertain the diagnosis. The awareness of the critical role of insulin resistance in the pathophysiology of "metabolic dysfunction" and SLD is also reflected in the new definitions (Table 1).

In early 2020, an international panel of experts led a consensus-driven process to develop a more appropriate term for the disease. Utilizing a 2-stage Delphi consensus, the proposed term was "metabolic dysfunction-associated fatty liver disease," or MAFLD (4,5). Later, in June 2023, a multi-society Delphi consensus statement on a new SLD nomenclature was published, introducing the term MASLD and effectively retiring the term NAFLD [6].

MAFLD definition is based on evidence of hepatic steatosis, in addition to one of the following three criteria, namely overweight/obesity (BMI >23kg/m^2), presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation (at least two of the following metabolic abnormalities: increased waist circumference, hypertension, elevated triglycerides, low HDL, pre-diabetes, insulin resistance or elevated plasma hs-CRP) [4, 5].

MASLD definition requires steatosis to be associated with at least one of five clinical comorbidities (steatosis plus ≥1 cardiometabolic risk factor) related to insulin resistance (hypertension, atherogenic dyslipidemia, overweight/obese or pre-diabetes/type 2 diabetes) (Table 2) [6].

MASLD should suspected in any individual with persistently elevated liver enzymes or hepatic steatosis identified commonly on imaging or rarely on biopsy. There are numerous benefits of using the term MASLD over NAFLD. The lack of need to exclude a secondary cause for liver steatosis, such as in the NAFLD definition, makes MASLD definitions more inclusive. The MASLD term improves understanding of the critical link between metabolic dysfunction and SLD and will enhance physicians' approach to patient awareness and engagement with their disease. Therefore, MASLD may better assist non-specialists and people with SLD in linking insulin resistance, metabolic abnormalities, and cardiovascular disease risk to hepatic steatosis.

MASLD will also facilitate diagnosis by identifying at-risk individuals with metabolic dysfunction. Therefore, MASLD has the potential for better public health messaging and prevention strategies. The change from using the term "fatty liver" in both NAFLD and MAFLD to "steatotic liver disease" in MASLD to describe liver fat accumulation is hoped to reduce the stigmata associated with defining this disease entity among obese patients. A uniformly accepted terminology will streamline clinical research and development of therapies.

There are potential drawbacks to using the term MASLD over NAFLD. MASLD needs further validation and refinement of the definition in different populations. A large body of data exists that was derived using the NAFLD definition. In contrast, there is limited data on the long-term implications of MASLD compared to NAFLD. By changing the nomenclature, there is potential disruption to ongoing research using NAFLD criteria. The applicability of findings of the older definition may not be directly applicable to patients with SLD defined using the new definition.

Table 1. Comparison of NAFLD, MAFLD and MASLD definitions

Terminology	*Definition*	*Strengths*	*Weaknesses*
NAFLD (Non-alcoholic Fatty Liver Disease)	The presence of fat in the liver exceeding 5% of liver weight, is not caused by alcohol or other secondary causes.	Simple, widely recognized, established research base.	Lacks specificity for disease severity, and does not consider metabolic risk factors.
MAFLD (Metabolic-Dysfunction Associated Fatty Liver Disease)	Presence of fat in the liver exceeding 5% of liver weight, with evidence of metabolic dysfunction.	More specific than NAFLD, emphasizes metabolic links.	New terminology, lacks an established research base, definition of metabolic dysfunction varies.
MASLD (Metabolic Dysfunction-Associated Steatotic Liver Disease)	Presence of steatosis (fatty liver) with at least one of five defined cardiometabolic risk factors (obesity, type 2 diabetes, hypertension, dyslipidemia, metabolic syndrome).	Focuses on metabolic risk factors, potentially better reflects disease severity.	New terminology, and complex definitions, require further validation.

Table 2. Summary of new nomenclature for SLD

Prior terminology	*New terminology*	*Clinical reference*
NAFLD	MASLD (metabolic dysfunction-associated steatotic liver disease)	Fatty liver in individuals who consume little or no alcohol plus at least one metabolic risk factor
NAFL	MASL (metabolic dysfunction-associated steatotic liver)	Non-progressive subtype of MASLD
NASH	MASH (metabolic dysfunction-associated steatohepatitis)	Progressive sub-type of MASLD
At-risk NASH	At risk MASH	Patients with MASH with ≥stage 2 fibrosis

MASLD comes with a simple set of criteria to enable easy diagnosis at the bedside for the general medical community, including primary care physicians. Key areas in which the superiority of MASLD over the traditional NAFLD terminology has been demonstrated include the risk of liver and extrahepatic mortality, disease associations, and identifying high-risk individuals. There will be a need for healthcare professionals to be educated and trained regarding the new MASLD terminology. There will be potential challenges in implementing MASLD in clinical settings. It is essential to tailor management strategies based on individual MASLD risk factors.

MASLD will influence future research directions in SLD by better unambiguously defining patient populations. Studies are needed to validate the MASLD definition and its prognostic value in SLD populations.

Recent studies have investigated the compatibility of existing research on NAFLD with the newly proposed criteria for MASLD. Two separate studies, one from Europe with a majority of participants of European descent and another from Asia with a majority of Asian descent, examined how applying the MASLD criteria would affect previously established patient groups with biopsy-confirmed NAFLD [11,12]. The results showed an overwhelming overlap – nearly all (99.9%) of the 1,783 patients with biopsied NAFLD met at least one of the metabolic risk factors. The most common risk factor was increased body mass index (BMI) at 97.5%, followed by

insulin resistance, hypertension and hypertriglyceridemia. The trends remained consistent even after including a third study with Swedish patients diagnosed by biopsy or imaging. In this larger group of 3,377 patients, 99.6% met at least one metabolic risk factor [13]. These findings were remarkably similar across all the studies despite differences in patient ethnicity. This suggests that existing research on NAFLD is likely still highly relevant for patients with MASLD.

MASLD nomenclature will also have an impact on preclinical research. Preclinical researchers studying MASLD should prioritize rodent models that reflect metabolic risk factors. Therefore, models that induce steatohepatitis and fibrosis through nutrient deficiencies alone may not accurately represent MASLD and should be described as such, while obesogenic diet models and the foz/foz mouse, which mimic these metabolic risk factors alongside liver disease, are more fitting for MASLD research [14].

The new MASLD nomenclature emphasizes the critical influence of metabolic dysfunction and cardiometabolic risk factors on the pathogenesis and progression of SLD. The use of "steatotic liver disease" in MASLD to describe liver fat accumulation is hoped to reduce the stigmata associated with defining this disease entity among patients. There is a growing body of evidence to suggest that existing research on NAFLD is likely still highly relevant for patients with MASLD. Therefore, the potential benefit seems to outweigh the challenges of the widespread adoption of MASLD in clinical practice and research.

Competing interests

The author has no conflict of interest to declare.

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References

1. Younossi, Zobair M, Golabi, Pegah, Paik, James M, Henry, Austin, Van Dongen, Catherine, Henry, Linda. The global epidemiology of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): a systematic review. *Hepatology* 2023; **77**(4): 1335-47.
2. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Non-alcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc.* 1980; **55**(7): 434-8.
3. Farrell GC, Chitturi S, Lau GK, Sollano JD Asia-Pacific Working Party on NAFLD, author. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. *J Gastroenterol Hepatol*. 2007; **22**: 775-7.
4. Eslam M, Newsome PN, Anstee QM, *et al*. A new definition for metabolic associated fatty liver disease: an international expert consensus statement, *Journal of Hepatology* 2020.
5. Eslam M, Sanyal AJ, George J International Consensus Panel, author. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* 2020; **158**: 1999-2014.
6. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, *et al*. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 2023.
7. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in non-alcoholic fatty liver disease: systematic review and meta-analysis. *Hepatology* 2017; **65**: 1557-65.
8. Chalasani N, Younossi Z, Lavine JE, *et al*. The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012; **55**(6): 2005-23.
9. Fan JG, Saibara T, Chitturi S, Sung JJY, Kim BI, Chutaputti A. Asia-Pacific Working Party for NAFLD. What are the risk factors and settings for non-alcoholic fatty liver disease in Asia-Pacific? *J. Gastroenterol. Hepatol.* 2007; **22**: 794-800.
10. Grander C, Grabherr F, Tilg H. Non-alcoholic fatty liver disease: pathophysiological concepts and treatment options, *Cardiovascular Research* 2023; **119**: 1787-98.
11. Ratziu V, Boursier J. AFEF Group for the Study of Liver Fibrosis. Confirmatory biomarker diagnostic studies are not needed when transitioning from NAFLD to MASLD. *J Hepatol.* 2024; **80**(2): e51-e52.12.
12. Song SJ, Lai JC, Wong GL, Wong VW, Yip TC. Can we use old NAFLD data under the new MASLD definition? *J Hepatol*. 2024; **80**(2): e54-e56.
13. Hagström H, Vessby J, Ekstedt M, Shang Y. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical. *J Hepatol.* 2024; **80**(2): e76-e77.
14. Gallage S, Avila JEB, Ramadori P, Focaccia E, Rahbari M, Ali A, Malek NP, Anstee QM, Heikenwalder M. A researcher's guide to preclinical mouse NASH models. Nat Metab. 2022; **4**(12): 1632-49.

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