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Editorial

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MASLD or MAFLD: fatty liver by any name will pose the same challenge

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Medical science has been struggling to understand fatty liver disease for centuries. In 1836, Addison was the first to describe this histological abnormality, and two years later, Rokitansly described its relationship to cirrhosis[1]. Within a few years, it became abundantly clear that diabetes and obesity, in addition to alcohol, can lead to the development of fatty liver. Furthermore, diabetic fatty liver may progress to cirrhosis. The term "non-alcoholic" was first used by the eminent pathologist Jurgen Ludwig in 1980 to describe steatohepatitis, a condition similar to that seen in alcoholic patients, among patients who denied any alcohol abuse[2]. The popular nomenclature of non-alcoholic fatty liver disease (NAFLD) is often credited to Shaffner and Thaler (1986)[3]. The spectrum of hepatic involvement in NAFLD ranges from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), cirrhosis, and the development of hepatocellular carcinoma (HCC). This nomenclature remained dominant for nearly four decades as the prevalence of NAFLD rapidly increased[4], driven by several socio-cultural factors. Today, it has become the most common indication for liver transplantation (LT) worldwide[5] and is also emerging as the leading cause of HCC in non-cirrhotic livers[6]. Despite ongoing efforts to understand its true pathogenesis[7] and find effective treatments, for reasons poorly understood by many, the nomenclature of this disease was changed twice within a span of 4 years, from NAFLD to metabolic (dysfunction)-associated fatty liver disease (MAFLD)[8] and later to metabolic dysfunction-associated steatotic liver disease (MASLD)[9].

The first change was announced in 2020, following a survey and Delphi process, where experts proposed the term MAFLD[10]. The primary aim of this change was to shift from a negative nomenclature of "non-alcoholic" to a more positive diagnosis[10]. The term MAFLD encompasses all patients with fatty liver who have at least two of the metabolic risk factors: waist circumference ≥ 102/88 in Caucasian men/women and ≥ 90/80 in Asian men/women; blood pressure ≥ 130/85 mm of Hg; plasma high-density lipoprotein levels < 40 mg/dL in men and 50 mg/dL in women; the presence of prediabetes, defined as fasting glucose levels between 5.6-6.9 nmol/L, or a 2-h postprandial glucose levels between 7.8-11.0 mmol/L, or HbA1c levels between 5.7%-6.4%; Homeostatic model assessment for insulin resistance (HOMA-IR) score ≥ 2.5; and plasma high-sensitivity C-reactive protein levels >2mg/L[10,11]. Initially, MAFLD was proposed as an umbrella term; however, concerns were later raised regarding the presence of other co-existing etiologies that may ultimately influence the natural course of the disease and must be addressed when treating these patients[12].

The need for this change in nomenclature is supported by the following reasons. The term "metabolic" reflects the pathophysiolsogic basis of the disease, focusing on a positive attribute rather than the exclusion of ethanol abuse. Therefore, the diagnosis can be made more quickly and simply, without the need to rule out other liver diseases. It is hoped that this change in nomenclature may generate renewed enthusiasm among healthcare personnel to identify these patients and promote a more holistic approach to managing the condition. Additionally, it helps identify patients with advanced fibrosis, enabling the stratification of those at high risk of mortality. Patients with dual etiologies of fatty liver (e.g., Hepatitis C and NAFLD), who were previously managed based on only one dominant cause, may receive a more comprehensive treatment approach. Finally, the potentially stigmatizing term "Alcohol" is avoided in MAFLD.

This nomenclature received wide acceptance[11,13,14,15] but was also criticized for several reasons. While it was widely believed that the pathogenesis of MAFLD was similar to that of metabolic syndrome, most of the drugs used to treat hypertension, diabetes, hyperlipidemia, and other related conditions proved ineffective in treating MAFLD. For example, statins, antihypertensive drugs, and many antidiabetic or lipid-lowing medications have not shown benefit for MAFLD patients. Additionally, the role of genetic factors, intestinal dysbiosis, and sarcopenia, which play a major role in the pathophysiology of MAFLD, was ignored due to the excess focus on metabolic components. MAFLD also failed to account for the additive/synergistic effects of viral hepatitis or ethanol abuse on the natural progression and prognosis of fatty liver disease. Furthermore, reports have highlighted a significant subset of patients with "lean NAFLD", where metabolic syndrome may not be prominent[16]. Some authors spoke frankly against the name change, stating that it is not supported in their regions[17,18,19].

Amid ongoing debates, the second change in nomenclature was introduced by another Delphi consensus meeting[11]. Surprisingly, many of the experts who participated in the first Delphi consensus were also involved in the second. The rationale for this second name change was threefold. First, the term "Fatty" was now considered stigmatizing for patients. Second, experts wanted to expand the spectrum to include alcohol and other causes of fatty liver, recognizing that many patients may have multiple contributing factors. Finally, the change aimed to address the "Potential negative impact of changes in diagnostic criteria for the disease in terms of biomarker and therapeutic development"[20]. To reflect these considerations, a new term, Met-alcoholic liver disease (ALD), was introduced, which represents a middle point in the spectrum of illness, positioned between MASLD (Ethanol abuse of less than 30 g per day in males and less than 20 g per day in females) at on one end and ALD at the other end (Ethanol abuse of more than 60 g per day in males and 50 g per day in females)[11]. Additionally, patients with uncommon etiologies of fatty liver, such as drug-induced steatosis, HCV infection, and monogenic causes of steatosis (Secondary SLD), were included under the classification of specific etiology MASLD. Monogenic causes, in particular, must be actively considered

in children when various inborn errors of metabolism commonly manifest as steatosis[21].

This latest nomenclature has also come under criticism, with experts quickly highlighting its limitations[20,22]. The Delphi consensus voting pattern showed that the term MASLD failed to reach the Delphi target of 67% (as it was the top choice of only 30% of experts) but was still accepted as a consensus. Some have suggested that the entire exercise may have been done to save billions of dollars already invested in biomarker and drug treatment research for NAFLD, as the earlier definition of MAFLD would have classified 20% of patients differently[23,24]. MASLD primarily focuses on liver fat, which may eventually be replaced by fibrosis as the disease progresses to cirrhosis. In such cases, patients without detectable fat in the liver may be mistakenly labeled as having cryptogenic cirrhosis. One major challenge in MASLD was the inclusion and stratification of alcohol intake, which largely relies on patient self-reported history. However, this approach is inherently unreliable, as patients may either misrepresent or underestimate their alcohol consumption[25]. Additionally, no effort was made to stratify the degree of metabolic dysfunction - an individual with only one cardiometabolic risk factor (CMRF) is considered equivalent to someone with five CMRFs.

This raises a fundamental question. How has this change in nomenclature improved our understanding or management of the condition? Whatever the name, patients will continue to progress from fatty liver to steatohepatitis, then to fibrosis, and ultimately to either cirrhosis or HCC. Is the new nomenclature truly evidence-based? A large number of papers have discussed the pros and cons of this change in recent years[10,26,27]. Now, efforts are being made to collect evidence to justify the revised terminology, and initial findings are yielding intriguing insights[28]. Perhaps the same level of enthusiasm should be directed toward addressing clinical questions that may directly impact patient outcomes.

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Authors' contributions

Involved in the manuscript preparation and contributed equally: Anand AC, Praharaj D
Read and approved the manuscript: Anand AC, Praharaj D

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Not applicable.

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