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Review



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From NAFLD to MASLD: transforming steatotic liver disease diagnosis and management

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Abstract

The transition from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD) represents a significant evolution in the nomenclature of steatotic liver disease. This updated terminology emphasizes metabolic dysfunction as a central criterion, offering greater precision and improved risk stratification. MASLD broadens the scope of liver disease classification by incorporating individuals with diverse metabolic profiles, including lean patients with hepatic steatosis, and aligns clinical practice with the multifactorial nature of this condition. The global adoption of MASLD creates opportunities for standardization in clinical and research settings, facilitating multicenter collaborations and enhancing the development of diagnostic tools and therapeutic strategies. However, the adoption of this new nomenclature poses challenges, including potential confusion during implementation, cultural and linguistic barriers, the integration of MetALD, and the need for educational initiatives targeting healthcare providers and patients. Further efforts are required to refine diagnostic criteria, address implementation challenges, and seamlessly incorporate MASLD into international coding systems. This review evaluates the key advantages and ongoing challenges associated with MASLD, providing a comprehensive analysis of its impact on clinical practice, research, and global health strategies.

Keywords: NAFLD, MAFLD, MASLD, steatotic liver disease, MetALD



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INTRODUCTION

The recognition of hepatic steatosis in patients with high alcohol consumption dates back to 1836, when Addison first described the condition^[1]. Later, in 1980, Ludwig *et al.* identified a similar histological pattern in patients without alcohol consumption, leading to the introduction of the term non-alcoholic steatohepatitis (NASH)^[2]. This discovery laid the foundation for the broader concept of non-alcoholic fatty liver disease (NAFLD), a term that encompasses a spectrum of conditions ranging from simple steatosis to NASH, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Over the past four decades, the prevalence of NAFLD has increased exponentially, paralleling the rise in obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS). Today, it is the most common chronic liver disease worldwide, affecting approximately 38% of the global population^[3]. In fact, NAFLD has become the second leading cause of endstage liver disease and primary liver cancer in adults. However, the impact of NAFLD extends far beyond liver-related complications. Cardiovascular disease (CVD) remains the leading cause of mortality in NAFLD patients, underscoring the strong association between liver disease and systemic metabolic dysfunction^[4]. The natural history of NAFLD involves a bidirectional relationship with components of MetS, particularly T2DM, which not only increases the risk of hepatic fibrosis and cirrhosis but is also exacerbated by NAFLD itself. NAFLD has been shown to impair glycemic control and increase the risk of both microvascular and macrovascular complications^[5]. This intricate interplay between hepatic and systemic metabolic dysfunction highlights the need for a classification that more accurately reflects the metabolic drivers of disease progression.

In response to these challenges, the terminology for steatosis-related liver diseases has evolved significantly. In 2020, Eslam *et al.* proposed the term "metabolic-associated fatty liver disease" (MAFLD) to emphasize the link between hepatic steatosis and metabolic dysfunction^[6]. However, the adoption of MAFLD met with resistance due to the absence of a global consensus. In 2023, following a four-round Delphi process, an international panel of 225 experts, including hepatologists, gastroenterologists, endocrinologists, primary care physicians, and patient advocates, endorsed the term "metabolic dysfunction-associated steatotic liver disease" (MASLD)^[7]. Supported by leading organizations such as the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Latin American Association for the Study of the Liver (ALEH), MASLD aimed to remove the stigma associated with the term "fatty" and to highlight the primary role of metabolic dysfunction in the disease's pathogenesis.

The broad international consensus achieved promotes uniformity in the application of this terminology. However, this consensus not only led to the adoption of the term MASLD but also introduced "steatotic liver disease" as an umbrella term encompassing all clinical entities characterized by hepatic steatosis. This shift breaks down the artificial division between the underlying causes of hepatic steatosis, acknowledging that these causes are often multifactorial and may co-occur, especially in cases where alcohol consumption and metabolic factors align, a condition now termed "metabolic and alcohol-related liver disease" (MetALD). This standardized terminology has raised awareness of this liver disease, creating opportunities to enhance the training of physicians across multiple specialties in this pathology. It also opens new avenues for research, treatment development, and the study of dual conditions such as MetALD.

Despite the broad international consensus supporting MASLD, several challenges remain. Some researchers and clinicians remain hesitant to abandon NAFLD, given its extensive use in scientific literature and clinical guidelines. Furthermore, the implementation of MASLD may pose educational and logistical challenges, especially in regions where clinical practice has yet to fully transition to the updated classifications. In this review, we emphasize the benefits of the new nomenclature as well as some of its controversial aspects. To

ensure a comprehensive and transparent analysis, we conducted a structured literature search in PubMed focusing on studies published between 2000 and 2024 related to the evolving nomenclature and its implications.

ENHANCED RISK STRATIFICATION THROUGH THE MASLD FRAMEWORK

The transition to MASLD is rooted in a proactive approach centered on identifying metabolic dysfunction. This new nomenclature classifies patients by the coexistence of hepatic steatosis with at least one cardiometabolic factor, such as obesity, T2DM, arterial hypertension, or dyslipidemia^[6]. These comorbidities are well-established not only for their role in liver disease progression but also for increasing cardiovascular risk, one of the leading causes of mortality in these patients^[8]. A major advantage of MASLD lies in its ability to identify patients at elevated risk of developing liver fibrosis^[9], the main risk factor for disease progression and adverse outcomes^[10]. Supporting this, a recent study analyzing data from over 230,000 patients with T2DM in Sweden demonstrated that accumulating MetS traits significantly increased the risk of major adverse liver outcomes (MALOS), including cirrhosis and its complications^[11]. Compared to patients with only T2DM, those with multiple MetS traits had a more than twofold higher risk of developing MALOs [adjusted hazard ratio (aHR) 2.33, 95%CI: 1.53-3.54]. Moreover, the risk of liver disease progression increased progressively with the number of metabolic traits present, with hypertension emerging as the most strongly associated risk factor (aHR 2.06, 95%CI: 1.57-2.71). These findings further support the rationale behind MASLD's emphasis on cardiometabolic dysfunction as a key determinant of liver disease progression and long-term outcomes.

By including cardiometabolic factors as a diagnostic criterion for MASLD, a more accurate assessment of mortality risk from both hepatic and non-hepatic causes is enabled. A recent study analyzing data from the third National Health and Nutrition Examination Survey (NHANES III) and its linked mortality data over a 26.9-year median follow-up found that MASLD was associated with a significantly higher risk of all-cause mortality (aHR 1.19, 95%CI: 1.06-1.34), particularly in individuals who met MASLD criteria but did not fulfill the NAFLD definition. Notably, NAFLD alone was not significantly associated with all-cause mortality, whereas MASLD and MAFLD identified a broader group of at-risk individuals, reinforcing the clinical relevance of metabolic dysfunction in risk stratification^[12]. Consequently, the MASLD framework extends beyond liver involvement, incorporating the systemic impact of metabolic dysfunctions such as insulin resistance and MetS, both of which are associated with increased overall mortality^[13,14].

Previous classifications often adopted a binary approach to comorbidities like T2DM, without distinguishing between complicated and uncomplicated cases. It is essential, however, to recognize that T2DM with macroangiopathy or microangiopathy profoundly impacts liver disease progression compared to uncomplicated cases^[15]. Similarly, the severity and control of arterial hypertension and dyslipidemia must be considered, as these factors can differently influence liver disease progression^[16,17]. The current classification also highlights the need for a more nuanced approach to obesity. While body mass index (BMI) is commonly used, metrics such as circumference or the waist-to-hip ratio are more accurate predictors of cardiovascular risk^[18]. Incorporating these distinctions into the MASLD classification is essential for more precise risk stratification.

DEFINITIONAL CHALLENGES OF MASLD: BALANCING OVERDIAGNOSIS AND UNDERDIAGNOSIS

The main differences between the definitions of MAFLD and MASLD are the amount of permitted alcohol consumption and the number of cardiometabolic factors required for diagnosis, particularly in normal-weight individuals [Figure 1]. MAFLD includes any condition of liver steatosis when associated with one of



Figure 1. Overlap and distinctions between NAFLD, MAFLD and MASLD. Overweight/obesity, type 2 diabetes mellitus, or lean/normal weight plus at least two metabolic risks: waist circumference \geq 102/88 cm in Caucasian men and women (or ethnic adjusted criteria), blood pressure \geq 130/85 mmHg or use of antihypertensive drug, prediabetes (defined as fasting plasma glucose levels 100-125 mg/dL or Hb A1c 5.7%-6.4% or 2-h post prandial plasma glucose levels 140-199 mg/dL, plasma triglycerides \geq 150 mg/dL or lipid-lowering treatment, plasma HDL-cholesterol < 40 mg/dL in men or < 50 mg/dL in women or lipid-lowering treatment, HOMA-IR score \geq 2.5, high sensitivity CRP level > mg/L; "(1) Body mass index \geq 25 kg/m² in Caucasians, or waist circumference > 94/80 cm in Caucasian men and women, or ethnic adjusted criteria; (2) fasting serum glucose \geq 100 mg/dL, or 2-h post-load glucose levels \geq 140 mg/dL, or HbA1c \geq 5.7%, or diagnosis of type 2 diabetes mellitus or antidiabetic treatment; (3) blood pressure \geq 130/85 mmHg or specific antihypertension treatment; (4) plasma triglycerides \geq 150 mg/dL or lipid-lowering treatment; (5) plasma HDL-cholesterol < 40 mg/dL in men or < 50 mg/dL in women or lipid-lowering treatment; (5) plasma HDL-cholesterol < 40 mg/dL in men or < 50 mg/dL in women or lipid-lowering treatment; NAFLD: Non-alcoholic fatty liver disease; MAFLD: metabolic-associated fatty liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease; Hb: hemoglobin; HOMA-IR: homeostasis model assessment of insulin resistance; CRP: C-reactive protein.

three additional conditions: overweight and obesity, T2D, or at least two cardiometabolic risk factors. This criterion led to the exclusion of a significant percentage of metabolically healthy or normal-weight patients^[19]. In contrast, the diagnosis of MASLD requires steatosis and only one cardiometabolic risk factor, making it more inclusive in terms of metabolic dysfunction. Therefore, while MASLD is more inclusive regarding metabolic risk factors, MAFLD represents a broader population because it allows the presence of other hepatic comorbidities as long as metabolic criteria are met.

The inclusion of patients with other liver diseases under MAFLD criteria may contribute to the higher allcause mortality observed in individuals with only MAFLD or overlapping MASLD/MAFLD compared to those with only MASLD^[20]. On the other hand, the MASLD definition allows for the inclusion of patients who, despite lacking overt obesity or diabetes, may exhibit a single metabolic alteration such as central obesity, hypertension, or prediabetes^[19]. This approach enables the identification of "lean" patients with liver steatosis who carry a risk of liver disease progression comparable to that of obese patients. Including these patients is critical, given that they have historically been underrecognized regarding their risk and potential to develop severe liver complications, such as advanced fibrosis or cirrhosis, without significant weight gain^[21]. Recognizing these at-risk patients helps prevent underdiagnosis and delays in initiating treatment. Therefore, MASLD facilitates better identification of lean patients who might otherwise be overlooked, representing a notable advantage over MAFLD.

However, several recent studies have investigated the implications of applying MASLD for disease diagnosis, raising serious concerns about its lack of specificity, potential for over-diagnosis, and lower performance in detecting hepatic and extrahepatic outcomes compared to the MAFLD definition^[22]. One of the most debated aspects of MASLD is its potential to include metabolically healthy individuals within its diagnostic category who do not have increased hepatic fibrosis or cardiovascular risk compared to healthy controls^[23]. It has been pointed out that various cardiometabolic risk factors may have different weights depending on their association with insulin resistance, which is the main etiological factor of the disease. Overdiagnosis can lead to overtreatment, which offers little to no benefit and can have significant physical, psychological, social, and financial consequences. However, some of these patients may have a fibrosis burden and cardiovascular risk comparable to those with manifest metabolic dysfunction^[24]. This suggests the need for adjustments in the MASLD definition to more precisely differentiate between those with a truly favorable metabolic profile and those at genuine risk.

In this context, some studies suggest that the MAFLD and MASLD classification may not adequately reflect individuals with a genetic predisposition to cirrhosis and hepatocellular carcinoma (HCC)^[25]. Metabolically healthy patients could be at risk of developing liver cancer due to genetic factors, even without meeting traditional metabolic criteria. Several genetic variants, particularly PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13, have been robustly associated with MASLD development and progression^[26]. The I148M polymorphism of PNPLA3 is the most well-documented genetic risk factor for hepatic steatosis, fibrosis, and HCC. Notably, individuals carrying this variant exhibit an increased risk of disease progression regardless of metabolic status, suggesting that genetic predisposition may help identify at-risk patients who do not meet the standard cardiometabolic criteria for MASLD. Furthermore, these genetic factors can interact with environmental and metabolic components, influencing disease phenotype and severity^[27]. This highlights the need for a more comprehensive evaluation that integrates not only metabolic but also genetic and molecular factors to better identify risk in these patients.

A small proportion of lean NAFLD patients may not meet MASLD criteria and could be classified as cases of "cryptogenic steatosis". It is important to note that steatosis and insulin resistance can exist in the absence of any of the five defined cardiometabolic risk factors, especially in younger individuals, and hepatic insulin resistance may precede the development of more overt cardiometabolic abnormalities^[28]. Additionally, hereditary metabolic diseases can contribute to hepatic steatosis in some cases^[29]. Therefore, these patients may require advanced genetic and metabolic testing to identify possible underlying etiologies.

CHALLENGES IN ASSESSING ALCOHOL INTAKE AND ITS IMPACT ON STEATOTIC LIVER DISEASE

As previously mentioned, MAFLD and MASLD differ in the amount of alcohol permitted in their definitions. While the diagnosis of MAFLD can be made regardless of alcohol consumption, MASLD excludes patients who consume more than 20 g of alcohol per day for women or 30 g per day for men. For individuals whose alcohol intake exceeds these limits, but who also present metabolic dysfunction, the

diagnosis of MetALD or Alcohol-Related Liver Disease (ALD) may apply^[7].

Recognizing alcohol as a contributing factor to disease progression represents one of the most novel and valuable aspects of the new nomenclature, with the introduction of the term MetALD. This term refers specifically to patients with metabolic dysfunction who consume alcohol in amounts greater than those allowed for MASLD but lower than the thresholds required for ALD. This includes alcohol consumption between 140-350 g per week for women and 210-420 g per week for men^[7]. This new entity will significantly enhance our understanding of the joint impact of alcohol and MetS on liver disease progression. However, several challenges remain, including the underreporting of alcohol consumption and irregular drinking patterns, which complicate the precise quantification of intake^[30]. To address these challenges, tools such as the "Alcohol Use Index" (ANI score) and specific direct biomarkers of alcohol consumption may improve detection in patients who report minimal or no alcohol intake. Ongoing research into more specific and reliable biomarkers is expected to further enhance the identification and management of patients with MetALD in the near future.

Another controversial aspect of this classification is considering alcohol consumption of up to 30 g per day in men and 20 g per day in women as "moderate"^[31]. Recent studies have shown that even lower alcohol intake than these thresholds is common in patients with MASLD and is associated with a significant risk of hepatic fibrosis and progression to MASH. The risk of fibrosis and complications increases with the amount of alcohol consumed weekly and the number of cardiometabolic risk factors present^[32]. Beyond the synergistic effect between alcohol consumption and MetS^[33,34], individual susceptibility to progress into advanced fibrosis is influenced by a combination of behavioral, environmental, genetic, and epigenetic factors^[35], which are not considered in the new definition. Additionally, the lack of clear evidence on the impact of previous alcohol consumption in individuals who have since ceased drinking generates uncertainty in clinical interpretation^[36]. It is crucial to discuss whether a history of alcohol use might still affect the prognosis and pathogenesis of steatotic liver diseases.

Although supported by a broad majority in a Delphi process, this change is not without controversy. Broader consensus and further studies will be required to fine-tune the alcohol consumption thresholds that maximize diagnostic accuracy and clinical management efficacy.

THE CARDIOVASCULAR ADVANTAGE OF MASLD

MASLD not only enhances the identification of patients at risk of liver disease progression but also improves cardiovascular risk stratification. The cardiometabolic factors that define MASLD play a central role in the pathogenesis of CVD, making MASLD a more precise diagnostic tool for identifying patients at risk of major cardiovascular events, such as myocardial infarction, stroke, or peripheral artery disease^[37]. In contrast to NAFLD, which may include individuals without metabolic dysfunction and, therefore, with lower cardiovascular risk^[38], MASLD ensures greater precision in identifying those at high risk for cardiovascular events.

This strong association between MASLD and CVD is largely explained by its underlying pathophysiological mechanisms, which involve hepatic lipotoxicity, oxidative stress, and systemic inflammation. The accumulation of intrahepatic lipids, particularly free fatty acids and toxic lipid intermediates such as ceramides, leads to mitochondrial dysfunction, increased reactive oxygen species (ROS) production, and endoplasmic reticulum stress, all of which promote hepatocyte injury and inflammation^[39]. Additionally, metabolic dysregulation in MASLD is closely linked to adipose tissue dysfunction, where excess visceral fat promotes hypoxia and oxidative stress, resulting in the release of proinflammatory cytokines (TNF- α , IL-6)

and chemokines^[40]. These cytokines not only contribute to hepatic insulin resistance and fibrosis but also act systemically, exacerbating low-grade chronic inflammation, which is a key driver of atherosclerosis and cardiovascular complications.

Several studies showed that MASLD is associated with a higher prevalence of arterial stiffness and atherosclerotic plaques^[41,42]. Arterial stiffness is an early marker of vascular damage, while the presence of atherosclerotic plaques is a strong predictor of adverse cardiovascular events. The elevated prevalence of these markers in MASLD patients, particularly those with advanced liver fibrosis, highlights an elevated cardiovascular risk profile. Regarding MAFLD, a recent comparative analysis evaluating the relationship between MASLD and MAFLD with coronary artery calcification (CAC) highlighted a distinct association between MASLD and the severity of CAC, with MASLD being uniquely linked to the advanced stage of CAC^[43]. However, another recent study found that MAFLD predicted CVD risk more effectively than MASLD^[44]. The authors reported that the proportion of patients with high CVD risk was higher in the MAFLD-only group (51.1%) compared to the MASLD-only group (35.0%). This finding aligns with expectations, as patients in the MASLD-only group typically have normal weight and no more than one feature of MetS. This reinforces the concept that, in cardiovascular medicine, the overall risk is largely determined by the number of concurrent metabolic abnormalities in each patient^[45]. Additionally, including patients with MetALD alongside those with MASLD is likely to identify a population with a similar CVD risk profile. In fact, while current data are preliminary, a recent meta-analysis of five studies involving nearly 10 million individuals found that MetALD was associated with worse outcomes compared to MASLD, primarily due to an increase in CVD- and cancer-related mortality^[46].

In conclusion, MASLD offers a significant advantage in cardiovascular risk management by more accurately linking metabolic dysfunction with increased cardiovascular risk. This improvement facilitates better stratification and clinical management of these patients, optimizing outcomes and reducing the burden of cardiovascular complications.

SIMPLIFYING DIAGNOSIS AND EXPANDING PRIMARY CARE INVOLVEMENT

The new classification of MASLD has proven to be an invaluable tool for the early identification of at-risk patients, particularly in primary care settings. This nomenclature facilitates the implementation of early intervention strategies, aiding in the prevention of liver fibrosis progression and the effective management of cardiovascular risk, offering a significant advantage over previous classifications^[47].

One of MASLD's key strengths is its simplicity and practicality in daily clinical practice. Unlike the MAFLD classification, which includes the less commonly used metabolic markers, such as the HOMA-IR index and high-sensitivity C-reactive protein (hs-CRP), MASLD relies on more accessible and routinely assessed criteria^[48]. The metabolic markers required by MAFLD, while valuable in specific contexts, are not widely employed in many clinical settings due to limited availability, making their broad application challenging. MASLD, in contrast, employs commonly used clinical parameters such as central obesity, hypertension, and blood glucose levels, factors that are readily available and integral to routine patient management in primary care. This approach streamlines the identification of at-risk patients of liver disease progression, enabling earlier intervention and improved management of liver disease from the primary care level.

The introduction of MASLD in place of NAFLD marks a paradigm shift in the approach to diagnosing this liver disease. One of the most significant changes is the reduced reliance on liver biopsy as a diagnostic standard, reflecting a transition toward more accessible, non-invasive diagnostic methods based on clinical criteria. This shift not only addresses the need for greater diagnostic accessibility but also aligns with

evidence highlighting the risks and limitations of liver biopsy. Non-invasive techniques, such as transient elastography and serum biomarkers for liver fibrosis, have greatly improved the early detection and monitoring of MASLD^[49]. These methods provide a safe and effective assessment of liver fibrosis without the risks inherent to biopsy. While liver biopsy continues to offer detailed insights into steatosis, inflammation, and fibrosis, the adoption of non-invasive techniques has lowered the barriers to diagnosing and monitoring MASLD, enhancing clinical workflow and patient care. However, histological assessment remains relevant in certain contexts, particularly for evaluating disease activity. The NAFLD Activity Score (NAS), originally developed for NAFLD, remains a widely used tool for grading steatosis, inflammation, and ballooning degeneration. Given that the histopathological features of MASLD largely overlap with those of NAFLD, the NAS score continues to be applicable.

The removal of liver biopsy as a diagnostic requirement for MASLD also has significant implications for primary care. It enables general practitioners to take a more active role in diagnosing and managing these patients, enabling evaluations and follow-ups without the immediate need for specialist referral^[50]. This shift enhances diagnostic accessibility but underscores the importance of proper training for primary care physicians in using and interpreting non-invasive diagnostic tools to ensure optimal patient management. The adoption of non-invasive tests not only reduces the risks associated with liver biopsy but also decreases the costs related to invasive procedures. However, it is crucial to ensure the standardized implementation of these methods in clinical practice^[51]. Clear guidelines and protocols must be established to guarantee consistent evaluation and minimize the risk of diagnostic errors.

Despite the advances in non-invasive methods, there remains a subset of patients for whom liver biopsy is still necessary. This is particularly true in cases where non-invasive test results are inconclusive or when dual or concomitant liver pathologies are suspected. In such scenarios, biopsy remains an indispensable tool for achieving a definitive diagnosis and guiding appropriate treatment.

THE IMPACT OF MASLD ON RESEARCH

The global adoption of the term MASLD has significant implications for research and treatment development. While this transition may initially raise concerns about the validity of previous studies on NAFLD and NASH, existing evidence indicates a high concordance between these classifications and MASLD, reducing the risk of invalidating earlier findings^[52-54]. Nevertheless, further studies are needed to validate biomarkers specifically within the MASLD framework, presenting opportunities to refine diagnostic and predictive tools.

The shift from NAFLD/NASH to MASLD/MASH introduces challenges in extrapolating data from prior research to the new nomenclature. Although MASLD's diagnostic criteria are simpler and more clinically applicable, patient selection for clinical trials may face complications, potentially affecting the generalizability of previous results. However, the updated criteria are expected to enhance patient stratification and foster greater homogeneity in future studies, ultimately benefiting clinical trials and drug development.

The unified MASLD criteria represent a major advancement for global research. By using simpler and more inclusive clinical parameters, MASLD facilitates data comparison across studies and populations, overcoming the limitations of the more complex NAFLD and NASH definitions. This standardization enhances collaboration between research centers, promotes multicenter clinical trials, and accelerates the development of new treatments^[55,56]. Moreover, MASLD's simplicity enables large-scale data collection, leading to more robust and reliable results. MASLD thus represents a critical step forward in aligning

research and therapeutic innovation in steatotic liver diseases.

The integration of MASLD and MetALD into international coding systems, such as the International Classification of Diseases (ICD), is crucial for ensuring consistency in epidemiological data collection, facilitating the comparison of clinical studies, and advancing long-term research efforts. A recent global expert consensus statement recommends that the currently available ICD codes for NAFLD and NASH can be used to define MASLD and MASH, respectively^[57]. However, the precise definition of MetALD remains a topic of ongoing debate, particularly concerning the alcohol consumption thresholds that will be used to distinguish MASLD and MetALD^[58]. This issue is especially significant in light of recent studies indicating that even small amounts of alcohol can negatively impact liver disease progression^[32]. Establishing clear and standardized alcohol consumption thresholds is essential for accurately classifying patients with MetALD. The differentiation between MASLD, MetALD, and ALD is not only critical for optimizing treatment and prevention strategies but also for ensuring that historical data can be effectively leveraged in future research. Such precision in classification will enhance the utility of these coding systems and promote consistency across clinical and research settings.

THE SOCIAL IMPACT OF MASLD TERMINOLOGY

The transition from the term NAFLD to more inclusive nomenclatures like MASLD not only represents an effort to more accurately characterize the disease but also seeks to reduce the associated stigma and better reflect the spectrum of individuals affected, regardless of their body weight or alcohol consumption habits^[59]. Individuals with NAFLD, particularly those with obesity, may face stigmatization not only due to their weight but also because of associated comorbidities, including the liver disease itself^[60-63]. Historically, terms like "fatty" and "non-alcoholic" have been identified as potentially stigmatizing^[63], and this perception may significantly impact health-related quality of life (HRQL)^[62,64].

Therefore, removing the term "fatty" from the MASLD nomenclature could reduce associated stigma, particularly for patients who experience feelings of guilt or negative self-perception related to their obesity or liver disease. While the term "fatty" has traditionally been associated with negative connotations, recent surveys indicate that many patients do not perceive it as highly stigmatizing^[65,66]. Nevertheless, patients who do perceive stigma due to their diagnosis or body weight tend to experience a greater psychological burden, negatively affecting their self-perception and overall well-being^[62]. The shift to MASLD nomenclature could alleviate part of this stigma by removing the term "non-alcoholic", which may reduce feelings of guilt and improve patients' emotional well-being. However, it is important to note that the stigma associated with obesity is likely to persist, as it remains a central factor in the pathogenesis of this disease^[67].

Additionally, the terminology used to describe liver diseases may vary in its cultural interpretation, influencing how these conditions are perceived and managed in different regions^[68]. Adopting a more inclusive term like MASLD could help reduce these disparities, promoting greater acceptance of the disease and facilitating its management in diverse cultural and socioeconomic contexts. However, it is crucial to ensure that diagnostic criteria are applied uniformly and do not present significant variations across populations.

Another key aspect that the new MASLD nomenclature must address is the integration of social determinants of health into its classification and management. Factors such as socioeconomic disparities, inequalities in access to healthy foods, and variability in lifestyle options play a crucial role in the progression of MASLD^[69,70]. Incorporating these determinants into clinical guidelines is essential to ensure that management strategies are accessible and applicable in all settings, particularly for vulnerable

populations or those with limited access to medical resources^[71].

To achieve a significant impact on equity in the management of MASLD, it is imperative to integrate this nomenclature and its implications into public health policies. The lack of integration into global strategies could limit the effectiveness of interventions aimed at preventing and treating these diseases^[72]. Raising global awareness of MASLD and its health impact through educational campaigns and outreach efforts is necessary, with a particular focus on addressing healthcare inequalities and prevention policies.

KEY FACTORS IN IMPLEMENTING MASLD

The transition to the MASLD nomenclature has not been universally accepted, and its abrupt adoption could lead to confusion in both research and clinical practice. Although MASLD is supported by major international scientific societies^[7], there are still divided opinions regarding its universal application^[73,74]. Some authors have suggested that the primary objective of the consensus process behind the MASLD definition may have been to resist the original proposal to adopt MAFLD^[75,76]. In fact, the Asian Pacific Association for the Study of the Liver (APASL) continues to support the MAFLD definition, and a recent global multi-society endorsement has advocated for MAFLD as an appropriate term^[77]. However, these controversies are of greater academic interest than clinical relevance and should not detract from the primary goals of raising awareness about this liver disease, ensuring its early identification, and promoting a multidisciplinary approach to its management.

This ongoing debate underscores the need for flexibility in adopting MASLD, particularly in clinical and research contexts where the term "steatotic" may not be fully understood or accepted. A flexible approach is essential to ensure that the adoption of MASLD does not cause unnecessary confusion, especially in settings where cultural and linguistic barriers may influence the understanding of the terminology.

One of the primary challenges in adopting MASLD lies in its implementation across different countries, where resistance to changes in established terminology may occur. This highlights the importance of educating both healthcare professionals and patients about the benefits of the new nomenclature and its clinical implications. Additionally, the transition must be carefully managed to prevent misunderstandings, particularly in coding systems such as the ICD, which will require timely updates to reflect these changes.

To facilitate this transition, a structured approach is required across multiple levels of healthcare. Table 1 summarizes key strategies to ensure a smooth implementation of MASLD, focusing on education, standardization, public health efforts, and adaptation for resource-limited settings.

ADAPTING SLD FOR THE FUTURE

The Delphi consensus statement recognized that MASLD and SLD terminology could dynamically evolve with emerging knowledge about the condition^[7]. It is well established that MASLD exhibits significant heterogeneity, with its clinical presentation and course influenced by various factors, including cardiovascular, metabolic, and neoplastic complications^[78]. Consequently, this condition does not follow a singular pathogenic, evolutionary, or therapeutic trajectory. For this reason, we believe it would be advantageous to reconsider the "D" in the nomenclature as "Disorder".

This change acknowledges the clinical reality that the term "Disease" may oversimplify the diverse manifestations and etiologies that define these conditions. "Disorder" better reflects the complexity of steatotic liver disease, which lacks a single etiology or clinical presentation [Figure 2]. By adopting

Implementation area	Recommended steps	
Education and training	-Implement targeted educational programs for healthcare professionals (primary care, hepatology, endocrinology) to ensure they understand MASLD's diagnostic criteria and implications -Develop online resources, workshops, and continuing medical education activities to facilitate knowledge dissemination	
Standardization of diagnostic protocols	-Establish clear clinical guidelines to ensure uniform MASLD diagnosis -Prioritize the use of non-invasive tools (FIB-4, transient elastography), making MASLD evaluation more accessible	
Integration into International and National Coding Systems	-Advocate for ICD-11 updates to incorporate MASLD -Provide guidance for policymakers and healthcare administrators on updating electronic records while ensuring data continuity	
Public health initiatives and awareness campaigns	reness -Launch awareness campaigns to educate patients and reduce confusion about the terminology change -Develop patient-friendly materials to improve engagement and promote early screening	
Adaptation for resource-limited settings	-Focus on cost-effective screening approaches, prioritizing metabolic risk assessment in primary care -Leverage telemedicine to expand access to education and diagnostic support	

MASLD: Metabolic dysfunction-associated steatotic liver disease; ICD: International Classification of Diseases.



Figure 2. The complexity of MASLD, highlighting its diverse etiological factors, complex pathophysiological mechanisms, heterogeneous clinical presentations, and variable disease progression, which may lead to both hepatic and extrahepatic complications. MASLD: Metabolic dysfunction-associated steatotic liver disease.

"Disorders", the nomenclature would expand to include all conditions associated with hepatic steatosis, ranging from genetic to metabolic, and environmental factors. This adaptation would more accurately reflect the multifaceted nature of steatotic liver disease, thereby promoting advances in hepatology research and education. It could also facilitate the development of more specific clinical guidelines tailored to the diverse presentations and needs of these patients.

We do not propose an immediate change to the nomenclature, as additional modifications may impede the widespread awareness required for this condition. However, when the necessary debate for the introduction of this new nomenclature in the ICD takes place, involving national and regional regulatory bodies and the World Health Organization (which maintains and updates the ICD system), why not adapt it with a minimal change, from "Disease" to "Disorder"? This simple proposal would make the term SLD truly serve as an umbrella for all disorders characterized by hepatic steatosis.

CONCLUSION

The transition from NAFLD to MASLD represents a significant advancement in the nomenclature of steatotic liver diseases, introducing a more inclusive and clinically relevant framework. By emphasizing metabolic dysfunction as a central criterion, MASLD captures the complex interplay of metabolic, cardiovascular, and environmental factors in disease progression, enhancing risk stratification and enabling more personalized patient management. This shift aligns clinical practice with the evolving knowledge of steatotic liver diseases, offering opportunities to improve patient outcomes and foster global research collaboration. However, the adoption of MASLD is not without challenges. To better understand the impact of this transition, Table 2 summarizes the key advantages and challenges associated with the different nomenclatures. This comparison highlights the strengths and limitations of each nomenclature, providing insight into the rationale for the recent shift to MASLD and the challenges that remain for its full implementation. Cultural and linguistic differences, as well as the need to educate healthcare professionals and patients, have emerged as significant hurdles. Additionally, integrating MASLD into international coding systems such as the ICD requires careful planning to address ongoing debates, such as defining alcohol consumption thresholds for differentiating MetALD and MASLD. These challenges underline the importance of continued efforts to refine and standardize the application of the new nomenclature.

MASLD marks a critical step forward in advancing the diagnosis and management of steatotic liver disease. Overcoming current obstacles through global cooperation, education, and research will be essential to fully realize its potential in improving clinical care and public health worldwide.

	NAFLD	MAFLD	MASLD
Definition	-Presence of hepatic steatosis in the absence of significant alcohol consumption or other causes of liver fat accumulation	-Hepatic steatosis with at least one metabolic risk factor (obesity, T2DM, or two metabolic risk factors)	-Hepatic steatosis plus at least one cardiometabolic risk factor, excluding cases with significant alcohol intake (> 20 g/day for women, > 30 g/day for men)
Advantages	-Extensive history in research and clinical practice -Familiarity in clinical practice -Established coding system -Strong foundation for clinical trials -Minimal need for changes in guidelines and protocols	-Explicitly incorporates metabolic dysfunction -Improves patient identification by focusing on metabolic dysfunction -Eliminates the "non-alcoholic" label -MAFLD allows for the coexistence of other liver diseases -Better alignment with cardiovascular risk stratification	-Global consensus and standardization -Explicit recognition of metabolic dysfunction -More inclusive and clinically relevant -Greater alignment with cardiometabolic risk -Less stigmatizing terminology -Encourages early detection and intervention -Promotes research and therapeutic advancements
Challenges	-Lack of explicit metabolic criteria -Exclusion of patients with coexisting liver diseases -Stigmatizing terminology -Negative definition by exclusion -Limited reflection of cardiovascular risk -Lack of comprehensive genetic evaluation	-Lack of global consensus -Incompatibility with existing coding systems -Use of less commonly measured metabolic markers (such as HOMA- IR and high-sensitivity CRP) -Potential for misclassification -Challenges in patient and provider education -Limited impact on reducing stigma -Lack of comprehensive genetic evaluation	-Transition and implementation difficulties -Potential disruption of historical data -Need for education and awareness -Integration into international coding systems -Linguistic and cultural adaptation -Lack of comprehensive genetic evaluation

Table 2. Summary of the key advantages and challenges of NAFLD, MAFLD, and MASLD nomenclatures

NAFLD: Non-alcoholic fatty liver disease; MAFLD: metabolic-associated fatty liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease; T2DM: type 2 diabetes mellitus; HOMA-IR: homeostasis model assessment of insulin resistance; CRP: C-reactive protein.

DECLARATIONS

Authors' contributions

Conducted the initial literature search and drafted the preliminary version of the manuscript: Iruzubieta P, Crespo J

Contributed to the final writing, critical revision, and refinement of the manuscript: Jimenez-Gonzalez C, Cabezas J

All authors read and approved the final version of the manuscript.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

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