Why MASLD Lags Behind MAFLD: A Critical Analysis of Diagnostic Criteria Evolution in Metabolic Dysfunction-Associated Liver Diseases

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Emerging in the 1800s under the label “fat in the liver” and later gaining prominence in the 1980s as non-alcoholic fatty liver disease (NAFLD), the disease predominantly attributed to metabolic dysfunction presents a formidable health issue marked by substantial morbidity and mortality. It was 2020 when a change of one letter “NAFLD” to metabolic dysfunction-associated fatty liver disease “MAFLD” linked with the change in the definition and diagnostic criteria began a new controversy around the globe. Metabolic dysfunction-associated fatty liver disease (MAFLD) criteria represent a substantial departure from previous diagnostic measures of NAFLD, and provide the first set of positive criteria for diagnosis of the disease in adults and children that emphasise the key attribute of metabolic dysfunction in the pathogenesis, and acknowledges that the disease is a continuum across the life span. In 2023, an adapted version of the diagnostic criteria of MAFLD was proposed to define a slightly modified term; metabolic dysfunction-associated steatotic liver disease (MASLD). The MASLD criteria did not provide any conceptual advantage, and emerging evidence suggests that it actually performs worse than the MAFLD criteria. This raises the intriguing question of why MASLD was unable to take advantage of being second? In this review, we will explore the possible reasons for this unique case and highlight the current evidence supporting the use of MAFLD instead of MASLD in defining metabolic dysfunction-associated fatty liver diseases.

Keywords: Diagnostic Errors • Fatty Liver • Metabolic Diseases • Terminology

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Introduction

Emerging in the 1800s under the label “fat in the liver” and later gaining prominence in the 1980s as non-alcoholic fatty liver disease (NAFLD), the disease predominantly attributed to metabolic dysfunction presents a formidable health issue marked by substantial morbidity and mortality. Despite its extensive historical recognition and terminology refinement, the field continues to confront significant challenges in redefining the disease, diagnostic criteria, and enhancing therapeutic strategies [1].

In 2020, a new term “metabolic dysfunction-associated fatty liver disease” (MAFLD) was proposed, changing one letter from “NAFLD” to “MAFLD”, which was linked with the change in the definition and diagnostic criteria and began a new controversy around the globe. Looking at what additional importance the MAFLD criteria hold, it is clear that while the 2020 MAFLD criteria signify a significant shift from the previous diagnostic approach of NAFLD, they also provide the first set of positive criteria for diagnosis of the disease in adults and children that emphasize the key role of metabolic dysfunction in the pathogenesis, and acknowledge that the disease occurs as a continuum across the life span [2-5]. Additionally, MAFLD has practical ramifications for treatment strategies and patient interactions [5]. Over the past few years “MAFLD” has become a popular term in research and practice and is widely endorsed [6], but it has also been resisted in some parts of the world, provoking division and controversy.

In 2023, an adapted version of the diagnostic criteria of MAFLD was proposed to define a slightly modified term – metabolic dysfunction-associated steatotic liver disease (MASLD) [7]. Scientific knowledge is the most solid and robust kind of knowledge that humans have because of the evolving character inherent in its own processes. Evolution of the performance of new versions of diagnostic criteria is typical in science, as subsequent criteria give the opportunity to capitalize on previous efforts. To our surprise, the MASLD criteria did not provide any conceptual advance; rather, the emerging evidence suggests that it performs worse than the MAFLD criteria. This raises the intriguing question of why MASLD did not benefit from being second.

Inability to achieve the target with a proposed definition or diagnostic criteria is a normal and critical part of the scientific process; however, admitting this inability remains large by 2 factors: over-detection and over-definition of disease. Over-diagnosis is a major issue in modern healthcare that can lead to harmful and costly outcomes. It can be caused by 2 factors: over-detection and over-definition of disease. Over-detection happens when medical professionals detect a disease too early or too often, leading to unnecessary procedures and treatments. Over-definition occurs when medical professionals redefine a disease to include more patients, leading to a broader diagnosis and more interventions. These issues can lead to an increase in healthcare costs, psychological stress for patients, and ethical concerns.

Figure 1. Limitations of the Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) definition.

The MAFLD criteria have made it easier to diagnose the disease in everyday clinical practice. This simplification lowers the barriers to reaching an early and accurate diagnosis of MAFLD while maintaining the same level of sensitivity and specificity. This means that the criteria can be used more confidently in clinical practice, leading to earlier diagnosis and better treatment decisions.

The effect of applying the MASLD to diagnose the disease has been investigated in several recent studies and serious concerns have been raised about lack of specificity, over-diagnosis, and lower performance in detecting hepatic and extra-hepatic diseases. We also offer our views on the best path forward.

MAFLD vs MASLD Evidence

The MAFLD criteria have made it easier to diagnose the disease in everyday clinical practice. This simplification lowers the barriers to reaching an early and accurate diagnosis of MAFLD while maintaining the same level of sensitivity and specificity. This means that the criteria can be used more confidently in clinical practice, leading to earlier diagnosis and better treatment decisions.

Over-Diagnosis

Over-diagnosis is a major issue in modern healthcare that can lead to harmful and costly outcomes. It can be caused by 2 factors: over-detection and over-definition of disease. Over-detection happens when medical professionals detect abnormalities that will not cause any harm to the patient or progress too slowly to cause symptoms or harm during the patient’s lifetime [12]. Over-definition is caused by lowering the
threshold for a risk factor or expanding disease definitions to include patients with mild symptoms. These patients are usually at lower risk than those diagnosed under earlier definitions. Over-diagnosis can lead to over-treatment, which offers little to no benefit and can have significant physical, psychological, social, and financial consequences (Figure 2). For instance, there is an increase in early forms of cancer or smaller abdominal aortic aneurysm diagnosis, without a reduction in advanced disease or death, which can be a sign of over-diagnosis through over-detection [13,14]. In regions with limited resources and high prevalence of fatty liver disease, it may be difficult to apply the MASLD criteria.

Lower Performance

The effectiveness of MASLD was compared to the existing criteria for MAFLD. Recent data strongly indicate that MAFLD is highly effective in identifying subjects at high risk for metabolic dysfunction, as well as hepatic and extra-hepatic outcomes [15-21]. This change in name and criteria to MASLD causes confusion without increasing utility.

Low Performance in Pediatric Populations

The definition of MASLD has been called into question, particularly in the context of children and adolescents [17]. However, the MAFLD definition provides a comprehensive framework for understanding pediatric fatty liver disease. The definition includes 3 types: Type 1, which is fatty liver associated with a systemic disorder; Type 2, which is MAFLD; and Type 3, which is fatty liver without an underlying defect (but one that may become apparent over time).

This classification is of utmost importance to prevent misclassification and to avoid unnecessary testing, which can cause physical, psychological, and economic harm to patients. In contrast, the MASLD concept does not account for these aspects. Moreover, the MAFLD definition includes age-specific criteria for children and adolescents, whereas the MASLD criteria do not. Therefore, it is essential to consider changes in body composition that contribute to the differential risk of metabolic dysfunction.

Furthermore, some of the obesity and metabolic factor cut-offs used in MASLD are factually incorrect, such as body mass index (BMI). These inaccuracies make it unsurprising that a recent study demonstrated the superiority of the MAFLD definition over the MASLD definition in pediatrics [17].

Inability to Consider a Global Perspective

For any new proposal to be adopted naturally without forcing it requires taking into consideration a global perspective. The MASLD definition falls short in this aspect. Staring from proposing changing MAFLD to MASLD, discarding the fact that for all non-Latin languages that are spoken by more than 5 billion people globally, there is no distinction between the 2 words. Another striking example is the proposed MetALD term to describe the coexistence of MASLD with excessive alcohol...
consumption above an arbitrary threshold. Therefore, apart from being flawed concept, it again reflects the self-centric approach of the MASLD proposal that ignores the global status. What about the coexistence of MASLD with other diseases such as hepatitis C and B, or autoimmune hepatitis, which it is more prevalent in other parts of the world [22]? Unfortunately, the MASLD definition did not take this into consideration.

Potential Causes of MASLD’s Inability to Better Define Fatty Liver Attributed to Metabolic Dysfunction

These findings raise the intriguing question of why the MASLD definition did not benefit from being proposed after MAFLD and could not provide any conceptual advance. Below, we analyze some of the potential key reasons for this.

Goal Missing

The main objective of the consensus process proposed in the MASLD definition was to resist the original proposal to adopt MAFLD, as pointed out by multiple recent articles [23,24]. This likely deviated the effort from providing a real conceptual advance.

Planning Problems

The MASLD concept is the birth of a consensus process that is formulated as a questionnaire of personal views rather than evidence. However, expert opinion is not a surrogate for evidence-based data. Science is not about consensus; it is about the truth [25]. An example of applying the Delphi-method to a transplant-related question incorrectly recommended high-dose chemotherapy and an auto-transplant for some women with high-risk breast cancer [26]. Subsequent randomized trials showed this approach was ineffective [27]. Consistently, in a recent analysis of over 100 consensus statements, the rigor of statement development was found to be one-third lower than that of evidence-based recommendations [28].

Execution Issues

The consensus of expert opinion is heavily influenced by the selection of participating experts and their perspectives, as well as the way the questionnaire is formulated. Unfortunately, the MASLD process has been criticized for selecting experts who favor one viewpoint over another, leading to a poor representation of most real-world physicians and active academics. Additionally, the questionnaire used in this process was not validated or transparent. However, without quality evidence, expert opinions may have little impact.

Conclusions

The above evidence suggests that, in retrospect, the process needed to “restate its objectives, seek out its rationale.” Going forward, there is an urgent need for a true consensus process that allows for the development of evidence-based guideline statements. This process should involve a systematic review of the evidence, with equal contribution from all regions of the world, patients, research, and clinical panelists. This is the only way to ensure that the outcomes will be widely adopted. It is important to note that identifying an objective-level consensus is only possible when gathering quantifiable data. In some qualitative Delphi studies, the judgement on consensus may be rather subjective on the part of the researcher, potentially leading to bias. We should learn from the problems associated with the concept of MASLD and use evidence to guide us. There is an urgent need for an appropriate consensus process.

Declaration of Figures’ Authenticity

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