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# The Paradigm Shift from NAFLD to MASLD: Clinical Implications and Future Directions

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**Abstract**

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease globally. Recently, its nomenclature has evolved to better reflect its metabolic underpinnings, transitioning first to metabolic dysfunction-associated fatty liver disease (MAFLD) and now to metabolic dysfunction-associated steatitis liver disease (MASLD). This shift from an exclusionary diagnosis to a positive, criterion-based definition represents a fundamental paradigm shift. This mini-review examines the rationale for this terminological evolution and discusses its significant implications for clinical practice, patient stratification, and future research. Additionally, it explores emerging evidence on MASLD-specific diagnostic tools, the interplay between MASLD and cardiovascular disease, and the potential for personalized treatment approaches.

**Keywords:** Non-alcoholic fatty liver disease; Metabolic dysregulated steatitis liver disease; MASLD; Diagnosis; Cardiovascular risk; Personalized medicine

**Abbreviations:** NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; HCC: Hepatocellular Carcinoma; MAFLD: Metabolic Dysfunction-Associated Fatty Liver Disease; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease

## Introduction

Non-alcoholic fatty liver disease (NAFLD) was historically defined by the presence of hepatic steatosis (>5%) in the absence of significant alcohol intake and after excluding other liver diseases. Its spectrum ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The term "non-alcoholic" has been criticized for its negative definition, which fails to capture the central role of metabolic dysfunction. Consequently, an international panel proposed renaming NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) in 2020, based on positive diagnostic criteria Eslam et al. [1]. A subsequent Delphi consensus (2023) further refined the terminology to metabolic dysfunction-associated steatotic liver disease (MASLD) to harmonize global nomenclature Rinella et al. [2]. This review explores the clinical significance of this redefinition and expands on emerging topics in the field.

## Rationale for the Change: From NAFLD to MASLD

### The NAFLD diagnosis had several key limitations

**a) Heterogeneity:** It encompassed a patho physiologically diverse patient population, hindering the development of targeted therapies.

**b) Stigmatization:** The term "non-alcoholic" can be perceived as attributing blame to patients, whereas "metabolic dysfunction-associated" is a more neutral and descriptive etiologic label Yki-Järvinen et al. [3].

**c) Inadequate Emphasis on Comorbidity:** The old framework did not explicitly require the presence of cardiometabolic risk factors, which are the primary drivers of disease progression.

The MASLD diagnosis requires hepatic steatosis plus one of the following five cardiometabolic risk factors: increased waist circumference, elevated blood pressure, triglycerides, or fasting glucose, or low HDL cholesterol. This positive-case definition better identifies individuals with a shared metabolic pathophysiology.

## Clinical Implications of the MASLD Criteria

### The new criteria have broad repercussions

**a. Epidemiology:** MASLD identifies a larger and more metabolically high-risk population compared to NAFLD. Some lean individuals with steatosis may be excluded, while those with mild alcohol consumption and metabolic dysfunction are now included, altering prevalence estimates and natural history studies Lin et al. [4].

**b. Risk Stratification:** The MASLD criteria inherently link liver disease to metabolic health, facilitating better identification of patients at high risk for NASH and advanced fibrosis, particularly those with T2DM Ng et al. [5].

**c. Management:** The paradigm mandates a holistic, patient-centered approach. Lifestyle intervention remains first-line, but there is a strengthened imperative to manage comorbid obesity, diabetes, and dyslipidemia. Pharmacotherapies with metabolic benefits, such as GLP-1 receptor agonists and SGLT2 inhibitors, are now central to the treatment armamentarium [6].

**d. Care Models:** Effective management necessitates deeper collaboration between hepatologists, endocrinologists, and primary care physicians to address both hepatic and extra-hepatic (e.g., cardiovascular, renal) complications.

## MASLD-Specific Diagnostic Tools and Biomarkers

The redefinition of MASLD has accelerated the search for more accurate non-invasive diagnostic tools. Traditional biomarkers like ALT and AST lack specificity for steatohepatitis or fibrosis. Emerging blood-based biomarkers, such as the Fibrosis-4 (FIB-4) index, Enhanced Liver Fibrosis (ELF) score, and PRO-C3, are gaining traction for risk stratification [7]. Additionally, imaging modalities like vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE) provide a reliable assessment of liver stiffness and steatosis. The MASLD criteria also encourage the integration of metabolic parameters into diagnostic algorithms, enabling a more comprehensive evaluation of liver disease within the context of systemic metabolic health.

## MASLD and Cardiovascular Disease: A Bidirectional Relationship

Cardiovascular disease (CVD) remains the leading cause of mortality in MASLD patients. The MASLD framework underscores the importance of assessing cardiovascular risk in all affected individuals. Evidence suggests that MASLD exacerbates insulin resistance, dyslipidemia, and systemic inflammation, all of which contribute to atherosclerosis and cardiovascular events [8]. Conversely, cardiovascular risk factors such as hypertension and diabetes accelerate liver disease progression. This bidirectional relationship necessitates integrated care models where cardiologists and hepatologists collaborate to manage both liver and cardiovascular health simultaneously.

## Current Challenges and Future Perspectives

### Despite its advantages, the MASLD framework presents challenges

I. Global Adoption: Widespread implementation of the new nomenclature across clinical guidelines, research protocols, and regulatory agencies is still ongoing Rinella et al. [2].

II. Non-Invasive Diagnostics: There is a pressing need for validated biomarkers and imaging tools to diagnose steatohepatitis and stage fibrosis non-invasively [7].

III. Drug Development: While several promising agents (e.g., resmetirom) are in advanced trials, no drug is yet approved for NASH/MASH. Future trials must target specific MASLD sub phenotypes defined by metabolic features [9].

IV. Public Health Policy: The redefinition underscores the need to integrate MASLD screening and prevention into broader strategies aimed at curbing the epidemics of obesity and diabetes [10].

## Conclusion

The transition from NAFLD to MASLD is a substantive advance that reframes the disease around its core metabolic etiology. This positive diagnostic framework promises to improve risk stratification, promote a more holistic and multidisciplinary approach to management, and stimulate research into targeted therapies. Overcoming challenges related to adoption, biomarker development, and drug approval will be crucial to translating this paradigm shift into improved patient outcomes. Future efforts should focus on validating MASLD-specific biomarkers, integrating multi-omics data for sub phenotyping, and developing personalized treatment strategies that address both hepatic and extra-hepatic manifestations.

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