ASIDE Gastroenterology

Review Article

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Multisystemic Narrative Review of Cardiovascular and Oncological Implications

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ARTICLE INFO

Article history:
Received 21 Dec. 2025
Received in revised form 3 Feb. 2026
Accepted 6 Feb. 2026
Published 26 Feb. 2026

Keywords:
MASLD
Cardiovascular disease
Hepatocellular carcinoma
FIB-4 index
Metabolic syndrome
Steatotic liver
Systemic inflammation
Resmetirom

ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has surpassed viral hepatitis as the primary driver of chronic liver disease globally. While traditionally viewed through the lens of hepatic progression, its clinical trajectory is increasingly defined by extrahepatic complications.
Objective: This narrative review evaluates MASLD as a manifestation of systemic metabolic failure, specifically analyzing its role in accelerating cardiovascular dysfunction and extrahepatic carcinogenesis—the two principal causes of mortality in this population.
Methods: A comprehensive literature synthesis was conducted from 2020 to December 2025, using databases including PubMed, Scopus, and the Egyptian Knowledge Bank (EKB) to identify high-impact studies and international guidelines.
Results: The pathophysiology involves a metabolic cascade whereby hepatic lipid accumulation and insulin resistance trigger systemic inflammatory signaling. Disrupted lipid handling and genetic determinants promote pro-atherogenic and pro-oncogenic environments. The review advocates a transition to risk-stratified approaches using noninvasive biomarkers, such as the FIB-4 index.
Conclusion: Addressing the bidirectional relationship between hepatic steatosis and systemic comorbidities requires a multidisciplinary therapeutic strategy. This framework provides a basis for early intervention to reduce the burden of cardiovascular events and malignancy among patients with MASLD.

1. Introduction

The specific diagnostic criteria and alcohol consumption thresholds for MASLD, alongside other subcategories of steatotic liver disease, are summarized in **(Table 1)** [1, 2].

In 2023, a global Delphi consensus reclassified non-alcoholic fatty liver disease (NAFLD) as metabolic dysfunction-associated steatotic liver disease (MASLD) to better reflect the underlying pathophysiological drivers of the condition. The transition from NAFLD to MASLD reflects a clinical effort to remove the stigma associated with the former terminology and to more accurately emphasize the central role of metabolic dysfunction in disease progression.

Globally, MASLD affects more than one-third of the adult population [2]. The diagnostic framework requires the identification of hepatic steatosis in combination with at least one of five cardiometabolic risk factors (CMRF): overweight/obesity, hyperglycemia, hypertension, hypertriglyceridemia, or low HDL-cholesterol. This requirement distinguishes MASLD from other forms of steatotic liver disease, emphasizing the systemic nature of the condition [2, 3].

Although hepatic steatosis itself is often clinically silent, MASLD is associated with an increased risk of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality. Paradoxically, however, cardiovascular disease remains the leading cause of death in affected individuals. This mortality is driven primarily by the systemic metabolic milieu rather than by hepatic steatosis in isolation [2]. This review aims to outline the current understanding of MASLD pathophysiology, evaluate its relationship with cardiometabolic risk, examine the mechanisms linking MASLD to cardiovascular and oncological outcomes, and summarize contemporary diagnostic and therapeutic strategies [1, 2].

1.1. Nomenclature and Definitions

To ensure clinical clarity, this review adopts the 2023 Multi-Society Consensus nomenclature: MASLD (Metabolic Dysfunction-Associated Steatotic Liver Disease): Defined by the presence of hepatic steatosis plus at least one of five cardiometabolic risk factors (CMRF), with no other discernible cause and minimal alcohol consumption (≤ 20g/day for females; ≤ 30g/day for males) [1, 3].

MetALD (Metabolic Dysfunction and Alcohol-Associated Liver Disease): Describes individuals who meet MASLD criteria but consume greater amounts of alcohol (20-50g/day for females; 30-60 g/day for males) [3, 4].

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Citation: Mohamed MMA, Taha MMMI, Ibrahim MMMR. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Multisystemic Narrative Review of Cardiovascular and Oncological Implications. ASIDE GI. 2026;2(2):15-25, doi:10.71079/ASIDE.GI.022626448

Table 1: Evolution of SLD Nomenclature and Diagnostic Criteria

Category	Definition	Alcohol Consumption Thresholds	Cardiometabolic Criteria
MASLD	Hepatic steatosis + ≥ 1 CMRF [1, 3]	≤ 20g/day (F); ≤ 30g/day (M) [3]	Required [3]
MetALD	Hepatic steatosis + ≥ 1 CMRF + Alcohol [1, 3]	20 – 50g/day (F); 30 – 60g/day (M) [3]	Required [3]
ALD	Steatosis driven by alcohol [1]	Not Required [3]	Not Required [3]
Cryptogenic SLD	Steatosis with no clear etiology [3]	Minimal to none [3]	None [3]

Acronyms: ALD, alcohol-associated liver disease; CMRF, cardiometabolic risk factors; F, female; M, male; MASLD, metabolic dysfunction–associated steatotic liver disease; MetALD, metabolic dysfunction–associated with increased alcohol intake; SLD, steatotic liver disease.
Notes: Alcohol consumption thresholds are defined as daily intake [1, 3]. Cardiometabolic criteria require the presence of at least one of five specific risk factors (e.g., BMI, fasting glucose, blood pressure, or lipid levels) [3].
Source: Adapted from Adinolfi et al., 2026. [1], based on the 2023 multi-society consensus [3].

MASH (Metabolic Dysfunction-Associated Steatohepatitis): The inflammatory stage of MASLD, characterized by hepatocyte ballooning and inflammation, with or without fibrosis [3, 5].

1.2. Literature Search Strategy

To ensure a comprehensive synthesis of the current evidence regarding MASLD and its multisystemic implications, a literature search was conducted in PubMed, Scopus, Elsevier (ScienceDirect), and the Egyptian Knowledge Bank (EKB). A primary search was conducted for 2020 – 2025, with the inclusion of landmark historical studies where appropriate for the pathophysiological context. Keywords and MeSH terms included "MASLD," "steatotic liver disease," "cardiovascular risk," and "extrahepatic malignancy." Selection was prioritized for high-impact longitudinal studies, meta-analyses, and international society guidelines to ensure the clinical relevance and quality of the narrative synthesis.

2. Epidemiology

2.1. Global Prevalence and Trends

MASLD is currently the most prevalent chronic liver disease worldwide. Recent epidemiological data indicate that global adult prevalence has reached approximately 38% [6], a significant increase from the 25% reported in the previous decade. This trend parallels the rising global incidence of obesity and type 2 diabetes mellitus (T2DM). Longitudinal projections suggest that if current metabolic trends persist, global prevalence may exceed 50% by 2040 [7, 8].

2.2. Regional Heterogeneity

The distribution of MASLD exhibits significant geographic variation, influenced by a combination of genetic predisposition, dietary patterns, and socioeconomic factors: North America: Prevalence is estimated to be between 35% and 40%, attributed to high caloric intake and sedentary lifestyles [6–8].

2.2.1. Asia

Historically lower, prevalence is increasing rapidly, currently estimated at 30 – 34%. This region is notable for the "Lean MASLD" phenotype, occurring in individuals with a normal Body Mass Index (BMI) [7, 9].

2.2.2. Europe

Estimates range from 25% to 30%. While the overall prevalence is lower than in North America, the aging demographic contributes to a higher burden of advanced hepatic fibrosis [6, 8].

2.2.3. MENA and Egypt:

The Middle East and North Africa (MENA) region reports the highest global prevalence, ranging from 36% to 42%. In Egypt, prevalence exceeds 40%, correlating with high regional rates of insulin resistance [6].

2.3. Prevalence in High-Risk Cohorts

The burden of MASLD is disproportionately concentrated within populations characterized by pre-existing metabolic dysfunction: Type 2 Diabetes: 65 – 70% of patients with T2DM are affected by MASLD, with a heightened risk for progression to advanced fibrosis [7].

2.3.1. Severe Obesity

In individuals with a BMI > 35 kg/m^2, prevalence exceeds 90% [7].

2.3.2. Type 1 Diabetes

Recent evidence suggests that MASLD affects approximately 22% of adults with Type 1 Diabetes, highlighting the impact of exogenous insulin-related weight gain and metabolic health in this cohort [4].

3. Pathophysiology

MASLD pathophysiology is characterized by the disruption of hepatic lipid homeostasis, where imbalances in lipid uptake, de novo lipogenesis, β-oxidation, and export lead to hepatocellular triglyceride accumulation. Lipotoxic intermediates induce oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction, activating proinflammatory and profibrotic signaling pathways. Persistent hepatocyte injury promotes hepatic stellate cell activation and extracellular matrix deposition, driving fibrosis and progressive liver dysfunction. The disease reflects systemic metabolic dysregulation, with contributions from adipose tissue, gut-derived factors, and insulin resistance amplifying hepatic pathology **(Figure 1)** [10].

3.1. Hepatic Lipid Metabolism

The disease initiates when at least one cardiometabolic criterion – such as obesity or T2DM – is present, shifting the liver into a state of chronic lipid surplus [3]. Hepatic steatosis develops when the delivery of free fatty acids (FFAs) and internal lipid synthesis surpasses the liver's capacity for oxidation or export via very-low-density lipoproteins (VLDL) [11, 12].

The FFAs supplying this overload originate from adipose-tissue lipolysis (≈ 59%), followed by hepatic DNL (≈ 26%), and dietary intake (≈ 15%) [13, 14]. In the setting of insulin resistance, the liver paradoxically increases DNL while failing to suppress the flux of fatty acids mobilized from peripheral fat stores [14, 15]. This

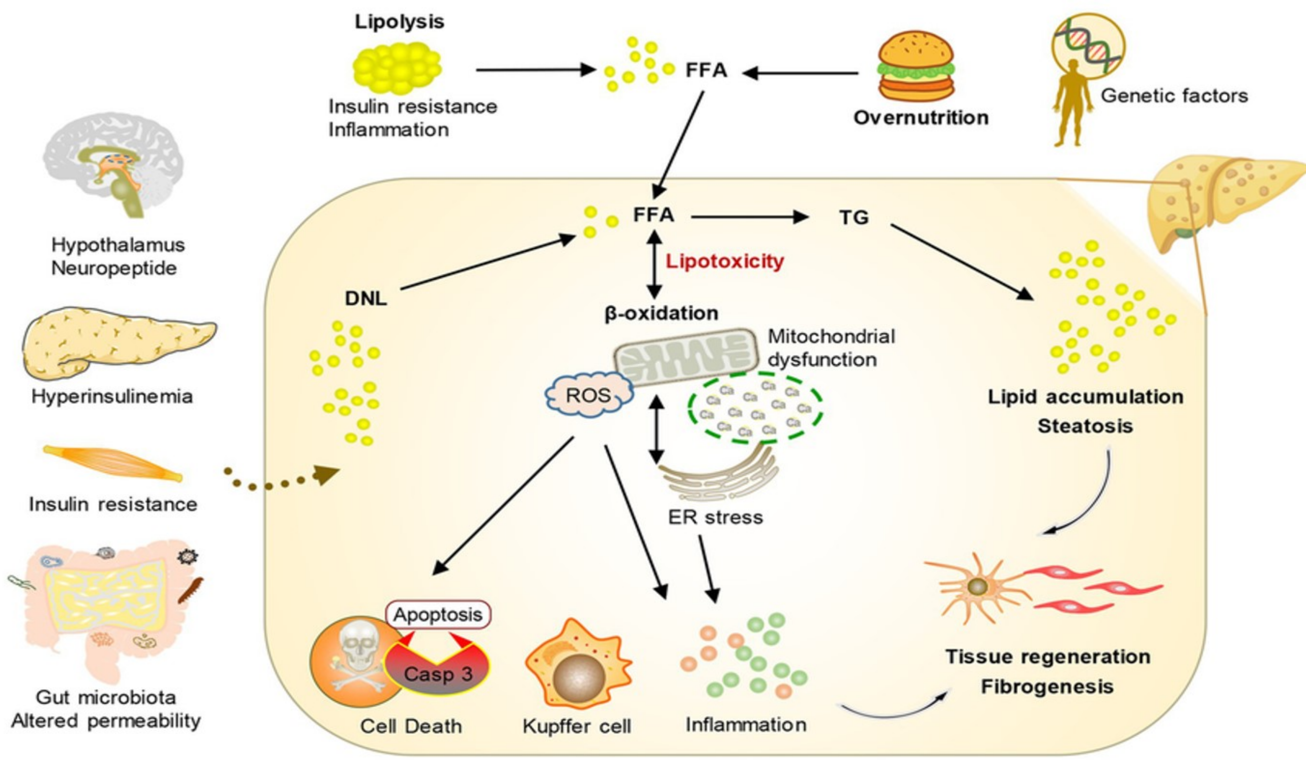

Figure 1: Conceptual diagram of the pathogenesis of MASLD. This diagram illustrates the complex interplay between overnutrition, insulin resistance, and mitochondrial dysfunction leading to hepatic fibrogenesis. Key drivers include the gut-liver axis (altered permeability), hypothalamic neuropeptide signaling, and lipotoxicity driven by free fatty acid (FFA) accumulation.
Acronyms: Casp 3, caspase-3; DNL, de novo lipogenesis; ER, endoplasmic reticulum; FFA, free fatty acids; ROS, reactive oxygen species; TG, triglycerides.
Mechanistic Note: Programmed cell death (apoptosis) and Kupffer cell activation serve as critical mediators of the transition from simple steatosis to inflammation and fibrogenesis.
Source: Adapted from Rao et al., 2023 [10].

imbalance generates toxic lipid intermediates that trigger oxidative stress and organelle dysfunction, marking the transition from simple storage to active hepatic injury [16, 17].

3.2. Insulin Resistance

This lipid buildup directly drives insulin resistance through a specific biochemical cycle [18]. As lipids like diacylglycerol (DAG) accumulate in hepatocytes, they activate PKCε, which impairs insulin receptor signaling and prevents the liver from regulating glucose production effectively [19–21].

Simultaneously, inflammatory signaling pathways – activated by excess saturated fatty acids – further disrupt insulin signaling through the phosphorylation of insulin receptor substrate-1 (IRS-1) [22, 23]. This creates a self-sustaining loop: insulin resistance promotes further lipid accumulation, which in turn exacerbates systemic inflammatory signaling and progressive metabolic failure [22, 24].

3.3. Inflammation and Cellular Injury

Metabolic stress triggers the innate immune system, characterizing the advanced stages of disease progression. Lipotoxicity-induced stress causes mitochondrial dysfunction and the leakage of reactive oxygen species (ROS), resulting in cellular damage and the release of damage-associated molecular patterns (DAMPs) [5, 25].

These DAMPs function as a critical bridge in the "multiple hit” cascade **(Figure 2)**, linking metabolic lipotoxicity to innate immune activation [5, 25, 26]. They activate Kupffer cells (resident macrophages) and trigger the NLRP3 inflammasome [5, 27]. This immune response produces pro-inflammatory cytokines (IL-1β and IL-18) and promotes distinct modes of cell death **(Table 2)** [27, 28]. This chronic cycle of hepatocyte death and inflammatory activation eventually triggers hepatic stellate cells to deposit collagen, driving the progression from simple steatosis to irreversible fibrosis [27].

4. Risk Factors and Associated Conditions

MASLD arises from a complex synergy of metabolic, genetic, and lifestyle factors. Insulin resistance (IR) serves as the central engine, stimulating hepatic de novo lipogenesis and increasing the flux of free fatty acids from dysfunctional adipose tissue [13, 14]. Visceral adiposity exacerbates this state by releasing pro-inflammatory cytokines that impair systemic lipid buffering [12]. Collectively, T2DM, dyslipidemia, and hypertension cluster to amplify the risk of advanced hepatic fibrosis and adverse cardiovascular outcomes [5, 6].

4.1. Major Risk Factors

4.1.1. Type 2 Diabetes (T2DM)

T2DM independently doubles the risk of hepatocellular carcinoma and liver-related mortality, significantly accelerating the transition from simple steatosis to advanced fibrosis [30–32].

4.1.2. Obesity and Dyslipidemia

Excess adiposity and atherogenic dyslipidemia increase the hepatic fatty acid load, triggering chronic oxidative stress [5, 6, 33].

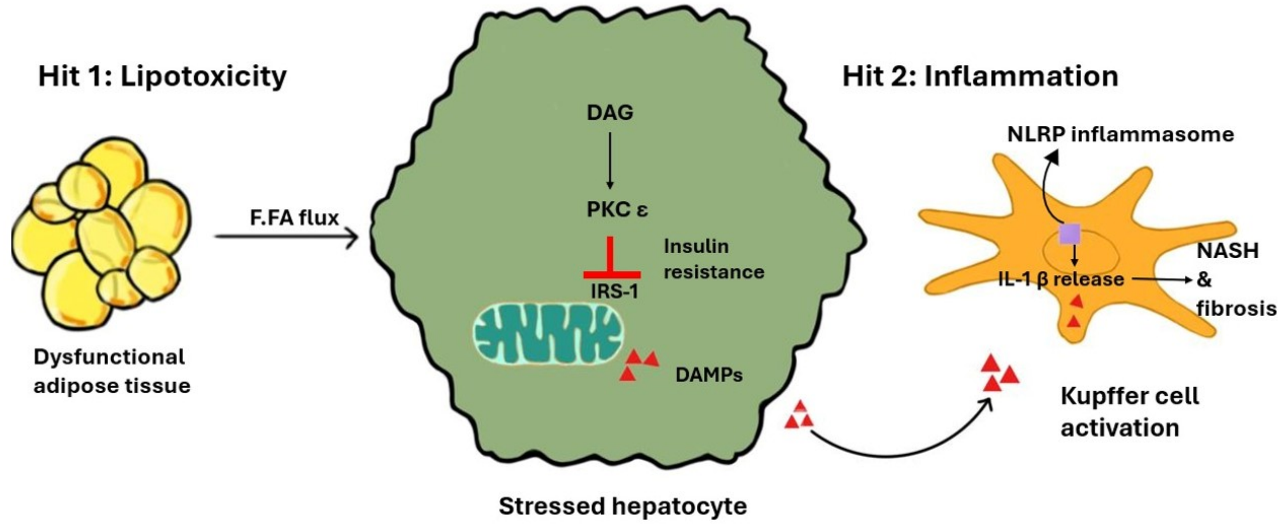

Figure 2: Multiple-Hit Pathogenesis. This illustration highlights how metabolic lipotoxicity (Hit 1) leads to innate immune activation, hepatocyte stress, and subsequent inflammation (Hit 2).
Acronyms: DAG, diacylglycerol; DAMPs, damage-associated molecular patterns; IRS-1, insulin receptor substrate 1; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; PKCε, protein kinase C epsilon.
Nomenclature: NASH is used here as the histological equivalent of MASH.
Source: Illustration by Takwa Mohamed Hathout. Data adapted from Rinella et al. (2023) [3].

Table 2: Modes of Hepatocyte Death in MASLD

Mode of Death	Primary Mechanism	Role in MASLD Progression	Key References
Apoptosis	Caspase-dependent programmed cell death.	Initial response to lipotoxic stress; markers (e.g., CK-18) correlate with disease activity.	[5, 28]
Pyroptosis	NLRP3 inflammasome-mediated; involves Gasdermin D.	Highly inflammatory; promotes rapid cytokine release (IL-1β) and stellate cell activation.	[27]
Ferroptosis	Iron-dependent lipid peroxidation.	Driven by ROS and impaired antioxidant capacity; critical in the transition to MASH.	[28]
Necroptosis	RIPK1/RIPK3-mediated regulated necrosis.	Promotes massive DAMP release and severe sterile inflammation.	[5]

Hepatocyte death is the primary driver of progression from simple steatosis to MASH (Metabolic Dysfunction-Associated Steatohepatitis), the inflammatory stage of metabolic liver disease [24, 29]. Each pathway contributes differently to liver injury: Apoptosis is a programmed cell death mediated by caspases; Pyroptosis is a highly inflammatory response involving the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome [25, 27]; Ferroptosis is an iron-dependent form of death caused by ROS (Reactive Oxygen Species) [26, 28]; and Necroptosis is a regulated necrosis involving RIPK1/RIPK3 that releases DAMPs (Damage-Associated Molecular Patterns) to trigger sterile inflammation [5].
Acronyms: CK-18, cytokeratin-18; MASH, metabolic dysfunction–associated steatohepatitis; RIPK, receptor-interacting protein kinase; ROS, reactive oxygen species.
Notes: This table summarizes the biochemical markers and triggers for various cell death pathways identified in steatotic hepatocytes.
Source: Synthesized from current literature (2020 – 2025).

4.1.3. Genetic Predisposition
Variants such as PNPLA3 (impaired lipid droplet hydrolysis) and TM6SF2 (disrupted VLDL export) significantly influence disease susceptibility and the velocity of fibrosis progression [13, 27, 34].

4.2. Associated Conditions
4.2.1. Dietary Factors
High-calorie diets rich in fructose and saturated fats are potent stimulators of fat synthesis. Fructose is particularly damaging as it bypasses normal metabolic checks to drive triglyceride production [13, 14, 16].

4.2.2. Gut-Liver Axis (SIBO)
Small-intestinal bacterial overgrowth promotes increased intestinal permeability. This facilitates the translocation of lipopolysaccharides (LPS) into the portal circulation, activating Toll-like receptors and exacerbating hepatocellular injury [15, 25].

4.2.3. Obstructive Sleep Apnea
Chronic intermittent hypoxia associated with OSA induces systemic oxidative stress and sympathetic overactivity, which intensify hepatic inflammatory signaling [13, 19, 25].

4.2.4. Endocrine and Hormonal Factors:
Hypothyroidism: Low thyroid hormones decrease the liver's ability to oxidize fat and export VLDL [6, 33].

Hyperuricemia: High uric acid promotes insulin resistance and stresses liver mitochondria [22, 24].

Polycystic Ovary Syndrome (PCOS): Hyperinsulinemia in PCOS promotes direct hepatic fat production [13, 19].

4.3. The "Lean MASLD" Phenotype

"Lean MASLD" occurs in individuals with a normal Body Mass Index (BMI 18.5 – 24.9 kg/m^2) who exhibit at least one cardiometabolic risk factor [2, 4].

Adipose Tissue Dysfunction: Pathogenesis is frequently driven by the limited expansion capacity of peripheral adipose tissue. When subcutaneous storage thresholds are exceeded, lipids are diverted to ectopic sites, resulting in significant hepatic accumulation [12, 13].

4.3.1. Genetic Influence

This phenotype is strongly associated with the PNPLA3 variant, explaining the presence of significant hepatic fat despite lower systemic adiposity [4, 13].

4.4. Metabolic Drivers of Malignancy

The pro-inflammatory and hyperinsulinemic state of MASLD creates a systemic environment conducive to carcinogenesis.

4.5. Established Associations:

4.5.1. Hepatocellular Carcinoma (HCC)

MASLD is a primary driver of primary liver malignancy. Distinctively, HCC in the context of MASLD frequently occurs in the absence of established cirrhosis, suggesting that lipotoxicity-induced DNA damage and chronic oxidative stress can initiate malignant transformation independently of advanced fibrosis [35–38].

4.5.2. Colorectal Cancer (CRC)

MASLD is associated with a 60% increase in CRC risk [39]. Pathophysiology likely involves the disruption of the gut-liver axis and the systemic elevation of insulin-like growth factor 1 (IGF-1), which promotes colonic epithelial proliferation and inhibits apoptosis [40].

4.6. Emerging Clinical Associations

4.6.1. Breast and Gynecological Malignancies:

MASLD is linked to a 20 – 40% higher incidence of breast cancer, particularly in postmenopausal women. The proposed mechanism involves the aromatization of androgens in adipose tissue and the resulting estrogenic stimulation of breast and uterine tissues [39, 41].

4.6.2. Thyroid and Pulmonary Malignancies

Recent data indicate an association between MASLD and more aggressive phenotypes of thyroid cancer. Furthermore, systemic inflammatory cytokines – specifically IL-6 and TNF-α – may synergize with environmental factors to increase lung cancer risk, though obesity remains a significant confounding variable in these cohorts [41].

5. Extrahepatic Manifestations

MASLD is a systemic multisystem disorder; its presence serves as a sentinel marker for clinical deterioration in other organ systems. While metabolic factors drive the initial liver injury, the resulting chronic systemic inflammation and shared pro-fibrotic pathways lead to significant complications outside the liver [34, 35, 42].

5.1. Cardiovascular Manifestations

Cardiovascular disease (CVD) is the leading cause of death in MASLD patients, often exceeding liver-related mortality. The liver's inflammatory state directly contributes to cardiac structural and electrical remodeling:

5.1.1. Heart Failure

MASLD independently raises the risk of incident heart failure, particularly Heart Failure with preserved Ejection Fraction (HFpEF), by approximately 50% [42, 43].

5.1.2. Structural Remodeling:

Patients frequently exhibit subclinical changes, including left ventricular hypertrophy and impaired diastolic filling, even in the early stages of liver fat accumulation [42].

5.1.3. Arrhythmias:

There is a robust association with Atrial Fibrillation, likely driven by pro-inflammatory cytokines originating from both the liver and epicardial adipose tissue [42–44].

5.2. Extrahepatic Malignancies

The pro-oncogenic environment of MASLD – characterized by hyperinsulinemia and chronic low-grade inflammation – extends beyond the liver to several extrahepatic sites [35, 36, 45]:

5.2.1. Colorectal Cancer (CRC):

MASLD is associated with a 60% higher risk of CRC and a significant increase in colorectal adenomas. This association is strongest in patients with advanced fibrosis, necessitating vigilant screening [39, 40, 46].

5.2.2. Gastrointestinal and Other Cancers:

Increased risks are noted for esophageal and gastric cancers [41]. Emerging evidence also suggests a higher incidence of breast and thyroid malignancies, often presenting with more aggressive clinical features [35, 41].

5.3. Renal and Endocrine Manifestations

The crosstalk between the liver and other metabolic organs creates a cycle of systemic decline:

5.3.1. Chronic Kidney Disease (CKD):

MASLD is an independent risk factor for CKD. Pro-inflammatory and pro-fibrotic signals (such as TGF-β) released by the liver promote glomerular damage and decline renal function [34, 43].

5.3.2. Metabolic Feedback Loops:

While insulin resistance drives MASLD, the presence of hepatic steatosis conversely makes glycemic control more difficult in patients with T2DM, increasing the likelihood of diabetic microvascular complications [29, 47].

6. Diagnosis and Risk Stratification

Diagnosis requires the identification of hepatic steatosis via imaging or histology, the presence of ≥ 1 cardiometabolic risk factor (CMRF), and the systematic exclusion of competing etiologies [2, 3].

6.1. Laboratory Assessment and Differential Diagnosis

Transaminases (ALT/AST) are poor exclusionary tests; a normal ALT does not exclude advanced fibrosis. Clinical suspicion should remain high in patients with T2DM or obesity regardless of enzyme levels [4, 33].

Table 3: Performance, thresholds, and limitations of non-invasive modalities for hepatic steatosis and fibrosis assessment

Modality	Performance and Thresholds	Limitations
Ultrasonography	High specificity (98%) for moderate/severe steatosis.	Sensitivity drops if fat content < 20% or BMI > 40 kg/m^2 [6].
FIB-4 Index	• < 1.3 (Low Risk): NPV > 90% for F3/F4 [4, 33]. • 1.3–2.67: Indeterminate [1, 3]. • > 2.67 (High Risk): Refer to hepatology [1, 4].	Accuracy decreases in patients < 35 or > 65 years old [4].
• VCTE (FibroScan)	• < 8 kPa (Low Risk): Rules out advanced fibrosis [33]. • 8-12 kPa: Indeterminate [3, 48]. • > 12–15 kPa (High Risk): Highly suggestive of F3/F4 [4, 33].	Reduced reliability in severe obesity (BMI > 35) without XL probes [33].
• MRI-PDFF	Gold standard for fat quantification (> 5% threshold) [1, 48].	High cost; limited availability for routine monitoring [6].

The diagnostic utility of these modalities depends on their ability to accurately stage fibrosis, as increasing stiffness values correlate with higher risks of liver-related complications. FIB-4 (Fibrosis-4 Index) serves as a high-sensitivity triage tool to rule out advanced disease in primary care [4, 33], whereas VCTE (Vibration-Controlled Transient Elastography) and MRI-PDFF (Proton Density Fat Fraction) provide quantitative assessments of liver stiffness and hepatic fat content, respectively [1, 33, 48]. While NITs (Non-Invasive Tests) offer a safe alternative to biopsy, their accuracy is influenced by the NPV (Negative Predictive Value), which remains the primary metric for excluding advanced fibrosis in at-risk populations [3, 48].
Acronyms: FIB-4, Fibrosis-4 Index; MRI-PDFF, Magnetic Resonance Imaging Proton Density Fat Fraction; NPV, Negative Predictive Value; VCTE, Vibration-Controlled Transient Elastography; LSM, Liver Stiffness Measurement; CAP, Controlled Attenuation Parameter; ELF, Enhanced Liver Fibrosis.
Notes: Performance ranges are based on evidence-based thresholds; operator dependence and patient obesity are noted as primary limitations [33].
Source: Compiled from AASLD and EASL clinical practice guidelines.

6.1.1. *Transaminase Thresholds:*
While lab ranges vary, an ALT > 30 U/L is increasingly recognized as the threshold for further evaluation in adults [4].

6.1.2. *Differential Diagnosis:*
To confirm MASLD, the following must be excluded:

- Metabolic Dysfunction-Associated and Increased Alcohol Intake (MetALD): A distinct category for patients meeting MASLD criteria but with higher alcohol intake (20-50g/day for females; 30-60g/day for males) [3].
- Alcohol-associated Liver Disease (ALD): Defined by chronic intake exceeding 50g/day in females or 60g/day in males. Clinical suspicion is supported by AUDIT/CAGE scores, and an AST:ALT ratio > 2; suggests alcohol use or advanced cirrhosis [3, 33].
- Viral Hepatitis: HBsAg and anti-HCV screening [6].
- Hereditary Hemochromatosis: Transferrin saturation > 45% and elevated ferritin [33].
- Drug-Induced Steatosis: Review use of amiodarone, methotrexate, or chronic corticosteroid use [13, 16].
- Rare Etiologies: Wilson disease or Autoimmune Hepatitis should be considered in younger cohorts or those with atypical biochemical profiles (e.g., low-titer autoantibodies and high IgG) [33].

6.2. Imaging and Non-Invasive Tests
The diagnostic goal is to identify Advanced Fibrosis (F ≥ 3), as this is the primary predictor of liver-related mortality.

While imaging is central to diagnosis, clinicians must recognize its technical boundaries. Conventional ultrasound has a sensitivity of only 60 – 90% for detecting steatosis, often failing when the fat fraction is below 20% [6, 24]. Furthermore, the accuracy of VCTE is highly operator-dependent and significantly limited by the 'skin-to-capsule' distance in patients with morbid obesity, which can lead to falsely elevated LSM readings [33]. Despite standardized cutoffs, diagnostic uncertainty persists within 'indeterminate' ranges (e.g., FIB-4 1.3 – 2.67 or VCTE 8 – 12 kPa), where guidelines vary on whether to prioritize immediate secondary testing or longitudinal monitoring [1, 3, 48] **(Table 3)**.

6.3. Clinical Referral and Management Pathway
Following the AASLD/EASL 2023 consensus, the clinical pathway follows a tiered approach **(Figure 3)**:

6.3.1. *Tier 1 (Low Risk)*
Calculate FIB-4 for all at-risk patients , including those with T2DM or obesity. If FIB-4 < 1.3, advanced fibrosis is ruled out with high negative predictive value; these patients should repeat non-invasive tests in 2 – 3 years and focus on cardiovascular disease (CVD) risk reduction. [3, 4, 33].

6.3.2. *Tier 2 (Indeterminate Risk)*
For FIB-4 1.3 – 2.67, perform a secondary non-invasive test such as VCTE or the Enhanced Liver Fibrosis (ELF) test. If results remain indeterminate, patients should be reassessed annually or referred based on clinical suspicion [3, 4].

6.3.3. *Tier 3 (Specialist Care)*
Patients with FIB-4 > 2.67 or LSM ≥ 12 kPa are considered high-risk and require hepatology referral. Confirmed advanced fibrosis (F3/F4) necessitates the initiation of MASH management, biannual HCC screening, and formal variceal risk assessment [3, 4, 33].

6.4. The Role of Liver Biopsy
Biopsy is no longer first-line but remains indicated when:

- NITs are indeterminate or discordant with clinical presentation.
- Alternative or co-existing liver diseases (e.g., Autoimmune Hepatitis) are suspected.
- Participation in clinical trials for MASH-targeted therapies [13].

6.5. Management of Advanced Fibrosis (F3) and Cirrhosis (F4)
Patients identified with advanced fibrosis (F3) or with compensated advanced chronic liver disease (cACLD) (F4) require a structured

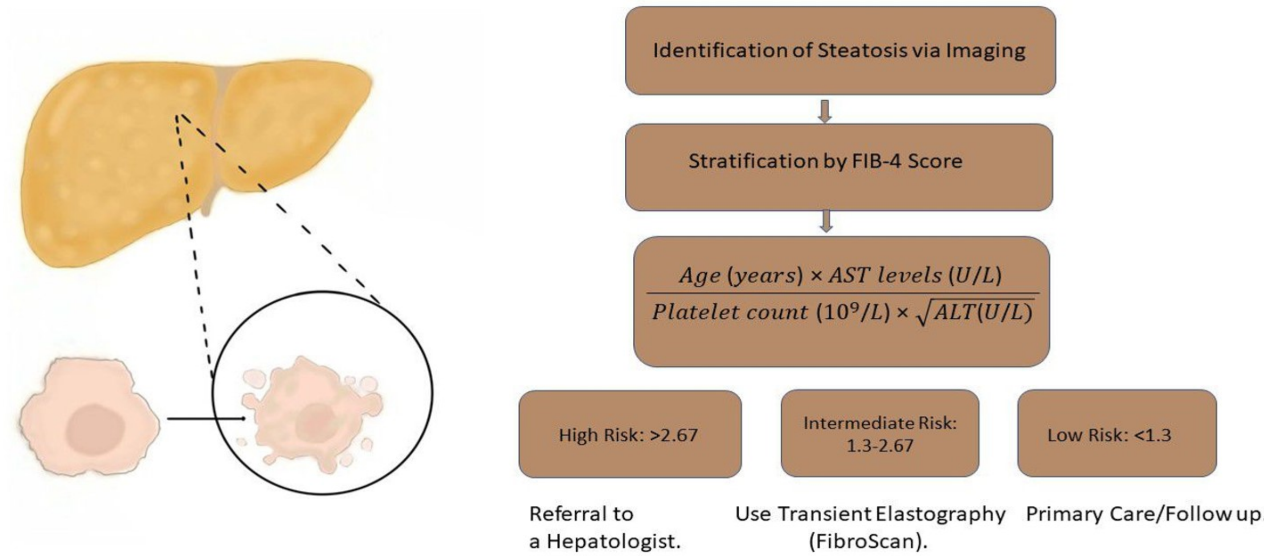

Figure 3: FIB-4 Risk Stratification Flowchart. A tiered clinical approach for primary care triage. Patients with a FIB-4 score < 1.3 (or < 2.0 for those aged > 65) are considered low risk [3, 33]. Those in the Indeterminate Risk category (FIB-4 1.3 – 2.67) require secondary testing [4]. Finally, patients with a score > 2.67 – or high-risk patients – require specialized hepatology referral [3].
Acronyms: ALT: alanine aminotransferase; AST: aspartate aminotransferase.
Source: Illustration by Gana Mohamed and Takwa Hathout. Adapted from AASLD/EASL 2023 guidelines.

care bundle to mitigate the risks of decompensation and mortality. This multifaceted approach includes:

6.5.1. HCC Surveillance
Mandatory biannual abdominal ultrasound (± alpha-fetoprotein) for all patients with cirrhosis (F4) and considered for those with F3 based on individual risk [30, 35, 38].

6.5.2. Portal Hypertension
According to the Baveno VII criteria, screening endoscopy for esophageal varices can be safely avoided in patients with a liver stiffness measurement < 20 kPa AND a platelet count > 150,000/L. Conversely, those not meeting these criteria require endoscopic screening [3, 4, 48].

6.5.3. Transplant Referral
Explicit referral for liver transplantation assessment is triggered by a MELD-Na score ≥ 15, the first occurrence of hepatic decompensation (ascites, encephalopathy, or jaundice), or HCC within Milan criteria [4, 48] Decompensation Monitoring: Regular clinical surveillance for complications such as ascites, hepatic encephalopathy, and variceal hemorrhage is essential for patients cACLD [3, 48].

6.5.4. Vaccination
Routine immunization against hepatitis A (HAV), hepatitis B (HBV), and pneumococcus, as well as annual influenza and COVID-19 boosters, is necessary to prevent acute-on-chronic liver failure [1, 4, 48].

6.5.5. Nutritional Support
Targeted intervention for sarcopenia involves a protein-rich diet (1.2 – 1.5 g/kg/day) and Vitamin D optimization to preserve bone mineral density [48].

6.5.6. Metabolic & Bone Health
Regular screening for osteoporosis/osteopenia and Vitamin D deficiency [1, 48].

6.6. Management and Treatment
The primary objectives in MASLD management are to achieve histological resolution of MASH and to cease or reverse fibrosis, thereby modifying the risk of cirrhosis, hepatocellular carcinoma, and liver-related mortality [1, 4, 24, 48]. Concurrent management of the cardiometabolic cluster – obesity, T2DM, dyslipidemia, and hypertension – is mandatory to reduce extrahepatic risks, including chronic kidney disease and heart failure [2, 29, 47].

6.7. Lifestyle and Behavioral Interventions
Lifestyle modification remains the non-pharmacological basis of therapy. Weight loss exhibits a dose-response relationship with histological improvement:

- >5% Weight Loss: Sufficient to reduce hepatic steatosis.
- 7–10% Weight Loss: Associated with significant MASH resolution (64% vs. 10% in those losing <5%) and improvement in inflammation [48].
- >10% Weight Loss: Offers the highest rates of benefit, with 90% MASH resolution and 45% fibrosis regression at 52 weeks [48].

6.8. Dietary and Physical Activity Protocols
6.8.1. Dietary Patterns
Beyond general weight loss, the Mediterranean Diet is uniquely effective due to its high concentration of monounsaturated fatty acids and antioxidants. These components directly influence hepatic de novo lipogenesis and systemic inflammation, leading to superior metabolic outcomes compared to standard low-fat diets [4, 48, 49].

Table 4: Comparing Pharmacotherapy for MASH

Agent	Class / Primary Indication	Key Histological Outcome
Resmetirom	THR-β Agonist; MASH with F2 – F3 fibrosis [1, 9].	25% Fibrosis improvement; 30% MASH resolution [9, 48].
Semaglutide	GLP-1 RA; Obesity and T2DM [48, 50].	
Tirzepatide	GIP/GLP-1 RA; Obesity and T2DM [9, 50].	62.8% MASH resolution; signal for fibrosis improvement [50].
Pioglitazone	PPAR-γ Agonist; T2DM (off-label for MASH) [4, 48].	Improved steatohepatitis; risk of weight gain [4, 48].

Therapeutic selection is increasingly guided by the patient's clinical phenotype. Resmetirom is prioritized for patients requiring direct fibrosis regression in non-cirrhotic (F2 – F3) stages, based on the MAESTRO-NASH trial outcomes [9]. Incretin mimetics (GLP-1 and dual GIP/GLP-1 RAs) are favored for those with high cardiometabolic risk, obesity, or Type 2 Diabetes Mellitus [48, 50]. Outcome data represent results from primary clinical endpoints: MASH resolution (defined as the disappearance of ballooning and inflammation) and/or fibrosis improvement [9, 50]. Non-invasive monitoring via MRI-PDFF and LSM provides surrogate assessments of treatment response [33, 42].
Acronyms: GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; MASH, metabolic dysfunction – associated steatohepatitis; RAs, receptor agonists; THR-β, thyroid hormone receptor-beta.
Source: Adapted from Rinella et al. (2023) [3], Eddowes et al. (2019) [33], and primary clinical trial data [9, 50].

6.8.2. Exercise
Guidelines recommend 150 minutes of moderate-intensity aerobic activity or 75 – 150 minutes of vigorous activity weekly. Exercise improves hepatic insulin sensitivity and reduces liver fat even in the absence of significant weight change [1, 4, 48].

6.9. Pharmacotherapy: The 2024 – 2025 Shift
Until recently, pharmacotherapy was limited to off-label use of vitamin E or pioglitazone. The landscape has been transformed by the approval of targeted agents and high-potency incretin therapies **(Table 4)**:

6.9.1. Resmetirom
A selective thyroid hormone receptor-β (THR-β) agonist approved for non-cirrhotic MASH. It achieved MASH resolution in ˜30% and fibrosis improvement in 25% of trial participants. [9].

6.9.2. Incretin Mimetics
Semaglutide and Tirzepatide have demonstrated MASH resolution rates exceeding 60%. While primary indications are obesity and T2DM, they significantly improve the metabolic environment and reduce liver stiffness [42, 50].

It is critical to distinguish between the evidence levels of current therapeutics [4]. Resmetirom and Tirzepatide have demonstrated efficacy based on histological endpoints (biopsy-proven MASH resolution and fibrosis reversal) [9, 50], which remain the gold standard for regulatory approval. Conversely, many early-stage incretin studies rely on surrogate outcomes, such as significant reductions in MRI-PDFF (Magnetic Resonance Imaging Proton Density Fat Fraction) or LSM, which correlate with clinical improvement but do not yet confirm tissue-level fibrosis regression [33, 42].

6.10. Bariatric Surgery
Bariatric procedures (Roux-en-Y gastric bypass or sleeve gastrectomy) are highly effective for patients with a BMI > kg/m^2 and refractory MASH [32, 48].

6.10.1. Long-term Outcomes
At 5 years post-surgery, up to 84% of patients achieve MASH resolution and 70% show fibrosis improvement [48].

6.10.2. Hard Outcomes
Large observational studies confirm that bariatric surgery reduces 10-year major liver-related events (2.3% vs. 8.5%) and cardiovascular events (8.5% vs. 15.7%) compared to non-surgical care [32, 48].

7. Complications
MASLD affects approximately 30% of the global adult population, with its prevalence having nearly doubled between 1991 and 2019 paralleling the surge in global obesity rates. MASH represents the progressive inflammatory phenotype, characterized by hepatocyte ballooning and lobular inflammation, and is the primary driver of advanced fibrosis. While cardiovascular disease (CVD) remains the leading cause of death in MASLD patients, liver-related mortality increases exponentially once patients reach advanced fibrosis stages (F3 – F4) [1, 24, 35, 48].

7.1. Type 2 Diabetes Mellitus
Type 2 Diabetes Mellitus (T2DM) is an independent risk factor for both MASH and accelerated fibrosis [51]. Because advanced fibrosis often remains asymptomatic until hepatic decompensation occurs, a risk-based assessment pathway is critical for diabetic patients:

7.1.1. Initial Screening
Utilize the FIB-4 Index as a primary case-finding tool for all diabetic patients, rather than relying on transaminases, which serve as poor rule-out tools [3, 7]

7.1.2. Confirmatory Testing
Elevated or indeterminate FIB-4 scores must be followed by Liver Stiffness Measurement via VCTE (Vibration-Controlled Transient Elastography) to improve positive predictive value [3, 4, 33].

7.2. Cardiovascular Disease (CVD)
The American Heart Association (AHA) recognizes MASLD as an independent, underappreciated risk factor for atherosclerotic cardiovascular disease. This risk is mediated by systemic metaflammation and pro-atherogenic lipid profiles [42, 43].

7.2.1. Management:
Statins are first-line, safe in MASLD, and may reduce the risk of HCC.

7.2.2. Preferred Agents
In patients with T2DM and high cardiovascular risk, SGLT2 inhibitors or GLP-1 RAs are preferred for their dual hepatic and cardioprotective benefits [42, 43]

7.3. Portal Hypertension and Variceal Risk
Clinically significant portal hypertension can manifest in compensated advanced chronic liver disease (cACLD) before symptoms appear.

7.3.1. *Risk Stratification*

- Liver stiffness measurement < 10 kPa: cACLD is unlikely [4, 33].
- Liver stiffness measurement > 15 kPa: Suggestive of cACLD [3, 33].
- CSPH Exclusion: Unlikely if Liver stiffness measurement < 15 kPa and platelets > 150×10^9/L [3, 48].

7.3.2. *Management*

Non-selective beta-blockers, particularly carvedilol, are the standard of care to reduce portal pressure and prevent the first episode of decompensation. Routine endoscopic screening for varices is not required if Liver stiffness measurement < 20 kPa and platelets > $150\times10^9/L$[3, 4, 48].

7.4. SARCOPENIA AND NUTRITIONAL OPTIMIZATION IN ADVANCED MASLD

Sarcopenia (the progressive loss of muscle mass, strength, and quality) frequently coexists with MASLD, creating a vicious cycle of physical inactivity and worsened insulin resistance. Modern clinical focus has shifted toward sarcopenic obesity (SO), which is characterized not just by low muscle volume, but by myosteatosis (fatty infiltration of the muscle). Patients with Sarcopenic obesity have a significantly higher risk of advanced fibrosis and mortality compared to those with obesity alone.

7.4.1. *The Incretin Paradox*

While GLP-1 and GIP/GLP-1 receptor agonists (e.g., Tirzepatide) are highly effective for weight loss, up to 25 – 40% of weight lost can be lean muscle mass. To prevent a decline in metabolic rate, these therapies must be paired with mandatory resistance training and optimized protein intake [10, 42, 50].

7.4.2. *Nutritional Strategy*

Overcoming "anabolic resistance" in MASLD requires a high protein intake (1.2 – 1.5 g/kg/day), distributed boluses of protein throughout the day. Adherence to a Mediterranean dietary pattern is the gold standard, as its monounsaturated fats and antioxidants specifically reduce systemic inflammation and de novo lipogenesis [16, 49].

7.4.3. *Physical Intervention*

Resistance exercise remains a cornerstone non-pharmacological 'liver-sparing' intervention. By improving the glucose-clearing capacity of the skeletal muscle – the body's largest metabolic organ – resistance training reduces the metabolic load on the liver independently of total weight loss [12, 19].

8. Conclusion

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a multisystem disorder driven by the convergence of hepatic lipotoxicity, insulin resistance, and systemic metaflammation [1, 48]. This cascade facilitates the progression from simple steatosis to MASH, a phenotype characterized by hepatocyte injury and fibrogenesis that may ultimately lead to cirrhosis or hepatocellular carcinoma (HCC) [4, 24]. Beyond the liver, evidence links MASLD to systemic complications, most notably cardiovascular disease and heart failure [42, 43].

The clinical approach is shifting toward risk-based screening using non-invasive tests (NITs) such as the FIB-4 index and VCTE (Vibration-Controlled Transient Elastography) [6, 12]. While these tools improve the identification of advanced fibrosis, their diagnostic accuracy can be affected by age and ethnicity, necessitating a cautious, tiered interpretation to ensure equitable care [4, 11]. Furthermore, access to these specialized diagnostic tools remains a challenge in underserved communities, which may delay diagnosis in high-risk "sentinel" populations.

Lifestyle modification, specifically a 7 – 10% reduction in body weight and adherence to a Mediterranean dietary pattern, remains the primary therapeutic recommendation [16, 49]. The recent approval of Resmetirom and the clinical promise of GLP-1 RAs represent significant progress [9, 50]. However, as these therapies move from clinical trials into general practice, ensuring broad and equitable access – regardless of socioeconomic status – is essential to preventing further health disparities in liver-related mortality [4, 9].

Ultimately, reducing the global burden of MASLD requires an integrated approach that connects hepatology with endocrine and cardiovascular care. Prioritizing early, inclusive, and evidence-based intervention is the most effective strategy to attenuate the long-term inflammatory and metabolic complications of this disease across all patient populations.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

Funding Source

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Acknowledgments

The authors would like to thank Gana Mohamed and Takwa Hathout for their assistance in the preparation of the figures and illustrations.

Ethical approval

Not applicable. This article is a literature review and does not contain any original studies with human participants or animals performed by any of the authors.

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The authors declare that Gemini (an AI tool by Google) was used to assist with structural editing and citation management during the preparation of this manuscript. The authors reviewed and verified all scientific content and take full responsibility for the integrity and accuracy of the final work.

Authors Contribution

All authors contributed to the study conception and design. The first draft of the manuscript was written by MM, and all authors provided critical revisions to previous versions of the manuscript. All authors read and approved of the final manuscript.

Data Availability

Data sharing is not applicable to this article as no new datasets were created or analyzed during the current study.

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