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REVIEW ARTICLE

Recent advances in metabolic dysfunction-associated steatotic liver disease

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD), commonly associated with obesity and type 2 diabetes mellitus, is characterized by excess intrahepatic fat and is accompanied by at least one metabolic risk factor, without significant alcohol consumption. It is a major etiology of chronic liver disease—including metabolic dysfunction-associated steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma—contributing substantially to liver-related morbidity and mortality. Accumulating evidence supports the notion that MASLD is a systemic condition with an increased risk of extrahepatic outcomes, including incident type 2 diabetes mellitus, cardiovascular disease, and various extrahepatic cancers. This review critically examines recent advances in key MASLD topics, including evolving clinical trial endpoints, novel insights into pathogenesis, genetic and non-genetic disease modifiers, cancer risk, and emerging pharmacological therapies. The review concludes that advances in disease stratification, biomarkers, and artificial intelligence may enhance patient care and research. With the rapid global rise in metabolic disorders, MASLD and metabolic dysfunction-associated steatohepatitis should be prioritized in health policy agendas. These conditions pose a challenge for clinical trial recruitment and patient management and should be integrated into the broader noncommunicable disease framework to prevent millions of avoidable cases and support goals to reduce premature noncommunicable disease deaths by 2030.

Keywords: Hypertension; Biomarkers; Genetics; Liver histology; Pathogenesis; Pharmacotherapy

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1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a specific subset of steatotic liver disease (SLD) characterized by excessive hepatic fat accumulation along with at least one metabolic risk factor, excluding significant alcohol consumption.[1]

Metabolic dysfunction-associated steatotic liver disease—encompassing metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC)—is the primary cause of chronic liver disease and contributes significantly to liver-related morbidity and mortality.[1] Additionally, MASLD is now

recognized as a systemic disorder associated with various extrahepatic outcomes, including incident type 2 diabetes (T2DM), cardiovascular disease (CVD), and extrahepatic cancers.[2] Various factors influence the epidemiology of MASLD, including age, sex, gender, and ethnicity.[3-6]

This review critically examines recent advances in key aspects of MASLD, including diagnostic strategies, evolving clinical trial endpoints, emerging disease modifiers, cancer risk, and novel pharmacological therapies. This review focuses on the most recent developments (2024–2026) in MASLD/MASH. This includes:

(i) New histology consensus statements (International MASLD Pathology Group [IMPG]) for clinical trials.
(ii) Evolving noninvasive endpoints and regulatory perspectives.
(iii) Emerging systemic modifiers of disease course (e.g., hypertension [HTN] and cancer risk.
(iv) Mechanistic insights (e.g., diurnal metabolic dysfunction and lipid droplet-mediated mechanical stress).
(v) The first wave of approved diseasemodifying pharmacotherapies (e.g., resmetirom, tirzepatide, and semaglutide).

2. Diagnosis

2.1. Histology

Assessing grading, namely the inflammatory changes, and staging (i.e., severity of liver fibrosis), is crucial for appropriate patient enrollment and the evaluation of responses to drug treatments in MASH clinical trials. However, the lack of universally accepted definitions for the histological features required for MASLD grading and staging, variability in interpretation among pathologists, and a lack of standardized guidelines for applying existing scoring systems contribute to significant interobserver variability.[7] These factors can also impact the performance of supervised machine learning algorithms.[7]

To address these limitations, the IMPG—consisting of 25 experienced hepatopathologists and a statistician—aimed to define standards for biopsy processing and standardize criteria for grading and staging of MASLD, thereby offering comprehensive guidance on histological assessment in MASH clinical trials.

Three IMPG working subgroups developed statements, which underwent evaluation through a Delphi consensus process. Initially, 278 statements were assessed in the first Delphi round, with 162 achieving agreement at or above the 80% threshold. The remaining 116 statements were subjected to review, revision, or exclusion. Upon further modification, 33 statements proceeded to a second Delphi round. Ultimately, 192 statements satisfied the established consensus criteria.[7] IMPG statements offer structured and standardized guidance to improve liver biopsy assessment and scoring in MASH clinical trials. These recommendations could also aid the future development of supervised machine learning algorithms for quantitative histological assessment in MASLD.[7]

2.2. Non-invasive assessment of liver fibrosis

Due to the aforementioned limitations of liver biopsy, several non-invasive diagnostic tests have been developed. These advances have significantly transformed the field of hepatology by enabling earlier identification of advanced fibrosis or cirrhosis, often before the development of liver-related complications.[8] Furthermore, with SLD now affecting approximately 30% of adults globally, the use of these tests has become essential for effective risk stratification.[9]

Although non-invasive tests (NITs) are now considered the standard of care in liver clinics, their use remains limited in other medical specialties—such as primary care, endocrinology, and cardiology. This is important because many patients with advanced fibrosis are managed in these settings.[10] Table 1 summarizes the main strengths and limitations of NITs for liver fibrosis according to Castera *et al.*[11]

It is important to note that distinct features differentiate these NITs. For example, the fibrosis 4 (FIB-4) index is age-dependent, enhanced liver fibrosis (ELF) has a proprietary nature, vibration-controlled transient elastography (VCTE) is limited in patients with obesity, and magnetic resonance elastography (MRE) is costly and has limited availability.[11]

The ELF test is a non-invasive serum test that combines three direct extracellular matrix biomarkers to assess liver fibrosis severity: hyaluronic acid, procollagen III amino-terminal peptide, and tissue inhibitor of matrix metalloproteinase-1.[12] A study among non-alcoholic fatty liver disease (NAFLD) patients found the ELF test to be sensitive but not very specific for ruling out advanced fibrosis at low cut-offs. Its accuracy decreases in low-prevalence settings and at higher thresholds. Clinicians should consider disease prevalence and select appropriate test thresholds for optimal results.[12]

Molecular markers that have emerged in recent investigations include cytokeratin18 fragments (CK-18) and *N*-terminal pro-peptide of collagen type 3 (PRO-C3). CK-18 or CK-18F serves as a non-invasive biomarker for MASLD and MASH. Elevated levels of this marker are associated with an increased risk of MASH, inflammation, and fibrosis, supporting its potential role in disease diagnosis and treatment monitoring.[13] A study

Table 1. Advantages and limitations of the most commonly used non-invasive tests for assessing liver fibrosis

Advantages and limitations	FIB-4 index	ELF	VCTE	MRE
Accuracy	↑↑	↑↑↑	↑↑	↑↑↑
Evidence	↑↑	↑	↑↑↑	↑
Availability	↑↑↑	↑	↑↑↑	↑
Cost	↑	↑↑	↑↑	↑↑↑

Abbreviations: ELF: Enhanced liver fibrosis; FIB-4: Fibrosis 4; MRE: Magnetic resonance elastography; VCTE: Vibration-controlled transient elastography.
Notes: Adapted from Castera *et al.*[11] ↑indicates limited/low, ↑↑ indicates good/intermediate, and ↑↑↑ indicates high/widespread.

recruited 700 participants from Hong Kong, San Diego, and Wenzhou to validate a three-parameter blood panel (N3-MASH: C-X-C motif chemokine ligand 10, CK-18, and body mass index [BMI]) for non-invasive diagnosis of MASH. N3-MASH distinguished MASLD from healthy controls with an area under the receiver operating characteristic curve [AUROC] of 0.954 and identified MASH within MASLD patients with an AUROC of 0.823, 90.0% specificity, 62.9% sensitivity, and 88.6% positive predictive value. Performance was confirmed across three cohorts (AUROC = 0.802–0.823), and the panel also tracked improvements in MASH (AUROC = 0.857). This tool may reduce the need for liver biopsies.[13] Furthermore, PRO-C3 is a biomarker of advanced fibrosis in MASLD and may be involved in renal fibrosis and atherosclerosis.[14,15]

A recent study evaluated how well various NITs detect a ≥ 1-point change in the histologic NAFLD activity score (NAS) among 173 patients with T2DM or severe obesity, all undergoing repeat liver biopsies and blood tests. Using paired analyses and logistic regression, PRO-C3 (together with soluble triggering receptor expressed on myeloid cells 2 and the homeostatic model assessment of insulin resistance) predicted NAS improvement (AUROC > 0.75; odds ratio [OR] = 1.13 per unit decrease; p = 0.001), whereas FIB-4 and the NAFLD fibrosis score did not accurately reflect NAS changes (AUROC < 0.60; OR < 1.05; p > 0.5). The study suggests that soluble triggering receptor expressed on myeloid cells 2, PRO-C3, and the homeostatic model assessment of insulin resistance are promising surrogate indicators for treatment response.[16]

It is important to note that, although numerous molecular markers demonstrate potential in research environments, many currently do not meet the required standards of accuracy, reproducibility, cost-effectiveness, or standardization necessary for adoption as independent diagnostic tests in routine clinical practice. Furthermore, many potential markers—such as several adipokines, general oxidative stress indicators, and certain experimental cytokines—currently lack adequate efficacy in clinical diagnostics for MASLD. Therefore, these markers are not recommended for routine laboratory implementation at this stage.

The available NITs are listed in Table 1, which combines simple scores and validated panels with elastography techniques to permit patient triaging. This may occur both in primary care and non-hepatology settings (e.g., diabetology, cardiology) to identify individuals who should be referred to hepatological care. Conversely, isolated molecular markers are still primarily utilized as research tools.

3. Advances in pathogenesis

3.1. Nighttime metabolic dysfunction

Hepatic lipid and glucose metabolism are tightly regulated by circadian rhythms in animal models, although it is unclear whether similar circadian variations affect the processes that control intrahepatic lipid accumulation in humans.

Marjot *et al.*[17] performed detailed metabolic phenotyping, including advanced stable isotope techniques, during both daytime and nighttime in subjects with MASLD and overweight controls. The primary endpoint was the diurnal variation in intrahepatic de novo lipogenesis (DNL). Secondary endpoints included variations in hepatic glucose production, glucose disposal,

plasma non-esterified fatty acids, and whole-body oxidation of glucose and lipids.

Their findings demonstrate that MASLD is characterized by pronounced nighttime metabolic dysfunction. Several pathogenic pathways, such as hepatic and peripheral insulin resistance, DNL, and systemic non-esterified fatty acid exposure, were significantly increased at night. Nighttime insulin resistance was further aggravated by lower plasma insulin concentrations, which were attributable to diminished insulin secretion and increased insulin clearance.

Notably, these diurnal disparities persist even following body weight loss and reductions in liver fat. This suggests that nighttime metabolic dysfunction may serve as a key driver in the development of steatosis. These insights may have practical implications for optimizing the timing of food intake, physical activity, and pharmacological treatment in MASLD patients. Additionally, integrated proteomic analyses of plasma, adipose tissue, and skeletal muscle during day–night cycles revealed specific molecular targets with potential therapeutic relevance for metabolic disease.

3.2. Lipid droplets

Lipid droplets (LDs), once considered passive disease biomarkers, are now recognized as active organelles involved in both physiological and pathological processes. They are key players in cellular signaling and metabolism. The dynamic behavior of LDs is strictly regulated by numerous proteins on their surface, which control lipid metabolism, trafficking, and signaling pathways.[18]

Loneker *et al.*[19] showed that exposure of human hepatocytes to oleate causes LDs to function as intracellular mechanical stressors. This leads to nuclear deformation, chromatin condensation, and reduced hepatocyte function—effects similar to those observed with tissue stiffening. Mathematical models, in which LDs were represented as mechanically interactive inclusions, supported these findings. Overall, the data indicate that lipid droplets generate internal mechanical stress and that nuclear membrane tension may coordinate cellular responses to both internal and external mechanical forces.[19] These pathogenic insights identify LDs as an ideal target for innovative therapies in the MASH field.

3.3. Mitochondrial dysfunction, energy metabolism, and cell death pathways

In MASLD, particularly among individuals with obesity, dysfunction in mitochondrial β-oxidation and the tricarboxylic acid cycle contributes to the accumulation of toxic lipid species and elevated electron leakage, which collectively promote increased production of reactive oxygen species (ROS).[20] In turn, mitochondrial ROS contribute to oxidative damage affecting lipids, proteins, and DNA, and facilitate the activation of pro-apoptotic signaling and necro-inflammatory pathways.[21]

Ferroptosis is distinguished by the iron-dependent accumulation of lipid peroxides and unique mitochondrial morphological changes, such as decreased volume, increased membrane density, heightened membrane potential, cristae depletion, and disruption of the outer membrane.[22] These features differ markedly from those observed in apoptosis, autophagy, and necrosis. Mitochondria play a significant regulatory role in ferroptosis by coordinating metabolic networks and maintaining redox balance. This process encompasses iron-dependent lipid peroxidation, glutathione (GSH) depletion, and the inactivation of GSH peroxidase 4.[23]

Collectively, these pathobiological processes contribute to hepatocyte death and fibrogenesis in MASLD.[24] In this context, the bidirectional relationship between mitochondrial dysfunction and systemic insulin resistance is emphasized in conditions such as obesity and T2DM, which exacerbate hepatic energy imbalance and lipotoxic stress.[25] These pathways provide a mechanistic rationale for therapies targeting mitochondrial function, oxidative stress, and ferroptosis in MASLD/MASH.[26]

Reduced GSH and the GSH/GSH disulfide ratio play a crucial role in maintaining redox balance, detoxifying lipid peroxides, and safeguarding mitochondria and other organelles against oxidative damage in MASLD.[27]

Chronic metabolic stress, inflammation, and mitochondrial ROS reduce GSH levels, disrupt the thiol-disulfide equilibrium, and promote protein S-oxidation as well as disulfide bond formation. These processes contribute to compromised insulin signaling, hepatocyte dysfunction, and the development of fibrosis.[28] GSH depletion is the primary trigger for ferroptosis, and this process is aggravated by high lipid availability and iron overload. Modulation of the thiol-disulfide system (e.g., boosting GSH) acts as an anti-ferroptotic defense.[29-31]

3.4. Nitric oxide and hepatic microvascular dysfunction

Endothelial nitric oxide (NO) synthase, located in the lining of blood vessels, is essential for producing NO. Insulin resistance reduces endothelial NO synthase activity, leading to decreased synthesis of NO and endothelial dysfunction (ED), both of which are linked to cardiovascular and metabolic diseases. Insulin and inflammation influence vascular health by promoting NO, which helps protect the endothelium. The mechanisms of

ED in MASLD are not fully understood, but factors such as insulin resistance, dyslipidemia, chronic inflammation, and elevated free fatty acids contribute to ED in patients with MASLD.[32]

Subclinical systemic chronic inflammation due to metabolic dysfunction and inherent cell stress upregulates inducible NO synthase and leads to excess production of NO, which can react with superoxide to form peroxynitrite, promoting nitrosative stress, mitochondrial dysfunction, and hepatocyte injury, thus contributing to a hepatotoxic phenotype.[33] The complex pathobiology of NO supports highly contextspecific therapeutic modulation, implying that future studies should clarify which components of the NO pathway can be safely and effectively targeted in MASLD/MASH.[34]

4. Evolving endpoints in metabolic dysfunction-associated steatohepatitis trials

To facilitate drug development for fibrosing MASH patients, clinicians, and researchers have expressed a growing interest in reducing reliance on liver histology as the primary endpoint. Currently, the United States Food and Drug Administration (FDA) grants accelerated approval based on surrogate endpoints. These endpoints are supported by limited evidence linking them to clinical outcomes (e.g., mortality or liver transplantation) and are considered reasonably likely surrogate endpoints (RLSEs) that may predict clinical benefit.

A recent publication outlines key regulatory considerations for the potential adoption of NITs as alternatives to liver histology and as RLSEs in the development of MASH drugs. It also describes FDA pathways and procedures for submitting data and proposals to support the use of NITs as RLSEs in place of liver histology.[35] Figure 1 summarizes the main regulatory considerations for evaluating non-invasive testing methods as reasonably likely surrogate endpoints in MASH drug development, serving as alternatives to liver histology.

It is plausible that these regulatory advances will facilitate patient recruitment in future MASH clinical trials, thereby improving the identification of therapies that may alter the natural course of the disease.

5. Modifiers of the natural course of disease

5.1. Genetic and non-genetic influences on histological changes in MASLD

Ethnic disparities in the prevalence and severity of MASLD are often seen as strong evidence supporting the role of genetics in its development and progression. For example, higher rates of the disease are observed among individuals of Hispanic descent[36] as well as variations in risk among East Asian and Africanpopulations.[37] These trends are partly due to the distribution of genetic variants,

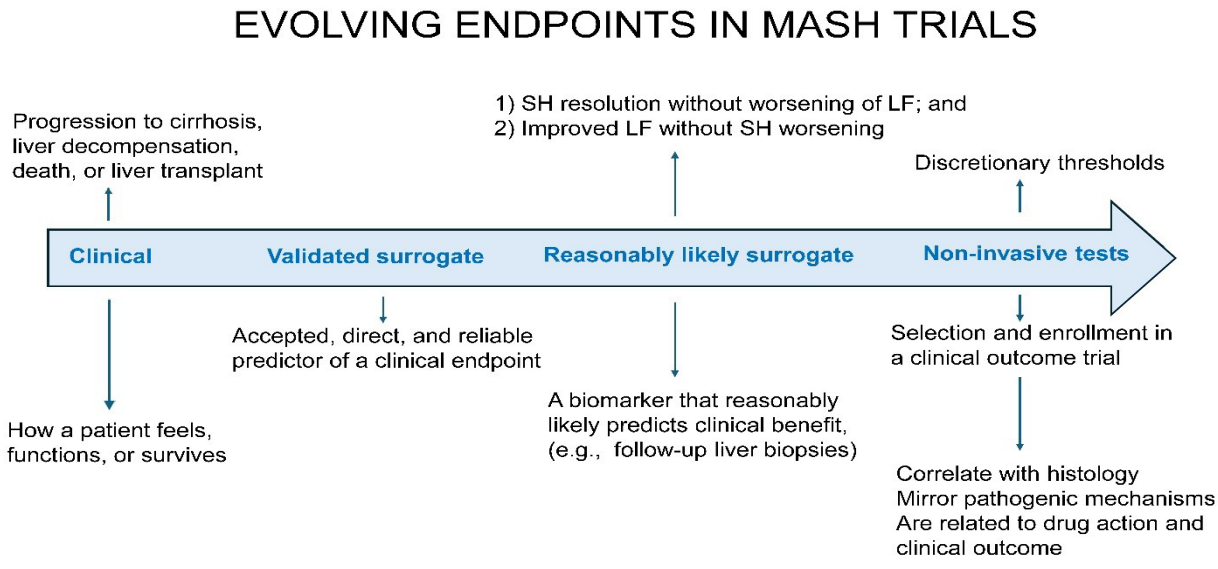

Figure 1. Overview of non-invasive tests used to evaluate treatment efficacy in metabolic dysfunction-associated steatohepatitis, extending assessment capabilities beyond traditional liver histology-based methods
Abbreviations: LF: Liver fibrosis; SH: Steatohepatitis.

such as those found in the *PNPLA3* and *HSD17B13* genes.[38,39] Additionally, Hispanic individuals, especially those of Mexican descent, tend to progress more rapidly to advanced liver fibrosis, while Black individuals often experience worse outcomes and higher mortality rates despite having a lower prevalence of the disease.[40] It is important to note that not only genetic factors but also socioeconomic and metabolic factors play a role in these disparities.

Vilar-Gomez *et al.*[41] investigated three single-nucleotide polymorphisms—*PNPLA3* rs738409, *TM6SF2* rs58542926, and *HSD17B13* rs72613567—in 671 patients (444 adults, 227 children) from NASH Clinical Research Network trials who had at least two liver biopsies. The *PNPLA3* G allele was associated with an increased risk of fibrosis (adjusted hazard ratio [aHR] = 1.31). In contrast, the *HSD17B13* allele was protective: it reduced progression from MASLD to MASH and fibrosis (aHR = 0.46 and aHR = 0.69, respectively) and increased rates of MASH resolution and fibrosis regression (aHR = 1.58 and aHR = 1.42, respectively). The *TM6SF2* T allele showed no significant effect. A three-single-nucleotide-polymorphism polygenic risk score was linked to a higher risk of progression from MASLD to MASH and fibrosis; the sum of non-risk alleles correlated with MASH resolution.

Non-genetic factors, such as T2DM and BMI, also influenced histological outcomes. Moreover, the effects of genetic variants were modified by age, sex, BMI, and T2DM. Overall, the study highlights the combined contribution of genetic and metabolic factors to MASLD progression and supports a more personalized management approach.

5.2. Role of arterial hypertension

Evidence supports a bidirectional (causal) relationship between MASLD and arterial HTN, implying complex and intertwined pathways that associate the regulation of blood pressure levels with metabolic dysfunction and liver histology changes.[42] In contrast to this perspective, research conducted in Japan indicated no association between MASLD and the development of arterial HTN.[43] Hirooka *et al.*,[43] utilizing data from a retrospective health-screening program, evaluated 24,384 Japanese adults. They found that MASLD explained 17.0% of all events of CVD and was associated with significantly elevated odds of CVD (aHR = 1.83, 95% confidence interval [CI] = 1.63–2.07, $p < 0.001$), with stronger correlations among younger adults. In contrast, MASLD did not demonstrate an association with new-onset arterial HTN (hazard ratio [HR] = 1.02, 95% CI = 0.95–1.09, $p = 0.634$). This distinction was further supported by competing risk analysis (interaction $p < 0.001$). They highlighted that MASLD is linked to a substantially increased odds of CVD events, while being minimally associated with HTN.[43] However, the retrospective design, possible selection bias, restriction to Japanese adults, and lack of advanced imaging for MASLD assessment limit generalizability. Despite adjustments, unmeasured confounders may also still influence the results.

Addressing these limitations, Zhou *et al.*[44] examined three large multicenter cohorts: 107,316 adults from the United Kingdom Biobank cohort, 8,169 from the VCTE-prognosis cohort, and 1,670 from the paired liver biopsy cohort. Adverse clinical outcomes included all-cause mortality, cardiovascular events, and liver-related events, as well as progression of both liver stiffness and liver fibrosis. In the United Kingdom Biobank cohort, HTN was associated with an increased risk of long-term adverse outcomes (aHR = 1.30, 95% CI = 1.26–1.33). In the VCTE-prognosis cohort, HTN raised the risk of liver stiffness progression (aHR = 1.57, 95% CI = 1.30–1.90), and in the paired liver biopsy cohort, it was linked to a higher risk of fibrosis progression (aHR = 1.41, 95% CI = 1.12–1.78). Subgroup and sensitivity analyses confirmed these results. Overall, HTN emerged as an independent and modifiable risk factor for adverse outcomes and liver disease progression in MASLD.

These findings indicate that HTN contributes not only to cardiovascular risk but also to hepatic fibrosis progression. Therefore, greater awareness among hepatologists, cardiologists, and primary care physicians is warranted. Incorporating non-invasive fibrosis assessments into standard care protocols for individuals with MASLD and HTN may improve risk stratification and facilitate timely intervention.

However, several key confounders, such as unhealthy diets (e.g., ultra-processed foods), physical activity, hypothyroidism, sedentary lifestyle, sleep quality, and other lifestyle factors, were not fully addressed in the observational study by Zhou *et al.*[44] To evaluate the potential impact of unmeasured confounding, Gao *et al.*[45] conducted E-value sensitivity analyses. The E-value gauges the minimum strength of association that an unmeasured confounder would need to fully explain the observed association between exposure and outcome.[46] Their analysis showed that the associations between HTN and long-term cardiovascular events, liver-related events, and mortality among MASLD patients remain generally robust. This highlights the critical importance of effective blood pressure control in individuals with MASLD.

Figure 2 schematically illustrates the pathomechanisms linking arterial HTN to fibrosis progression in MASLD.

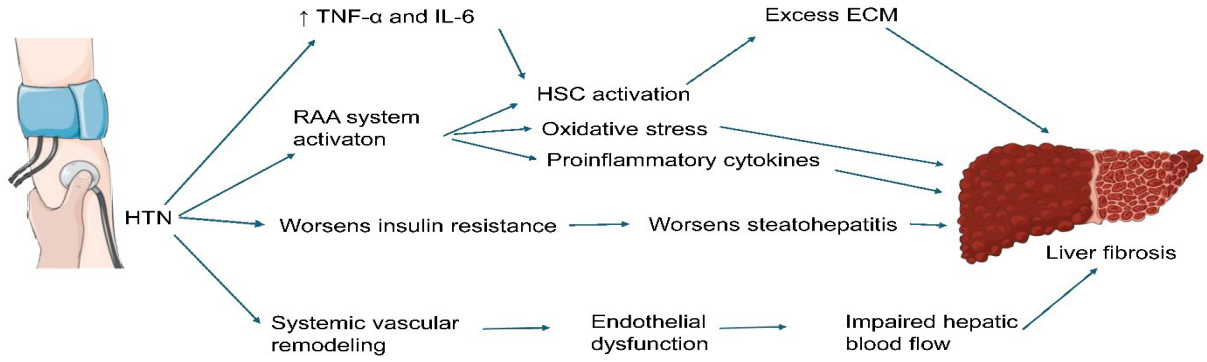

Figure 2. Overview of the various mechanisms that may potentially associate arterial HTN with liver fibrosis. Image created by the authors using Servier Medical Art (SMART) based on studies by Lonardo *et al.*,[42] Zhou *et al.*,[44] and Ratziu *et al.*,[47] and licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0).
Abbreviations: ECM: Extracellular matrix; HTN: Hypertension; IL-6: Interleukin 6: RAA: Renin–angiotensin–aldosterone; TNF-α: Tumor necrosis factor α.

HTN increases proinflammatory cytokines (e.g., tumor necrosis factor α and interleukin 6), which activate hepatic stellate cells and promote liver fibrosis. Oxidative stress and insulin resistance further intensify cellular damage, fat accumulation, and inflammation, while dyslipidemia contributes to tissue injury. Additionally, vascular remodeling and endothelial dysfunction impair hemodynamics, and activation of the renin–angiotensin–aldosterone system amplifies inflammatory and fibrotic pathways.

To better understand how different ethnicities affect MASLD epidemiology and pathobiology, future studies should be conducted using geographically consistent and ethnically homogenous cohorts.

6. Metabolic dysfunction-associated steatotic liver disease and cancer

Growing evidence indicates that MASLD is associated not only with primary liver malignancies but also with several extrahepatic malignant neoplasms.[48]

Using longitudinal data, Chung *et al.*[49] investigated the influence of variations in MASLD status over time on the risk of cancer. The study included 3,536,172 Korean adults who underwent two consecutive health screening check-ups, with a 10.6-year median follow-up. Compared to MASLD-free subjects, those with persistent MASLD had the most elevated overall cancer risk (HR = 1.15, 95% CI = 1.13–1.18). Participants with incident MASLD also had an increased risk, although more modest (HR = 1.03, 95% CI = 1.00–1.06). In contrast, individuals in the resolved MASLD group did not show a statistically significant increase in the risk of cancer.

Persistent MASLD was particularly linked to elevated risk of larynx, biliary tract, kidney, liver, pancreas, and colorectal cancers. Additionally, women with persistent MASLD had increased risks of cancers of the uterine corpus, cervix, and ovaries.[49] In summary, MASLD, especially when persistent, is associated with an increased risk of overall and site-specific cancers. Importantly, individuals whose MASLD resolved did not have a significantly elevated cancer risk. The results indicate that prompt recognition and treatment of MASLD could potentially mitigate the risk of subsequent cancer development. However, this study by Chung *et al.*[49] is based on a large Korean cohort; therefore, its findings cannot be automatically extended to different ethnicities, as cancer risks associated with MASLD may vary depending on baseline cancer epidemiology and genetic background in various geographical regions.

The putative pathomechanisms linking MASLD to various cancers are complex and multifactorial. Compared to extrahepatic cancers, primary liver cancer may involve different molecular and cellular pathways.

Figure 3 schematically illustrates the pathobiology of MASLD-associated cancers. Within the context of systemic metabolic dysfunction, characterized by insulin resistance, a prothrombotic state, hypercholesterolemia, and altered cytokine balance, MASLD may promote tumor development, particularly among individuals with liver fibrosis. The risk of HCC, which is more common in men, increases with advancing fibrosis stage. Conversely, women appear to have a higher risk of extrahepatic cancer, which may occur irrespective of liver fibrosis severity.

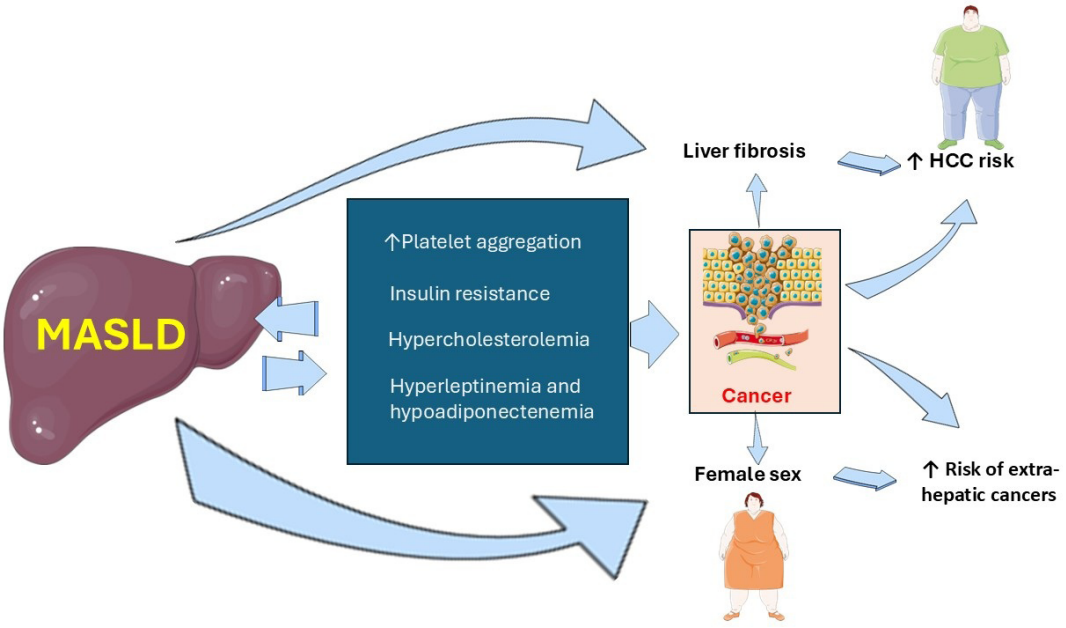

Figure 3. Schematic illustration of sex and liver fibrosis as key modifiers of MASLD-associated cancer risk. Image created by the authors using Servier Medical Art (SMART) based on the study by Loneker *et al.*,[19] and licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0). Abbreviations: HCC: Hepatocellular carcinoma; MASLD: Metabolic dysfunction-associated steatotic liver disease.

Nitric oxide signaling plays a crucial role in oncogenesis during the progression from MASLD to HCC. While NO is essential for normal physiological processes, elevated levels produced by inducible NO synthase, due to persistent inflammation and lipotoxicity in MASLD/MASH, create a microenvironment conducive to cancer development. This occurs through mechanisms such as DNA damage, altered apoptosis, and enhanced angiogenesis.[50]

Taken together, increasing awareness of the increased risks of extrahepatic cancer among those with MASLD will increasingly guide research and clinical practice in the MASLD field.

7. Drug treatment

The main goal of MASH trials is to assess the prevention of cirrhosis, decompensated liver disease, and mortality from all causes. Meeting these clinical endpoints requires extended follow-up. For this reason, the FDA grants conditional approval based on surrogate histological measures. At least one of the following must be demonstrated: MASH resolution without worsening of fibrosis, or fibrosis improvement by at least one stage without MASH worsening. In contrast, the European Medicines Agency requires both MASH resolution and fibrosis improvement to be shown.[51]

In recent years, there have been significant advancements in disease-modifying therapies for metabolic disease. These new therapies, such as resmetirom, tirzepatide, semaglutide, and others in development, have proven to be more effective than the outdated "hepatoprotective" agents previously used as adjunctive treatments. Since 2024, three randomized controlled trials (RCTs) have reported promising results for pharmacological treatment of MASH. These studies led to FDA approval of resmetirom and semaglutide for fibrosing MASH. A summary of these trials is presented in Table 2.[52-54]

Hartman *et al.*[55] examined histological responses in clinically relevant subgroups within the Phase 2b SYNERGY-NASH trial. This study included subjects with biopsy-proven MASH, F2–F3 fibrosis, and an NAS of ≥4. During the trial, additional inclusion criteria were introduced (FibroScan–aspartate aminotransferase score >0.35 and an increased aspartate aminotransferase entry threshold from >20 to >23 U/L), allowing assessment of their impact on participant qualification rates.[56] A total of 190 participants were randomized to weekly subcutaneous tirzepatide (5, 10, or 15 mg) or placebo for 52 weeks. Among 155 evaluable participants, tirzepatide improved MASH resolution without worsening fibrosis across various subgroups. Significant risk differences for tirzepatide were observed in many subgroups, depending on dose. However, statistical power for fibrosis improvement was limited by small sample sizes. Notably,

Table 2. Summary of Phase II and III clinical trials of effective and specific pharmacotherapies for NASH/MASH and liver fibrosis

Study	Drug; drug class; mechanism of action; manufacturer; trial	Patient population	Endpoints	Findings	Side effects	Conclusion
Harrison *et al.*[52]	Res; liver-selective THR agonist; counters intrahepatic hypothyroidism, reduces LFC, liver enzymes, LDL-C, and LF development; Madrigal; pharmaceuticals Phase III trial	966 adults with biopsy-proven NASH and an LF stage ranging from F0 to F4. Patients were randomized in a 1:1:1 ratio to receive once-daily Res (80 mg [n = 322] or 100 mg [n = 323]) or PL (n = 321)	At week 52: NASH resolution (defined as a reduction in NAS by ≥2 points with no worsening of fibrosis) and fibrosis improvement by ≥ 1 stage with no worsening of NAS	NASH resolution without fibrosis worsening was achieved in 25.9% of patients in the 80-mg Res group and 29.9% in the 100-mg Res group, compared with 9.7% in the PL group ($p < 0.001$ vs. PL). LF improvement by at ≥1 stage without worsening of NAS was observed in 24.2% of patients in the 80-mg Res group and 25.9% in the 100-mg Res group, compared with 14.2% in the PL group ($p < 0.001$ vs. PL). Changes in LDL-C from baseline to week 24 were 0.1% in the PL group, −13.6% in the 80-mg group, and −16.3% in the 100-mg group ($p < 0.001$ vs. PL)	Res was associated with a higher incidence of GI AEs, including diarrhea and nausea, compared with PL; however, the rates of serious AEs were similar between groups	Res demonstrated superior efficacy compared with PL in achieving NASH resolution and LF improvement by at least one stage
Loomba *et al.*[53]	Tirze; dual GIP/GLP-1 RA; ameliorates glycemic control and determines body weight loss; Eli Lilly; phase II, dose-finding, multicenter, double-blind, RCT	190 participants with histological evidence of MASH and fibrosis stages F2 or F3. Participants were randomized to once-weekly subcutaneous Tirze (5 mg, 10 mg, or 15 mg) or PL for 52 weeks	Primary: MASH resolution without worsening of LF at week 52; secondary: a decrease of ≥1 LF stage without MASH worsening	Among 157 participants with evaluable liver histology at week 52[a], Tirze showed significant improvements vs. PL. Differences in MASH resolution were 34% (95% CI = 17–50), 46% (95% CI = 29–62), and 53% (95% CI = 37–69) ($p < 0.001$ for all doses). Fibrosis improvement by ≥1 LF stage without MASH worsening was observed with differences of 25% (95% CI = 5–46), 22 (95% CI = 1–42), 21% (95% CI = 1–42) for the 5 mg, 10 mg, and 15 mg groups, respectively	GI events were the most common, predominantly mild to moderate in severity	Once-weekly Tirze demonstrated superior efficacy compared with PL in achieving MASH resolution without LF worsening
Sanyal *et al.*[54]	Sema; GLP-1RA; improves insulin sensitivity, reduces global body weight, visceral adiposity, BP, and CRP levels, and improves the lipid profile; Novo Nordisk; Phase III, multicenter, double-blind RCT	1,197 subjects with histology-proven MASH and LF stages 2 or 3, randomized in a 2:1 ratio to receive once-weekly subcutaneous Sema (2.4 mg) or PL for 240 weeks	MASH resolution without LF worsening and fibrosis improvement without MASH worsening	At the interim analysis (week 72; first 800 patients), Sema showed a significant benefit over PL. MASH resolution without LF worsening demonstrated an estimated difference of 28.7% (95% CI = 21.1–36.2; $p < 0.001$). An LF improvement without MASH worsening showed an estimated difference of 14.4% (95% CI = 7.5–21.3; $p < 0.001$). Mean body weight was greater in the Sema group (−8.5%; 95% CI = −9.6 to −7.4; $p < 0.001$)	GI AEs occurred more frequently in the Sema group compared with PL	Once-weekly Sema at 2.4 mg demonstrated significant improvements in MASH resolution, fibrosis outcomes, and body weight compared with PL in patients with moderate to advanced LF

Abbreviations: AE: Adverse event; BP: Blood pressure; CI: Confidence interval; CRP: C-reactive protein; F0: Fibrosis absent; F4: Cirrhosis; GI: Gastrointestinal; GIP: Gastrointestinal peptide; GLP-1: Glucagon-like peptide 1; LDL-C: Low-density lipoprotein cholesterol; LF: Liver fibrosis; LFC: Liver fat content; MASH: Metabolic dysfunction-associated steatohepatitis; NAS: Non-alcoholic fatty liver disease fibrosis score; NASH: Non-alcoholic steatohepatitis; PL: Placebo; Sema: Semaglutide; THR: Thyroid hormone receptor; Tirze: Tirzepatide; RA: Receptor agonist; RCT: Randomized, placebo-controlled trial; Res: Resmetirom.

Note: [a]Missing values were imputed based on the assumption that they would exhibit the same pattern of results as observed in the placebo group.

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significant fibrosis improvement was noted at the 5 and 15 mg doses in patients with stage 3 fibrosis. In summary, post hoc analyses suggest that tirzepatide consistently improves MASH resolution without worsening fibrosis across demographic, histological, and biomarker-defined subgroups compared to placebo.[55]

The availability of various drug options within the MASH setting presents potential advantages for combined therapy. Using drugs with complementary pharmacological activities may allow lower doses, reduce adverse effects associated with each drug class, while simultaneously enhancing treatment efficacy.[57] Combining agents that improve metabolic dysfunction, including conventional antidiabetic agents, hypo-lipidemic drugs, antihypertensive therapies, and antioxidants, with specific MASH-directed therapies may be particularly beneficial.[57]

Targeting patient-specific pathogenic pathways may address the underlying drivers of MASH. However, the high cost and ethical considerations of advanced drug pharmacotherapies must be acknowledged, especially given global disparities where some regions use these treatments for lifestyle-related liver disease while others continue to face food scarcity.[57]

8. Strengths, limitations, and future perspectives

This review synthesizes recent advancements in MASLD and MASH, focusing on developments in diagnostics, pathogenesis, disease course modifiers, cancer risk, and newly validated pharmacotherapies, including their practical and research implications. However, it is limited by its narrative (non-systematic) approach, potential selection bias in studies, rapidly evolving evidence that may require updates, and limited availability of long-term outcome data for some new therapies discussed.

While metabolic disorders are rapidly increasing worldwide, MASLD and MASH—dynamic metabolic liver diseases[58]—remain overlooked in public health policies and pose challenges in recruiting patients for enrollment in clinical trials and in routine clinical management. Therefore, MASLD and MASH should be prioritized within the broader noncommunicable disease agenda to prevent millions of avoidable cases and help achieve the global target of reducing premature noncommunicable disease deaths by 2030.[59] MASH, closely linked to obesity and T2DM, significantly increases the risk of chronic liver disease. Current therapeutic strategies focus on targeting metabolic dysfunction, inflammation, and fibrosis. Although regulatory approval still relies on histological endpoints, non-invasive biomarkers and more personalized therapies are gaining ground. Several new drugs have recently emerged, and recent trials have shown encouraging results.

Figure 4 schematically summarizes the most recent advances discussed in this review. Genetic susceptibility interacts with environmental and lifestyle exposures—such as obesity, T2DM, unhealthy dietary patterns, and physical inactivity—to drive systemic and hepatic insulin resistance. Insulin resistance leads to adipose tissue dysfunction, impaired lipid buffering, and pro-inflammatory adipokine signaling. This also increases the hepatic influx of non-esterified fatty acids, while simultaneously stimulating hepatic DNL and impairing appropriate lipid handling and export. These processes promote hepatocellular lipid accumulation and lipotoxicity, generating toxic lipid species such as saturated fatty acids, diacylglycerols, and ceramides. This can contribute to organelle dysfunction and lipid droplet remodeling and expansion, leading to mechanical stress.

Additionally, lipotoxic stress triggers mitochondrial dysfunction, reduced β-oxidation efficiency, and electron leak, as well as endoplasmic reticulum stress with activation of the unfolded protein response. This results in the production of reactive oxygen species, oxidative and nitrosative injury, and engagement of regulated cell-death pathways such as apoptosis, pyroptosis, and ferroptosis. Hepatocyte injury and the release of damage-associated signals activate resident macrophages (Kupffer cells) and promote immune cell recruitment, amplifying inflammatory signaling and cytokine/chemokine production. Paracrine crosstalk between injured hepatocytes, immune cells, and the hepatic microvasculature leads to activation of hepatic stellate cells and extracellular matrix deposition, driving progressive fibrosis, cirrhosis, and eventual HCC.

Figure 4 also highlights clinically relevant extrahepatic consequences of MASLD/MASH, including increased cardiometabolic risk (atherosclerotic CVD and HTN), worsening glycemic control and T2DM progression, chronic kidney disease, and elevated risk of selected extrahepatic malignancies. Mechanistic advances discussed in Sections 3, 5, and 6 are integrated into Figure 4, including diurnal/circadian metabolic dysfunction, the role of genetics, lipid droplet pathobiology and mechanotransduction, vascular/hemodynamic modifiers, and links between MASLD and cancer.

The mechanistic insights highlighted in this review support metabolism-directed therapies, including thyroid hormone receptorβ agonists, glucagon-like peptide-1 receptor agonists (GLP1RAs), dual GIP/GLP1RAs, and other metabolic agents. For example, a recent meta-analytic review of 13 phase II or phase III RCTs comprising 1,811 participants demonstrated that, regardless of diabetes

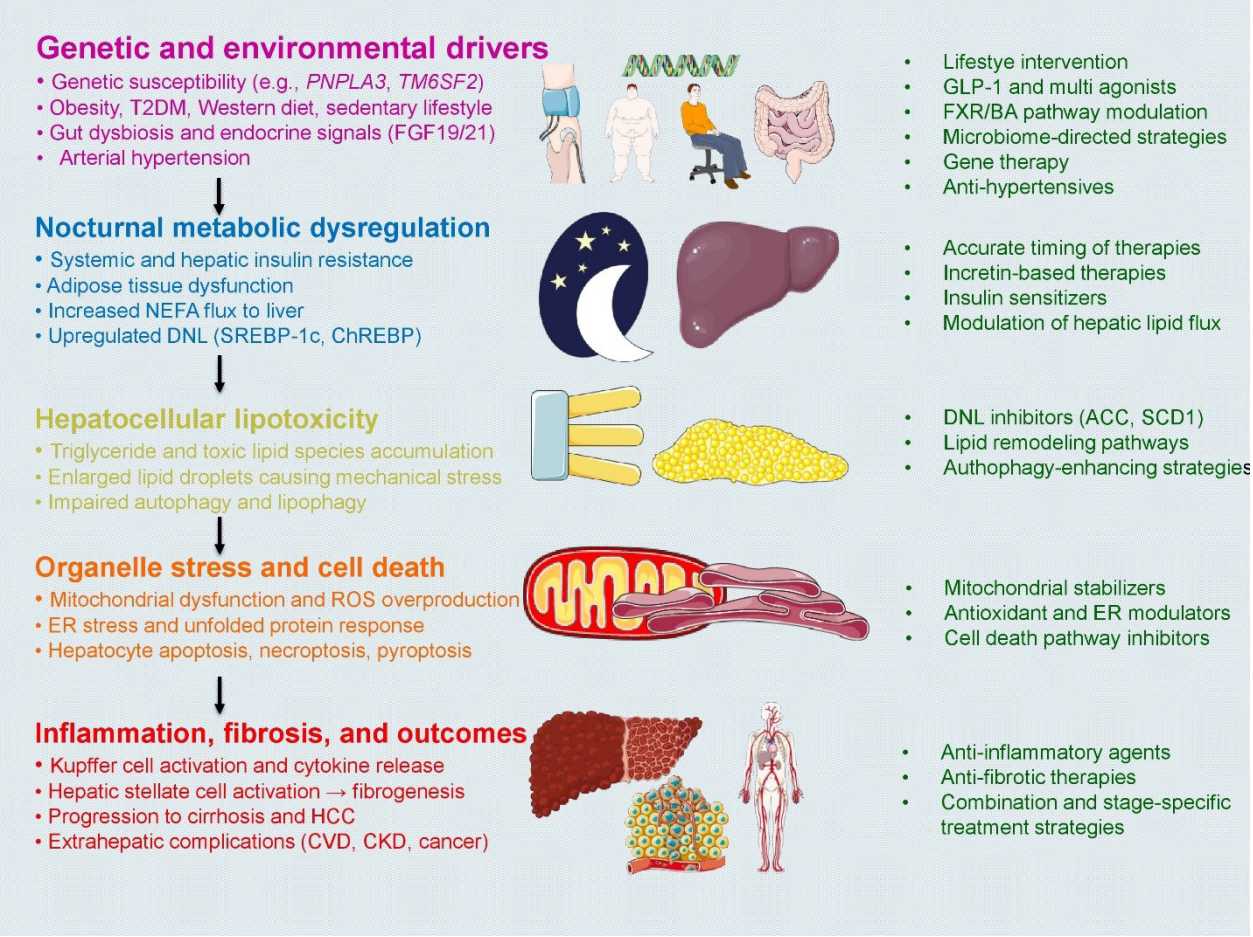

Figure 4. Overview of metabolic dysfunction-associated steatotic liver disease/metabolic dysfunction-associated steatohepatitis pathophysiology and potential therapeutic objectives. Image created by the authors using Servier Medical Art (SMART) and licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

Abbreviations: BA: Bile acid; CKD: Chronic kidney disease; CVD: Cardiovascular disease; DNL: De novo lipogenesis; ER: Endoplasmic reticulum; FXR: Farnesoid X receptor; GLP-1: Glucagon-like peptide-1; HCC: Hepatocellular carcinoma; NEFA: Non-esterified fatty acid; ROS: Reactive oxygen species; T2DM: Type 2 diabetes mellitus.

status, GLP-1RAs, particularly semaglutide at 2.4 mg/week for up to 72 weeks, were significantly more effective than placebo in achieving MASH resolution among individuals with MASH and moderate-to-advanced fibrosis (n = 3 RCTs; pooled random-effects OR = 3.48; 95% CI = 2.69–4.51; I^2 = 0%), as well as in improving liver fibrosis (pooled OR = 1.79; 95% CI = 1.37–2.35; I^2 = 0%).[60] In contrast, for those with MASH-related compensated cirrhosis (n = 1 RCT), semaglutide did not result in MASH resolution or improved fibrosis compared to placebo. Additionally, GLP-1RAs were found to reduce magnetic resonance-measured liver fat content (n = 9; pooled mean difference: −4.50%, 95% CI = −6.60 to −2.40%; I^2 = 95.9%). The findings suggest that GLP-1RAs are a promising therapeutic option for non-cirrhotic MASLD or MASH.

Considering the limited efficacy of medications targeting metabolic dysfunction in patients with advanced liver disease, direct antifibrotic agents and macrophage-based therapies may be more appropriate for later stages of MASH.[61] Nevertheless, these approaches are still under development. Current research indicates that macrophage transplantation, hepatocyte-specific oligonucleotides, and chimeric antigen receptor T-cell–based treatments could potentially be incorporated into stage-specific or combination regimens. By addressing distinct pathogenic pathways and cellular targets, such strategies may enhance the proportion of MASH patients achieving fibrosis reduction.[61]

Redox and mitochondria-oriented interventions in

MASLD and MASH target the core pathophysiological cycle of lipid overload, oxidative stress, and iron-dependent cell death. These strategies aim to restore mitochondrial oxidative phosphorylation, enhance antioxidant defenses (particularly GSH), and inhibit ferroptosis to halt fibrosis.[62,63] Finally, combination therapies may be customized to address patient-specific factors such as genetic predispositions, T2DM, obesity, and HTN.[64]

9. Future research directions

Future research directions and pharmacological targets need further precise definition. Key knowledge gaps include determining the optimal treatment duration, identifying appropriate patient populations (considering genetic profiles and co-morbidities such as T2DM and HTN), and evaluating the long-term safety and efficacy of novel therapeutic agents. Emerging pharmacological targets include regulators of circadian metabolism and meal timing, molecules implicated in lipid droplet pathobiology and intracellular mechanotransduction, mitochondrial and ferroptosis pathways (including GSH peroxidase 4, iron metabolism, and mitochondrial biogenesis), inflammatory and fibrogenic cascades (e.g., stellate cell activation and matrix remodeling), pathways linking MASLD to HTN and vascular dysfunction, as well as mechanisms connecting MASLD to oncogenesis.

Combination therapies that address metabolic dysfunction, inflammation, and fibrosis simultaneously show promise for advancing the management of MASLD/MASH but are largely underexplored at present. Consequently, the success of treatment is now defined not only by histological improvement but also by patient-reported outcomes, particularly as combination therapies and precision medicine approaches continue to evolve.[65] In this regard, sex-specific investigations and considerations of systemic health remain fundamental and yet unmet priorities in the MASLD field.[66,67]

Recent advances in disease stratification, biomarker development, and artificial intelligence (AI) have the potential to enhance patient care and clinical research. AI-assisted digital pathology offers the possibility of using supervised and deep learning algorithms to standardize grading and staging of liver biopsies, minimize interobserver variability, and provide quantitative measurements of steatosis, inflammation, ballooning, and fibrosis. Integrating IMPG consensus criteria into AI workflows may harmonize histologic endpoints in clinical trials. Furthermore, AI-based systems may facilitate the combination of non-invasive tests, such as machine learning models that incorporate serum biomarkers (e.g., FIB-4, ELF components), elastography, imaging data, and clinical variables to improve the non-invasive prediction of advanced fibrosis, decompensation, or hepatocellular carcinoma. AI can also support patient identification and trial enrichment; electronic health record–driven algorithms are valuable for identifying high-risk MASLD/MASH patients at scale, optimizing clinical trial recruitment, and enriching study cohorts for targeted endpoints such as fibrosis progression or cardiovascular events. Lastly, AI-driven methodologies that integrate genetics, metabolomics, imaging, and longitudinal clinical data to characterize MASLD subphenotypes, predict therapeutic response (e.g., to resmetirom, tirzepatide, semaglutide), and inform personalized treatment strategies may advance precision medicine in MASLD.

10. Conclusion

Metabolic dysfunction-associated steatotic liver disease presents significant risks for chronic liver diseases and systemic conditions, including CVD and cancer. This review highlights current developments in MASLD pathogenesis, clinical trials, risk factors, its associations with cancer, and emerging therapeutic strategies. Progress in patient stratification, biomarker identification, and applications of AI may further improve clinical management. Addressing MASLD through targeted health policies and incorporating it within comprehensive disease frameworks is vital to minimize preventable cases and mortality by 2030.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

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Writing – original draft: All authors
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Availability of data

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