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Non-Alcoholic Fatty Liver Disease and Metabolic Dysfunction-Associated Fatty Liver Disease: Current Insights into Epidemiology, Diagnosis, Treatment, and Global Health Challenges

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent chronic liver disorder globally, affecting over 30% of adults. It is increasingly recognized as a multisystem disease with significant cardiometabolic and oncologic consequences. Recent advances have substantially transformed its conceptual understanding, diagnosis, and clinical management. This review aims to critically evaluate global progress in NAFLD research and management with emphasis on epidemiology, pathophysiology, diagnostic innovations, therapeutic developments, and the emergence of precision hepatology, while addressing the transition toward metabolic dysfunction-associated fatty liver disease (MAFLD). A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science databases, covering studies published between Relevant clinical trials, guidelines, and high-impact research articles were systematically analyzed across key domains including epidemiology, molecular mechanisms, diagnostics, therapeutics, and public health strategies. The global prevalence of NAFLD has increased across diverse populations, including pediatric, elderly, lean, and socioeconomically disadvantaged groups. The MAFLD terminology has gained traction for better reflecting metabolic dysfunction, although debates persist. Mechanistic insights highlight the roles of insulin resistance, lipotoxicity, mitochondrial dysfunction, impaired autophagy, and gut microbiota dysbiosis. Advances in genomics and epigenetics have identified key variants such as *PNPLA3* and *TM6SF2*, along with circulating biomarkers including miR-122 and Pro-C3. Non-invasive diagnostic tools, particularly imaging modalities and artificial intelligence-based systems, are increasingly replacing liver biopsy. Although no pharmacological therapy has yet received full regulatory approval, several agents, including obeticholic acid, resmetirom, lanifibranor, and semaglutide, are in advanced stages of clinical development. Lifestyle modification remains the cornerstone of management. NAFLD is strongly associated with increased risk of cardiovascular disease, type 2 diabetes, chronic kidney disease, and malignancies. Emerging precision hepatology approaches integrating multi-omics, artificial intelligence, and digital health technologies are enabling personalized disease management. NAFLD is evolving from a liver-specific disorder into a global multisystem health challenge. Despite significant advances, key challenges remain in standardizing diagnostic criteria, ensuring equitable access to therapies, and addressing global health disparities. The integration of precision medicine, digital technologies, and public health strategies holds promise for reducing the burden of NAFLD in the coming decade.

Keywords: NAFLD; MAFLD; NASH; fibrosis; metabolic syndrome; gut–liver axis; genomics; non-invasive diagnostics; biomarkers; artificial intelligence; precision hepatology; global health

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of hepatic conditions characterized by the accumulation of fat in more than 5% of hepatocytes in individuals who consume little or no alcohol (less than 20 g/day in women and 30 g/day in men). NAFLD encompasses two major histological subtypes: simple steatosis (non-alcoholic fatty liver, NAFL) and non-alcoholic steatohepatitis (NASH). NASH is a progressive form of the disease marked by hepatocellular injury, inflammation, and varying degrees of fibrosis that may eventually lead to cirrhosis, liver failure, or hepatocellular carcinoma (HCC)[1].

NAFLD is closely linked to metabolic comorbidities, such as obesity, insulin resistance, type 2 diabetes mellitus (T2DM), dyslipidaemia, and hypertension. Given these associations, NAFLD is increasingly considered a hepatic manifestation of metabolic syndrome[2]. NAFLD is also independently associated with cardiovascular disease, chronic kidney disease, and certain malignancies, making it a major contributor to overall morbidity and mortality[3].

As of 2023, it is estimated that over 30% of the global adult population is affected by NAFLD, with prevalence rates exceeding 40% in certain regions such as the Middle East, South America, and parts of Asia. The prevalence continues to rise in parallel with increasing rates of obesity and T2DM[4].

NASH affects approximately 20% of individuals with NAFLD and is responsible for the majority of liver-related morbidity and mortality. The global prevalence of NASH has been rising steadily and is projected to become the leading cause of liver transplantation in the United States by 2030[5].

The economic burden of NAFLD is substantial. In the United States alone, the annual direct medical costs for NAFLD are estimated at $100 billion, while in Europe, this burden reaches nearly €35 billion annually[6]. Indirect costs related to productivity loss, absenteeism, and premature death further exacerbate the societal impact.

In 2021, an international expert panel proposed a shift in nomenclature from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD). This change was aimed at better reflecting the underlying pathophysiology and removing the exclusionary emphasis on alcohol consumption[7]. According to the new criteria, MAFLD is diagnosed based on hepatic steatosis in conjunction with at least one of the following: overweight/obesity, presence of T2DM, or evidence of metabolic dysregulation.

Rationale for Change

• The term NAFLD was considered insufficiently descriptive and confusing for patients.
• MAFLD criteria offer a more inclusive and positive diagnostic framework.
• Better aligns with current understanding of disease mechanisms linked to metabolic dysfunction[8].

Controversies

• The transition may lead to confusion in ongoing clinical trials and longitudinal cohort studies.
• Critics argue that MAFLD does not address liver-specific outcomes effectively and may obscure non-metabolic causes of fatty liver disease[9].

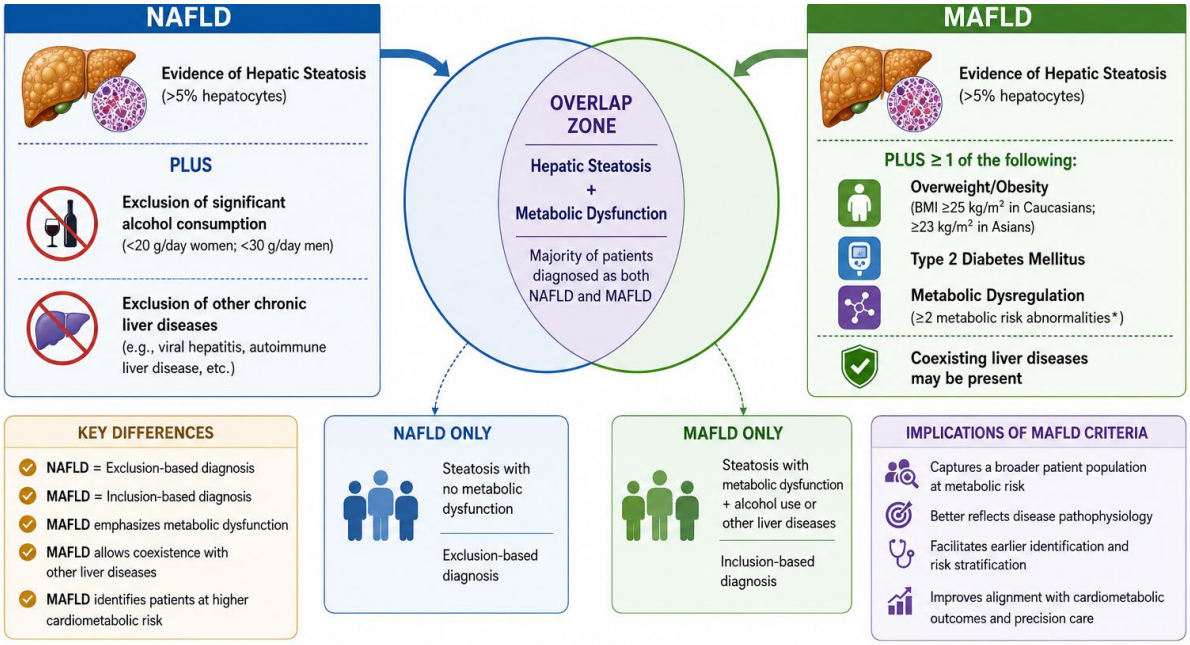

Figure 1. Comparison of NAFLD and MAFLD diagnostic criteria and population overlap. The figure illustrates the fundamental differences between the traditional non-alcoholic fatty liver disease (NAFLD) definition and the newer metabolic dysfunction-associated fatty liver disease (MAFLD) criteria. NAFLD is diagnosed based on hepatic steatosis in the absence of significant alcohol consumption and other chronic liver diseases, whereas MAFLD requires hepatic steatosis in the presence of overweight/obesity, type 2 diabetes mellitus, or metabolic dysregulation. The overlap region represents patients fulfilling both definitions, while MAFLD additionally captures individuals with metabolic dysfunction and concurrent liver diseases. This paradigm shift reflects the growing recognition of metabolic dysfunction as the central driver of fatty liver disease pathogenesis. Despite the debates, several hepatology societies have begun integrating MAFLD terminology into their guidelines and research initiatives, signifying a paradigm shift in the field.

2. Epidemiology

Recent estimates suggest that NAFLD affects approximately 30% of the global adult population, although substantial regional variation exists. According to a 2022 meta-analysis, prevalence rates are highest in the Middle East (38–40%) and South America (35–38%), followed by North America (32–35%), Asia-Pacific (27–32%), and Europe (25–30%)[10]. The prevalence has increased significantly in low- and middle-income countries due to rapid urbanization, sedentary lifestyles, and the adoption of Western dietary patterns.

NAFLD is now considered the most common liver disorder worldwide and a leading cause of chronic liver disease, surpassing viral hepatitis in several countries. NASH, the more progressive form of NAFLD, has an estimated global prevalence of 1.5–6.5% and continues to rise[11]. Pediatric NAFLD has also emerged as a major public health concern. The prevalence among obese children is estimated to range from 40% to 70%, and the disease may progress to NASH and fibrosis even during early life[12]. Alarmingly, autopsy studies have revealed that NAFLD is now among the most common liver disorders affecting adolescents in developed nations.

Advancing age is associated with altered lipid metabolism and a greater prevalence of metabolic comorbidities such as type 2 diabetes mellitus (T2DM) and hypertension. Consequently, NAFLD prevalence among individuals older than 60 years is estimated to exceed 40%, with a substantially increased risk of progression to fibrosis and cirrhosis[13].

Importantly, NAFLD is not restricted to obese individuals. Lean individuals (BMI < 25 kg/m^2) may also develop NAFLD, particularly in Asian populations, where up to 20% of NAFLD patients are non-obese. These individuals frequently exhibit visceral adiposity, insulin resistance, or genetic predispositions, including polymorphisms in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene[14]. Lean NAFLD presents significant diagnostic and therapeutic challenges because affected individuals may not meet conventional screening criteria.

Ethnic background plays a significant role in disease susceptibility. Hispanic populations demonstrate the highest prevalence of NAFLD, followed by individuals of South Asian and Middle Eastern ancestry. In contrast, African American populations exhibit comparatively lower prevalence rates, likely due to favorable patterns of fat distribution and protective genetic factors[15].

Socioeconomic status also influences NAFLD prevalence and disease burden. Individuals from lower-income populations are more likely to experience poor dietary habits, limited access to healthcare services, and reduced levels of physical activity, all of which contribute to increased NAFLD risk. Furthermore, under-resourced communities frequently lack adequate screening programs and early intervention strategies, resulting in delayed diagnosis and poorer clinical outcomes[16].

3. Pathophysiology

Insulin resistance (IR) is central to the pathogenesis of NAFLD. It impairs insulin's ability to suppress lipolysis in adipose tissue, leading to an increased influx of free fatty acids (FFAs) into the liver. These FFAs are either stored as triglycerides or contribute to the formation of toxic lipid intermediates, such as diacylglycerols and ceramides. This process, known as lipotoxicity, triggers hepatocellular injury, oxidative stress, inflammation, and apoptosis[17].

IR also enhances hepatic de novo lipogenesis (DNL), which further exacerbates lipid accumulation and promotes mitochondrial dysfunction and endoplasmic reticulum (ER) stress. The net result is hepatic steatosis with a heightened risk of progression to NASH and fibrosis.

Mitochondrial dysfunction plays a pivotal role in the transition from benign steatosis to NASH. Impaired mitochondrial β-oxidation and electron transport chain activity lead to increased reactive oxygen species (ROS) production. This oxidative stress causes lipid peroxidation, DNA damage, and inflammatory signaling[18].

ER stress, resulting from protein misfolding and calcium imbalance, activates the unfolded protein response (UPR). Chronic activation of the UPR induces inflammation and apoptosis, contributing to hepatocellular damage in NASH[19].

Autophagy, a lysosome-mediated degradation pathway, is essential for lipid turnover and organelle quality control. Dysregulated autophagy has been implicated in NAFLD by promoting lipid droplet accumulation, mitochondrial damage, and hepatic inflammation[20]. Enhancing autophagic flux may represent a potential therapeutic strategy.

Emerging evidence highlights the gut-liver axis as a critical regulator in NAFLD pathophysiology. Dysbiosis, characterized by alterations in gut microbiota composition, can influence intestinal permeability, endotoxemia, and bile acid metabolism. Bacterial metabolites such as lipopolysaccharides (LPS), ethanol, and short-chain fatty acids (SCFAs) can modulate hepatic inflammation and fat accumulation[21].

Metagenomic studies have identified NAFLD-associated microbial signatures, including an increase in Gram-negative and ethanol-producing bacteria. These changes may serve as non-invasive biomarkers or therapeutic targets. Probiotics, prebiotics, and fecal microbiota transplantation (FMT) are under investigation as potential interventions to restore gut microbial homeostasis.

4. Genetics and Epigenetics

Genetic susceptibility significantly influences the development and progression of NAFLD. Among the most studied variants is the PNPLA3 (patatin-like phospholipase domain-containing 3) I148M polymorphism, which is strongly associated with increased hepatic fat accumulation, inflammation, and fibrosis risk[22]. Similarly, the TM6SF2 (transmembrane 6 superfamily member 2) E167K variant impairs VLDL secretion, promoting lipid retention in hepatocytes and fibrosis[23].

Other emerging variants include MBOAT7, involved in phospholipid remodeling, and GCKR (glucokinase regulator), which affects glucose and lipid metabolism. These polymorphisms, individually and cumulatively, shape the interindividual variability in disease risk and response to treatment.

Epigenetic mechanisms, such as DNA methylation, histone modification, and non-coding RNA regulation, have been implicated in NAFLD progression. Hypomethylation of genes involved in lipogenesis and inflammation (e.g., SREBP-1c, TNF-α) has been observed in patients with NASH[24]. Conversely, hypermethylation of protective genes may impair hepatocyte resilience.

MicroRNAs (miRNAs), particularly miR-122, miR-34a, and miR-21, modulate lipid metabolism, inflammation, and fibrosis. These small RNA molecules are being explored as potential non-invasive biomarkers for early diagnosis and staging[25].

Histone acetylation and methylation patterns also influence hepatic gene expression. Drugs targeting epigenetic enzymes, such as histone deacetylase inhibitors, are currently being evaluated for NAFLD therapy.

The integration of multiple risk variants into polygenic risk scores (PRS) offers promise for personalized NAFLD risk stratification. PRS may enhance screening efficiency, predict disease progression, and guide therapeutic choices[26]. However, their clinical utility is still evolving, particularly across diverse ethnic groups.

5. Diagnostic Advancements

Given the limitations and risks associated with liver biopsy, considerable effort has been directed toward the development of non-invasive diagnostic tools for assessing steatosis, inflammation, and fibrosis in NAFLD. Commonly used scoring systems include the NAFLD Fibrosis Score (NFS), FIB-4 Index, and AST-to-Platelet Ratio Index (APRI). These tools rely on routine clinical and biochemical parameters and are particularly effective for excluding advanced fibrosis[27].

Advanced imaging modalities such as transient elastography (FibroScan®) and magnetic resonance elastography (MRE) provide quantitative assessments of liver stiffness and hepatic fat content with excellent reproducibility. MRI-proton density fat fraction (MRI-PDFF) is currently regarded as the gold standard for hepatic fat quantification in clinical trials[28].

Artificial intelligence (AI) and machine learning (ML) models are increasingly being integrated into radiological workflows to improve NAFLD diagnosis. AI-driven platforms enhance the detection of subtle alterations in liver morphology and texture, thereby improving fibrosis staging accuracy and treatment monitoring[29].

AI has also facilitated the development of predictive models that integrate clinical, biochemical, genetic, and imaging data to identify patients at elevated risk of progression to NASH or cirrhosis. These decision-support systems show significant promise for personalized care pathways in NAFLD.

Serum biomarkers have emerged as valuable tools for diagnosing and staging NAFLD. Cytokeratin-18 (CK-18) fragments, released during hepatocyte apoptosis, are elevated in NASH and correlate with disease activity. Other promising biomarkers include Pro-C3, a marker of fibrogenesis, and hyaluronic acid, an indicator of fibrosis[30].

Recent studies have highlighted the diagnostic potential of circulating microRNAs, particularly miR-122 and miR-192, which are associated with hepatic inflammation and fibrosis. These biomarkers may facilitate early disease detection and reduce the need for invasive diagnostic procedures.

6. NAFLD and Systemic Complications

NAFLD is not solely a hepatic disorder but also a systemic condition associated with significant cardiovascular consequences. Cardiovascular disease (CVD) represents the leading cause of mortality among patients with NAFLD, surpassing liver-related complications[31]. The pathophysiological relationship is driven by shared risk factors, including obesity, insulin resistance, dyslipidaemia, and chronic systemic inflammation.

Studies have demonstrated that individuals with NAFLD, particularly those with NASH, exhibit increased carotid intima-media thickness, coronary artery calcification, and endothelial dysfunction. NAFLD is also associated with cardiac arrhythmias such as atrial fibrillation and QT interval prolongation, likely resulting from oxidative stress and myocardial fat infiltration[32].

A bidirectional relationship exists between NAFLD and type 2 diabetes mellitus (T2DM). NAFLD increases the risk of developing diabetes through hepatic insulin resistance and chronic inflammation, whereas T2DM accelerates progression from NAFLD to NASH and cirrhosis[33]. Up to 70% of individuals with T2DM may have NAFLD, and approximately 30% may develop NASH.

This interaction complicates disease management, as patients with both T2DM and NAFLD experience a substantially greater risk of cardiovascular and renal complications. Glycaemic control, particularly through agents such as GLP-1 receptor agonists and SGLT2 inhibitors, has demonstrated promising effects on both hepatic and metabolic outcomes.

Emerging evidence also suggests a strong association between NAFLD and several extrahepatic malignancies, particularly colorectal, breast, and pancreatic cancers. Proposed mechanisms include insulin resistance, chronic inflammation, and alterations in the gut microbiome[34].

NAFLD-related metabolic dysfunction may create a pro-tumorigenic environment by promoting cellular proliferation, angiogenesis, and immune evasion. Consequently, regular cancer surveillance in patients with NAFLD, particularly those with metabolic syndrome, may be warranted.

NAFLD is independently associated with an increased risk of chronic kidney disease (CKD), even after adjustment for diabetes and hypertension. Proposed mechanisms include systemic

inflammation, accelerated atherogenesis, and renal lipotoxicity. Importantly, the severity of hepatic fibrosis is a strong predictor of renal impairment in patients with NAFLD[35].

Management of CKD in the setting of NAFLD requires a multidisciplinary approach focused on blood pressure control, glycaemic management, and lifestyle interventions.

7. Transition from NAFLD to MAFLD

In 2021, an international consensus panel proposed renaming non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated fatty liver disease (MAFLD). This initiative was intended to better reflect the underlying pathophysiology, emphasize positive diagnostic criteria, and eliminate the exclusion of alcohol consumption as a defining feature[36].

The MAFLD definition requires evidence of hepatic steatosis in addition to at least one of the following conditions: overweight/obesity, type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation. Unlike the NAFLD framework, MAFLD acknowledges the coexistence of other liver diseases, including alcohol-related liver disease and viral hepatitis, provided that metabolic dysfunction is present.

Recent studies indicate that individuals meeting MAFLD criteria exhibit a higher risk of liver fibrosis, cardiovascular events, and all-cause mortality compared with individuals classified using traditional NAFLD criteria[37].

Professional societies remain divided regarding the nomenclature change. Several organizations, including Chinese, Latin American, and Middle Eastern liver associations, have adopted the MAFLD terminology, whereas others, including the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), have not yet fully endorsed the transition[38].

The shift toward MAFLD has prompted revisions in clinical guidelines, clinical trial eligibility criteria, and public health strategies. Importantly, MAFLD may better capture the systemic nature of the disease, encouraging multidisciplinary collaboration among hepatologists, endocrinologists, cardiologists, and primary care physicians.

8. Management Strategies (2021–2025)

Lifestyle modification remains the cornerstone of NAFLD/MAFLD management. Sustained weight loss of at least 7–10% of body weight has been associated with significant histological improvements, including NASH resolution and fibrosis regression[39].

The Mediterranean diet, characterized by high consumption of monounsaturated fats, fruits, vegetables, legumes, and whole grains, has demonstrated substantial benefits in reducing hepatic steatosis and improving insulin sensitivity.

Low-carbohydrate dietary approaches and intermittent fasting regimens have also shown promising effects on reducing intrahepatic fat accumulation and improving metabolic health.

Physical Activity

- A minimum of 150–300 minutes per week of moderate-intensity aerobic exercise is recommended.
  • Resistance training complements aerobic exercise by reducing hepatic fat content and improving metabolic parameters.
  • Behavioral support interventions, including cognitive behavioral therapy and digital health technologies, improve adherence and long-term sustainability of lifestyle modifications.

Pharmacological Therapies

Currently, no medications have received specific FDA approval for the treatment of NAFLD or NASH; however, several promising therapeutic agents are undergoing clinical evaluation.

- Obeticholic acid (FXR agonist): Demonstrates fibrosis improvement but may be associated with pruritus and alterations in lipid profiles[40].
  • Resmetirom (MGL-3196, THR-β agonist): Reduces hepatic fat accumulation and improves lipid metabolism.
  • Lanifibranor (pan-PPAR agonist): Exhibits anti-inflammatory and anti-fibrotic effects in Phase II clinical studies.
  • Semaglutide (GLP-1 receptor agonist): Promotes weight loss and facilitates NASH resolution.

- Metabolic and Cardiovascular Risk Management
- Effective management of metabolic comorbidities remains critical.

- Statins are considered safe in NAFLD and significantly reduce cardiovascular risk.
  • SGLT2 inhibitors and GLP-1 receptor agonists demonstrate both metabolic and hepatoprotective benefits.
  • Blood pressure and lipid management should follow established cardiovascular prevention guidelines.

Emerging and Adjunctive Therapies

• **Anti-fibrotic agents:** Novel compounds targeting hepatic stellate cells and extracellular matrix remodeling are under development.
• **Probiotics and microbiome modulators:** These therapies aim to restore gut-liver axis homeostasis.
• **Vitamin E:** May provide benefits in non-diabetic patients with biopsy-confirmed NASH, although long-term safety remains under evaluation.

Farnesoid X receptor (FXR) is a nuclear receptor that regulates bile acid synthesis, lipid metabolism, and glucose homeostasis. FXR agonists, including obeticholic acid, have demonstrated anti-fibrotic and metabolic benefits in NAFLD, although adverse effects such as pruritus and increased LDL cholesterol remain important limitations[41].

Second-generation FXR agonists with improved safety profiles, including tropifexor, are currently under development. These agents aim to reduce hepatic inflammation and fibrosis through modulation of bile acid signaling and lipotoxicity pathways.

Thyroid hormone receptor-beta (THR-β) is selectively expressed in the liver and plays a central role in lipid metabolism. Agonists such as resmetirom target this receptor to reduce intrahepatic triglyceride accumulation and improve lipid profiles. Clinical studies have demonstrated significant reductions in MRI-PDFF-measured liver fat without affecting systemic thyroid function[42].

These agents may provide both hepatic and cardiovascular benefits and are being investigated as monotherapies and combination therapies.

9. Emerging Therapeutic Targets and Novel Interventions

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that regulate glucose and lipid metabolism. Lanifibranor, a pan-PPAR agonist, activates PPAR-α, PPAR-γ, and PPAR-δ pathways and has demonstrated efficacy in reducing NASH activity and hepatic fibrosis in Phase II clinical trials[43].

Other selective PPAR agonists, including elafibranor (PPAR-α/δ agonist) and saroglitazar (PPAR-α/γ agonist), are also under investigation and may provide personalized therapeutic approaches based on patient-specific metabolic phenotypes.

Hepatic fibrosis is a major determinant of prognosis in NAFLD and MAFLD. Consequently, several anti-fibrotic agents have been developed to target different stages of the fibrogenesis pathway.

• **Simtuzumab:** An anti-LOXL2 monoclonal antibody designed to inhibit collagen cross-linking, although clinical efficacy has been limited.
• **Cenicriviroc:** A CCR2/CCR5 antagonist that targets macrophage recruitment and hepatic inflammation.
• **Galectin-3 inhibitors:** These compounds block fibrosis-associated signaling pathways and are being evaluated as novel anti-fibrotic therapies.

These agents are increasingly being explored as part of combination treatment strategies alongside metabolic-targeted therapies.

Targeting the gut microbiome has emerged as one of the most promising frontiers in NAFLD treatment. Fecal microbiota transplantation (FMT), probiotics, prebiotics, and postbiotics aim to restore intestinal microbial balance and reduce endotoxemia.

Modulators of bile acid metabolism, including bile acid transporter inhibitors, and therapies targeting microbial metabolites are also being investigated as indirect approaches to reducing hepatic inflammation and steatosis.

10. Personalized Medicine and Precision Hepatology

The emergence of precision medicine has transformed the management paradigm of non-alcoholic fatty liver disease (NAFLD), recently redefined as metabolic dysfunction-associated fatty liver disease (MAFLD). Advances in genomics, bioinformatics, and digital health technologies have enabled a more individualized approach to disease prediction, diagnosis, and treatment. Genetic susceptibility plays a crucial role in disease development and progression, with variants in genes such as PNPLA3, TM6SF2, MBOAT7, and GCKR being strongly associated with hepatic steatosis, fibrosis progression, and hepatocellular carcinoma risk. Genetic profiling therefore provides valuable information for identifying high-risk individuals and predicting therapeutic response[43].

Recent developments in next-generation sequencing (NGS) and polygenic risk score (PRS) models have further enhanced risk assessment by integrating the cumulative effects of multiple genetic variants. These approaches are increasingly being explored for patient stratification, personalized surveillance programs, and targeted therapeutic interventions. Simultaneously, artificial intelligence (AI) and machine learning technologies are revolutionizing clinical decision-making by analyzing large-scale datasets derived from electronic health records, laboratory investigations, imaging modalities, and wearable devices. AI-driven predictive models facilitate early disease detection, fibrosis risk assessment, and personalized treatment planning, thereby improving clinical efficiency and patient outcomes.

The application of multi-omics technologies has significantly expanded understanding of the complex molecular mechanisms underlying NAFLD and MAFLD. Comprehensive integration of genomics, transcriptomics, proteomics, metabolomics, lipidomics, and microbiomics provides a systems-level perspective of disease pathogenesis and progression. These approaches have enabled the identification of distinct molecular subtypes of NAFLD, highlighting the biological heterogeneity that exists among patients with seemingly similar clinical presentations[44].

Multi-omics investigations have also facilitated the discovery of novel biomarkers for early diagnosis, disease staging, fibrosis prediction, and treatment monitoring. Furthermore, these technologies support the identification of previously unrecognized therapeutic targets and improve prediction of drug responsiveness. The integration of omics-derived biomarkers with clinical and imaging data through advanced computational models is increasingly generating actionable insights that can be translated into personalized patient care.

Effective risk stratification represents a cornerstone of precision hepatology. Contemporary models combine clinical characteristics, non-invasive fibrosis assessments, metabolic risk factors, genetic information, and biomarker profiles to categorize patients into low-, intermediate-, or high-risk groups. Such stratification assists clinicians in determining surveillance frequency, selecting candidates for pharmacological interventions, prioritizing specialist referral, and identifying individuals who may benefit from clinical trial participation.

Personalized therapeutic strategies are increasingly being developed to address the heterogeneous nature of NAFLD and MAFLD. Treatment plans may incorporate tailored

dietary interventions, structured physical activity programs, targeted pharmacotherapies, bariatric procedures, and gut microbiota modulation based on individual metabolic and molecular profiles. In addition, emerging therapies directed at specific pathogenic pathways, including insulin resistance, inflammation, oxidative stress, lipid dysregulation, and fibrosis, are expected to further enhance individualized treatment outcomes.

The convergence of genomics, multi-omics technologies, artificial intelligence, and digital health platforms is driving a paradigm shift toward precision hepatology. Future clinical practice is expected to increasingly rely on integrated molecular and clinical data to facilitate early diagnosis, individualized risk prediction, and personalized therapeutic decision-making. As these technologies become more accessible and clinically validated, precision medicine approaches have the potential to improve treatment efficacy, reduce disease progression, and optimize long-term outcomes for patients with NAFLD and MAFLD.

11. Public Health and Policy Interventions: Screening and Early Detection Programs

Given the rapidly increasing prevalence and systemic burden of non-alcoholic fatty liver disease (NAFLD), recently redefined as metabolic dysfunction-associated fatty liver disease (MAFLD), early detection and risk stratification have become critical public health priorities. Current recommendations from major hepatology societies advocate targeted screening of high-risk populations, particularly individuals with obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome, and other cardiometabolic risk factors. Early identification of disease allows timely intervention and may prevent progression to advanced fibrosis, cirrhosis, and hepatocellular carcinoma[45].

Primary healthcare settings play a central role in screening and disease surveillance. Non-invasive assessment tools, including the Fibrosis-4 Index (FIB-4), NAFLD Fibrosis Score (NFS), transient elastography, and emerging serum biomarkers, are increasingly utilized to identify patients requiring specialist referral. Furthermore, the integration of automated risk calculators, clinical decision-support systems, and electronic health record alerts has improved risk assessment and facilitated early diagnosis in routine clinical practice.

Recent international and regional clinical practice guidelines emphasize a multidisciplinary management strategy involving hepatologists, endocrinologists, cardiologists, nutritionists, and primary care physicians. Leading organizations, including the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and the Asian Pacific Association for the Study of the Liver (APASL), recommend standardized diagnostic pathways, broader implementation of non-invasive biomarkers, and comprehensive patient education programs focused on lifestyle modification and disease prevention[46]. These recommendations increasingly incorporate the MAFLD nomenclature, reflecting contemporary understanding of the central role of metabolic dysfunction in disease pathogenesis.

NAFLD has now emerged as a major non-communicable disease (NCD) of global importance and is increasingly recognized within international health policy frameworks. Organizations such as the World Health Organization (WHO) and the Global Liver Institute (GLI) have advocated for the incorporation of NAFLD into national and international NCD prevention programs. Similarly, initiatives such as the Lancet Commission on Liver Disease and the European NAFLD Policy Review have emphasized the need to integrate NAFLD screening within diabetes and cardiovascular disease management programs, establish national surveillance systems and disease registries, and promote public health policies that encourage healthy nutrition, regular physical activity, and liver health awareness.

Advances in digital health technologies are further transforming NAFLD prevention and management strategies. Artificial intelligence (AI)-driven risk prediction models, telemedicine platforms, mobile health applications, and digital lifestyle intervention programs are increasingly being employed to improve disease monitoring, patient engagement, and personalized healthcare delivery. Tools such as fatty liver risk calculators, wearable activity trackers, and digital coaching platforms facilitate self-management and support long-term adherence to lifestyle interventions. Moreover, public awareness initiatives utilizing social media campaigns, community-based education programs, and school health interventions are playing an essential role in reducing disease stigma, improving health literacy, and promoting early healthcare-seeking behavior.

Collectively, these integrated approaches have the potential to improve early diagnosis, optimize disease management, reduce healthcare burden, and ultimately mitigate the growing global impact of NAFLD/MAFLD.

12. Future Directions and Research Gaps

The COVID-19 pandemic has highlighted the increased vulnerability of individuals with metabolic disorders and has significantly influenced the landscape of NAFLD/MAFLD research. Accumulating evidence indicates that patients with NAFLD/MAFLD experience more severe COVID-19 outcomes, including higher rates of hospitalization, intensive care unit admission, mechanical ventilation, and mortality. Furthermore, the systemic inflammatory response associated with SARS-CoV-2 infection may exacerbate underlying hepatic steatosis, fibrosis progression, and metabolic dysfunction[47].

Consequently, post-pandemic research efforts are increasingly focused on evaluating the long-term hepatic consequences of COVID-19, particularly its effects on liver function, fibrosis progression, and metabolic health. Additional areas of interest include the integration of telemedicine and digital health technologies for remote liver disease management, as well as the incorporation of NAFLD screening protocols into post-COVID metabolic rehabilitation and follow-up programs.

A major challenge in NAFLD research remains the limited availability of long-term prospective data describing disease progression, treatment response, and clinical outcomes. Large-scale longitudinal cohort studies and international registries are therefore essential for improving risk prediction and guiding evidence-based management strategies. Several

collaborative initiatives, including the Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) consortium, the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN), and the EASL-Lancet Liver Commission, are actively addressing these knowledge gaps. These programs aim to validate novel non-invasive biomarkers, improve disease classification systems, refine risk stratification models, and establish standardized outcome measures across diverse populations[48].

Despite substantial advances in therapeutic development, several challenges continue to hinder the successful translation of NAFLD therapies into clinical practice. Current clinical trials frequently encounter difficulties related to endpoint standardization, variability in histological assessment, and limited representation of diverse patient populations. In addition, evolving diagnostic criteria and the transition from NAFLD to MAFLD terminology have created challenges in patient selection and trial design.

Future clinical investigations should prioritize the development of combination therapies targeting multiple pathogenic pathways, including insulin resistance, inflammation, oxidative stress, lipotoxicity, and fibrosis. Greater emphasis should also be placed on underrepresented populations such as pediatric patients, elderly individuals, lean NAFLD patients, and those with mixed-etiology liver disease. Furthermore, the incorporation of precision medicine approaches, including genetic, metabolic, and multi-omics profiling, may facilitate personalized therapeutic strategies and improve treatment efficacy.

Given the complex and multisystem nature of NAFLD/MAFLD, future healthcare systems must adopt integrated and patient-centered models of care. Multidisciplinary clinics involving hepatologists, endocrinologists, cardiologists, nutritionists, and primary care physicians are increasingly recognized as an effective approach for comprehensive disease management. Such collaborative frameworks enable simultaneous management of hepatic, metabolic, and cardiovascular comorbidities, thereby improving clinical outcomes.

Advances in digital health technologies offer additional opportunities to enhance patient care through remote monitoring, lifestyle coaching, and continuous risk assessment. Digital health hubs, wearable monitoring devices, telemedicine platforms, and artificial intelligence (AI)-driven clinical decision-support systems have the potential to facilitate early intervention and individualized treatment planning. AI-based algorithms may further assist in disease screening, fibrosis prediction, patient stratification, and treatment optimization[49].

Although significant progress has been made in understanding the epidemiology, pathophysiology, diagnosis, and management of NAFLD/MAFLD, substantial research gaps remain. Future studies should focus on identifying reliable non-invasive biomarkers, validating emerging therapeutic targets, improving clinical trial design, and expanding the application of precision medicine technologies. Strengthening international collaborations, developing global surveillance networks, and integrating digital health innovations into routine clinical practice will be crucial for reducing the growing burden of NAFLD/MAFLD and improving patient outcomes worldwide.

13. Discussion

From 2021 to 2025, nonalcoholic fatty liver disease (NAFLD) has undergone a dramatic transformation in how it is understood, diagnosed, and managed. Once considered a liver-specific concern, it is now widely acknowledged as a complex, multisystem disease with profound global health implications. The continued rise in NAFLD prevalence, particularly in pediatrics, lean individuals, and low- to middle-income populations, highlights an urgent need for targeted prevention and intervention strategies. This epidemiological shift, coupled with increasing metabolic complexity, has prompted a nomenclature change from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD). Although this transition remains debated, MAFLD better reflects the underlying metabolic pathophysiology and is gaining traction in research and clinical guidelines.

Advancements in pathophysiology have further refined our understanding of disease mechanisms. Insulin resistance, lipotoxicity, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and impaired autophagy contribute to hepatocyte damage and progression to nonalcoholic steatohepatitis (NASH) and fibrosis. The gut–liver axis, particularly microbiota-derived endotoxins and metabolites, has emerged as a pivotal regulator of hepatic inflammation and steatosis. Parallel breakthroughs in genomics have identified gene variants such as PNPLA3, TM6SF2, and MBOAT7 that significantly influence susceptibility, disease progression, and treatment response. Moreover, epigenetic mechanisms and circulating microRNAs offer novel biomarkers and therapeutic targets, further supporting the application of precision medicine in hepatology.

Simultaneously, diagnostic strategies have shifted toward non-invasive, scalable tools. While liver biopsy remains the gold standard for definitive diagnosis, its limitations have accelerated the adoption of imaging-based modalities such as FibroScan® and MRI-PDFF, as well as serum biomarkers including CK-18 and Pro-C3. These tools improve fibrosis assessment, facilitate early detection, and reduce patient burden. Artificial intelligence (AI) and machine learning algorithms have been integrated into diagnostic imaging and electronic health records, enabling real-time risk prediction and individualized care pathways.

NAFLD's systemic burden is increasingly recognized, particularly its role in cardiovascular disease, type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and extrahepatic cancers. Cardiovascular complications remain the leading cause of mortality in this population, underscoring the need for comprehensive, multidisciplinary care. The bidirectional relationship between T2DM and NAFLD complicates management and necessitates therapies that address both glycemic and hepatic outcomes. Likewise, the growing evidence linking NAFLD to renal impairment and malignancies has expanded the clinical impact of this disease beyond hepatology alone.

Despite these developments, the therapeutic landscape remains limited. No pharmacotherapies are currently approved specifically for NAFLD or NASH, though several agents are in advanced clinical trials. FXR agonists (e.g., obeticholic acid), thyroid hormone receptor β agonists (e.g., resmetirom), PPAR modulators (e.g., lanifibranor), and GLP-1 receptor agonists (e.g., semaglutide) show promise in improving fibrosis and hepatic steatosis. However,

lifestyle modification centered on weight loss, dietary adjustment, and physical activity remains the foundation of care. Digital health tools and behavioral support programs are being used to enhance patient adherence and long-term sustainability of lifestyle changes.

Personalized hepatology is emerging as a viable paradigm through the integration of genomics, multi-omics profiling, and AI. These tools enable early risk stratification, identification of molecular phenotypes, and prediction of therapeutic responsiveness. However, clinical translation remains limited by data heterogeneity, high costs, and lack of standardized infrastructure. Expansion of multi-ethnic biobanks, improved machine learning models, and global research consortia are needed to bridge these gaps and support equitable access to personalized liver care.

On a public health level, NAFLD has gained recognition as a priority non-communicable disease (NCD). Regional and international guidelines now promote early screening in primary care settings using non-invasive tools and risk-based algorithms. Policy integration efforts such as incorporating NAFLD screening into diabetes and cardiovascular disease programs are underway, supported by digital health platforms and mobile applications that engage patients in self-care and monitoring. The COVID-19 pandemic has further catalyzed telemedicine and remote liver care strategies, particularly for high-risk patients with metabolic comorbidities.

While significant progress has been made, research gaps persist. Standardizing diagnostic endpoints, improving inclusion of pediatric and elderly populations, and expanding representation of lean and non-obese NAFLD patients remain priorities. Future clinical trials should adopt combination therapies targeting multiple disease pathways and explore interventions that address the gut microbiome, fibrosis, and systemic inflammation. Multidisciplinary liver-metabolic clinics and digital care hubs may offer scalable solutions to improve adherence, outcomes, and population health impact.

In conclusion, NAFLD/MAFLD represents a growing public health and clinical challenge that demands integrated solutions. The field is advancing rapidly in diagnostics, therapeutics, and precision medicine, yet widespread implementation remains uneven. Bridging this gap requires sustained global collaboration, innovative care models, and robust health policy support. With continued investment in translational research, digital tools, and multidisciplinary care, the coming decade holds the potential to significantly reduce the burden of fatty liver disease worldwide[48–60].

14. Conclusion

Over the past five years, significant progress has been made in understanding the complex pathogenesis, systemic implications, and evolving management strategies of nonalcoholic fatty liver disease (NAFLD), now increasingly referred to as metabolic dysfunction-associated fatty liver disease (MAFLD). The global burden of the disease has expanded markedly, affecting diverse populations including children, elderly individuals, lean patients, and those in low- and middle-income countries. Advances in molecular research have revealed roles for insulin resistance, lipotoxicity, mitochondrial and endoplasmic reticulum stress, gut microbiota dysbiosis, and genetic predisposition in disease onset and progression. These insights have fostered the emergence of novel diagnostic tools especially non-invasive biomarkers and

imaging modalities as well as early applications of artificial intelligence and multi-omics technologies in personalized hepatology.

Despite the absence of approved pharmacotherapies, multiple promising agents targeting nuclear receptors, fibrotic pathways, and metabolic regulators are currently in late-stage clinical trials. Lifestyle intervention remains the cornerstone of treatment, supported increasingly by digital health platforms and behavioral modification tools. Importantly, NAFLD is now recognized as a multisystem disorder linked to increased cardiovascular risk, type 2 diabetes, chronic kidney disease, and malignancies, requiring integrated and multidisciplinary care models. The shift to the MAFLD nomenclature, while still under debate, reflects a broader movement toward redefining fatty liver disease within the context of metabolic dysfunction and systemic health.

Looking forward, future success will depend on closing critical research gaps, particularly in biomarker discovery, combination therapy development, and inclusion of underrepresented populations. The integration of real-world data, global registry initiatives, and longitudinal cohort studies will be essential to refining diagnostic thresholds and therapeutic targets. Policymakers and healthcare systems must prioritize early detection, public awareness, and care coordination to reduce disease burden. As we enter the next decade, the convergence of precision medicine, digital innovation, and public health collaboration offers a transformative opportunity to improve outcomes and reshape the landscape of fatty liver disease on a global scale.

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