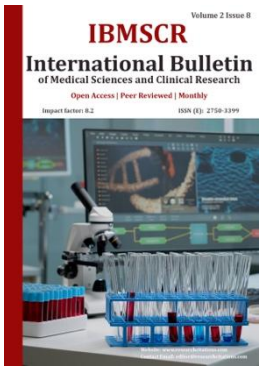

NON-ALCOHOLIC FATTY LIVER DISEASES AS A LEADING CAUSE TO LIVER CIRRHOSIS

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Abstract:

Non-alcoholic fatty liver disease (NAFLD) has emerged as the most prevalent chronic liver disorder globally, closely associated with obesity, insulin resistance, and metabolic syndrome. This review aims to analyze NAFLD as a leading cause of liver cirrhosis by summarizing current evidence on its epidemiology, risk factors, pathogenesis, and clinical significance. Epidemiological studies indicate that approximately 24–30% of adults worldwide are affected by NAFLD, with prevalence rising even among adolescents and young adults. Key mechanisms driving disease progression include hepatic fat accumulation, insulin resistance, oxidative stress, and chronic inflammation. NAFLD can progress from simple steatosis to non-alcoholic steatohepatitis (NASH), advanced fibrosis, and ultimately cirrhosis, leading to significant morbidity and mortality. Early recognition, lifestyle modification, and targeted interventions are essential to reduce the clinical burden and prevent long-term hepatic complications.

Keywords: Non-alcoholic fatty liver disease, NAFLD, NASH, liver cirrhosis, metabolic syndrome, epidemiology, pathogenesis

Introduction. Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disorder worldwide, reflecting the global increase in obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (Younossi Z.M. et al., 2016; Estes C. et al., 2018). NAFLD is characterized by excessive fat accumulation in hepatocytes (>5% of liver weight) in the absence of significant alcohol consumption or other secondary causes of liver disease (Powell E.E. et al., 2021). Its spectrum ranges from simple steatosis, which is often asymptomatic, to non-alcoholic steatohepatitis (NASH), which is associated with inflammation, hepatocyte injury, fibrosis, and potential progression to cirrhosis and hepatocellular carcinoma (Friedman S.L. et al., 2018).

Recently, a global consensus renamed NAFLD to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) to better categorize its metabolic drivers (Rinella M.E. et al., 2023). This shift is supported by international guidelines that aim to reduce the stigma associated with 'fatty' liver language (Newsome P.N. et al., 2024). Additionally, the diagnostic criteria now place more emphasis on metabolic dysfunction even in the presence of other liver diseases (Eslam M. et al., 2020).

Globally, the prevalence of NAFLD is estimated at 24–30% of the adult population, with regional variations reflecting differences in obesity rates, lifestyle, and genetic predisposition (Younossi Z.M. et al., 2016; Estes C. et al., 2018). Middle Eastern and South American populations have the highest reported prevalence, while African populations show lower rates. NAFLD is increasingly diagnosed in younger individuals, including adolescents, raising concerns about earlier onset of liver complications and increased lifetime risk of cirrhosis (Powell E.E. et al., 2021).

Genetic factors also play a pivotal role in disease susceptibility and progression. Polymorphisms in the PNPLA3 (I148M) and TM6SF2 genes have been linked to higher hepatic fat content and accelerated fibrosis, explaining part of the ethnic variability in NAFLD prevalence (Romeo S. et al., 2008; Anstee Q.M. et al., 2020). Beyond genetics, lifestyle factors such as high-calorie diets, sedentary behavior, and insulin resistance are key contributors to the pathogenesis of NAFLD (Powell E.E. et al., 2021).

The clinical significance of NAFLD lies not only in its potential progression to cirrhosis but also in its systemic impact, including increased cardiovascular risk, chronic kidney disease, and type 2 diabetes (Anstee Q.M. et al., 2020). Early identification of high-risk patients, preventive strategies, and appropriate management are essential to reduce the burden of NAFLD-related liver disease and associated comorbidities.

This review aims to summarize current evidence on the epidemiology, risk factors, pathogenesis, and clinical impact of NAFLD, with a focus on its progression to liver cirrhosis. Understanding these aspects is crucial for guiding clinical practice, public health interventions, and future research in the field of metabolic liver disease.

Epidemiology of NAFLD

Non-alcoholic fatty liver disease (NAFLD) is now recognized as the most prevalent chronic liver disease worldwide, affecting nearly one in four adults globally (Younossi Z.M. et al., 2016). Meta-analytic assessments estimate the global prevalence of NAFLD at approximately 24–30%, with notable geographic variation (Estes C. et al., 2018). The Middle East and South America report the highest prevalence, exceeding 30%, whereas Africa shows the lowest rates, around 13–14%. This variation reflects differences in obesity prevalence, lifestyle factors, and genetic susceptibility across populations. NAFLD prevalence is increasing in both developed and developing countries, largely driven by the parallel rise in obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and sedentary lifestyles (Powell E.E. et al., 2021). In Western countries, up to 25–30% of adults are affected, while in Asian populations, prevalence varies between 15–30%, highlighting the influence of regional metabolic and lifestyle factors. Notably, NAFLD is no longer restricted to middle-aged or older adults; it is increasingly identified in adolescents and young adults, which raises concerns about early progression to advanced liver disease over a lifetime (Younossi Z.M. et al., 2016).

Epidemiological studies also reveal sex differences in NAFLD prevalence. Men generally exhibit higher prevalence than premenopausal women, but postmenopausal women show increasing rates, likely due to hormonal changes influencing fat distribution and insulin resistance. Additionally, NAFLD coexists frequently with metabolic comorbidities, including obesity (particularly central obesity), T2DM, hypertension, and dyslipidemia, further emphasizing its role as a multisystem metabolic disorder (Anstee Q.M. et al., 2020). The World Health Organization emphasizes that NAFLD/MASLD is now a critical component of the global non-communicable disease crisis, closely following the trajectory of the obesity pandemic (WHO, 2024).

The burden of NAFLD is expected to grow substantially in the coming decades. Projections indicate that NAFLD-related liver cirrhosis and hepatocellular carcinoma (HCC) will increasingly contribute to liver transplantation demand, especially as viral hepatitis becomes better controlled through vaccination and antiviral therapy (Younossi Z.M. et al., 2019). These epidemiological trends underscore the urgent need for population-level interventions targeting

obesity, diabetes, and sedentary lifestyles, alongside early detection and management strategies for high-risk individuals.

Risk Factors and Predisposition

NAFLD is a multifactorial disease influenced by a combination of metabolic, genetic, and environmental factors. Among these, obesity is the most significant risk factor, particularly central or visceral obesity, which correlates strongly with hepatic fat accumulation and insulin resistance (Powell E.E. et al., 2021). Individuals with a body mass index (BMI) ≥30 kg/m^2 exhibit a markedly higher prevalence of NAFLD, although the disease can also occur in non-obese individuals, especially in Asian populations, reflecting the role of visceral adiposity over total body weight. Type 2 diabetes mellitus (T2DM) is another major contributor to NAFLD. Insulin resistance in T2DM promotes hepatic de novo lipogenesis and impairs fat oxidation, leading to steatosis. Patients with diabetes are also at increased risk of progressing to non-alcoholic steatohepatitis (NASH) and advanced fibrosis (Anstee Q.M. et al., 2020).

Dyslipidemia, characterized by elevated triglycerides and low high-density lipoprotein (HDL) cholesterol, further exacerbates hepatic fat accumulation and oxidative stress. Hyperlipidemia often coexists with obesity and diabetes, forming the metabolic syndrome cluster, which is strongly associated with both the development and progression of NAFLD (Powell E.E. et al., 2021).

Genetic predisposition plays a crucial role in individual susceptibility. Polymorphisms in the PNPLA3 gene, particularly the I148M variant, have been consistently linked to increased hepatic fat deposition, NASH, and fibrosis progression (Romeo S. et al., 2008). Other genetic loci, such as TM6SF2 and MBOAT7, also influence lipid metabolism and fibrogenesis, partially explaining the variability in disease severity among individuals with similar metabolic risk profiles. Age and sex are additional important factors. NAFLD prevalence increases with age and is higher among men than premenopausal women. Postmenopausal women, however, demonstrate rising prevalence, likely due to estrogen deficiency affecting lipid metabolism and insulin sensitivity.

Lifestyle factors contribute substantially to NAFLD risk. Diets high in saturated fats, simple sugars (particularly fructose), and excessive caloric intake promote hepatic lipid accumulation. Sedentary behavior exacerbates insulin resistance and obesity, further amplifying risk. Conversely, physical activity and weight loss have been shown to reduce liver fat content and improve metabolic profiles (Powell E.E. et al., 2021). Finally, ethnic differences influence NAFLD prevalence and outcomes. Hispanic populations display higher susceptibility and more severe liver disease, while African ancestry appears somewhat protective, likely due to differences in PNPLA3 allele frequency and lipid handling (Anstee Q.M. et al., 2020).

Pathogenesis of NAFLD

The pathogenesis of non-alcoholic fatty liver disease (NAFLD) is complex and multifactorial, involving metabolic, genetic, and environmental interactions. Traditionally, the "two-hit hypothesis" was proposed, suggesting that simple hepatic steatosis ("first hit") sensitizes the liver to additional insults such as oxidative stress, inflammation, and mitochondrial dysfunction ("second hit"), which ultimately leads to non-alcoholic steatohepatitis (NASH) and fibrosis (Powell E.E. et al., 2021). More recent models have adopted a "multiple parallel hits" concept, emphasizing the simultaneous contribution of various pathogenic factors, including adipose tissue dysfunction, gut microbiota alterations, and

genetic predisposition (Anstee Q.M. et al., 2020). The progression from simple steatosis to NASH is driven by complex molecular mechanisms, including lipotoxicity and endoplasmic reticulum stress, which trigger cellular apoptosis and long-term scarring (Loomba R. et al., 2021). Hepatic lipid accumulation is central to NAFLD development. Insulin resistance, commonly associated with obesity and type 2 diabetes, drives excessive lipolysis in adipose tissue, increasing the flux of free fatty acids (FFAs) to the liver. At the same time, hyperinsulinemia stimulates de novo lipogenesis, further promoting triglyceride deposition in hepatocytes. Impaired mitochondrial fatty acid oxidation and export of very-low-density lipoproteins (VLDL) exacerbate hepatic fat accumulation (Powell E.E. et al., 2021).

Oxidative stress and mitochondrial dysfunction represent key mechanisms in progression from simple steatosis to NASH. Excessive FFAs undergo β-oxidation in mitochondria, generating reactive oxygen species (ROS) that damage hepatocellular membranes, proteins, and DNA. ROS-induced lipid peroxidation promotes activation of Kupffer cells and hepatic stellate cells, triggering inflammatory cascades and fibrogenesis (Anstee Q.M. et al., 2020). Inflammatory signaling plays a critical role in NAFLD progression. Adipose tissue dysfunction in obesity leads to increased secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and leptin, which exacerbate hepatic inflammation. Conversely, anti-inflammatory adipokines, including adiponectin, are reduced, further tilting the balance toward hepatocellular injury and fibrosis (Powell E.E. et al., 2021).

Gut-liver axis alterations contribute to NAFLD pathogenesis. Dysbiosis and increased intestinal permeability allow translocation of bacterial endotoxins into the portal circulation, activating hepatic Toll-like receptors and promoting inflammatory responses. Short-chain fatty acids, bile acids, and other microbial metabolites also modulate hepatic lipid metabolism and immune responses, linking gut health directly to liver pathology (Anstee Q.M. et al., 2020). Genetic and epigenetic factors influence susceptibility and disease severity. The PNPLA3 I148M variant is strongly associated with hepatic fat accumulation, NASH, and fibrosis progression, while TM6SF2 and MBOAT7 polymorphisms affect triglyceride secretion and lipid remodeling. Epigenetic modifications, including DNA methylation and microRNA expression, further regulate genes involved in lipid metabolism, inflammation, and fibrogenesis, explaining inter-individual variability in disease outcomes (Romeo S. et al., 2008).

Progression from Steatosis to Cirrhosis

Non-alcoholic fatty liver disease (NAFLD) encompasses a continuum of hepatic pathology, beginning with simple steatosis and potentially advancing to non-alcoholic steatohepatitis (NASH), fibrosis, and ultimately cirrhosis. Understanding this progression is crucial for timely intervention and prevention of liver-related morbidity and mortality (Powell E.E. et al., 2021). Simple Steatosis (NAFL): The earliest stage of NAFLD is characterized by accumulation of triglycerides in hepatocytes without significant inflammation or hepatocellular injury. Patients at this stage are often asymptomatic, and liver function tests may be normal or mildly elevated. Simple steatosis is considered reversible with lifestyle modifications, including weight loss, dietary changes, and increased physical activity (Anstee Q.M. et al., 2020).

Non-Alcoholic Steatohepatitis (NASH): Progression from simple steatosis to NASH involves hepatocellular injury, inflammation, and ballooning degeneration. This stage represents a higher risk of fibrosis development due to chronic inflammatory signaling and oxidative stress. NASH is frequently associated with metabolic syndrome components,

including insulin resistance, central obesity, and dyslipidemia (Powell E.E. et al., 2021). Histologically, NASH is identified by hepatocyte ballooning, lobular inflammation, and varying degrees of fibrosis, often requiring liver biopsy for definitive diagnosis.

Fibrosis Development: Persistent hepatocellular injury triggers activation of hepatic stellate cells, which deposit extracellular matrix proteins and collagen, leading to fibrosis. Fibrosis initially occurs in a perisinusoidal and periportal distribution but can progressively involve bridging fibrosis, distorting hepatic architecture. The rate of fibrosis progression is influenced by metabolic factors, genetic predisposition (e.g., PNPLA3 I148M variant), age, and comorbidities such as type 2 diabetes (Romeo S. et al., 2008; Anstee Q.M. et al., 2020).

Cirrhosis: Advanced fibrosis ultimately culminates in cirrhosis, characterized by nodular regeneration, architectural distortion, and portal hypertension. NAFLD-related cirrhosis is increasingly recognized as a major cause of end-stage liver disease and a leading indication for liver transplantation globally (Younossi Z.M. et al., 2019). Unlike viral hepatitis, NAFLD cirrhosis is often diagnosed late due to subtle early symptoms, highlighting the importance of regular monitoring in at-risk individuals.

Risk Factors for Rapid Progression: Several factors accelerate NAFLD progression to cirrhosis: Metabolic comorbidities: Type 2 diabetes, obesity, and hyperlipidemia increase hepatocyte lipotoxicity and inflammatory signaling.

Genetic variants: PNPLA3, TM6SF2, and MBOAT7 polymorphisms modulate lipid metabolism and fibrosis risk. Age and sex: Older age and male sex are associated with more severe fibrosis. Lifestyle factors: Sedentary behavior, high-calorie diets, and alcohol consumption exacerbate liver injury.

Clinical Implications: Early identification of patients at risk for fibrosis progression is essential. Non-invasive scoring systems (e.g., FIB-4, NAFLD fibrosis score) and imaging modalities (transient elastography, MRI-PDFF) aid in risk stratification, guiding clinical management and the timing of liver transplantation consideration (Powell E.E. et al., 2021).

Clinical Impact of NAFLD-Related Cirrhosis

NAFLD-related cirrhosis represents the advanced stage of chronic metabolic liver disease and is associated with substantial morbidity, mortality, and healthcare burden. As NAFLD prevalence rises globally, the clinical implications of cirrhosis due to this etiology are becoming increasingly significant (Younossi Z.M. et al., 2019; Powell E.E. et al., 2021).

1. Hepatic Complications: Cirrhosis disrupts normal liver architecture and function, leading to portal hypertension, variceal bleeding, ascites, hepatic encephalopathy, and hepatocellular carcinoma (HCC). NAFLD-related cirrhosis is particularly concerning because patients may remain asymptomatic until decompensation occurs, delaying diagnosis and treatment (Powell E.E. et al., 2021). HCC risk is rising among NAFLD patients, even in the absence of viral hepatitis or significant alcohol consumption (Younossi Z.M. et al., 2019).

2. Metabolic Comorbidities: Patients with NAFLD cirrhosis often have coexisting metabolic disorders, including type 2 diabetes mellitus, obesity, and cardiovascular disease. These comorbidities not only exacerbate liver injury but also contribute to higher overall morbidity and mortality. Cardiovascular disease remains a leading cause of death in NAFLD patients, often surpassing liver-related complications (Anstee Q.M. et al., 2020).

3. Impact on Quality of Life: Cirrhosis significantly impairs physical, psychological, and social functioning. Fatigue, muscle wasting, sleep disturbances, and cognitive dysfunction are

common. Studies have shown that patients with NAFLD cirrhosis experience decreased health-related quality of life, particularly in domains related to physical health and daily activities (Powell E.E. et al., 2021).

4. Healthcare Burden: The rising prevalence of NAFLD-related cirrhosis increases the demand for healthcare resources, including hospitalizations, endoscopic procedures, imaging studies, and liver transplantation. Predictive models indicate that NAFLD may soon become the leading indication for liver transplantation in Western countries, reflecting both the success in controlling viral hepatitis and the uncontrolled rise of metabolic liver disease (Younossi Z.M. et al., 2019).

5. Prognosis and Mortality: Cirrhosis from NAFLD carries a variable prognosis depending on the stage at diagnosis and presence of comorbidities. Decompensated cirrhosis, marked by jaundice, ascites, and encephalopathy, significantly increases mortality risk. Furthermore, the presence of metabolic syndrome components accelerates disease progression and worsens outcomes (Anstee Q.M. et al., 2020).

Clinical Implications: Early identification of at-risk individuals is crucial for timely intervention. Screening high-risk populations—patients with obesity, diabetes, or advanced age—can enable preventive strategies, including lifestyle modification, pharmacotherapy targeting metabolic risk factors, and regular surveillance for HCC and portal hypertension complications. Multidisciplinary care involving hepatologists, endocrinologists, nutritionists, and primary care providers improves outcomes and reduces progression to decompensated cirrhosis. NAFLD-related cirrhosis is no longer an isolated hepatic issue; it is a multisystem disorder that significantly increases the risk of cardiovascular events and chronic kidney disease (Dufour J.F. et al., 2022). Effective management requires intensive lifestyle interventions, as significant weight loss has been histologically proven to reverse even advanced stages of fibrosis (Vilar-Gomez E. et al., 2023).

Diagnostic Approaches

Early and accurate diagnosis of NAFLD and its progression to cirrhosis is crucial for preventing complications and guiding management. Diagnosis involves a combination of clinical evaluation, laboratory tests, imaging modalities, and, in selected cases, liver biopsy (Powell E.E. et al., 2021; Anstee Q.M. et al., 2020).

1. Clinical Assessment:The initial evaluation begins with a thorough patient history and physical examination. Risk factors such as obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, and family history of liver disease should be identified. Physical signs, including hepatomegaly, stigmata of chronic liver disease, and central obesity, provide initial clues for NAFLD (Powell E.E. et al., 2021).

2. Laboratory Tests: Biochemical evaluation includes liver function tests (AST, ALT, ALP, bilirubin), which may indicate hepatocellular injury. However, these markers are often normal in NAFLD patients, particularly in early stages, making them insufficient for diagnosis alone. Additional assessments include fasting glucose, HbA1c, lipid profile, and inflammatory markers, which help evaluate associated metabolic disorders (Anstee Q.M. et al., 2020).

3. Imaging Techniques: Non-invasive imaging plays a pivotal role in detecting hepatic steatosis and evaluating fibrosis: Ultrasound: Widely available and cost-effective, useful for detecting moderate-to-severe steatosis, though less sensitive in early disease or in obese individuals. Transient Elastography (FibroScan): Measures liver stiffness to estimate fibrosis

and can quantify hepatic fat content using controlled attenuation parameter (CAP). Magnetic Resonance Imaging (MRI) and Proton Density Fat Fraction (PDFF): Highly accurate in quantifying liver fat and assessing fibrosis, particularly in research or complex cases.

4. Non-invasive Fibrosis Scoring Systems: Several scoring algorithms help stratify patients by fibrosis risk without invasive procedures. Commonly used scores include:

NAFLD Fibrosis Score (NFS): Incorporates age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio. Fibrosis-4 (FIB-4) Index: Based on age, AST, ALT, and platelet count; useful for identifying advanced fibrosis. Enhanced Liver Fibrosis (ELF) Test: Measures serum biomarkers reflecting extracellular matrix remodeling and fibrosis. These tools guide clinical decision-making and determine the need for further evaluation or referral to hepatology specialists (Anstee Q.M. et al., 2020). Leading clinical associations now prioritize the use of non-invasive tests, such as the FIB-4 index, to stratify patients at risk of advanced fibrosis in primary care settings before considering invasive procedures (Cusi K. et al., 2022).

5. Liver Biopsy: Although invasive, liver biopsy remains the gold standard for diagnosing NASH and assessing fibrosis stage. It is typically reserved for patients with diagnostic uncertainty, suspected advanced fibrosis, or those being considered for clinical trials or experimental therapies. Histological assessment distinguishes simple steatosis from steatohepatitis and provides prognostic information regarding progression to cirrhosis (Powell E.E. et al., 2021).

6. Emerging Diagnostic Modalities: Recent research focuses on molecular biomarkers, elastography-based imaging, and artificial intelligence–driven analysis to improve non-invasive diagnosis. These approaches aim to enhance sensitivity and specificity, reduce the need for biopsy, and facilitate large-scale screening in high-risk populations.

Clinical Implications: Timely and accurate diagnosis of NAFLD and fibrosis is essential to implement lifestyle interventions, pharmacological treatments, and surveillance strategies. Non-invasive tests and imaging facilitate early detection, patient stratification, and longitudinal monitoring, improving outcomes and reducing progression to cirrhosis and its complications.

Conclusion

Non-alcoholic fatty liver disease (NAFLD) has emerged as a major global health challenge, reflecting the escalating prevalence of obesity, metabolic syndrome, and type 2 diabetes. Epidemiological data indicate that approximately one-quarter of the adult population worldwide is affected, with significant variation across regions due to genetic, ethnic, and lifestyle factors (Younossi Z.M. et al., 2016; Estes C. et al., 2018). NAFLD represents a spectrum of liver pathology, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and ultimately cirrhosis.

The progression is influenced by a complex interplay of metabolic, genetic, inflammatory, and environmental factors. Notably, the PNPLA3 polymorphism has been consistently associated with increased hepatic fat accumulation and accelerated fibrosis, emphasizing the role of genetic predisposition in disease severity (Romeo S. et al., 2008; Anstee Q.M. et al., 2020).

The clinical significance of NAFLD extends beyond liver-related morbidity. Patients with NAFLD are at elevated risk of cardiovascular disease, type 2 diabetes, and hepatocellular carcinoma. Importantly, NAFLD-related cirrhosis is projected to become one of the leading

indications for liver transplantation globally, underscoring the urgent need for early detection and intervention (Younossi Z.M. et al., 2019).

Early diagnosis, risk stratification, and monitoring of NAFLD progression are essential components of effective disease management. Non-invasive imaging, laboratory assessments, fibrosis scoring systems, and selective liver biopsy enable accurate detection and guide treatment decisions. Lifestyle modification, including dietary changes, physical activity, and metabolic risk factor control, remains the cornerstone of therapy, while emerging pharmacological agents hold promise for advanced disease.

In conclusion, NAFLD has evolved from a relatively benign metabolic condition to a leading cause of advanced liver disease and cirrhosis worldwide. Its high prevalence, potential for progression, and systemic implications highlight the need for proactive screening, multidisciplinary management, and ongoing research. Addressing NAFLD through early recognition, personalized intervention, and public health strategies is imperative to reduce the global burden of liver-related complications and improve patient outcomes.

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