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Nonalcoholic Fatty Liver Disease: A Literature Review of Epidemiology, Pathophysiology, and Diagnostic Approaches

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Abstract— This literature review provides an in-depth analysis of nonalcoholic fatty liver disease (NAFLD), a common metabolic condition that affects a worldwide population. This review outlines the disease's scope, epidemiological trends, pathophysiology, noninvasive diagnostic criteria, and approaches. NAFLD presents as continuum of hepatic conditions ranging from mild steatosis to more serious illnesses such as nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. A combination of clinical examination, laboratory tests, and imaging methods are used to make a diagnosis, with a liver biopsy serving as the confirmed gold standard for both diagnosis and disease severity assessment. Because of the intricacy and multifaceted etiology of NAFLD, successful diagnosis, treatment, and prevention need a multidisciplinary approach.

Keywords: Non-alcoholic fatty liver disease (NAFLD); Metabolic dysfunction associated steatotic liver disease (MASLD); diagnosis; epidemiology; pathophysiology.

1. Introduction

Nonalcoholic Fatty Liver Disease (NAFLD) is characterized by hepatic fat buildup and insulin resistance (IR), which is closely linked to Type 2 Diabetes (T2DM), hyperlipidemia, obesity, and other metabolic comorbidities. The diagnosis now relies on imaging or liver biopsy to reveal hepatic steatosis, defined as the presence of more than 5% hepatocytes affected by fat, while eliminating secondary causes such as drug or alcohol-induced steatosis. Furthermore, NAFLD is ruled out if a person's daily alcohol intake surpasses 30g for men and 20g for women (1).

These alcohol intake thresholds, however, are impacted by factors such as liquor type, individual peculiarities, and the existence of metabolic risk factors. Surprisingly, individuals with metabolic risk factors tend to be more susceptible to hepatic steatosis compared to individuals who only consume alcohol (2).

NAFLD, far from being a monolithic entity, manifests along a spectrum encompassing nonalcoholic fatty liver disease (NAFL), nonalcoholic steatohepatitis (NASH), and cirrhosis. These categories exhibit distinct pathologies and prognoses (3). NAFL is characterized by ≥ 5% hepatic steatosis without evidence of hepatocellular damage, linked to a relatively low incidence of cirrhosis and liver failure. In contrast, NASH is defined by ≥ 5% hepatic steatosis with cellular injury, although fibrosis is not necessarily present. Fibrosis plays a pivotal role in the progression to cirrhosis in adults (4), a significant precursor to hepatocellular carcinoma (HCC) (5). It is the leading indication for liver transplantation (6, 7). Table 1 outlies the different NAFLD stages and their characteristics (3).

The aim of the literature review is to provide a comprehensive synthesis focused on NAFLD, encompassing its epidemiology, pathophysiology, and various diagnostic methods. Understanding the epidemiology of NAFLD is crucial for elucidating its prevalence, distribution across populations, and associated risk factors, thereby informing targeted preventive strategies and healthcare resource allocation. The review also aims to explore the underlying pathophysiological mechanisms implicated in NAFLD development and progression, shedding light on the intricate interplay between metabolic dysregulation, IR, oxidative stress, inflammation, and hepatic lipid metabolism, thus providing a comprehensive understanding of the disease process and potential therapeutic targets. Furthermore, this review aims to elucidate the diverse diagnostic methods employed in identifying NAFLD, encompassing mainly non-invasive imaging techniques and serological biomarkers. By synthesizing evidence from a range of studies, this review seeks to elucidate the strengths, limitations, and comparative efficacy of different diagnostic modalities, ultimately facilitating informed clinical decision-making and enhancing patient care in the context of NAFLD.

2. Epidemiology

NAFLD is a major public health issue across the world. A thorough meta-analysis revealed that it affects around 25% of the world's population, as determined by modern imaging

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Table 1. NAFLD Spectrum (8)

NAFLD Spectrum	Characteristics
NAFL	≥5% hepatic fat without cell damage or ballooning; seldom progresses to cirrhosis or liver failure.
NASH	Hepatic fat >5% with cell ballooning and inflammation, independent of fibrosis; higher risk of advancing to liver complications than NAFL.
NASH Cirrhosis	Liver cirrhosis with evidence of past/current fat accumulation or inflammation.
Cryptogenic Cirrhosis	Cirrhosis without clear etiology, commonly associated with metabolic disorders and obesity.

NAFL: Non-alcoholic fatty liver; NASH: Non-alcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease.

techniques (9). While the impact of NAFLD is felt over the world, its prevalence varies significantly. In Western nations, 17% to 46% of individuals suffer from this illness, with variations due to diagnostic techniques, age, gender, and ethnicity (10, 11). The Middle East and South America have the greatest prevalence (31.79% and 30.45%, respectively), whilst Africa has the lowest rate of occurrence (13.48%)(9).

Yet, the scope of NAFLD goes beyond basic prevalence. Along with it, there is NASH, a disorder which global incidence is difficult to determine due to the lack of practicality of doing liver biopsies in the general population. According to present estimations, the prevalence of NASH ranges between 1.5% and 6.5% (9). Surprisingly, NASH is discovered in 59.10% of NAFLD patients for whom a clinical indication needs a liver biopsy, but in situations where precise clinical grounds are lacking, NASH's prevalence ranges from 6.67% to 29.85% (9).

Furthermore, the prevalence of NAFLD, particularly in the general population, was assessed in a limited number of studies. Depending on the examination techniques used, such as liver enzymes and ultrasonography, studies have found varied incidence rates ranging from 20 to 86 per 1,000 person-years. The incidence rate with proton magnetic resonance spectroscopy was 34 per 1,000 per year (12). For instance, Whalley et al. estimated an incidence rate of 29 per 100,000 person-years based on the International Classification of Diseases (ICD-10), albeit administrative coding mistakes may have resulted in underestimating the condition (13). Sung et al., on the other hand, discovered a 12% incidence of NAFLD among 11,448 participants monitored for five years (14).

Younossi et al.'s meta-analysis across Asia indicates an incidence of 52.34 per 1,000 person-years based on the continent's aggregated incidence. Another study reported the incidence rate to be 28 per 1,000 person-years (9, 15). In addition, Younossi et al. did a study on NAFLD occurrence among normal-weight individuals, indicating a 7% incidence rate, particularly impacting younger females with normal enzyme levels (16).

However, it is important to note that the reliability of ultrasonography, the primary screening technique for NAFLD, decreases when hepatic steatosis is less than 20%. This raise the possibility that the global prevalence of NAFLD is being understated (17).

3. Historical perspectives and outcomes

The previous two decades indicate a well-documented natural course of NAFLD, with NAFLD patients having a higher mortality rate than the overall population (18). Regardless of other metabolic comorbidities, cardiovascular disease (CVD) is the primary cause of mortality among NAFLD patients, followed by liver and cancer-related diseases. Notably, the liver-related death rate is 0.77/1,000 person-years, but the total mortality rate for NAFLD patients is 11.77/1,000 person-years. NASH had significantly higher rates, with 15.44/1,000 person-years for liver-related causes and 25.56/1,000 for total mortality (9, 19).

Because of its high prevalence, NAFLD is now the third most common cause of HCC in the United States (5). The prevalence of HCC linked with NAFLD has increased by 9% every year, a tendency related to the growing obesity pandemic. Furthermore, these HCC patients are older, with shorter survival periods due to a higher risk of CVD and HCC-related mortality when compared to HCC patients who do not have NAFLD (20).

Surprisingly, a considerable number of people with a diagnosis of cryptogenic cirrhosis, which is cirrhosis with no known etiology, may have 'burned out' NAFLD. Their clinical characteristics are strongly associated with metabolic syndrome (MetS) and its risk factors, including T2DM and obesity (21).

The vital relevance of early identification and intervention in improving patient outcomes and reducing the economic and healthcare burden of NAFLD cannot be emphasized given the significance of these strong findings. Given a lack of understanding among frontline medical professionals, NAFLD frequently goes undetected in real-world healthcare settings (22, 23).

4. NAFLD and metabolic syndrome

NAFLD lies at the intersection of metabolic complexities, where the confluence of many causes amplifies its importance

in modern healthcare. MetS, a condition defined by the existence of three out of five requirements. Waist circumference, triglyceride levels, blood pressure, high-density lipoprotein cholesterol, and fasting blood sugar are among the requirements (3). The rising incidence of NAFLD is inextricably linked to rising obesity and MetS rates among populations, leading current guidelines advocate for full metabolic risk factor evaluations in asymptomatic individuals with hepatic steatosis. The growing body of research relating metabolic comorbidities to advanced liver fibrosis has prompted this move (24, 25).

Obesity, ranging from overweight to severe obesity, is a significant risk factor for NAFLD. Patients with excessive obesity, over the 95th percentile, are especially vulnerable to NAFLD after bariatric surgery (26). The increased presence of visceral adipose tissue in obese MetS patients, combined with raised amounts of inflammatory adipokines such as leptin, creates a setting favorable to IR and the development of CVD (27-30).

Dyslipidemia, characterized by elevated triglyceride levels and decreased high-density lipoprotein (HDL), is a significant characteristic of MetS and is closely associated to NAFLD. Patients with high HDL/cholesterol and triglyceride/cholesterol ratios were more likely to have NAFLD than those with low ratios (31, 32). Ismaiel et al.'s assessment of the literature underlines the relationship between dyslipidemia and postprandial hyperlipidemia, demonstrating how NAFLD shares features with these abnormal lipid profiles, exacerbating cardiovascular risk in NAFLD patients (3, 33). Atherosclerosis and a higher risk of CVD have also been linked to postprandial hyperlipidemia (34, 35).

T2DM, which is common in NAFLD patients, shows the complex link between metabolic disease. NAFLD affects up to two-thirds of diabetics (36-39). The European investigation conducted by Gastaldelli et al. revealed a substantial relationship between poor insulin sensitivity and an increased risk of CVD in NAFLD patients. Furthermore, Rocha et al.'s study indicated that 98% of NAFLD patients had IR, with 39% also having diabetes (40). This bidirectional link between NAFLD and T2DM highlights the complicated interaction between the two diseases (41).

IR is a major risk factor for NAFLD and MetS. It is characterized by aberrant cellular responses to insulin and is linked to metabolic changes in glucose and lipids (42). Hyperinsulinemia might aggravate IR by altering insulin signaling in critical organs (43). Subclinical inflammation, altered adipokines, and ectopic fat buildup in organs are all repercussions of IR, all of which contribute to an elevated risk of poor cardiovascular outcomes (3).

Latest recommendations support prompt detection and treatment of MetS components related to liver fat storage, regardless of the body mass index (BMI), in response to this sophisticated web of metabolic linkages. Recognizing the high links between both disorders, the discovery of MetS should prompt examinations for NAFLD, and vice versa (44). Individuals with MetS should have hepatic steatosis and NAFLD tests, whereas NAFLD patients should have MetS components and risk factors evaluated, since these metabolic comorbidities increase the likelihood of severe liver fibrosis. This all-encompassing strategy is critical for lowering cardiovascular and liver-related mortality (24).

NAFLD is caused by a complex combination of inflammatory, genetic, and metabolic variables involving iron metabolism, genetic predispositions and immune responses mediated by Kupffer cells. Iron has a key impact on the progress of NAFLD, as the increase in iron deposition in hepatic cells leads to oxidative stress and apoptosis. Kuppfer cells, being the iron loaded macrophages of the liver, will therefore activate NF-κβ, progressing the conditions towards NASH, a more severe type (45-47). In fact, Kuppfer cells play a substantial part in the inflammatory processes in NAFLD. Hepatic steatosis results from the production of inflammatory cytokines which disrupt hepatocytes' metabolic pathways. Upon their activation, often due to lipotoxicity resulting from free fatty acid buildup in the liver, Kuppfer cells subsequently adopt a more pro-inflammatory M1 phenotype and release cytokines such as TNF-α and IL-1β. the further worsening of the liver's inflammation and fibrosis (48, 49).

Nonetheless, the genetic side has a crucial role, notably in the likelihood of developing NAFLD. Particular polymorphisms, including those in the IL-1β and IL-6 genes, have been found to be correlated with the extent of NASH severity (50). Moreover, poor NAFLD outcomes such as accelerated fibrosis and NASH development, have been associated with mutations at level of the hemochromatosis gene and PNPLA3 I148M (51, 52). Likewise, more recent studies show the link between MBOAT7-TMC4 locus and increased HS and liver injury in general (53). Furthermore, recent genome-wide association studies that a missense variant in the PYGO1 gene and an intronic variant near the LEPR gene, both had genome-wide significance for steatosis and NASH, respectively (54). Moreover, the study performed by Parisinos et al. showed that variants SLC30A10 and SLC39A8 in metal ion transporters genes were significantly correlated with the approximation of NASH severity provided by MRI-based corrected T1 score coupled with elevated liver enzymes (55). In addition, a loss of function mutation was HSD17B13 was linked of decreased rates of NASH, but not simple steatosis, suggesting it may be implicated in more severe forms of NAFLD (55). Table 2 provides an overview of the pathophysiological mechanisms involved in NAFLD (56).

5. NAFLD EVALUATION

The complicated landscape of NAFLD diagnosis warrants a sophisticated approach that considers varied guidelines from various medical associations. Despite some advocates for mass screening, current recommendations advise against routine NAFLD screening in the general population. This caution stems from the lack of effective drugs, uncertainty regarding long-term benefits, and cost-effectiveness issues (8, 57). Instead, the focus is on identifying high-risk populations for specialized examinations.

Table 2 Overview of the pathological mechanisms involved in nonalcoholic fatty liver disease

Mechanism	Description
Hepatic insulin resistance	Insulin resistance is the primary cause of hepatic steatosis, distinguished by increased free fatty acids influx as well as de novo lipogenesis, while whilst there is a decrease fatty acid oxidation and VLDL export. The resulting impairment allows for an excessive build up in hepatocytes.
Adipose tissue dysfunction	FFAs are released into the liver more readily when adipose tissue is dysfunctional, which is frequently caused by obesity. This stimulates lipid production and gluconeogenesis in the liver, which contributes to NAFLD. Adipose tissue also produces adipokines, which can aggravate insulin resistance and inflammation, worsening liver disease.
Gut Microbiome Dysbiosis	An altered microbiota can increase intestinal permeability, enabling more bacterial products to reach the liver through the portal vein, triggering inflammatory responses and contributing to liver damage and NAFLD.
Genetic factors	Variants in the genome affect lipid metabolism and linked to the severity and advancement of NAFLD, such as PNPLA3, TM6SF2, and MBOAT7 gene. These genes have an influence on inflammatory reactions, fat storage, and lipogenesis.
Inflammatory Cytokines and Chemokines	In NAFLD, adipocytes, hepatic macrophages, and other liver cells produce more pro-inflammatory cytokines and chemokines. The aforementioned mediators activate hepatic stellate cells and induce fibrogenesis, resulting in liver inflammation and, potentially, fibrosis.
Oxidative stress and Lipotoxicity	Excess FFAs lead to oxidative stress by releasing ROS. ROS induces cellular injury methods such as lipid peroxidation. Furthermore, lipotoxicity from fatty acids causes cell malfunction and death, adding to liver damage in NAFLD.
Activation of Kuppfer Cells	Kuppfer cells, are hepatic macrophages that upon activation produce cytokines promoting inflammation and fibrosis. Their activation can by various factors, including gut-derived toxins and cellular stress.
Iron overload	Hepatic iron accumulation exacerbates oxidative stress and inflammation, leading to more severe liver injury.

VLDL: very low-density lipoprotein; FFA: free fatty acid; NAFLD: nonalcoholic fatty liver disease.

The diagnosis of NAFLD is based on four criteria: (1) verified liver steatosis by imaging or histology, (2) lack of significant alcohol consumption, (3) exclusion of secondary causes of hepatic steatosis, and (4) absence of concurrent etiologies of chronic liver disease. Other secondary reasons leading to hepatic steatosis, such as hepatotoxic medications, viral infections, autoimmune liver illnesses, and hereditary abnormalities, must be ruled out during early examinations (3).

Similarly with autoimmune antibodies and serum ferritin, serology-based examinations in NAFLD patients may result in false positives. Serum ferritin increase, which is prevalent in NAFLD, is not always symptomatic of liver iron excess. Nonetheless, serum ferritin levels greater than 1.5 times the upper normal range have been linked to progressive fibrosis (58). Patients with increased blood ferritin and transferrin levels should be investigated for hereditary hemochromatosis,

and a liver biopsy to measure hepatic iron buildup ought to be investigated (46]).

Several essential steps must be taken by physicians in order to establish a NAFLD/NASH diagnosis. First, confirm the existence of NAFLD with confirmed hepatic steatosis and eliminate excessive alcohol use. Second, investigate other causes of chronic liver disease, such as viral hepatitis, autoimmune illness, and medication-induced liver damage. Third, evaluate the possibility of NASH. Fourth, examine fibrosis and, if found, its degree of severity (10, 59). This approach ensures that the challenging NAFLD diagnostic landscape is well understood.

5.1 *Hepatic steatosis*

5.1.1 *Imaging based diagnosis of hepatic steatosis*

The first assessment of NAFLD involves a careful selection of imaging modalities, each with its own set of pros and cons.

Ultrasonography (USG) is a widely available, non-invasive, and cost-effective diagnostic method. It has a high sensitivity (>90%) for diagnosing hepatic steatosis above 20% and a variable specificity (84-95%) (3, 9, 11). When the hepatorenal index reaches 1.34, the Ultrasonographic Fatty Liver Indicator, which is based on liver-kidney contrast, has a sensitivity of 92% and a specificity of 85% (60).

Controlled Attenuation Parameter (CAP) assesses liver fat level within a particular range (100-400 dB/m) and is used in transient elastography (FibroScan). While CAP is effective at identifying hepatic steatosis, it struggles grading its severity, with results varying between studies (61-63). The primary use of CAP is to detect steatosis, although it falls short in grading, predicting non-hepatocellular carcinoma, and measuring cardiovascular risk (64).

Computed tomography (CT) Scan evaluates hepatic steatosis by evaluating attenuation in contrast and non-contrast enhanced images. Based on liver attenuation values (40–42 HU) and hepatic:splenic ratios, it has a 100% specificity for detecting moderate to severe steatosis (65, 66). However, its drawbacks include radiation exposure, high costs, and a poorer sensitivity in diagnosing mild steatosis (67).

Magnetic resonance imaging (MRI) is emerging as a complete technique for qualitative and quantitative hepatic steatosis evaluation. It has a high sensitivity (76.7–90.0%) and specificity (87.1–91%), even at minimal fat concentrations (5–10%) with no radiation exposure (68, 69). Furthermore, regardless of demographic characteristics, histological activity, or concomitant hepatic diseases, it stays sensitive to steatosis changes across the liver parenchyma, rendering it operator-independent (70).

Hydrogen-1 Magnetic Resonance Spectroscopy (1H-MRS) distinguishes hepatic steatosis grades and removes the requirement for liver biopsy. It measures the region just beneath the lipid resonance peak and isn't influenced by confounding factors. It is, however, complicated, expensive, and requires patient cooperation (70).

Proton Density Fat Fraction (PDFF) is performed using shift-encoded molecules, being another MRI-based approach that provides high diagnostic accuracy. It offers a promising quantitative strategy for assessing hepatic steatosis (71).

Xe133 Liver Scan is a non-invasive approach that can identify hepatic steatosis with greater sensitivity (94.3%) and specificity (87.5%) than ultrasonography. However, it only recognizes adipose tissue, making discrimination among NAFLD spectra difficult and offering no anatomical information (72).

5.1.2 *Scoring based hepatic steatosis diagnosis*

NAFLD Liver Fat Score (NLFS) when > -0.640, NLFS has a sensitivity of 86% and a specificity of 71% in diagnosing hepatic steatosis surpassing 5.56%. Although NLFS is useful for detecting hepatic steatosis, it does not distinguish between NAFLD stages, limiting its staging value (73).

The Fatty Liver Index (FLI) which ranges from 0 to 100 has a remarkable specificity and sensitivity, showing values of 87% and 86%, respectively, in establishing hepatic steatosis when FLI is 60. FLI 30, on the other hand, effectively rules out hepatic steatosis. Furthermore, FLI correlates with cancer and cardiovascular mortality independently, making it a useful indication for these illnesses. It also acts as an indirect marker for MetS, providing a simple method for detecting hepatic steatosis (74)

Hepatic Steatosis Index (HSI) has gained popularity as a reliable NAFLD diagnostic tool. It has a remarkable sensitivity of 93.1% in ruling out NAFLD and a specificity of 92.4% in diagnosing NAFLD with an HSI value of less than 30. HSI, which is based on a regression model, is promising for screening individuals with hepatic steatosis detected by ultrasonography (69, 74).

SteatoTest is useful since a cut-off value of 0.30 provides 90% sensitivity and a cut-off value of 0.70 provides 90% specificity. It helps to accurately diagnose hepatic steatosis (75).

NAFL screening score has a positive predictive value of 84% and a specificity of 90% when using the high cut-off value. At the reduced cut-off, the NAFL's screening score has a negative predictive value of 95% and a sensitivity of 92% for ruling out NAFLD. It provides a promising way to assessing the risk of NAFLD (75). **Table 3** lays down the above-mentioned scores and their corresponding formulas (76).

5.1.3 *Breath test*

Verdam et al. work takes a fresh method to NASH differentiation. This approach efficiently distinguishes patients with NASH from those without by analyzing three volatile organic chemicals ("n-tridecane," "3-methyl-butanonitrile," and "1-propanol") in exhaled breath. Positive and negative predictive scores of 82% and 81%, respectively, highlight its diagnostic potential. This non-invasive breath test has the potential to improve patient care and risk assessment by providing a viable path for NASH diagnosis (77).

Table 3. Hepatic steatosis diagnosis scores and their formulas

Hepatic steatosis scores	Formula
NAFLD liver fat score (NLFS)	$1.18 \times \text{metabolic syndrome} + 0.45 \times \text{diabetes(2,if yes; 0,if no)} + 0.15 \times \text{FSI}\left(\frac{\text{mU}}{\text{L}}\right) + 0.04 \times \text{AST}\left(\frac{\text{U}}{\text{L}}\right) - 0.94 \times \left(\frac{\text{AST}}{\text{ALT}}\right) - 2.89$
Fatty Liver Index (FLI)	$[e^{0.953} \times \log_e(\text{TG}) + 0.139 \times \text{BMI} + 0.718 \times \log_e(\gamma\text{-GT}) + 0.053 \times \text{WC} - 15.745] \times \frac{100}{1 + e^{0.953 \times \log_e(\text{gamma-GT}) + 0.053 \times \text{WC} - 15.745}}$
Hepatic steatosis index (HSI)	$8 \times \frac{\text{ALT}}{\text{AST}} + \text{BMI} + 2\ (\text{if woman}) + 2\ (\text{if diabetic})$
Lipid accumulation product (LPA)	$[\text{WC (cm)} - 58] \times \text{triglycerides}\left(\frac{\text{mmol}}{\text{l}}\right)$
SteatoTest	Proprietary, but built upon the following: α-2-macroglobulin, apolipoprotein A1, haptoglobin, γ-glutamyl transferase, ALT, AST, total cholesterol, and fasting glucose and adjusted by age and sex
NAFL screening score	Derived from age, FPG, UA, ALT/AST ratio, BMI and TG.
Visceral adiposity index	Men: VAI = $\left(\frac{\text{WC}}{39.68 + (1.88 \times \text{BMI})}\right) \times \left(\frac{\text{TG}}{1.03}\right) \times \left(\frac{1.31}{\text{HDL}}\right)$ Women: VAI = $\left(\frac{\text{WC}}{36.58 + (1.89 \times \text{BMI})}\right) \times \left(\frac{\text{TG}}{0.81}\right) \times \left(\frac{1.52}{\text{HDL}}\right)$

FSI: Fasting serum insulin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: Body mass index; WC: Waist circumference; FPG: Fasting blood glucose; UA: Uric acid; TG: Triglycerides; HDL: High-density lipoprotein; VAI: Visceral adiposity index.

5.2 NASH

5.2.1 *Breath test*

Verdam et al. work takes a fresh method to NASH differentiation. This approach efficiently distinguishes patients with NASH from those without by analyzing three volatile organic chemicals ("n-tridecane," "3-methyl-butanonitrile," and "1-propanol") in exhaled breath. Positive and negative predictive scores of 82% and 81%, respectively, highlight its diagnostic potential. This non-invasive breath test has the potential to improve patient care and risk assessment by providing a viable path for NASH diagnosis (77).

5.2.2 *Imaging based NASH diagnosis*

1H-MRS (Proton Magnetic Resonance Spectroscopy) is an approach that has a high sensitivity of 87.4% and a specificity of 74.3% in identifying NASH. 1H-MRS provides important insights into NASH detection, resulting in more precise diagnosis (78).

Magnetic Resonance Elastography (MRE) is another useful method for identifying NAFL. MRE greatly improves diagnostic accuracy, with a sensitivity of up to 94% and a specificity of 73% when using a cut-off of 2.74 kPa. This method assists in the accurate diagnosis of NASH patients (79).

5.2.3 *Scoring based NASH diagnosis*

NashTest is a simple scoring method that divides NASH into three categories: NASH with an area under the curve (AUROC) of 0.79, Borderline NASH (AUROC: 0.6), and No-NASH (AUROC: 0.77–0.83). It is a potential method for classifying NAFLD patients based on NASH severity (80).

HAIR (Hypertension, ALT, insulin resistance) score with a sensitivity of 80% and specificity of 89%, is very predictive in obese individuals when at least two of its components are present. This score assists in the precise identification of NASH (81).

NASH Diagnostic Index (NDI) presents when using values over 22 and 50, respectively, an 82% specificity for "simple steatosis" and an 86% specificity for NASH. This tool aids in the proper detection of NASH (82).

National Institute for Health and Care Excellence (NICE) Model has an ideal cutoff of 0.14 for this model, yielding 84% sensitivity, 86% specificity, 44% positive predictive value, and 98% negative predictive value for diagnosing NASH. It is very effective in excluding NASH patients (83).

Palekar Score differentiates NASH from steatosis using a collection of risk variables with a sensitivity of 73.7% and specificity of 65.7% when more than three risk factors are present (84).

NAFIC score has a promising ability to predict NASH, with an AUROC curve of 0.851 (85).

NASH Predictive Index (NPI) with an amazing accuracy range (AUROC: 0.87–0.90) in predicting NASH, has tremendous promise, albeit external validation is required (86).

Table 4 shows these scores and their corresponding formulas (76, 87).

5.2.4 *Biomarkers for NASH diagnosis*

Cytokeratin-18 (CK-18) in serum measures hepatocyte apoptosis, at a cut-off value of > 240 U/L and a sensitivity of 76.7% and specificity of 95%, being the most accurate single indicator for separating steatosis NASH.

Serum aminotransferases with elevated alanine transaminase (ALT) values beyond the usual threshold (>70 U/L) had a 50% sensitivity and a 61% specificity in diagnosing NASH. However, whilst these values are commonly employed to detect hepatic inflammation, they have a low positive predictive value for NASH and cannot quantify liver fibrosis (88).

Serum Adiponectin generated by fatty tissue acts as a negative predictor of NASH in the setting of NAFLD and NASH, where MetS plays a key role. A threshold value of 29.16 g/L can help differentiate people with fatty liver (89, 90).

Fibroblast Growth Factor 21 (FGF21) levels in patients with obesity and T2DM are correlated with the severity of NASH. This biomarker may be employed to detect and predict disease development, with NASH patients having greater FGF21 levels, averaging 453.262 picograms per milliliter (91). The combination of FGF21 and CK-18 improves diagnostic accuracy (92).

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) as reported by Ruscia et al. can play a role as a steatosis biomarker due to its participation in low-density lipoprotein (LDL) receptor degradation and lipogenesis (93, 94).

Tumour Necrosis Factor-Alpha (TNF-α) levels according to Tilg et al. are elevated in NASH patients, implying a bigger disease load and a higher risk of severe liver outcomes (95).

5.2.5 *Imaging based liver fibrosis diagnosis*

Transient Elastography (TE) determines liver stiffness measure (LSM) based on wave transmission velocity, with higher LSM indicating more stiffness. The dependability, rapidity, and applicability of TE for obese individuals are its distinguishing features. It excels in excluding liver fibrosis, with a negative predictive value ranging from 94% to 100%. Notably, LSM < 6.0 kPa eliminates the possibility of severe fibrosis. Nevertheless, TE is not appropriate in the presence of ascites or congestive liver disease, and a kPa ≥ 20 may indicate significant portal hypertension (92).

Shear Wave Elastography (SWE) measures shear wave velocity to quantify liver elasticity. It categorizes fibrosis using the following values: F1 (7.1 kPa), ≥ F2 (7.8 kPa), F3 (8 kPa), and F4 (>11.5 kPa). While SWE has a sensitivity of 93.8% for detecting F2 at a threshold of 7.19 kPa, its specificity is just 52%. Sensitivity and specificity for F3 are 93.1% and 80.8% at 9.1 kPa, respectively, whereas for F4, they are 75.3% and 87.8% at 13 kPa. A higher threshold of 15.73 kPa increases sensitivity to 100% and specificity to 82%, respectively. However, food consumption might cause erroneous results, therefore measurements should be taken at least four hours following a meal (92).

Magnetic Resonance Elastography (MRE) overcomes the limitations of ultrasound-based procedures, and it works well in situations of ascites and obesity. It has 94% sensitivity and 95% specificity for distinguishing between F0-F1 and F2-F4 fibrosis, and 98% sensitivity and 94% specificity for F0-F3 vs F4 (96). Using a threshold of >3.63 kPa, MRE has 86% specificity and 91% sensitivity, resulting in a high negative predictive value (97%) and a moderate positive predictive value (68%) for discriminating advanced fibrosis (F3-F4) from F1 and F0. MRE, on the other hand, it cannot be utilized in individuals who have specific pacemakers, claustrophobia, or iron excess (97).

5.2.6 *Diagnostic scores for liver fibrosis*

Aspartate aminotransferase (AST)/Platelet Ratio Index (APRI) with a cutoff of 0.7 has a sensitivity of 77% and a specificity of 72% for diagnosing F2 fibrosis, whereas an APRI cutoff of 1 has a sensitivity of 61% to 76% and a specificity of 64% to 72% for identifying advanced liver fibrosis (F3 and F4). It is highly effective for ruling out liver fibrosis, although it cannot distinguish between all of its stages (98) .

Fibrosis-4 (FIB-4) score of more than 3.25 has an 82.1% positive predictive value and a 98.2% specificity for severe liver fibrosis. When the score is 1.45, however, FIB-4 has a negative predictive value of more than 90%, giving it a dependable and cost-effective method for firmly confirming or eliminating severe liver fibrosis (99).

BARD score, while frequently being used for its convenience, has a low positive predictive value of less than 42%, resulting in false positives and classifying many patients with moderate NAFLD as being at high risks (100).

NAFLD Fibrosis Score (NFS) makes a distinction between NAFLD with and without fibrosis. A cutoff value of -1.455 has a strong negative predictive value of 93% for excluding fibrosis, whereas a cutoff value of 0.676 has a positive predictive value of 90% for accurately excluding severe fibrosis. NFS also has predictive significance and can screen patients for liver-related complications (101).

King's Score, originally used to diagnose hepatitis C, with a score of >16.7 efficiently rules out cirrhosis with a 96% negative predictive value and provides 86% sensitivity and 80% specificity in detecting liver fibrosis in NAFLD/NASH (102).

Table 4. NASH diagnosis scores and their corresponding formulas

NASH scores	Formula
NASH Test	age, sex, height, weight, serum levels of triglycerides, cholesterol, α-2-macroglobulin, apolipoprotein A1, haptoglobin, γ-glutamyl transferase, aminotransferases ALT, AST, and total bilirubin
HAIR score	A score between 0 and 3, calculated by adding Hypertension = 1, ALT > 40IU = 1, and IR index> 5.0 = 1
NASH diagnostic index	serum insulin, glucose, triglycerides, ALT, and waist-to-hip ratio
NICE model	$-5.654 + 3.780E-02 \times$ ALT (IU/L) $+ 2.215E-03 \times$ CK–18 fragment levels (IU/L) $+ 1.825 \times$ (presence of MS = 1)
Palekar score	The sum of the following risk factors: age ≥50 years, female sex, AST ≥45 (U/L), BMI ≥30 (kg/cm2), AST/ALT ratio, and hyaluronic acid ≥55 (mcg/L).
NAFIC score	The sum of the following: serum ferritin ≥200 (ng/mL; women) or ≥300 (ng/mL; men) = 1 point; fasting insulin ≥ 10 μU/mL = 1 point; and type IV collagen 7s ≥5.0 (ng/mL) = 2 points
NASH predictive index	Comprised of age, female sex, BMI, HOMA-IR, and log [AST× ALT]
Visceral adiposity index	Men: VAI = $(\frac{WC}{39.68 + (1.88 \times BMI)}) \times (\frac{TG}{1.03}) \times (\frac{1.31}{HDL})$ Women: VAI = $(\frac{WC}{36.58 + (1.89 \times BMI)}) \times (\frac{TG}{0.81}) \times (\frac{1.52}{HDL})$

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; IR: Insulin resistance; MetS: Metabolic syndrome; BMI: Body mass index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; WC: Waist circumference; TG: Triglycerides; HDL: High-density lipoprotein.

FI (Fibrosis Index Score) with a value of 3.30 results in 70.8% sensitivity and 81.0% positive predictive value for advanced fibrosis (103).

ELF Panel provides three cutoff values for distinguishing across fibrosis stages, with unique sensitivities and specificities for each stage (97).

FibroTest has a sensitivity and positive predictive value at particular cutoffs, with a 90% negative predictive value for severe fibrosis (97). Nevertheless, in some settings, it may yield false positives (104).

HepaScore at 0.2 has a 98% negative predictive value for excluding fibrosis, but a poor 62% positive predictive value when at 0.8 (105, 106).

Table 5 summarizes the liver fibrosis diagnosis scores and with their formulas (76, 87).

6. Conclusions

NAFLD is a multidimensional and complex disease that requires a careful approach to both diagnosis and therapy. Its worldwide incidence is increasing, with tight links to a variety of metabolic comorbidities such as obesity, T2DM, and dyslipidemia. The combination of clinical, laboratory, and imaging characteristics is critical for accurate NAFLD diagnosis, with liver biopsy acting as the definitive approach for differentiating between NAFL and NASH. Significant research efforts are required to unravel the complex pathophysiology, understand the natural disease development, and develop optimum therapy approaches for NAFLD is key in halting disease progression and improving patient outcomes, emphasising the importance of addressing this growing global health concern.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 5. Liver fibrosis assessment scores and their corresponding formulas

Liver fibrosis score	Formula
APRI	$\frac{\left[\left(\frac{AST}{upper\ limit\ of\ the\ normal\ AST\ range}\right) X\ 100\right]}{Platelet\ count}$
FIB-4	$\frac{(Age\ (years) \times AST\ (U\ /\ L))}{Platelet\ count\ \left(10^9/_L\right) \times \sqrt{ALT\ (U/L)}}$
BARD Score	The total points of: (BMI ≥ 28 = 1 point; AST-to-ALT Ratio ≥ 0.8 = 2 points, the presence of diabetes = 1 point), and cumulative score ≥ 2 is indicative of advanced fibrosis
King's score	$age\ \times AST\ (U/L)\ \times INR/platelet\ count\ (10^9/L)$
NAFLD fibrosis score	$-1.675\ +\ 0.037 - age\ (years) +\ 0.094 - BMI\ (kg/m2) + 1.13 \times \frac{IFG}{diabetes}\ (yes\ =\ 1, no\ =\ 0) + 0.99 \times \frac{AST}{ALT} - 0.013 \times platelet\ count\ (10^9/l) - 0.66 \times albumin\ (g/dl)$
Fibrosis index score	$8\ -\ 0.01\ \times\ number\ of\ platelets\ (10^9/L)\ -\ albumin\ (g/dL)$
Enhanced liver Fibrosis score	$2.494\ +\ 0.846\ In\ (CHA)\ +\ 0.735\ In\ (CPIIINP)\ +\ 0.391\ In\ (CTIMP-1)$
FibroTest	$4.467 \times log[\alpha 2-macroglobulin(g/L)] - 1.357 \times log[Haptoglobin\ (g/L)] + 1.017 \times log\|GGT\ (IU/L)] + 0.0281 \times [Age\ (years)] + 1.737 \times log[TBil\ (umol/L)] - 1.184x\ [Apo\ A1\ (g/L)] + 0.301 \times Gender\ (Female\ =\ 0, Male =\ 1) - 5.540$
HepaScore	$Y = e^{(-4.185818 - (0.0249 \times age) + (0.7464 \times sex) + (1.0039 \times \alpha 2-macroglobulin) + (0.0302 \times hyaluronic\ acid) + (0.0691 \times total\ bilirubin) - (0.0012 \times GGT))}$ $HepaScore = \frac{Y}{1+Y}$ with 1 for men and 0 for women
Visceral adiposity index	Men: VAI = $(\frac{WC}{39.68 + (1.88\ \times\ BMI)}) \times (\frac{TG}{1.03}) \times (\frac{1.31}{HDL})$ Women: VAI = $(\frac{WC}{36.58 + (1.89\ \times\ BMI}) \times (\frac{TG}{0.81}) \times (\frac{1.52}{HDL})$

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BMI: Body mass index; INR: International normalized ratio; IFG: Impaired fasting glucose; CHA: Hyaluronic acid; PIIINP: Amino-terminal propeptide of type III procollagen; TIMP1: metallopeptidase inhibitor 1; GGT: Gamma-glutamyl transferase; TBil: Total bilirubin; WC: Waist circumference; TG: Triglycerides; HDL: High-density lipoprotein

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