Non-alcoholic fatty liver disease: Definition and subtypes

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Running title: Definition and subtypes of NAFLD

Abbreviations

AASLD, American Association for the Study of Liver Disease; BMI, body mass index; CRN, Clinical Research Network; EASL, European Association for the Study of Liver; HSD17B13, hydroxysteroid 17\(\beta\)-dehydrogenase 13; MAFLD, metabolic (dysfunction)-associated fatty liver
disease; MHO, metabolically healthy obesity; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NAS, NAFLD activity score; $PNPLA3$, patatin-like phospholipase domain-containing protein 3; $TM6SF2$, transmembrane 6 superfamily member 2.
Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide, with a global prevalence of approximately 30%. However, the prevalence of NAFLD has been variously reported depending on the comorbidities. The rising prevalence of obesity in both the adult and pediatric populations is projected to consequently continue increasing NAFLD prevalence. It is a major cause of chronic liver disease worldwide, including cirrhosis and hepatocellular carcinoma (HCC). NAFLD has a variety of clinical phenotypes and heterogeneity due to the complexity of pathogenesis and clinical conditions of its occurrence, resulting in various clinical prognoses. In this article, we briefly described the basic definition of NAFLD and classified the subtypes based on current knowledge in this field.

Keywords
Non-alcoholic fatty liver disease, steatohepatitis, fibrosis, definitions, subtypes

Introduction

The term non-alcoholic fatty liver disease (NAFLD) was first introduced by Schaffner in 1986. It is characterized by excessive hepatic fat accumulation, associated with insulin resistance and defined as the histological presence of steatosis in >5% hepatocytes. As non-invasive measurement, proton magnetic resonance spectroscopy or quantitative fat/water selective magnetic resonance imaging (MRI) can be used to measure steatosis by determining the proton density fat fraction (rough estimation of the fat volume fraction in the liver; steatosis >5.6%)\(^2-4\). A diagnosis of NAFLD is made after excluding other obvious factors that influence the liver profile or could induce steatosis, such as significant alcohol intake, viral hepatitis, and medications that cause fatty changes. NAFLD is an integrated term for heterogeneous pathological states; therefore, the therapeutic approach should be chosen considering each cause and subtype. In recent years, there have been several attempts to refine NAFLD stages and phenotypes.

The diagnosis of NAFLD is based on radiological or histopathological findings that demonstrate
fatty changes in the liver. Biopsy is the gold standard for confirming fatty changes, but there are limitations of sampling error, intraobserver discrepancy, and invasiveness. Non-invasive modalities, such as computed tomography (CT), ultrasonography (US), and MRI, are used to detect fatty changes in the liver. Therefore, the incidence and prevalence of NAFLD have been reported differently depending on the diagnostic tool.

The annual incidence (diagnosis made using abdominal US) in the general population was approximately 48.2 cases/1,000 persons (range, 13.4–77.7)\textsuperscript{5,7}. Using another diagnostic method, the hepatic steatosis index, the annual incidence rate was 21.1 cases/1,000 persons per year\textsuperscript{8}. In a meta-analysis, the annual incidence rate in Korea was 45.1 cases/1,000 persons\textsuperscript{9,10}. The prevalence of NAFLD varied from 21–44\%\textsuperscript{11-13}. In a meta-analysis conducted in Korea, the prevalence rate of NAFLD was reported as 12.6–51\%\textsuperscript{9,14,15} according to diagnostic modality. However, the data of incidence and prevalence, according to various classification and subtypes of NAFLD, were insufficient until now.

**Traditional definition and classifications**

NAFLD is a generic term that encompasses the spectrum of non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), and NASH-related cirrhosis. NASH is the inflammatory subtype of NAFLD, and it is characterized by steatosis, evidence of hepatocyte injury (ballooning), and inflammation with or without fibrosis. NASH-cirrhosis is the presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis\textsuperscript{4}.

The 2018 American Association for the Study of Liver Diseases (AASLD) NAFLD guidelines recommend that the classification of biopsy specimens should include a distinction between NAFL (steatosis), NAFL with inflammation, and NASH (steatosis with lobular and portal inflammation and hepatocellular ballooning). A comment on severity (mild, moderate, or severe) may be useful\textsuperscript{2}. Specific scoring systems, such as NAFLD activity score (NAS) and/or steatosis, activity, and fibrosis score, and the presence of fibrosis may be used in description\textsuperscript{2,16}. In 2005,
the NASH Clinical Research Network (CRN) published the NAS\textsuperscript{16} to provide a standard measure for assessing histological changes in NAFLD during clinical trials. This score can be used for assessing the full spectrum of NAFLD, including simple steatosis. The score is calculated as the unweighted sum of the scores for steatosis (0–3), lobular inflammation (0–3), and hepatocellular ballooning (0–2), and it ranges from 0 to 8. The main purpose of the NAS is to evaluate histological changes over time rather than to serve as diagnostic criteria for NASH.

However, some studies have used the threshold values of NAS, specifically NAS ≥ 5, as a surrogate for the histological diagnosis of NASH because NAS ≥ 5 has been reported to correlate with a diagnosis of NASH, and biopsies with scores ≤ 2 were diagnosed as ‘not NASH’\textsuperscript{16}. Brunt et al. reviewed biopsies obtained from 976 adults in NASH CRN studies and reported that only 75% of the biopsies with definite NASH had NAS ≥ 5, whereas 28% of the borderline NASH and 7% of the ‘not NASH’ biopsies had NAS ≥ 5. In addition, 3% of the patients with NAS ≥ 5 were ‘not NASH’, and 29% of the patients with NAS ≤ 4 were diagnosed as NASH\textsuperscript{17}. Therefore, caution is needed in the clinical application of NAS, and it should not be confused with diagnostic or classification criteria.

\textbf{(1) Non-alcoholic fatty liver (simple steatosis)}

Hepatocellular steatosis is the hallmark of NAFL, and presence of more than 5% is required for diagnosis\textsuperscript{18-20}. It is classified into two types: macrovesicular and microvesicular steatosis. Steatosis in NAFLD is usually macrovesicular; however, microvesicular steatosis may also be present in approximately 10% patients\textsuperscript{21,22}.

Many previous studies have suggested that NAFL is a benign disease. Through the several studies performing paired or repeat liver biopsy, NAFL showed significantly superior overall prognosis, including progression to cirrhosis rather than NASH\textsuperscript{23,24}. However, the concept that NAFL is a benign disease was challenged with the accumulation of evidence; it is now regarded as a progressive disease. Recent data suggest that nearly 25\% of the patients with NAFL may develop fibrosis\textsuperscript{25}. In another study that included patients with NAFLD who underwent serial biopsy (25
with simple steatosis and 45 with NASH), 64% of the 25 patients with steatosis showed rapid progression to NASH after 3.7 years. The increasing severity of steatosis has been reported to be positively associated with lobular inflammation, zone 3 fibrosis, and definite steatohepatitis. In a meta-analysis comparing NAFL and NASH, the percentage of patients who progressed by one or more stage of liver fibrosis was similar (39.1% and 34.5%, respectively). In a prospective study of 52 patients with paired liver biopsies, 28% of the patients with NAS < 5 showed progression to fibrosis. Overall, roughly 30–40% of patients with NAFL show fibrosis progression in studies with sequential biopsies. Therefore, follow-up can be considered even in patients with simple NAFL without evidence of inflammation.

The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines recommend that patients with NAFL without metabolic risk factors should be monitored at 2–3-year intervals considering the low risk of progression. The clinical factors associated with progression to NASH include hypertension, diabetes or insulin resistance, and low aminospartate transferase/ aminoaalanine transferase (AST/ALT) ratio at the time of liver biopsy. Rapid progression was also often observed with concomitant hepatic injury related to alcohol, toxin exposure, nutrients, drugs, chronic hepatitis C, or autoimmune liver disease. In contrast, there are no consensus for surveillance guideline about NAFLD with risk factors.

(2) Non-alcoholic steatohepatitis without fibrosis

NASH was first described in 1980 and represents a state of chronic liver inflammation. NASH is currently defined as very heterogeneous, especially according to the presence or absence of fibrosis. A diagnosis of NASH requires a biopsy with histological findings demonstrating hepatocellular ballooning degeneration and hepatic lobular inflammation with hepatic steatosis. However, histological confirmation is not frequent; thus, the accurate estimation of the prevalence of NASH in the general population is limited. The prevalence of NASH has been known to be approximately 1.4–15% in the general population, and 20% of the patients with NAFLD histologically show NASH in biopsy specimens. The incidence of NASH doubled between
1990 and 2017, and its age-standardized incidence rate has increased by 1.35% per year, from 3.31 to 4.81 per 1,000,000 persons. Current guidelines from the AASLD recommend biopsy for patients with NAFLD who are at increased risk of steatohepatitis and/or advanced fibrosis and for those in whom the coexisting liver disease cannot be ruled out. As mentioned above, high-risk factors for progression to NASH include coexisting metabolic diseases (hypertension, diabetes mellitus, or obesity), elevated levels of aminotransferases, older age (> 60 years), and Hispanic ethnicity. Non-invasive scoring systems and methods for the prediction of fibrosis include NAS, Fibrosis-4 index, AST-to-platelet ratio index (APRI), and enhanced liver fibrosis (ELF) panel and Vibration Controlled Transient Elastography and magnetic resonance elastography (MRE).

Brunt et al. classified the inflammatory grades of NASH as grade 1 (mild), grade 2 (moderate), and grade 3 (severe). The NASH CRN later subclassified grade 1 according to the degree and location of fibrosis (Table 1). Intralobular inflammation is also present in NASH and usually consists of a mixed inflammatory cell infiltrate. In NAFLD/NASH, portal inflammation is usually absent or mild and mainly involves lymphocytic infiltration. When portal inflammation is disproportionately severe, the possibility of concurrence with other liver diseases (such as hepatitis C and autoimmune hepatitis) should be considered. Hepatocellular ballooning is characterized by swollen hepatocytes with rarefied cytoplasm, reflecting hepatocellular injury. Hepatocellular ballooning is believed to result from the alteration of the intermediate filament cytoskeleton. In a meta-analysis of 10 longitudinal histological studies, older age and parenchymal or portal inflammation on initial biopsy were independent predictors of progression to advanced fibrosis in NASH.

Data about the relationship between the degree of inflammation and prognosis are insufficient. Therefore, the clinical importance between simple NAFL and NASH (without fibrosis) has not yet been fully investigated. A recent study showed that the presence of biopsy-proven NASH was not related to liver-specific morbidity or overall mortality. More prospective studies on the prognosis of NASH without fibrosis are needed.
Non-alcoholic steatohepatitis with fibrosis

The characteristic pattern of fibrosis in NASH is perisinusoidal/pericellular fibrosis, which typically begins in zone 3. Fibrosis in NAFLD typically involves an active neuroinflammatory reaction. As NASH progresses, portal/periportal and bridging fibrosis and liver cirrhosis may develop.

Those with histologic evidence of NASH with pronounced fibrosis have a higher risk of adverse hepatic outcomes (hepatic decompensation, HCC, and liver-related mortality), and this risk increases exponentially as fibrosis advances to cirrhosis. In addition, many observational studies have shown that biopsy-confirmed liver fibrosis is a major predictor of not only liver-related but also overall mortality in patients with NAFLD. A recently published systematic analysis including 4,428 patients with biopsy-confirmed NAFLD, of which 2,875 patients (65%) had a histologically proven NASH, revealed that the unadjusted risk increased with increasing stage of fibrosis relative to no fibrosis stage (stage 0); all-cause mortality relative risk, 3.42 (95% confidence interval [CI], 2.63–4.46) and liver-related events relative risk, 12.78 (95% CI, 6.85–23.85). Sanyal et al. from the NASH CRN also reported a prospective study on the outcomes of NAFLD, including the entire spectrum of NAFLD. In this study, all-cause mortality increased with increasing fibrosis stages, with 0.32 deaths per 100 person-years for stage F0 to F2, 0.89 deaths per 100 person-years for stage F3, and 1.76 deaths per 100 person-years for stage F4. The incidence of other complications of cirrhosis also increased as the fibrosis grade increased.

Therefore, many clinical trials on NASH treatment aim to reduce fibrosis.

NASH-related cirrhosis

In advanced fibrosis or cirrhosis, steatosis and necroinflammatory reactions may disappear; this condition is known as burn-out NASH. Patients with this presentation could be diagnosed with cryptogenic cirrhosis, of which the leading cause is believed to be NAFLD/NASH. The prevalence of NASH-related cirrhosis was 0.178% in a study including 417,524 American adults.
performed between 2009 and 2012, which showed a 2–2.5-fold increase from the values obtained between 1999 and 2002\textsuperscript{49}. Recently, rapid progression to NASH-cirrhosis was reported in advanced fibrosis patients. In these studies, approximately 20% of the patients with NASH with advanced fibrosis (F3) may develop cirrhosis rapidly within 2 years\textsuperscript{37,48}. Prospective studies for the natural courses for NASH-cirrhosis need to be accumulated.

NASH-related cirrhosis is most commonly macronodular or mixed\textsuperscript{50}, and the pathological assessment seldom reports histological features related to NASH or even steatosis\textsuperscript{44}. Most patients with cryptogenic cirrhosis in the United States have been diagnosed with ‘burnt-out’ NASH\textsuperscript{51-54}. This concept was indirectly supported by the fact that patients with cryptogenic cirrhosis who undergo liver transplantation had higher rates of obesity and other metabolic risk factors and a higher risk of developing recurrence of NASH and metabolic conditions after transplantation\textsuperscript{52,53}. A study that compared 103 and 144 patients with cryptogenic cirrhosis and biopsy-proven NASH, respectively, reported that cryptogenic cirrhosis was demographically similar to NASH-related cirrhosis\textsuperscript{55}.

The diagnosis of NASH cirrhosis is based on: (1) having risk factors for progression to cirrhosis, (2) excluding the other causes of cirrhosis, and (3) having cirrhosis complications. The majority of patients with NASH-cirrhosis are women, older than 50 years, and with obesity and/or diabetes mellitus and dyslipidemia as comorbidities. Patients with NASH-advanced fibrosis (F3-4) showed an overall 10-year survival of 81.5% during the follow-up period. NASH-cirrhosis had lower rates of liver-related complications and HCC than cirrhosis related with hepatitis C infection\textsuperscript{56}. In a recent study, all-cause mortality rate in NASH-cirrhosis is 1.76 deaths per 100 person-years. Patients with NASH-cirrhosis also had a higher risk of diabetes and chronic renal disease\textsuperscript{41}. In a retrospective study that included the United Network for Organ Sharing Data, the authors reported that the number of NASH-related transplant cases increased\textsuperscript{57}. With the increasing prevalence of risk factors, the number of NASH-cirrhosis cases would consistently increase.
Variants in classification of non-alcoholic fatty liver disease

(1) Lean non-alcoholic fatty liver disease

Risk factors for NAFLD include insulin resistance and metabolic syndrome i.e. three or more of the following: obesity, diabetes mellitus, hypertension, low high-density lipoprotein levels, and high triglyceride levels\(^2\). Among these, obesity is the most common risk factor. However, people with normal body weight (body mass index [BMI; kg/m\(^2\)] <23 kg/m\(^2\) for Asians and <25 kg/m\(^2\) for Westerners) or non-obese weight (BMI <25 kg/m\(^2\) for Asians and <30 kg/m\(^2\) for Westerners) can also be diagnosed with NAFLD, referred to as lean or non-obese NAFLD.

The lean NAFLD is more prevalent in Asia\(^4,5,8\). Data on the prevalence of lean NAFLD in the general population varies from 7.8–74\% across studies\(^5,8-1\) This variation is mainly because of the variation in the BMI cut-off used to define lean individuals. In one Asian study that included 307 biopsy cases, 23.5\% were diagnosed as lean NAFLD\(^6,2\).

Compared to healthy people, patients with lean NAFLD had higher metabolic syndrome occurrence, diastolic blood pressure, hemoglobin A1c, and insulin resistance\(^6,3,4\). Additionally, biochemical and hematologic markers, such as serum ALT, AST, Gamma glutamyl peptidase (\(\gamma\)-GT), and total bilirubin levels, were higher in patients with lean NAFLD than in healthy participants\(^6,0,6,1,6,3\). Although the prevalence of metabolic syndrome in lean NAFLD was lower than in obese NAFLD, the impact of lean NAFLD was a stronger risk factor for higher all-cause mortality, cirrhosis, and HCC than obese NAFLD\(^6,3\). Zou et al., reported that patients with lean NAFLD showed advanced fibrosis stage and a higher incidence of metabolic comorbidities\(^6,5\).

Additionally, Hagstrom et al. reported that patients with lean NAFLD had a higher all-cause mortality\(^6,5,6,6\). Most studies reported a poorer prognosis in lean NAFLD than in obese NAFLD. These results suggest the important role of metabolic disorders in this population.

The etiology of lean NAFLD is assumed to be based on central obesity and visceral fat\(^6,7\). Therefore, the BMI-driven approach for NAFLD may need to be reappraised. BMI does not entirely explain the association between visceral fat and NAFLD. Moreover, the relationship
between lean NAFLD and metabolic syndrome is still not fully understood, and more long-term studies are required.

(2) Metabolically healthy non-alcoholic fatty liver disease

Obese patients present with significant variations in metabolic abnormalities, such as hyperglycemia, hypertension, and dyslipidemia. Recently, these patients have been classified into different subphenotypes depending on their metabolic health status. Metabolically healthy obesity (MHO) is a concept derived from clinical observations that some obese people do not present with common metabolic abnormalities\(^{68}\); the implications of this for the development of NAFLD across its subphenotypes remain vague.

In a study that included 4,432 MHO people, 2,145 patients (48.4%) were presented NAFLD simultaneously\(^ {67}\). On the contrary, in 225 patients with NAFLD, 14 (6.2%) were metabolically healthy\(^ {61}\). MHO was considered as a risk factor of NAFLD development. Chang, et al. reported that the metabolic health obesity was an independent risk factor for NAFLD development with hazard ratio as 2.15–3.55 then lean patients\(^5\). Metabolic healthy people with NAFLD had a favorable biochemical profile i.e. lower $\gamma$-GT, fasting glucose, and triglycerides levels and higher high-density lipoprotein cholesterol than metabolic unhealthy people. However, they had been diagnosed with NAFLD at a younger age, similar to metabolically unhealthy people\(^ {69}\).

Despite the consensus that obesity is a prerequisite for MHO, more than 30 different definitions of metabolic health are used in clinical studies\(^ {70}\). According to the previous studies, MHO is still considered as preliminary status toward metabolic syndrome and NAFLD; therefore, surveillance strategy of these groups has not been established. A consensus on the concept of MHO between researchers and a cohort study that includes a large number of patients is required.

(3) Metabolic (dysfunction)-associated fatty liver disease

As mentioned earlier, the definition of NAFLD must exclude other causes that can result in inflammation and fatty changes. The significant daily alcohol intake amount that differentiates
NAFLD from alcoholic fatty liver disease ranges from 10 to 40 g (pure alcohol) a day, and this range varies between studies. The EASL guideline defined the amount of significant alcohol consumption as ≥ 210 g in men and ≥ 140 g in women weekly. These criteria were also applied in the Korean Association for the Study of Liver NAFLD guidelines. In the AASLD guidelines, the standard alcohol drink was defined as 14 g of pure alcohol, and significant alcohol consumption was defined as more than 21 standard drinks in men and 14 in women per week.

Recently, it has been suggested that the term NAFLD does not reflect the heterogeneous pathogenesis or various courses of fatty liver disease. Furthermore, the overestimation of the exclusion of alcohol has induced debate about the threshold of ‘significant’ alcohol consumption required for the diagnosis of NAFLD. In 2019, a consensus by 32 experts suggested an alternative terminology, metabolic (dysfunction)-associated fatty liver disease (MAFLD), to more accurately reflect the pathogenesis of this disease. The diagnosis of MAFLD is based on the evidence of fat accumulation in the liver in the presence of one of the following three criteria: overweight/obesity, type 2 diabetes mellitus, and evidence of metabolic dysregulation.

Prevalence of MAFLD was estimated to be approximately 50.7%, and it varied substantially across countries and regions, from 22.3% to 81.5%. According to a recently published study, the prevalence of MAFLD in Korea was reported to be 33.9%. Patients with MAFLD were significantly older and had higher BMI and prevalence of metabolic comorbidities (diabetes and hypertension) than those with NAFLD. In a study that included 756 Japanese patients with fatty liver, the MAFLD definition better identified a group with fatty liver and significant fibrosis, which were evaluated using non-invasive tests.

The term MAFLD implies that fatty change is a risk factor in patients with other causes of chronic liver disease, including viral hepatitis B and C, autoimmune diseases, or alcohol intake above the threshold levels. Whether MAFLD can replace NAFLD is still under debate in several studies. Further research and comparative analyses of the risk associated with fatty changes are needed to validate this term.
Genetic factors play a major role in NAFLD development. Many studies have explored the genetic drivers of NAFLD beyond metabolic syndrome and insulin resistance. Typically, patatin-like phospholipase domain-containing protein 3 (PNPLA3) and transmembrane 6 superfamily member 2 (TM6SF2) nucleotide polymorphisms affect the development and progression of the disease. Furthermore, homozygous carriers of p.148M mutations show a 12-fold increased risk of developing HCC, suggesting the potential for monogenic inheritance. The mutation occurs with the greatest frequency in Hispanics, followed by non-Hispanic whites, and the least in African Americans.

The rs738409[G] allele of PNPLA3 has been consistently shown to be associated with higher liver fat content and necroinflammatory scores and a substantially increased risk of developing fibrosis. The PNPLA3 rs738409[G] allele is more common in Asians with lean NAFLD without metabolic syndrome, which could account for the observation that Asian and Caucasian populations have a similar prevalence of NAFLD. In another study, patients with cryptogenic cirrhosis had a similar prevalence of PNPLA3 rs738409 genotypes as those with NASH. These associations were independent of the presence of type 2 diabetes mellitus and obesity. However, high PNPLA3 allele expression was related to other factors, such as lifestyle, viral infection, and alcohol consumption.

Another genetic variant that is associated with NASH is the rs58542926 allele of TM6SF2. The TM6SF2 E16K variant is associated with an increased risk of progressive NASH, although a recent study has reported that the variant may reduce the risk of cardiovascular disease. In a more comprehensive discussion on NAFLD genetics, including TM6SF2 and MBOAT7 gene variants, genetic risk factors for liver fibrosis were identified.

Another example is the enzyme hydroxysteroid 17β-dehydrogenase 13 (HSD17B13), a member of a large family of enzymes primarily involved in sex hormone metabolism, which is a novel liver-specific lipid droplet-associated protein in mice and humans with NAFLD. Hepatic overexpression of HSD17B13 promotes lipid accumulation in the liver, suggesting the pathogenic
role of *HSD17B13* in NAFLD. A recent study showed that a loss-of-function variant of *HSD17B13* was associated with a reduced risk of chronic liver disease and progression from steatosis to steatohepatitis, highlighting it as a potential therapeutic target.

Many other genes involved in carbohydrate and lipid metabolism, insulin signaling pathways, inflammatory pathways, oxidative stress, and fibrogenesis have been shown to play a role in the development and progression of NAFLD/NASH. Some of these include *GCKR, APOB, LPIN1, UCP2*, and *IFLN4*. Although these genetic advancements have increased our understanding of the pathogenesis of NAFLD, routine testing for these genetic variants is currently not advocated. The relationship between genetic diversity and NAFLD progression requires further investigation.

**Conclusion**

NAFLD affects a heterogeneous patient population. Although the primary driver in many patients is metabolic syndrome, a complex and dynamic heterogeneous interaction of different factors are involved. Therefore, the response to therapy differs among patients depending on sex, the presence of genetic variants, coexistence of different comorbidities, diverse microbiota composition, and various amounts of alcohol consumption. In this review, we addressed this heterogeneity and subtypes of NAFLD by analyzing published data on the differential contributions of known factors to the pathogenesis and clinical expression of NAFLD. We need to consider this heterogeneity and the dominant drivers of this disease in patients according to subtypes and make predictions to provide precision-targeted therapy for NAFLD.

**Authors’ contribution:** All authors contributed to the study conception and design, material preparation, data collection. The first draft of the manuscript was written by Seul Ki Han and Moon Young Kim. All authors commented on previous versions of the manuscript. All authors
read and approved the final manuscript.

**Conflict of interest statement:** The authors have no conflict of interest to disclose.

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<table>
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<tr>
<th>Grading</th>
<th>Grade 1 (mild)</th>
<th>Grade 2 (moderate)</th>
<th>Grade 3 (severe)</th>
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<td></td>
<td>Steatosis</td>
<td>Steatosis</td>
<td>Steatosis</td>
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<td></td>
<td>Up to 66%</td>
<td>Any degree</td>
<td>Panacinar</td>
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<tr>
<td>Ballooning</td>
<td>Occasional in zone 3</td>
<td>Obvious, predominantly zone 3</td>
<td>Ballooning and disarray obvious, predominantly in zone 3</td>
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<td>Intralobular inflammation: scattered polymorphs ± lymphocytes</td>
<td>Polymorphs and chronic inflammation noted</td>
<td>Scattered polymorphs ± mild chronic inflammation</td>
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<td>Portal inflammation</td>
<td>Portal inflammation: No or mild</td>
<td>Mild to moderate</td>
<td>Mild or moderate</td>
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<tr>
<td></td>
<td>Zone 3 perisinusoidal/pericellular fibrosis, focal or extensive</td>
<td>Zone 3 perisinusoidal/pericellular fibrosis + focal or extensive periportal fibrosis</td>
<td>Zone 3 perisinusoidal/pericellular fibrosis + portal fibrosis + bridging fibrosis</td>
<td>Cirrhosis</td>
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Table 2. The definition and subtypes of non-alcoholic fatty liver disease

<table>
<thead>
<tr>
<th>Traditional classification</th>
<th>Definition</th>
<th>Prevalence</th>
<th>Clinical implications</th>
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| NAFL                      | 5% of steatosis in hepatocytes  
Without any cause of fatty change | 5–30% of general populations | 30–40% of patients with NAFL seem to experience progression of fibrosis |
| NASH                      | NAFLD + hepatocyte ballooning degeneration and hepatic lobular inflammation | 2–30% of NAFLD  
3%–6% of the general population | Fibrosis is a major prognostic predictor of liver-related and overall mortality |
| NASH-Cirrhosis            | NAFLD + necroinflammatory reactions may disappear, and cirrhosis without other specific causes may be present. | 20% of patients with NASH  
0.178% of the general population | Cryptogenic cirrhosis is presumed to be an advanced form of NASH. |
<p>| Variants of NAFLD         | Definition | Prevalence | Clinical implications |
| Lean NAFLD               | NAFLD in people with  | 23.5% of the | Compared with non-lean |</p>
<table>
<thead>
<tr>
<th>normal body weight</th>
<th>general population</th>
<th>NAFLD, lean NAFLD had a stronger correlation with metabolic deterioration.</th>
<th>The risk of fibrosis is increased</th>
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<tr>
<th>Metabolically healthy NAFLD</th>
<th>Steatosis above 5% Does not meet any metabolic syndrome criteria</th>
<th>6.2% of NAFLD</th>
<th>Diagnosed with NAFLD at a younger age</th>
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<td></td>
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<td>The disease progression from Metabolic healthy to unhealthy is higher in obesity group than normal weight group</td>
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| MAFLD | Steatosis above 5% The presence of one of the following three criteria: overweight/obesity, type 2 diabetes mellitus (T2DM), and evidence of metabolic dysregulation | 50.7% of the general population; varies across countries and regions | Paradigm shift from NAFLD to MAFLD |

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<tr>
<th>Genetics</th>
<th>Subtypes</th>
<th>Clinical implications</th>
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<tr>
<td>PNPLA3</td>
<td>Common in Asians with lean NAFLD Associated with cryptogenic cirrhosis</td>
<td></td>
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<tr>
<td>TM6SF2</td>
<td>Increased risk for progressive NASH</td>
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<tr>
<td>HSD17B13</td>
<td>Loss-of-function variant was associated with liver disease progression</td>
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NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; BMI, body mass index; MAFLD, metabolic (dysfunction)-associated fatty liver disease
PNPLA3, patatin-like phospholipase domain-containing protein 3; HSD17B13, hydroxysteroid 17β-dehydrogenase 13; TM6SF2, transmembrane 6 superfamily member 2