

World Journal of *Gastroenterology*

World J Gastroenterol 2017 December 21; 23(47): 8263-8438



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World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents[®]/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch[®]), Journal Citation Reports[®], Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports[®] cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29th among 79 journals in gastroenterology and hepatology (quartile in category Q2).

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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PUBLICATION DATE
December 21, 2017

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Clinical epidemiology and disease burden of nonalcoholic fatty liver disease

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Author contributions: Perumpail BJ, Khan MA, Kim D, Cholankeril G and Ahmed A drafted the manuscript; Cholankeril G and Ahmed A critically revised intellectual input; all authors approved the final manuscript.

Conflict-of-interest statement: All authors have no conflicts of interest or financial disclosure relevant to this manuscript.

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Manuscript source: Invited manuscript

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Received: October 22, 2017

Peer-review started: October 25, 2017

First decision: November 8, 2017

Revised: November 8, 2017

Accepted: December 4, 2017

Article in press: December 4, 2017

Published online: December 21, 2017

Abstract

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic fat accumulation after the exclusion of other causes of hepatic steatosis, including other causes of liver disease, excessive alcohol consumption, and other conditions that may lead to hepatic steatosis. NAFLD encompasses a broad clinical spectrum ranging from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and finally hepatocellular carcinoma (HCC). NAFLD is the most common liver disease in the world and NASH may soon become the most common indication for liver transplantation. Ongoing persistence of obesity with increasing rate of diabetes will increase the prevalence of NAFLD, and as this population ages, many will develop cirrhosis and end-stage liver disease. There has been a general increase in the prevalence of NAFLD, with Asia leading the rise, yet the United States is following closely behind with a rising prevalence from 15% in 2005 to 25% within 5 years. NAFLD is commonly associated with metabolic comorbidities, including obesity, type II diabetes, dyslipidemia, and metabolic syndrome. Our understanding of the pathophysiology of NAFLD is constantly evolving. Based on NAFLD subtypes, it has the potential to progress into advanced fibrosis, end-stage liver disease and HCC. The increasing prevalence of NAFLD with advanced fibrosis, is concerning because patients appear to

experience higher liver-related and non-liver-related mortality than the general population. The increased morbidity and mortality, healthcare costs and declining health related quality of life associated with NAFLD makes it a formidable disease, and one that requires more in-depth analysis.

Key words: Nonalcoholic fatty liver disease; Hepatic steatosis; Fatty liver; Prevalence; Incidence; Fibrosis; Risk factor; Epidemiology; Outcomes; Nonalcoholic steatohepatitis

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Core tip: Nonalcoholic fatty liver disease (NAFLD) is a term for a host of histological findings stemming from hepatic steatosis and remains the most common liver disease globally with increasing prevalence. The vast variation in disease presentation complicates diagnosis, leading to an underestimate of actual disease occurrence. NAFLD is associated with many metabolic comorbidities, including obesity, type II diabetes, dyslipidemia, and metabolic syndrome. Its potential to develop into more severe liver conditions, such as nonalcoholic steatohepatitis, advanced fibrosis, cirrhosis and hepatocellular carcinoma, can lead to a state in which liver transplantation is the only treatment option available. The population at risk of developing progressive liver disease creates a challenge to the healthcare system in terms of screening for this evolving epidemic of liver disease.

Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. *World J Gastroenterol* 2017; 23(47): 8263-8276 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i47/8263.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i47.8263>

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become a common cause of chronic liver disease in the world^[1] since its first description in 1980 as the “unnamed disease”^[2]. It has been studied in-depth subsequently with continuous myriad of further investigations being carried into this soon to be common indication for liver transplantation (LT). Figure 1 summarizes some of the most landmark studies in the current literature on NAFLD.

NAFLD CLASSIFICATION

NAFLD encompasses a wide histological variety: Nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), fibrosis, NASH cirrhosis, and

NASH-related hepatocellular carcinoma (HCC) (Figure 2). NAFLD is characterized by $\geq 5\%$ of hepatic fat accumulation in the absence of any secondary causes and is a diagnosis of exclusion. Therefore, other etiologies leading to similar hepatic histology must be ruled out including excessive alcohol consumption; viral hepatitis; other chronic liver disease such as, Wilson’s disease, hemochromatosis, viral hepatitis, autoimmune hepatitis, cholestatic liver disease and other chronic liver diseases; starvation; lipodystrophy; celiac disease; Cushing’s disease; and medications (corticosteroids, methotrexate, diltiazem, oxaliplatin, amiodarone, isoniazid, highly active anti-retroviral therapy, etc.). Current guidelines recommend utilizing criteria requiring an alcohol exposure of less than 30 g/d for men and less than 20 g/d for women as a component of NAFLD diagnosis^[1].

EPIDEMIOLOGY

NAFLD has diverse manifestations described in all ethnicities all over the world and present in both sexes^[3]. The variable presentations probably contribute to the underreported new and existing cases of NAFLD as well as the limited studies undertaken to elucidate the exact incidence and prevalence of NAFLD.

Disease burden

It is currently estimated that the global prevalence of NAFLD is as high as one billion^[4]. In the United States, NAFLD is estimated to be the most common cause of chronic liver disease, affecting between 80 and 100 million individuals, among whom nearly 25% progress to NASH.

Incidence of NAFLD

A study from Japan which followed 3147 patients over 414 d found a 10% annual incidence rate^[5]. Another Japanese study evaluated elevated aminotransferase levels, weight gain and insulin resistance development over 5 years to classify patients with NAFLD and their incidence was reported as 31 per 1000 person-years^[6]. A retrospective study done in England later demonstrated a much lower incidence of 29 per 100000 person-years^[7]. A recent extensive meta-analysis described a pooled regional incidence of NAFLD in Asia and Israel to be 52 [95% confidence interval (CI): 28-97] per 1000 person-years and 28 (95%CI: 19-41) per 1000 person-years, respectively^[3]. Current data on incidence for NAFLD are limited in some regions of the world due to the limited number of studies. Further studies seem warranted to determine the true incidence in general population.

Prevalence of NAFLD

In general, the prevalence of NAFLD has increased over the last 20 years. In addition to the gold standard

Hamaguchi *et al*^[5] The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med* 2005; 143: 722-728

- **Study design:** A prospective cohort study done over 414 d to investigate the effect of metabolic syndrome on pathogenesis of non-alcoholic fatty liver disease.
- **Summary results:** Participants with metabolic syndrome had 4 to 11 times higher risk of future non-alcoholic fatty liver disease.
- **Limitations:** Abdominal ultrasonography, which is not the gold standard, was used to classify non-alcoholic fatty liver disease.

Szczepaniak *et al*^[14] Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab* 2005; 288: E462-E468

- **Study design:** Randomized controlled clinical trial to measure hepatic triglyceride content (HTGC) using magnetic resonance spectroscopy (MRS).
- **Summary results:** A value of 5.56% or greater of HTGC defined as abnormal in patients with no risk factors. Estimated prevalence of NAFLD as 33.6% in the Dallas heart study cohort.
- **Limitations:** 43% of the study population was obese contributing to the higher prevalence reported in comparison to general population.

Younossi *et al*^[16] Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol* 2011; 9: 524-530

- **Study design:** A retrospective analysis of National health and nutrition examination surveys used to estimate changes in the prevalence and predictors of chronic liver disease (CLD).
- **Summary results:** Prevalence of CLD is increasing: 11.78% \pm 0.48% (1988-1994), to 14.78% \pm 0.58% (2005-2008) ($P < 0.0001$). Prevalence of NAFLD has increased steadily as well: 5.51% \pm 0.31% (1988-1994) to 11.01% \pm 0.51% (2005-2008) ($P < 0.0001$).
- **Limitations:** The analysis and results are limited to adults only. There was no histological definition of NAFLD or NASH used to account for prevalence.

Younossi *et al*^[3] Global epidemiology of nonalcoholic fatty liver disease- Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; 64: 73-84

- **Study design:** A systematic review and meta-analytic approach to report the incidence, prevalence, disease progression and burden of NAFLD.
- **Summary results:** Pooled incidence rate from Asia and Israel were 52 and 28 per 1000 person-year respectively. Prevalence of NAFLD in US has increased from 15% to 25% between 2005 and 2010. Prevalence of NASH is between 1.5% to 6.45%. 9% of NASH patients had advancements in their fibrosis.
- **Limitations:** High unexplained heterogeneity of included studies. Under representation of under-developed countries and besides two studies all others were from countries with high human development index.

Schwimmer *et al*^[21] Prevalence of fatty liver in children and adolescents. *Pediatrics* 2006; 118: 1388-1393

- **Study design:** A retrospective review to determine the prevalence of pediatric fatty liver as diagnosed by histology in a population-based sample.
- **Summary results:** Prevalence of fatty liver in pediatric age group 2-19 yr old was 9.6% (95%CI: 7.4 - 11.7). Prevalence increases with increasing age. Ages 2-4: 0.7 (95%CI: 0.0-2.0), ages 15-19: 17.3 (95%CI: 13.8-20.8).
- **Limitations:** A specific cause of fatty liver disease could not be determined.

Wong *et al*^[98] Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. *Gut* 2010; 59: 969-974

- **Study design:** Prospective longitudinal hospital based cohort study to investigate disease progression over 36 months of different degrees of NAFLD.
- **Summary results:** 13 patients with simple steatosis at baseline, three (23%) continued to have simple steatosis at month 36, five (39%) developed borderline NASH and three (23%) developed NASH. Among 17 patients with NASH at baseline, 10 (59%) continued to have NASH and six (35%) had borderline NASH at month 36. Only one (6%) patient regressed to simple steatosis.
- **Limitations:** All patients received lifestyle advice and regular monitoring of metabolic factors. This might have altered the natural history of the disease. Patients with NAFLD in a hospital clinic may have more advanced disease than those in the community. Small Sample size precluded more detailed analysis of factors associated with disease progression. Liver biopsy might be limited by sampling bias.

Angulo *et al*^[113] Liver Fibrosis, but no other Histologic Features, Associated with Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2015; 149: 389-397

- **Study design:** A retrospective analysis of 619 patients diagnosed with NAFLD from 1975 through 2005 underwent analysis of their laboratory and biopsies results.
- **Summary results:** Features associated with death or liver transplantation included fibrosis stage 1 (HR = 1.88; 95%CI: 1.28-2.77), stage 2 (HR = 2.89, 95%CI: 1.93-4.33), stage 3 (HR = 3.76, 95%CI: 2.40-5.89), and stage 4 (HR = 10.9, 95%CI: 6.06-19.62) compared with stage 0. Survival free of liver transplantation in patients with non-NASH was significantly lower in those with fibrosis as compared to those without fibrosis ($P < 0.001$).
- **Limitations:** Lack of a specific protocol for patient follow-up with regards to endoscopy and imaging procedures in non-cirrhotic patients, and thus it is possible that the number of liver-related events was underestimated. Over-representation of the white population.

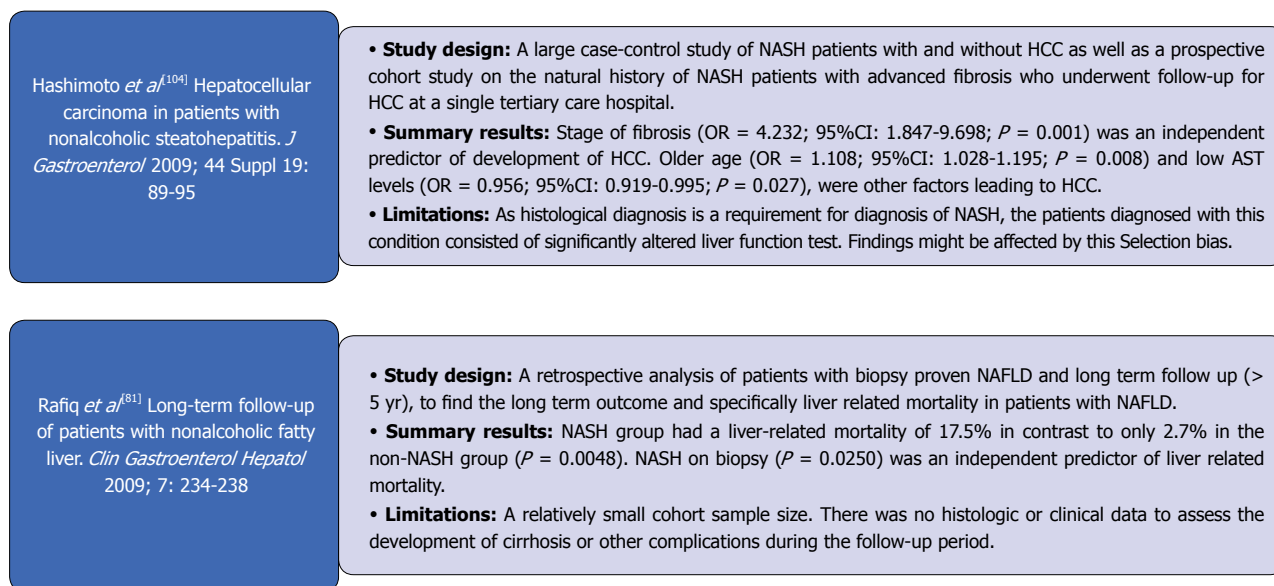


Figure 1 Summary of landmark literature.

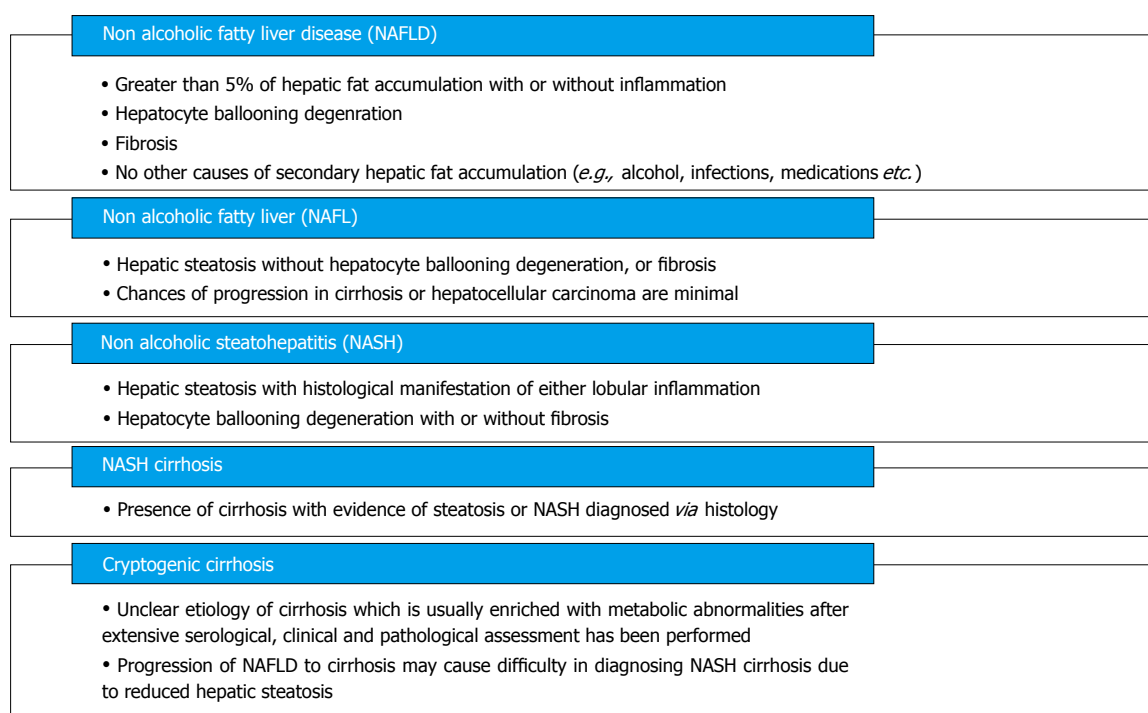


Figure 2 Definitions of nonalcoholic fatty liver disease and its subsets.

diagnostic test of liver biopsy, there are some non-invasive modalities available to diagnose NAFLD. Hepatic ultrasonography, computed tomography (CT), and MRI are accepted modalities for detecting hepatic fatty infiltration. The difference in sensitivity of diagnostic modalities may account for the discrepancy in prevalence data for NAFLD. Using aminotransferase levels as a screening laboratory test for liver disease, prevalence of elevated aminotransferases was 7.9% in the United States general population (1988-1992) with unexplained liver disease in 69% of these subjects^[8,9].

In a recent meta-analysis, hepatic ultrasonography allowed for the reliable and accurate detection of moderate-to-severe fatty liver and is now considered the screening modality of choice^[10]. Prevalence of ultrasonographic diagnosis of NAFLD ranged between 17% in India to 46% in the United States^[8,11,12]. MRS remains one of most sensitive and accurate noninvasive tests available with a NAFLD prevalence of 33% reported in the Dallas Heart Study^[13,14]. The Middle East and South America have the highest NAFLD prevalence at 31% and 32% respectively with

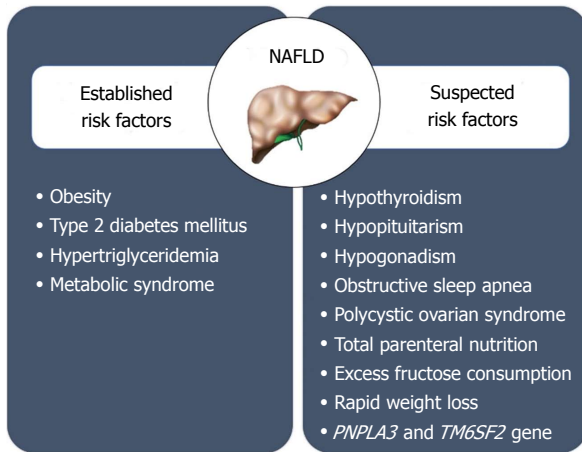


Figure 3 Established and suspected risk factors for nonalcoholic fatty liver disease. NAFLD: Nonalcoholic fatty liver disease.

the lowest prevalence in Africa at 13.5%^[3]. Recently, Asia has been facing the highest obesity epidemic and thus not surprisingly has been experiencing a rapid rate of increase in the prevalence of NAFLD. Chinese adolescents on a “westernized” diet have a greater than 25% prevalence of NAFLD. Studies from Korea, China, Japan and Taiwan have all reported a prevalence ranging from 11%-45%^[15]. Along with the global drift, United States has not been immune to the uptrend in NAFLD. A recent United States-based study using the National Health and Nutrition Examination Surveys (NHANES) conducted between 1988 and 2008 found that the prevalence of NAFLD using elevated alanine aminotransferase (ALT) doubled in the United States during this time period (5.5% to 11.0%)^[16]. Based on the NHANES-III data collected between 1988 and 1994, the prevalence of ultrasonography-diagnosed NAFLD was 34%^[17]. Meta-regression of studies done globally also displayed an increased prevalence of NAFLD from 15% in 2005 to 25% in 2010^[3]. The discrepancy in the prevalence of NAFLD among studies is most likely due to differences in sample selection, diagnostic modalities, dietary and lifestyle habits.

Economic impact

The current annual medical and societal costs of NAFLD are estimated at \$292 billion in the United States^[18]. The projected cost of caring for patients is expected to increase by 18% from 2000 to 2035 and health-related quality of life of NAFLD patients is described as declining^[19,20].

HOST AND ENVIRONMENTAL RISK FACTORS FOR NAFLD

Based on our current knowledge, it appears that a combination of genetic, demographic, clinical and environmental factors may play a role in determining the likelihood of NAFLD in a given individual (Figure 3).

Therefore, the pathogenesis of NAFLD is a multifactorial and multi-step process.

Genetic predisposition to NAFLD

Although obesity, lifestyle variation, and insulin resistance are the most prevalent risk factors leading to the development of NAFLD in a person, NAFLD varies substantially among subjects with comparable lifestyle, environmental impact, and metabolic abnormalities, indicating that other factors contribute to pathogenesis. The heritability^[21] and interethnic variations in susceptibility^[13] suggest that genetic factors may play an important role in determining the phenotypic manifestation and overall risk for NAFLD. NAFLD clusters in families with certain genetic variants on or near *TM6SF2*, *PNPLA3*, *NCAN*, and *PPP1R3B* genes that increase the heritability of NAFLD by up to 27% within families^[22,23]. One genetic variant that is associated with NAFLD is a missense mutation [Ile148 - > Met148 (I148M)] in the palatin-like phospholipase domain-containing 3 gene (*PNPLA3*)^[24]. A recent meta-analysis showed that *PNPLA3* exerts a strong influence not only on hepatic fat accumulation (GG homozygous individuals showed a 73% higher hepatic fat content compared with CC homozygous individuals, $P < 1 \times 10^{-9}$) but also on the susceptibility to develop more severe histologic liver damage (GG homozygous individuals had a 3.24-fold greater risk of higher necro-inflammatory scores and a 3.2-fold greater risk of developing fibrosis compared with CC homozygous individuals, $P < 1 \times 10^{-9}$, respectively)^[22]. These associations were maintained irrespective of the degree of obesity or the presence of diabetes^[23,25,26]. A single variant in *PNPLA3* gene (I148M) has been observed in highest frequency in Hispanics, followed by non-Hispanic whites and least in African Americans^[24]. A minor allele in transmembrane 5 superfamily member 2 (*TM6SF2*) was associated with MRS-measured hepatic triglyceride content from the Dallas Heart Study^[27]. In addition, a minor allele of *TM6SF2* was noted to increase the risk for hepatic fibrosis independent of age, obesity, diabetes, and *PNPLA3* genotype^[28].

Gender and age-related risk for NAFLD

Generally, gender differences exist in NAFLD. Prevalence of NAFLD and NASH was higher in men^[12]. Women are at a reduced risk of NAFLD compared with men at their reproductive period, whereas after menopause women lose the protective effect and have a comparable prevalence of NAFLD as men^[29]. These associations were consistent with children^[30]. Superseding gender, age trends have been associated with NAFLD. Based on the NHANES data, suspected NAFLD prevalence defined as elevated ALT rose from 3.9% in 1988-1994 to 10.7% in 2007-2010, with increases among all race/ethnic subgroups, males and females ranging 12-19 years in age^[30]. These trends

were also consistent among adolescent and young adults aged 15-39 years^[31]. Although the majority of studies are among people aged 30 to 70 years, the general trend of increased prevalence is observed with age with peak prevalence of NAFLD noted between age 50-60 in men^[32]; with 16.1% in ages 30 to 40 years old, 22.3% in 41 to 50 years old, 29.3% in 51 to 60 years old, and 27.6% in over 60 years old based on NHANES III^[33]. In women, prevalence of NAFLD increased with age especially after menopause; with 12.5% in ages 30 to 40 years old, 16.1% in 41 to 50 years old, 21.6% in 51 to 60 years old, and 25.4% in over 60 years old^[33]. A study with octogenarians admitted in a geriatric hospital showed a higher than usual prevalence of 46%^[34].

Differences in NAFLD from race/ethnicity

Race/ethnicity is another variable affecting the prevalence of NAFLD, with the highest prevalence among Hispanics followed by non-Hispanic whites, and lowest prevalence in African Americans^[12,13,35]. The numbers cited are at times double for Hispanics (45%-58%) in comparison to African Americans (24%-35%), with Latinos of Mexican origin having the highest prevalence in a subgroup analysis of the Latino population^[13,36]. These findings hold true even in studies in the pediatric population^[30]. Underlying genetic and lifestyle variations amongst these ethnicities could further account for the skewed prevalence of NAFLD.

Linking obesity and NAFLD

The prevalence of NAFLD among the obese population ranges from 30% to 37%^[8]. Abdominal obesity with increased waist circumference is specifically more strongly correlated with NAFLD^[37]. In a recent cohort study of 2017 subjects during a median 4.4 year follow-up, the visceral adiposity was associated with incident NAFLD in a dose-dependent manner, with an adjusted hazard ratio [HR, per 1-standard deviation (SD) increase] for incident NAFLD of 1.36 (1.16-1.59)^[38]. In addition, this study found significant relationships with subcutaneous adiposity for regressed NAFLD of HR = 1.36 (95%CI: 1.08-1.72) independent of visceral adiposity^[38]. Furthermore, a recent study reported that visceral adiposity increased the risk for NAFLD without significant fibrosis and NAFLD with significant fibrosis after adjusting for known risk factors^[39]. Multivariate analysis showed that the visceral adipose tissue area was independently associated with increased risks of NASH and significant fibrosis^[39]. These studies suggest that certain types of abdominal fat are risk factors for NAFLD and more advanced NAFLD-related fibrosis, whereas other types could reduce risk for NAFLD. In recent years, several cohort studies demonstrated an association between body weight change and incident NAFLD^[40-43]. Even a modest gain in body weight of 2 kg within the normal range has been shown to increase the risk of developing NAFLD^[41]. Obesity has also

been noted to be an additive factor causing a two-fold increase in steatosis in the setting significant alcohol use^[28]. While it is common to have NAFLD in obese population, it is even more common to have obesity in patients with NAFLD. The pooled prevalence of obesity in NAFLD globally is reported to be 51%^[3].

Contribution of diet composition to NAFLD

Due to the evidence supporting that obesity is associated with NAFLD, some macro- and micro-nutrients contribute more to the epidemic of NAFLD. Fructose is a major player, either from sucrose or high fructose corn syrup found in beverages. Consumption of such beverages has increased five-fold in the United States since 1950, and drinking two average size sugar containing beverage servings for 6 mo ends up mirroring many features of NAFLD^[44]. It is hypothesized that sugars promote de novo lipogenesis and trigger inflammatory response leading to hepatocyte apoptosis via the c-Jun-N-Terminal pathway^[45].

Diabetes as a risk factor for NAFLD

Pre-existing metabolic disorders, specifically type 2 diabetes mellitus (T2DM), have a close association with NAFLD, with more than three-quarters of diabetic patients reportedly having NAFLD^[46]. T2DM and insulin resistance promote lipolysis of the adipose tissue leading to release of free fatty acids and their deposition in the liver leading to steatosis^[45]. T2DM is a significant risk factor to cause progressive NASH, fibrosis, cirrhosis and an independent risk factor of mortality in addition to liver-related mortality^[47].

Sleep deprivation as a risk factor for NAFLD

Sleep disturbances and disorders are common medical problems in the current era. Epidemiological studies^[48,49] have provided evidence that poor sleep quality and sleep deprivation is associated with obesity which plays a key role in the pathogenesis of NAFLD. Recently, population cohort studies^[50-52] reported that sleep deprivation may be independently associated with NAFLD with odds ratio 1.28 (1.13-1.44) in men and 1.71 (1.38-2.13) in women. Further, poor quality sleep was found to be a positive predictor of NAFLD in men and women 1.10 (1.02-1.19) and 1.36 (1.17-1.59) respectively^[52]. Biologic plausibility for this independent association has been explored by evaluating the role of inflammatory cytokines interleukin 6 and TNF- α ^[53,54]. These cytokines are increased by sleep disturbances and play a role in pathogenesis of NAFLD by increasing adipocyte lipolysis which in turn can cause hepatic overflow of free fatty acids^[55]. Further, sleep deprivation can affect hypothalamus pituitary adrenal axis, which in turn affects cortisol metabolism leading to hepatic fat accumulation^[56,57].

Medical conditions associated with NAFLD

In addition to the above listed risk factors, other

emerging contributors such as hypothyroidism, hypopituitarism, polycystic ovarian disease and obstructive sleep apnea (Figure 3) should be kept in mind^[1].

METHODOLOGY FOR NAFLD DIAGNOSIS

NAFLD is diagnosed based on clinical history, laboratory and radiographic studies which are further complemented by histologic information. Abdominal imaging revealing hepatic steatosis may be sufficient for diagnosis of NAFLD and liver biopsy may not be required if clinical and laboratory data have ruled out other causes of liver disease. However, role of liver biopsy is important in differentiating NASH from simple steatosis and this may have implications in management as NASH has a higher risk of disease progression as compared to simple steatosis^[58]. NASH is confirmed when all four features viz. steatosis, inflammation, cellular ballooning and fibrosis are present on histology^[58,59]. Apart from imaging and liver biopsy, certain non-invasive tests can help in clinical decision making regarding the presence of advanced fibrosis in NAFLD patients. NAFLD fibrosis score (NFS) is one of the most commonly employed non-invasive tests to assess severity of hepatic fibrosis by utilizing six variables: age, BMI, hyperglycemia, platelet count, albumin and aspartate aminotransferase (AST)/ALT ratio. It is calculated using the published formula available at (*Hepatology* 2007; 45: 846-854 DOI: 10.1002/hep.21496). A meta-analysis of 3064 patients reported that NFS has an area under the receiver operating curve (AUROC) of 0.85 for predicting bridging fibrosis with nodularity or cirrhosis. A score < -1.45 had 90% sensitivity to exclude advanced fibrosis, whereas a score > 0.67 had a 97% specificity to identify presence of advanced fibrosis^[60]. FIB-4 index is another algorithmic score utilized in studies to predict advanced fibrosis. It is based on age, platelet count, AST and ALT and is calculated using published formula (*Hepatology* 2006; 43: 1317-1325 DOI: 10.1002/hep.21178). Using this formula, patients with score > 3.25 are likely to have advanced fibrosis whereas, those with score < 1.45 are unlikely to have advanced fibrosis. Imajo *et al.*^[61] compared various risk scores and elastography against liver histology and showed that NFS and FIB-4 were better than other non-invasive scoring indices like AST to platelet ratio index and AST/ALT ratio. Further, NFS and FIB-4 were as good as MR elastography (MRE) in predicting advanced fibrosis in patients with biopsy-proven NAFLD.

Abdominal imaging as a means of measuring hepatic steatosis

A variety of imaging tools can be utilized for the diagnosis of NAFLD. Abdominal ultrasound is limited by low sensitivity in patients with less than 30% steatosis on histology^[62]. However, it is noninvasive,

widely available and does not require contrast. On the other hand, CT can be associated with radiation hazard and contrast linked nephropathy. It is also limited by low sensitivity hepatic mapping and is expensive^[62]. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) provide the highest precision (sensitivity and specificity) in quantifying steatosis and liver fat mapping^[63] and may become the test of choice in management of NAFLD^[64,65]. Hepatic stiffness measurement with MRE is superior to MRI for the non-invasive diagnosis of significant liver fibrosis and cirrhosis^[66], but the role of transient elastography may be limited in subjects with high body mass indices^[67]. Further, MRE has the advantage of identifying individuals with steatohepatitis, even before the onset of significant fibrosis^[68]. NAFLD with inflammation but without fibrosis demonstrates greater hepatic stiffness than simple steatosis and lower mean stiffness than NAFLD with fibrosis^[68]. Despite this, abdominal imaging studies are currently unable to accurately diagnose NASH.

Role of liver biopsy in the diagnosis of NAFLD

Liver biopsy with key histologic features is essential for confirmation of NASH. However, due to its invasive nature experts recommend selective use in NAFLD patients who have a higher probability of progressing to NASH. An individualized assessment is needed with discussion of risks and benefits of a diagnostic liver biopsy. Early diagnosis of NASH has crucial management implications and these patients can benefit from newly approved medications, off-label therapy with promising agents and treatment in the setting of a clinical trial in an attempt to retard the progression of liver disease^[69-74]. Steatosis may be absent in the setting of advanced fibrosis or cirrhosis^[58,69]. Inter-observer variability among experienced pathologists can occur during the histologic evaluation of hepatic balloon degeneration on a liver biopsy sample^[58,59,75,76]. Poor inter-observer agreement among pathologists regarding sampling error or identification of hepatic ballooning may have resulted in a lower number of patients meeting the entry criteria in clinical trials^[69]. Therefore, liver biopsy although considered as a gold standard for diagnosis of NASH may have several limitations. Patients with isolated hepatic steatosis with any degree of necroinflammation on an index liver biopsy are at risk for progressive histologic damage^[77,78]. In addition, patients with metabolic syndrome or those with individual components of metabolic syndrome coupled with isolated hepatic steatosis on liver biopsy may be at risk for more rapidly worsening histologic damage^[77,78]. Figure 2 organizes the predictors of histologic evidence of NASH on an index liver biopsy in patients with NAFLD. Liver biopsy is indicated in NAFLD patients who have persistently elevated ALT and/or AST levels with abdominal imaging consistent with fatty liver age

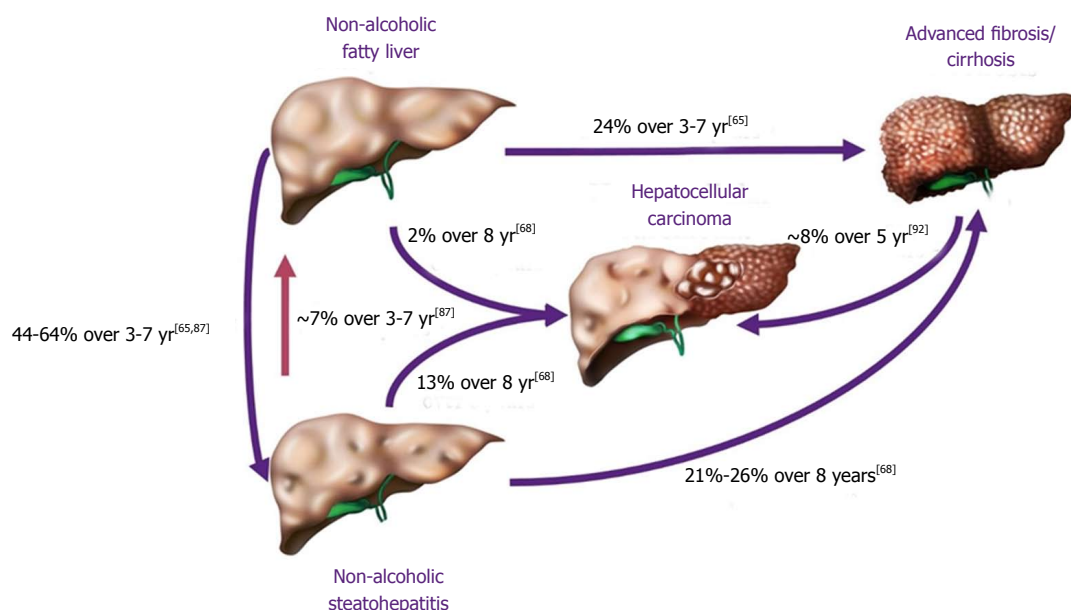


Figure 4 The natural history of nonalcoholic fatty liver disease.

65 years or older, suspicion of other coexisting liver disease, suspicion that another liver disease has been misdiagnosed as NAFLD and those with metabolic syndrome or its components^[1,79-84].

Alternative methods to differentiate NAFLD and NASH

Due to high prevalence of NAFLD along with limitations of liver biopsy and clinical predictors of NASH, there has been a need to develop next generation of noninvasive biomarkers for early diagnosis of NASH^[85]. These noninvasive markers may be able to differentiate lack of fibrosis or mild fibrosis from advanced bridging fibrosis or cirrhosis^[85,86]. However, they are limited in their ability to consistently detect intermediate grade and stage of hepatic fibrosis^[85,86]. Further, abdominal ultrasound have low sensitivity to diagnose NAFLD with less than 30% steatosis^[87]. Keratin 8/18 immunostaining and other next generation noninvasive biomarkers may become available in the near future^[88]. Based on preliminary data, levels of cytokeratin 18 are associated with the presence of NASH, but lacks sensitivity and the histologic details provided by a liver biopsy^[89,90]. Several panels have been developed and studied to predict the presence of advanced fibrosis in patients with NASH^[91]. NAFLD fibrosis score^[92] and FIB-4 are derived from readily available clinical markers for the assessment of advanced fibrosis^[93]. The Enhanced Liver Fibrosis panel utilizes an extracellular matrix marker panel to predict the stage of fibrosis in patients with chronic liver disease^[94].

NAFLD PROGRESSION FROM SIMPLE STEATOSIS TO NASH AND HCC

In terms of progression of NAFLD, the cohort of

patients falls in two broad categories, NASH and NAFL (Figure 4). They are primarily divided by the likelihood of progression; NAFL which represents simple steatosis and steatosis with non-specific inflammatory changes, following a more indolent course of progression, while NASH may progress more rapidly to end-stage liver disease.

Clinical assessment of NAFLD

NAFLD activity score (NAS) has gained popularity in defining NASH, yet histology is still the gold standard. As NASH advances to cirrhosis, it loses its characteristic histologic features, including inflammation and steatosis. Thus, it is increasingly being recognized as "cryptogenic cirrhosis" which essentially means cirrhosis of unclear etiology. Cryptogenic cirrhosis is referred to as 'burnt out' NASH by experts in the medical literature^[8,95]. Patients with cryptogenic cirrhosis have clinical manifestations commonly observed in patients with NASH, such as obesity, dyslipidemia, insulin resistance, T2DM and metabolic syndrome.

Histologic progression and risk factor for NAFLD

NAFL is more readily reversible if lifestyle modifications are implemented in a timely fashion. The benign progression of NAFL and rapid progression of NASH has also been supported by earlier cohort studies from United Kingdom^[96] and Denmark^[97]. In one of the earliest histology-based studies, biopsy-proven NAFLD was divided into 4 types with type 3 (fatty liver and ballooning degeneration) and type 4 (fatty liver, ballooning degeneration, and either Mallory bodies or fibrosis) representing the modern-day definition of NASH^[80]. Over follow up periods of 8 years, 21% to 26% of patients with histological type 3 and type 4 developed cirrhosis compared to only 3% of patients

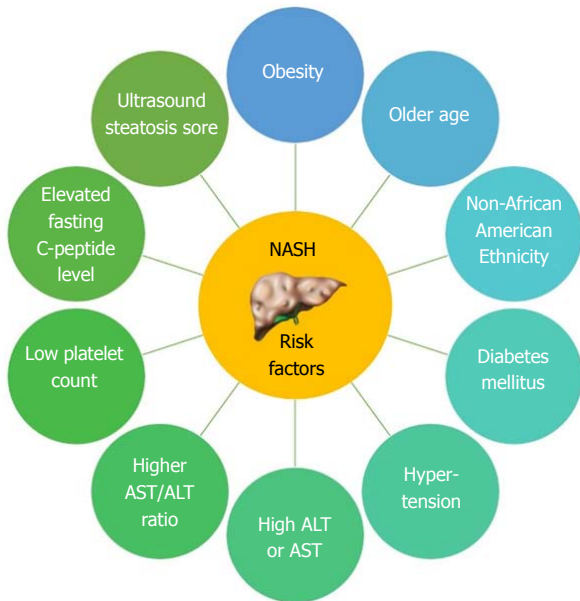


Figure 5 Risk factors for nonalcoholic steatohepatitis subset. NASH: nonalcoholic steatohepatitis.

with type 1 (fatty liver alone) and type 2 (fatty liver and lobular inflammation)^[80]. Recent studies are challenging the widespread belief that non-NASH (simple steatosis) has a benign course. Based on histological diagnosis and follow up biopsies of 52 patients, NAFL advanced to NASH in 23% of cases over a period of 3 years^[98]. The evolution into NASH can be as high as 44%-64% and progression of simple steatosis into advanced fibrosis was reported in up to 24% of the patients with NAFL^[77,99] (Figure 4). Risk factors causing increasing NASH likelihood include obesity, older age, female sex, non-African American race/ethnicity, diabetes mellitus, and hypertension (Figure 5)^[100]. With fibrosis staging and its progression from one stage to another being an important marker of mortality, recent studies reported around 9% to 25% of the patients developed NASH^[101].

Risk of progression from NASH to NASH-related cirrhosis

The risk of progression of NASH into cirrhosis has been delineated in previous studies, and is estimated to be between 21% and 26% in 8 years^[80,102]. Although development of cirrhosis further increases the risk of progression to HCC and/or hepatic decompensation, the stage of fibrosis is also an excellent predictor of outcome.

Risk of HCC development from NAFLD

The incidence of HCC has been increasing in parallel with the rise in NAFLD and its subsets. HCC incidence has grown four-fold from 1973 to 2011^[103]. Advanced fibrosis is a reliable risk factor for HCC with 8% 5-year cumulative incidence rate of developing HCC in patients with advanced fibrosis^[104]. The annual incidence of NAFLD-related HCC (0.44 per 1000

person-years) is rare at this moment and 15-35 times lower than the incidence of HCC in chronic hepatitis B^[3]. In comparison, the annual incidence rate of NASH-related HCC was a significant 5.29 cases per 1000 person-years^[3]. This highlights the increased need of preventative measures that should be adopted; as the prevalence of NAFLD increases so will the incidence of NASH-related HCC. Younossi *et al.*^[105] described a 9% annual increase of HCC cases related to NAFLD over a period of six years from 2004 to 2009. While previous studies have described progression of advanced fibrosis and cirrhosis as a major link between NAFLD and HCC, the latest studies are describing 35% to 50% of HCC without cirrhosis^[106,107]. Understanding of underlying pathogenetic pathways remains unclear at best. A few potential mechanisms to explain the link between NAFLD and HCC include hyperinsulinemia or metabolic syndrome, functioning of hepatic progenitor cells activated by hepatocyte damage, activation of CD8+/CD4+ T lymphocyte and natural killer cells activation causing self-damage and *PNPLA3*-related pathways^[108].

NAFLD OUTCOMES

Liver transplantation in NAFLD patients

NASH is characterized by histologic evidence of progressive hepatocellular injury (ballooning) which can progress to cirrhosis and its complications including HCC with eventual need for liver transplant^[1,109,110]. During last decade, NASH-related LT increased from 1.2% in 2001 to 9.7% in 2009 to become the third most common indication for LT in the United States^[110]. A 2013 population cohort study based on data from the United Network for Organ Sharing/Organ Procurement Transplant Network revealed that NASH has become the second leading etiology of liver disease among adults awaiting LT in the United States and is predicted to become the leading indication in the near future^[110,111]. In addition, NASH is also the second leading etiology for HCC in adults requiring LT in the United States^[112].

Mortality rates associated with NAFLD

A retrospective longitudinal study during 12.6 years showed that increasing fibrosis stage from 1 (HR = 1.88) to stage 4 (HR = 10.49) increased mortality, liver-related events and need for LT^[113]. Over a 8 years follow-up period, liver-related mortality increased in NASH and NASH-related cirrhosis compared to NAFL (11% vs 2%)^[80]. A more recent study using follow-up data from the same cohort reported 18% liver-related mortality in NASH patients compared to 3% in non-NASH patients during 18.5 years^[81].

Predictors of mortality in NAFLD

Previous studies comparing NAFLD to the general

population have consistently shown increased mortality in NAFLD. However, these studies did not adjust for metabolic confounders in the setting of NAFLD. Data from NHANES III revealed no significant difference in the overall survival of ultrasonography-diagnosed subjects with NAFLD compared with the non-NAFLD population after adjusting for multiple metabolic factors^[17]. These results suggest that NASH and/or fibrosis may be the major driver contributing to significant long-term outcomes^[17].

Causes of mortality in NAFLD

NAFLD is associated with increased overall mortality, with ranges for the standardized mortality ratio (SMR) of 1.34-2.6 compared to the general population^[114]. An early landmark study by Adams *et al*^[82] documented that patients with NAFLD ($n = 435$) from Olmsted County, diagnosed histologically or by ultrasonography demonstrated a significantly higher risk of mortality during 7.6 years of follow-up (SMR = 1.34, 95%CI: 1.00-1.76). In this study, liver-related mortality was the third most common cause of death, after malignancy and cardiovascular disease^[82]. This is in contrast to the general population where liver-related mortality is reported 12th most common cause of death^[115]. NASH cirrhosis has been compared to hepatitis C-related cirrhosis in multiple studies with majority of the studies showing decreased or comparable mortality and lower or similar cirrhosis-related complications and/or HCC^[101,114]. However, the cardiovascular mortality was higher in NASH cirrhosis^[100]. The increased risk for cardiovascular mortality can be explained by the decreased morbidity when compared to chronic hepatitis C-related cirrhosis. Thus, most patients may outlive their liver disease but develop fatal complications from cardiovascular disease and malignancies.

CONCLUSION

NAFLD is a term for a host of histological findings stemming from hepatic steatosis and remains the most common liver disease globally with increasing prevalence. The vast variation in disease presentation complicates diagnosis, leading to an underestimate of actual disease occurrence. NAFLD is associated with many metabolic comorbidities, including obesity, type II diabetes, dyslipidemia, and metabolic syndrome. Its potential to develop into more severe liver conditions, such as NASH, advanced fibrosis, cirrhosis and HCC, can lead to a state in which LT is the only treatment option available. The population at risk of developing progressive liver disease creates a challenge to the healthcare system in terms of screening for this evolving epidemic of liver disease. Further research must be conducted to understand NAFLD pathophysiology and its treatment, as well as, define accurate incidence, current disease burden, and

socioeconomic effects of this disease.

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P- Reviewer: Blanco JR, Inzaugarat E, Trovato GMM
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ISSN 1007-9327

