



Non-alcoholic Fatty Liver Disease: Growing Burden, Adverse Outcomes and Associations

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a systemic disorder with a complex multifactorial pathogenesis and heterogeneous clinical manifestations. NAFLD, once believed to be an innocuous condition, has now become the most common cause of chronic liver disease in many countries worldwide. NAFLD is already highly prevalent in the general population, and owing to a rising incidence of obesity and diabetes mellitus, the incidence of NAFLD and its impact on global healthcare are expected to increase in the future. A subset of patients with NAFLD develops progressive liver disease leading to cirrhosis, hepatocellular carcinoma, and liver failure. NAFLD has emerged as one of the leading causes of cirrhosis and hepatocellular carcinoma in recent years. Moreover, HCC can occur in NAFLD even in absence of cirrhosis. Compared with the general population, NAFLD increases the risk of liver-related, cardiovascular and all-cause mortality. NAFLD is bidirectionally associated with metabolic syndrome. NAFLD increases the risk and contributes to aggravation of the pathophysiology of atherosclerosis, cardiovascular diseases, diabetes mellitus, and chronic kidney disease. In addition, NAFLD is linked to colorectal polyps, polycystic ovarian syndrome, osteoporosis, obstructive sleep apnea, stroke, and various extrahepatic malignancies. Extended resection of steatotic liver is associated with increased risk of liver failure and mortality. There is an increasing trend of NAFLD-related cirrhosis requiring liver transplantation, and the recurrence of NAFLD in such patients is almost universal. This review discusses the growing burden of NAFLD, its outcomes, and adverse associations with various diseases.

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Abbreviations: AP, acute pancreatitis; CC, cryptogenic cirrhosis; CI, confidence interval; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HR, hazard ratio; IR, insulin resistance; LT, liver transplantation; MetS, metabolic syndrome; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Surveys; OSA, obstructive sleep apnea; OR, odds ratio; PCOS, polycystic ovarian syndrome; SS, simple steatosis; T2DM, type 2 diabetes mellitus. Received: 10 October 2019; Revised: 3 December 2019; Accepted: 9 December 2019

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by accumulation of fat in $\geq 5\%$ of hepatocytes in the absence of significant alcohol consumption (< 30 g/day for men and < 20 g/day for women) or secondary causes of hepatic steatosis.¹ Histologically, the spectrum of NAFLD ranges from simple steatosis (SS) that in some patients can progress to nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC), and liver failure. NAFLD, once believed to be an innocuous condition, has emerged as the leading cause of chronic liver disease in many countries worldwide.^{2,3} NAFLD is now pandemic worldwide and its prevalence has increased considerably over the last two decades.^{4–7}

The changing epidemiology of NAFLD in Asia during the past two decades is well-documented.^{4,6,7} NAFLD is strongly associated with metabolic syndrome (MetS), the components of which include hypertension, hyperglycemia, abdominal obesity, and dyslipidemia.⁸ However, NAFLD is not merely a hepatic manifestation of MetS but rather both a consequence as well as a predecessor of MetS. Compared with the general population, NAFLD patients are at increased risk of liver-related, cardiovascular and all-cause mortality. NAFLD has been associated with a large number of extrahepatic conditions, such as type-2 diabetes mellitus (T2DM), atherosclerosis, cardiovascular disease (CVD), chronic kidney disease (CKD), polycystic ovarian syndrome (PCOS), obstructive sleep apnea (OSA), extrahepatic malignancies, etc.^{9,10} Recent data suggest that NAFLD increases the susceptibility and/or worsen outcome of acute pancreatitis (AP), cerebrovascular accident (CVA), and osteoporosis.^{11–13}

There is growing trend of patients with NASH-related cirrhosis requiring liver transplantation (LT).^{14,15} The risk of developing progressive liver disease and associated extrahepatic diseases presents a challenge to the healthcare system to develop effective strategies in order to prevent an exponential increase in morbidity and mortality related to it. This review will focus on the growing burden of NAFLD, its outcomes and adverse associations with various extrahepatic diseases; of note, this review is not intended to discuss the therapeutic aspects of NAFLD and its complications.

Global burden and rising prevalence

According to current estimate, the global prevalence of NAFLD among the general population may be as high as one billion.² In a recent meta-analysis of 86 studies,

encompassing a sample size of 8,515,431 from 22 countries, the prevalence of NAFLD in the general population was 25.24%, with the highest prevalence rates in the Middle East and South America.⁵ That meta-analysis also demonstrated an increased prevalence of NAFLD, from 15% in 2005 to 25% in 2010, and comparable prevalence rates between the West and the East.

The National Health and Nutrition Examination Surveys (NHANES) data collected from 1988 to 2008 show that the prevalence of NAFLD has doubled in the USA during that time period. From 1988 to 1994, NAFLD accounted for 46.8% of chronic liver disease cases; from 1994 to 2004, its prevalence further increased to 62.84%, and then to 75.1% from 2005 to 2008.¹⁶ NAFLD is no longer a disease confined to the Western world, as studies from China, Korea, Taiwan, Japan and India have also found a high community prevalence of NAFLD, ranging from 15–49.8%^{5,17} (Table 1). Current USA projections using a Markov model indicate a 21% increase in NAFLD from 2015 to 2030, leading to a 33.5% overall prevalence by 2030. The projected increase in the prevalence of NASH is 63%, which will cause a 168% increase in the number of patients with decompensated cirrhosis, and a 137% increase in the numbers of patients developing HCC by 2030.¹⁸ Thus, with growing prevalence rates of NAFLD affecting both adults and children, it is likely to emerge as the leading cause of end-stage liver disease in the years to come.

Obesity and T2DM are important risk factors for NAFLD. The prevalence of NAFLD is about 50–90% in obese subjects.¹⁹ The pooled prevalence of NAFLD in patients with T2DM is 59.67% (95% confidence interval (CI): 54.31–64.92%) according to a meta-analysis of 24 studies.²⁰ The growing epidemic of obesity and T2DM have fueled an increasing prevalence of NAFLD worldwide.^{19–23} Moreover, obesity and T2DM also increase the risk of NAFLD progression to NASH, cirrhosis, and HCC.^{22,23} In Asia, NAFLD can occur in lean subjects with central obesity, which may be partly because of a higher metabolic activity of visceral fat and genetic predisposition, such as the patatin-like phospholipase domain-containing 3 (PNPLA3) polymorphism.^{24,25} It is worth noting that a wide variation in clinical presentation and

sensitivity of diagnostic tools complicate diagnosis of NAFLD, often leading to an underestimate of the actual disease burden.

Progression of NAFLD

The natural course of liver disease progression in NAFLD is still incompletely defined. A subset of such patients develops progressive liver disease leading to NASH, cirrhosis, HCC, and liver failure (Fig. 1). Though early studies in 1990's suggested that SS does not progress to NASH or cirrhosis, subsequent studies with paired liver biopsies have shown that SS is more progressive than originally believed.^{26–28} Apart from components of MetS, genetic polymorphisms, such as PNPLA3 I148M gene and transmembrane 6 superfamily member 2 E167K gene variants, have a significant impact on NAFLD susceptibility and progression.²⁵ Identification of such variants may help to identify NAFLD patients at higher risk for liver disease progression and HCC.

Progression from SS and NASH

Prospective studies have revealed progression from SS to NASH in 23–44% of patients over a period of 26 months to 6.6 years.^{7,28} In a meta-analysis of 11 studies including 411 patients with paired liver biopsy performed at least 1 year apart, liver fibrosis progression occurred not only in patients with NASH but also in patients with nonalcoholic fatty liver (NAFL), defined as SS alone or associated with mild inflammation. One stage of fibrosis progression occurred over 14.3 years in patients with NAFL (95% CI: 9.1–50.0 years) and 7.1 years among patients with NASH (95% CI: 4.8–14.3 years).²⁹ A very slow rate of progression of SS may partly account for the discrepancy between clinical and histological studies, as such patients may die from other causes before developing advanced liver disease. In a systematic review of 10 studies, Argo *et al.* have found that 37.6% of 221 patients with NASH had progressive fibrosis over a mean follow-up interval of 5.3 years.³⁰ A recent meta-analysis also revealed occurrence of fibrosis progression in 41% of NASH patients, with 20% of them identified as being rapid progressors.⁵ Yet

Table 1. Recent Population-based prevalence studies on NAFLD based on ultrasonography

Study	Country/region	Year published	Screened population, <i>n</i>	NAFLD detected, <i>n</i> (%)
Kim <i>et al.</i> ⁵⁶	USA	2013	12317	4188 (34.00%)
Caballería <i>et al.</i> ¹¹¹	Spain	2010	766	198 (25.80%)
Suomela <i>et al.</i> ¹¹²	Finland	2015	1621	246 (15.20%)
van der Voort <i>et al.</i> ⁹⁵	Netherlands	2014	2292	779 (34.00%)
Ruhl <i>et al.</i> ¹¹³	USA	2013	12232	2446 (20.00%)
Shen <i>et al.</i> ¹¹⁴	Taiwan	2014	6511	1769 (27.17%)
Younossi <i>et al.</i> ¹¹⁵	USA	2013	6709	1448 (22.00%)
Chang <i>et al.</i> ¹¹⁶	South Korea	2013	43166	11652 (26.99%)
Cai <i>et al.</i> ¹¹⁷	China	2013	10605	3906 (36.83%)
Dassanayake <i>et al.</i> ¹¹⁸	Sri Lanka	2009	2985	974 (32.63%)
Kim <i>et al.</i> ⁶⁵	South Korea	2012	4023	1617 (40.20%)
Chalmers <i>et al.</i> ¹⁷	India	2019	2158	1075 (49.8%)

Abbreviation: NAFLD, nonalcoholic fatty liver disease.

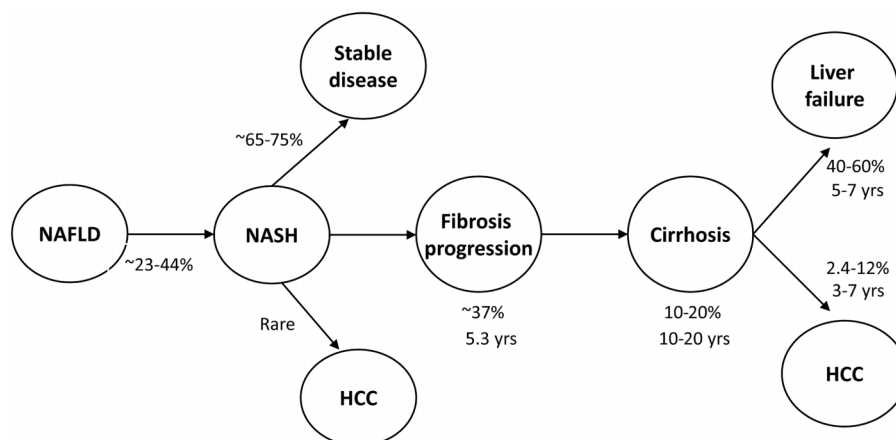


Fig. 1. Progression of liver disease in patients with NAFLD. Data adapted from references: 9, 27, 28, 30 and 40.

Abbreviations: HCC, hepatocellular carcinoma; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis.

another study has revealed a rapid fibrosis progression in one-third of NASH patients who had any-stage of fibrosis progression.³¹ To summarize, studies utilizing paired liver biopsies suggest that approximately 23–44% of patients with SS progress to NASH and 37–41% of patients with NASH develop progressive fibrosis.

NASH-cryptogenic cirrhosis

Clinical-histological study has revealed silent cirrhosis in 10% (8/80) of NAFLD patients with normal liver enzymes.³² Around 9–25% of patients with NASH progress to cirrhosis over a period of 10–20 years. In a recent study, French investigators identified 125,052 NAFLD/NASH patients from the French National Database on Hospital Care, of whom 1.2%, 6.3%, and 0.9% were diagnosed with compensated cirrhosis, decompensated cirrhosis, and HCC respectively. During 7 years of follow-up, 5.6% of the NAFLD/NASH patients progressed to cirrhosis and 27.5% of the compensated cirrhosis patients developed decompensation.³³ Powell *et al.*³⁴ have suggested that NASH should be recognized as a potential cause of cryptogenic cirrhosis (CC).

Many of the patients with CC have features of MetS in varying proportions.^{35,36} However, needle biopsy studies have failed to demonstrate histological features of NASH in patients with CC. It seems that the features of NASH usually regress concurrently with fibrosis progression.^{34,35} In contrast to studies based on needle biopsy samples, explants from CC patients undergoing LT have revealed steatosis (80%) and ballooning (70%) in a significant proportion.³⁷ A study from India that assessed explants from patients with CC revealed NASH to be the etiology in 63% patients.³⁸ Another study of explants from CC revealed NASH to be the most common etiology (33%).³⁴ Moreover, the recurrence of steatosis in the allograft of CC patients is remarkably high (100% in 5 years).³⁹ Therefore, NASH-cirrhosis cases appear to constitute a significant proportion of patients previously labelled as CC.

NAFLD and HCC

HCC is the second leading cause of cancer - related death worldwide. NAFLD has emerged as one of the leading causes

of HCC in recent years. Multiple risk factors, such as components of MetS, ethnicity and hepatic siderosis, appear to have an incremental effect on the risk of developing HCC among NAFLD patients. The cumulative incidence of HCC in patients with NASH-related cirrhosis is quite high, ranging from 2.4 % over 7 years to 12.8 % over 3 years.⁴⁰ However, alarmingly, HCC can develop *de novo* in patients with NASH in the absence of cirrhosis.^{41,42} Kawada *et al.*,⁴³ in a study of 1,168 HCC patients who underwent hepatic resection, found NASH as an etiology of HCC in 8 patients, 6 of who (75 %) had noncirrhotic NASH. Similarly, Takuma *et al.*⁴⁴ reported 7 out of their studied 11 (65%) patients with NASH-related HCC had noncirrhotic liver. In a review of 94 published cases of NASH-related HCC, the patients were found to be predominantly elderly males, with 26% having noncirrhotic liver and the majority (69%) having large (mean size 3.5 cm) and multifocal HCC.⁴⁴

Several reports have confirmed the increasing burden of NAFLD - related HCC worldwide. A recent large population - based Surveillance, Epidemiology and End Results (known as the SEER) study has demonstrated a 9% annual increase in NAFLD-related HCC between 2004 and 2009.⁴⁵ Dyson *et al.*⁴⁶ noted a nearly 10 - fold increase in NAFLD - related HCC cases in the UK from 2000 to 2010. Another study from a hepatitis B - endemic area in Korea has also demonstrated an increasing proportion of NAFLD - related HCC cases over time.⁴⁷ Moreover, patients with NAFLD-related HCC had a shorter survival time, more cardiovascular events, and more cancer-related mortality than patients without NAFLD.⁴⁸ In a study from Germany, where 1119 patients with HCC treated in an 11 year period were retrospectively analyzed, the overall survival among the patients with NASH-related HCC ($n = 45$) was lower compared to those with HCC of other etiologies.⁴⁹ However, it appears that the worse natural history in such patients is not related to a more aggressive behavior of NAFLD - HCC, but mainly to detection at a later stage.

Long-term outcomes

Multiple studies have found that the overall mortality in NAFLD patients is higher than that in matched individuals from a healthy population.^{50–55} A community-based cohort

study with mean follow-up duration of 7.6 years found that mortality in NAFLD patients was significantly higher than in the general population (standardized mortality ratio of 1.34; 95% CI: 1.003–1.76). Death was most commonly due to malignancy and CVD.⁵⁰ Using the third set of NHANES data, Ong *et al.*⁵¹ found NAFLD to be associated with higher overall (hazard ratio (HR): 1.038; 95% CI 1.036–1.041) and liver-related (HR: 9.32; 95% CI 9.21–9.43) mortality compared with the reference population. In both studies, liver disease was the third leading cause of death among NAFLD subjects.

Two recent longitudinal studies have uniformly found that stage of liver fibrosis irrespective of severity of hepatic necroinflammation is independently associated with overall and disease-specific mortality in patients with NAFLD.^{50,53} In one study involving 619 NAFLD patients with median follow-up period of 12.6 years, the risk of death or LT ($n = 193$) increased progressively with increasing stages of fibrosis (HR for stage 1: 1.88, stage 2: 2.89, stage 3: 3.76, and stage 4: 10.9). Patients with fibrosis, regardless of NASH, had shorter survival times than patients without fibrosis.⁵⁰ Another longitudinal study with mean follow-up of 26.4 years found that NAFLD patients ($n = 229$) had an increased mortality compared with the reference population (HR: 1.29; 95% CI 1.04–1.59) and CVD constituted the most common cause of death. Overall mortality was not increased in patients with NASH and mild fibrosis, whereas patients with fibrosis stage >2, irrespective of NASH, had increased mortality (HR: 3.3; 95% CI 2.27–4.76, $p < 0.001$).⁵³

In a meta-analysis of seven studies with follow-up ranging from 7.3–24 years, liver-related mortality was higher in patients with NASH compared to those with SS (OR: 5.71; 95% CI: 2.31–14.13).⁵⁴ Kim *et al.*,⁵⁶ in a large prospective cohort study of 11,154 USA adult participants from the NHANES population found that NAFLD itself did not increase the risk of mortality. However, advanced fibrosis, as determined by noninvasive fibrosis markers, significantly predicted the mortality, mainly from CVD causes, independent of other known factors. In a systematic review and meta-analysis of five studies including 1,495 NAFLD patients with 17,452 patient years of follow-up, Dulai *et al.*⁵⁷ found an increased risk for all-cause mortality with increase in the stage of fibrosis, and such risk was more pronounced with regard to liver-related mortality.

It appears that higher stages of liver fibrosis are a strong determinant of all-cause mortality in NAFLD, most likely because of the pronounced effect on liver-related mortality, whereas CVD accounts for an increased proportion of mortality at lower stages of fibrosis. Thus, compared with the general population, NAFLD increases the risk of liver-related, cardiovascular and all-cause mortality, and the impact of NAFLD on mortality appears to differ according to its severity (Table 2). The disparity in estimates of risk across studies might be attributed to variations in characteristics of study populations or follow-up.

Extrahepatic association of NAFLD

NAFLD is closely associated with several extrahepatic diseases, such as T2DM, CVD, malignancy, CKD, OSA, and PCOS (Fig. 2). These associations do not truly represent extrahepatic manifestations of NAFLD. However, the implications of such association may influence clinical evaluation and treatment decisions in NAFLD patients. Although these associations may result from common risk factors, there are lines

of evidence to suggest that NAFLD is associated with many of these diagnoses, independent of traditional risk factors, such as components of MetS. Also, for some of the diseases, the association appears to be bidirectional. Therefore, severity of NAFLD may influence the severity of associated disease and vice versa. Similarly, management of one condition may influence management of the associated one.

T2DM

The association between NAFLD and T2DM is complex and bidirectional. NAFLD is not only a consequence but also a cause of T2DM. NAFLD is associated with increased risk of developing DM after adjustment for several metabolic confounders.^{54,58,59} Two large meta-analyses have confirmed the association between NAFLD and incident T2DM.⁵⁴ In a prospective study of 129 biopsy-proven NAFLD patients, 78% developed either T2DM (58%) or impaired glucose tolerance (20%) during the 13.7 years follow-up.⁵⁸ Moreover, the risk of incident T2DM was threefold higher among patients with NASH compared to those with SS. Moreover, T2DM increases the risk of NAFLD progression to NASH, cirrhosis, and HCC.²³

Because of systemic insulin resistance (IR), NAFLD worsens the glycemic control in patients with T2DM. In diabetic subjects, NAFLD increases risk of all-cause mortality by 2.2-fold compared with those without NAFLD.⁶⁰ NAFLD and T2DM interact adversely to enhance the risk of atherosclerosis, CKD, and retinopathy.²³ Substantial evidence links NAFLD with an increased risk of developing CVD and arrhythmic complications in patients with DM.⁶¹ Thus, the coexistence of NAFLD and DM increases the risk of developing not only the more severe forms of NAFLD but also the vascular complications of DM and all-cause mortality.

CVD

Several studies have unequivocally demonstrated a strong association between NAFLD and increased risk of CVD. NAFLD has been linked with increased biomarkers of endothelial dysfunction,⁶² increased carotid artery intima-media thickness,⁶³ increased arterial stiffness,⁶⁴ coronary artery calcification,⁶⁵ and impaired flow-mediated vasodilatation.⁶⁶ A recent meta-analysis of 27 studies supported the association of NAFLD with markers of subclinical atherosclerosis independent of traditional CVD risk factors and MetS.⁶⁷ Moreover, persistent and progression of NAFLD is associated with increased risk and progression of subclinical carotid atherosclerosis, in a study comparing to subjects without NAFLD and those with regression of NAFLD.⁶⁸

The widely prevalent dyslipidemia in NAFLD patients is highly atherogenic, being characterized by hypertriglyceridemia, high levels of low-density lipoprotein cholesterol, and low levels of high-density lipoprotein cholesterol—all of which are key risk factors for CVD.⁶⁹ Studies in patients with NAFLD have shown abnormal left ventricular morphology and diastolic dysfunction when compared with controls.^{70,71} Various factors have been implicated in the causation of left ventricular dysfunction in NAFLD, including hyperinsulinemia-induced myocyte growth and interstitial fibrosis, alteration in myocardial metabolism of fatty acids, upregulation of angiotensin II (a neurohormone), decrease in myocardial perfusion reserve, and increase in aortic stiffness.

Table 2. Community-based longitudinal studies determining all-cause and cause-specific mortality in patients with NAFLD

Study, year	Population	Follow-up	Diagnostic method	Results
Adams <i>et al.</i> ¹¹⁹ , 2005	420 community-based USA NAFLD patients	7.6 years	Histology and ultrasonography	Patients with NAFLD had higher rates of all-cause, CVD and liver-related mortality than the matched general population (standardized mortality ratio: β 1.34; 95% CI: 1.003–1.76)
Ekstedt <i>et al.</i> ⁵⁸ , 2006	129 Swedish biopsy-proven NAFLD patients	13.7 years	Histology	Mortality was not increased in patients with simple steatosis but patients with NASH had higher rates of all-cause (~2-fold), cardiovascular (~2-fold) and liver-related (~10-fold) mortality than the matched reference population
Rafiq <i>et al.</i> ¹²¹ , 2009	173 USA patients with biopsy-proven NAFLD	13 years	Histology	All-cause mortality did not differ between the NAFLD subtypes, but liver-related mortality was higher in patients with NASH The most common causes of mortality were CVD, malignancy and liver-related complications
Söderberg <i>et al.</i> ⁵² , 2010	256 Swedish subjects with raised liver enzymes, including 118 biopsy-proven NAFLD	28 years	Histology	40% of the 118 NAFLD subjects died during follow-up. Compared with the matched Swedish population, subjects with NAFLD exhibited 69% increased mortality, more so with NASH (86%)
Ekstedt <i>et al.</i> ⁵³ , 2015	229 Swedish patients with biopsy-proven NAFLD	26.4 \pm 5.6 years	Histology	Patients with NAFLD have increased all-cause mortality (HR: 1.29, 95% CI: 1.04–1.59), with a high risk of death from CVD and liver-related disease. The fibrosis stage rather than presence of NASH predicts the mortality
Jepsen <i>et al.</i> ³⁸ , 2003	7,372 Danish patients with fatty liver, including 1,800 patients with NAFLD	6.2 years	Ultrasound and liver enzymes	Patients with NAFLD had higher rates of all-cause (2.6-fold), cardiovascular (2.1-fold) and liver-related (19.7-fold) mortality than the general population
Haring <i>et al.</i> ¹²⁰ , 2009	4,160 community-based cohort of German adult subjects	7.3 years	Ultrasound	NAFLD was independently associated with increased risk of all-cause and CVD mortality in men (HR: 6.2, 95% CI: 1.2–31.6)
Zhou <i>et al.</i> ⁵⁵ , 2012	3,543 community-based cohort study of Chinese adult subjects	4 years	Ultrasound	Patients with NAFLD had ~3-fold higher rates of all-cause and CVD mortality than those without NAFLD
Kim <i>et al.</i> ⁵⁶ , 2013	11,154 USA adult participants, including 34.0% NAFLD, from the Third NHANES-1988-94.	14.5 years	Ultrasound and noninvasive markers of liver fibrosis	NAFLD with advanced fibrosis, not NAFLD in general, is associated with increased mortality independent of other known factors
Zeb <i>et al.</i> ¹²² , 2016	4,119 USA adult subjects, including 728 NAFLD, without CVD at baseline	Median 7.6 years	Computed tomography	Overall 253 deaths reported, including 40 NAFLD subjects. NAFLD was independently associated with incident CVD and all-cause event (HR: 1.42, 95% CI: 1.00–2.03)

Abbreviations: CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

NAFLD is also associated with an increased risk of atrial fibrillation.⁷² NAFLD has also been reported as independently associated with QT prolongation.⁷³ Notably, the duration of the QT interval is a predictor for CVD death in the general

population, and a prolonged QT interval increases the risk of cardiac arrhythmias and sudden cardiac death.⁷⁴

NAFLD contributes to the prothrombotic state by increasing plasma levels of plasminogen activator inhibitor 1, the

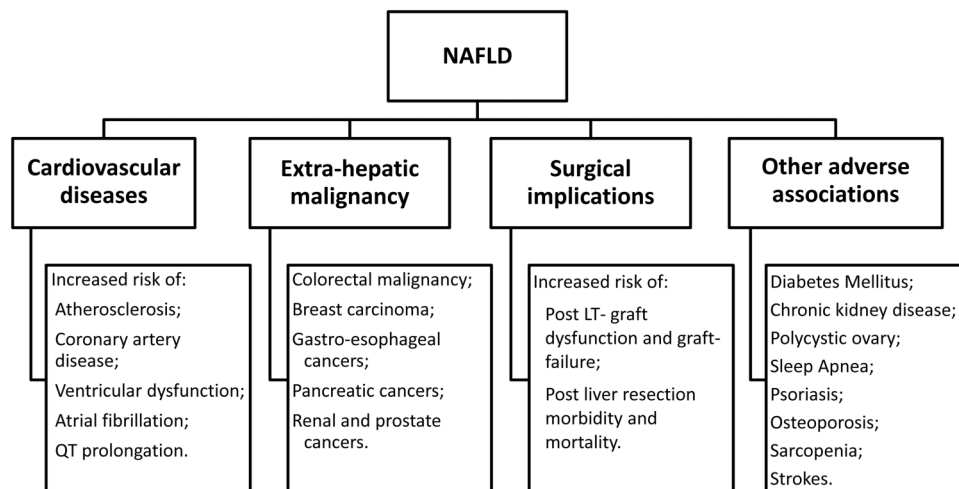


Fig. 2. Association of NAFLD with cardiovascular diseases, extrahepatic malignancy, surgical complications, and various other diseases.
Abbreviations: LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease.

elevated levels of which are related to increased risk of myocardial infarction.⁷⁵ In a recent prospective study among patients with clinical indication of coronary angiogram ($n = 612$), the presence of NAFLD was associated with severity of coronary artery stenosis and need for coronary intervention.⁷⁶ In a large meta-analysis of 164,494 participants from 21 cross-sectional and 13 cohort studies, NAFLD was associated with an increased risk of incident (HR: 1.37; 95% CI: 1.10–1.72) and prevalent (OR: 1.81; 95% CI: 1.23–2.66) CVD but not with CVD mortality.⁷⁷ However, there was marked heterogeneity among studies and nonuniform definition of important variables, including DM, which could have affected the results of mortality. Moreover, another meta-analysis of 40 studies assessing the natural history of NAFLD revealed that patients with NAFLD, irrespective of SS or NASH, had a considerably greater risk of CVD mortality than the matched control population.⁵⁴

Many prospective studies have demonstrated that CVD-related death occurs in higher proportion than liver-related death among patients with NAFLD.^{50,51} A meta-analysis of a total 16 observational studies with 34,043 adult individuals, including 36.3% NAFLD and approximately 2,600 CVD outcomes over a median period of 6.9 years, revealed that NAFLD is significantly associated with an increased risk of fatal and nonfatal cardiovascular events (OR: 1.64). However, the observational design of the studies included does not prove that NAFLD causes CVD.⁷⁸ Thus, there seems to be little doubt that NAFLD is associated with increased incidence and prevalence of CVD, some controversies surround as to whether NAFLD by itself is associated with increased CVD mortality. Also, whether the association between NAFLD and CVD is because of the shared risk factors or NAFLD itself confers an additional risk is the subject of further extensive scrutiny.

Extrahepatic malignancy

NAFLD has been associated with several extrahepatic malignancies. Malignancy is among the leading cause of death in NAFLD patients.^{50,51,54} In meta-analyses of seven longitudinal studies with follow-up ranging from 7.3 to 24 years,

malignancy was the most common (28%) cause of death in NAFLD.⁵⁴ In a recent longitudinal study comprising a community cohort of 4,722 NAFLD and 14,441 age- and sex-matched control subjects, 2,224 incident cancers occurred during a median follow-up of 8 years and NAFLD was associated with 90% higher risk of developing cancers.⁷⁹ The highest increase in the risk was noted for HCC, followed by uterine, gastric, pancreatic and colonic cancer. Moreover, the association between obesity and cancer risk was small in the absence of NAFLD, suggesting that NAFLD may potentiate obesity-cancer relationship.⁷⁹

In a cohort study of 129 biopsy-proven NAFLD patients, 5.6% of the patients with NASH died because of extrahepatic malignancy during a mean follow-up of 13.7 years.⁵⁸ Several studies have found a higher prevalence of colorectal neoplasm in patients with NAFLD compared to patients without NAFLD.^{80–82} A large cohort study ($n = 5517$) from Korea has found a two-fold increase in the occurrence of colorectal adenoma and a three-fold increase in the risk of colorectal cancer in patients with NAFLD compared to controls.⁸⁰ Another study revealed that among NAFLD, patients with NASH have a higher prevalence of adenomas (51.0% vs. 25.6%) and advanced neoplasms (34.7% vs. 14.0%) than those with SS. Moreover, NASH remained significantly associated with a risk of adenomas and advanced neoplasms after adjusting for demographic and metabolic factors.⁸¹

In a retrospective cohort study on 1,522 subjects who underwent two consecutive colonoscopies between 2003 and 2010, NAFLD was an independent risk factor (OR: 1.45; 95% CI: 1.07–1.98) for adenoma formation after a negative baseline colonoscopy.⁸² The adenoma group had a higher prevalence of NAFLD than the non-adenoma group (55.6% vs. 38.8%; $p < 0.05$). NAFLD patients are more likely to have multiple polyps localized more often in the right hemi-colon. In a case-control study, NAFLD was found to have a significant association with breast cancer.⁸³ NAFLD has also been found to be associated with malignancy of the esophagus, stomach, pancreas, kidney, and prostate.^{9,54,79} However, concurrent presence of features of MetS and too little available data limit drawing definite conclusions about a causal role of NAFLD in such association.

CKD

The link between NAFLD and CKD has drawn considerable attention during recent times. Various studies have suggested that NAFLD can accelerate the development and progression of CKD independent of traditional risk factors.^{10,84,85} A recent meta-analysis, that included near 64,000 subjects, found that NAFLD was associated with an approximately 2-fold increase in risk of both prevalent (OR: 2.12; 95% CI: 1.69–2.66) and incident CKD (HR: 1.79; 95% CI: 1.65–1.95).⁸⁴ Furthermore, histologically severe NAFLD is more positively correlated with CKD. Both NASH and NAFLD with advanced fibrosis are associated with a higher prevalence (OR: 2.53 for NASH, OR: 5.20 for advanced fibrosis) and incidence of CKD (HR: 2.12 for NASH, HR: 3.29 for advanced fibrosis), as compared to those with SS.⁸⁴

In a large longitudinal study, NAFLD was found to be associated with declining renal function in CKD patients independent of traditional risk factors, and the association was stronger in patients with advanced NAFLD.⁸⁵ The pathophysiological basis of the linkage between the two appear to be multifactorial. The pro-inflammatory milieu in NAFLD along with IR, dyslipidemia, oxidative stress, hypertension, and the activated renin-angiotensin system may hasten the development and progression of CKD. Compared to other etiologies of cirrhosis, the risk of CKD and requirement of simultaneous liver-kidney transplantation are greater in patients with NASH-related cirrhosis.⁸⁶ Furthermore, CKD may aggravate NAFLD through uremic toxins, intestinal dysbiosis, altered gut-barrier function, and alterations in glucocorticoid metabolism.⁸⁷ Interestingly, there is evidence to suggest that in patients with NASH, improvement in liver histology by lifestyle modification leads to improved kidney function.⁸⁵

PCOS

PCOS is one of the most common endocrine disorders in women during reproductive ages. It is associated with a plethora of metabolic consequences, including glucose intolerance, dyslipidemia, and NAFLD. Several studies have consistently found that the prevalence and severity of NAFLD is markedly increased in women with PCOS, independent of coexisting features of MetS.⁸⁸ A recent systematic review and meta-analysis of 17 studies has revealed that PCOS patients ($n = 2,734$) have increased prevalence of NAFLD (OR: 2.54, 95% CI 2.19–2.95) and the presence of NAFLD among them is associated with hyperandrogenism, in addition to IR and adiposity.⁸⁹ The prevalence of NAFLD among women with PCOS is estimated to vary from 15% to 55%, whereas amongst the reproductive-aged women with NAFLD, the prevalence of PCOS is as high as 71%.⁹⁰

OSA

OSA is strongly associated with NAFLD independent of traditional risk factors. In a meta-analysis of over 2,000 subjects from 18 studies, OSA was associated with an increased risk of NAFLD (OR: 2.99), NASH (OR: 2.37), and advanced fibrosis (OR: 2.30).⁹¹ This association is related to the degree of nocturnal hypoxemia caused by repetitive upper airway obstruction during sleep. Intermittent hypoxia can result in oxidative stress, IR, abnormal lipid metabolism, overactivation of the sympathetic nervous system, inflammation, and mitochondrial dysfunction, each of which plays important roles in

development and progression of NAFLD.⁹² Intermittent hypoxia activates hypoxia-inducible factors, which leads to increased synthesis of hepatic fat, upregulated hepatic inflammation, and fibrosis. The chronic intermittent hypoxia in morbidly obese subjects contributes to the severity of hepatic necroinflammation and fibrosis independent of adiposity.⁹³ Furthermore, NAFLD in patients with OSA is associated with higher CVD risks. Minville *et al.*⁹⁴ have recently demonstrated that in patients with OSA, hepatic steatosis was independently associated with endothelial dysfunction after adjustment for confounders. Therefore, among obese patients with OSA, screening for the presence of underlying NAFLD and subsequent monitoring for NAFLD progression should be considered. In patients with NAFLD, treatment of OSA with continuous positive airway pressure may impact outcomes of future CVD.

Psoriasis

NAFLD is highly prevalent in patients with psoriasis. In a large prospective population-based cohort study of 2,292 subjects with 118 (5.1%) patients with psoriasis, NAFLD prevalence was higher among those with psoriasis (46.2% vs. 33.3%) even after adjustment for important risk factors.⁹⁵ The prevalence of NASH in patients with psoriasis is much higher (22%) than that in the general population (2–6%). Moreover, data also suggest that the presence of NAFLD may increase severity of psoriasis.^{96,97} Future studies are needed to assess whether there is a causal relationship between NAFLD and psoriasis.

Osteoporosis

Several studies have demonstrated that NAFLD patients have lower bone mineral density compared to non-NAFLD subjects.⁹⁸ In a study from China, NAFLD was independently associated with a ~2.5-fold increased odds of osteoporotic fractures among men.⁹⁹ A recent meta-analysis of six studies has revealed that obese children with NAFLD are more susceptible to osteoporosis than children with only obesity.¹³ The potential contribution of NAFLD to development of osteoporosis warrants further study. Chronic inflammatory processes, vitamin D deficiency, disturbances of growth hormone/insulin-like growth factor 1 axis are the proposed pathophysiological factors linking NAFLD with decreased bone mass.

Sarcopenia

NAFLD has been recently associated with sarcopenia which is defined as a generalized, and progressive and loss of skeletal muscle mass, quality, and strength.^{100,101} Sarcopenia is associated with increased risks and histological severity of NAFLD, independent of obesity and metabolic risk factors.¹⁰⁰ In a longitudinal study, Kim *et al.*¹⁰¹ has demonstrated that increases in relative skeletal muscle mass over time had significant beneficial association with incident NAFLD (adjusted HR: 0.69; 95% CI: 0.59–0.82) and resolution of baseline NAFLD (adjusted HR: 4.17; 95% CI: 1.90–6.17). The pathophysiological mechanisms linking sarcopenia and NAFLD may include IR and chronic inflammation. IR promotes accumulation of triglycerides in muscles and exacerbates protein catabolism in association with the chronic inflammatory milieu, leading to muscle depletion.

CVA

NAFLD appears to be associated with an increased risk and severity of stroke as well as with a worse functional outcome in stroke patients. In a prospective study including a total of 25,800 subjects, Hadda *et al.*¹⁰² found an increased frequency of CVA in NAFLD compared to the controls. A meta-analysis of seven studies with a total of 6,183 subjects revealed a significant association of NAFLD with elevated risk of CVA.¹² Also, there are data to suggest a role of NAFLD in subclinical ischemic stroke and cognitive impairments.¹⁰² These observations are clinically relevant because strategies to prevent the progression of asymptomatic brain lesions to overt CVA can be explored in patients with NAFLD. Further studies are warranted to throw more light on these aspects.

AP

NAFLD increases the severity of AP. A recent study demonstrated that the presence of NAFLD at admission portends a higher risk of severe and moderately severe AP, as well as a higher risk of organ failure.¹¹ The mechanism by which NAFLD exacerbates pancreatitis remains unclear. The potential reasons could be imbalance of adipocytokines, increased activity of hepatic Kupffer cells, and reduction of alpha-1-antitrypsin levels. Pancreatic steatosis, which is frequently associated with NAFLD, may lead to a higher incidence of AP and may be an etiological factor in pancreatic cancer.

Surgical implications of NAFLD

Post-liver resection liver failure

A normal liver has remarkable capacity to regenerate, which makes it possible for surgeons to do a large liver resection without causing significant hepatic impairment. However, extended liver resection may lead to the development of progressive liver failure in the postoperative period which is associated with very high mortality rate.¹⁰³ Steatotic liver have poor ability to regenerate and reduced tolerance against ischemic injury. Therefore, patients with NAFLD are at higher risk of post-liver resection liver failure. In a series of 135 patients who had undergone major hepatic resection at the Mayo Clinic, acute liver failure occurred in 14% of patients with fatty liver versus 4% in those with normal liver.¹⁰⁴ In a cohort of 478 liver resection patients, Belghiti *et al.*¹⁰⁵ demonstrated that steatosis was an independent risk factor for postoperative complications. Another study on outcome after liver-resection for colorectal liver metastases in 406 patients has found that patients with steatohepatitis have a significantly higher 90-day mortality than those without it (14.7 vs. 1.6%; OR: 10.5).¹⁰⁶ In conclusion, major hepatic resection of steatotic liver, particularly in patients with NASH, is associated with increased risk of liver failure and death.

Influence on LT

Transplantation of steatotic grafts is associated with an increased risk of primary nonfunction, early allograft dysfunction, and posttransplant vascular and biliary complications in cadaveric as well as living-donor LT.¹⁰⁷ A study involving large series of LT patients has demonstrated that patients receiving up to 30% of fatty liver had a higher rate of primary nonfunction

(5.1% vs. 1.8%) and worse patient (77% vs. 91 %) and graft (70% vs. 82%) survival at 2 years compared to patients receiving a nonsteatotic graft.¹⁰⁸ NAFLD is an independent predictor of occurrence of post-LT MetS that increases the risk of steatosis in the graft liver.^{109,110} Within a few months of LT, steatosis developed in 60–100% of the patients and NASH in 10–40% of the patients. Approximately 10% of the patients progressed to advanced fibrosis or cirrhosis in a decade.¹¹⁰

In conclusion, NAFLD is highly prevalent in the general population, and its prevalence is expected to increase in the coming years. It has emerged as one of the leading causes of cirrhosis and HCC in recent years and is a growing indication for LT. NAFLD is associated with various extrahepatic diseases and increased risk of all-cause mortality. Increased awareness about consequences of NAFLD and development of strategies to change the course of this disease are needed to control its emerging global threat. The optimal treatment of NAFLD remains a clinical challenge, as there is no approved pharmacotherapies. While traditional pharmacological therapies, such as insulin sensitizer (pioglitazone) and antioxidative agent (vitamin E), significantly improve steatosis and inflammation, they have no significant effect on liver fibrosis and have long-term safety issues. Currently, the therapeutic options for NAFLD include diet and lifestyle modification and pharmacological interventions targeting the components of MetS. Lifestyle changes, if sustained, can make significant difference in the trajectory of liver disease and overall outcomes. Finally, morbidly obese NASH patients can benefit from bariatric surgery, which may reduce liver fibrosis but carries a risk of decompensation in patients with cirrhosis.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception of the study (RK, RNP, UA), design of the study and drafting of the manuscript (RK), data collection (RK, RNP, UA), manuscript revision (RNP).

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