TITLE

Causes of mortality in Non-Alcoholic Fatty Liver Disease (NAFLD) and Alcohol related Fatty Liver Disease (AFLD)

AUTHORS

Michael P Johnston[1], Janisha Patel[1], Christopher D Byrne[2,3,]

[1] Department of Hepatology, University Hospital Southampton NHS Foundation Trust, Southampton, UK. ORCID (MPJ): 0000-0002-4704-8349, ORCID (JP): 0000-0002-4634-0751

[2] Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK. ORCID

[3] National Institute for Health Research Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton National Health Service (NHS) Foundation Trust, Southampton, UK. ORCID: 0000-0001-6322-7753

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ABSTRACT [247 words]

Non-alcoholic fatty liver disease (NAFLD) and alcohol related fatty liver disease (AFLD) both represent a spectrum of liver disease severity from hepatic steatosis to fibrosis and cirrhosis. Both NAFLD and AFLD are common diseases in the general population. NAFLD affects ~25% of the adult global population whilst AFLD has become the commonest indication for liver transplantation in the United States. It is often not possible to distinguish between NAFLD and AFLD on examination of liver histology, consequently, differentiation between NAFLD and AFLD is heavily reliant on a history of alcohol consumption.

Age, smoking, alcohol consumption and sex appear to influence risk of mortality in NAFLD or AFLD. In NAFLD and AFLD, the key causes of increased liver-related mortality are advanced liver fibrosis and cirrhosis leading to complications such as hepatocellular carcinoma and decompensated cirrhosis. NAFLD and AFLD are also associated with an increased risk of all-cause mortality including an increased risk of extra-hepatic malignancy. Non-invasive biomarkers of liver disease severity in NAFLD and AFLD perform poorly to predict mortality. However, alanine aminotransferase, gamma-glutamyl transpeptidase, FIB-4 and the NAFLD Fibrosis Score are independently associated with increased mortality in NAFLD.

Both NAFLD and AFLD are associated with extra-hepatic risk factors and complications such as metabolic syndrome encompassing obesity, hypertension, type 2 diabetes mellitus, and chronic kidney disease. AFLD is associated with hypertension and cardiovascular disease as well as other organ damage.

This narrative review discusses the associations, risk factors and diagnostic biomarkers linking NAFLD and AFLD with increased mortality.

1. Introduction

Fatty liver disease encompasses a spectrum of disease predominantly comprising non-alcoholic fatty liver disease (NAFLD) and alcohol related fatty liver disease (AFLD). In

NAFLD, the early stages of the disease, comprise non-alcoholic fatty liver (NAFL) that may progress in a proportion of patients to a more severe form of disease, termed non-alcoholic steatohepatitis (NASH) (with or without liver fibrosis). Similarly, AFLD begins with alcoholic fatty liver (AFL) and may progress to alcoholic steatohepatitis (ASH) (with or without liver fibrosis). In both conditions, the disease may progress to cirrhosis and in both conditions the development of liver fibrosis markedly increases the risk of development of hepatocellular carcinoma (HCC).

The gold standard for distinguishing the presence of NAFL/NASH or for distinguishing between the two is a liver biopsy. The use of liver biopsy may also be used to distinguish the presence of AFL/ASH or distinguish between the two. However, liver biopsy in AFLD is normally reserved for cases where there is diagnostic uncertainty, where precise staging is required or for clinical trials. These are the recommendations from the European Association for the Study of the Liver (EASL).[1] Importantly, distinguishing between NAFL/NASH and AFL/ASH cannot be reliably undertaken by interpretation of histology,[2,3] with clinicopathological correlation required, mainly in the form of a reliable history of long standing excess alcohol consumption.

Fatty liver disease presents a significant public health problem. There is a lot of effort into improving understanding of the drivers of disease development; namely alcohol consumption and obesity.[4] In the United States the prevalence of AFLD has been quoted to be 2.0-2.5%.[5] In a Northern Italian cohort, amongst individuals at 'risk' from AFLD (defined as >30g alcohol per day for either sex) the prevalence of liver cirrhosis was 2.2% and the prevalence of non-cirrhotic liver disease (either steatosis or steatohepatitis) was 3.3.[6] These studies were not based on biopsy data and so unable to comment on prevalence of steatosis versus steatohepatitis.

There is a significant burden of liver-related mortality due to AFLD given the propensity to progress to liver cirrhosis with continued drinking. Recently AFLD became the leading indication for liver transplantation in the United States.[7] In contrast, the rate of progression of fibrosis in NAFLD is comparatively slow with patients' associated comorbidity presenting the more imminent mortality risk.[8] Obesity is not the only driver of NAFLD development but it is a strong contributor and undoubtedly the scale of the obesity epidemic has meant that the most recent estimates show that NAFLD affects ~25% of the global adult population.[8]

To establish a diagnosis of NAFLD there must be evidence of hepatic steatosis either on imaging or histology and the absence of secondary causes of hepatic fat accumulation such as excess alcohol consumption.[9] Simple steatosis or NAFL is defined as steatosis > 5% in the absence of hepatocellular injury. The more severe form of liver disease i.e. NASH, is defined as steatosis >5% with evidence of inflammation and hepatocyte injury (e.g. ballooning) with or without fibrosis.[9] Normal alcohol intake according to the American Association for the Study of Liver Diseases (AASLD) definition is <21 standard drinks for a man and <14 drinks for a woman in a week; a standard drink is <14g alcohol.[9]

In this review we will discuss the causes of mortality in fatty liver disease, including NAFLD and AFLD. The definitions of NAFLD and AFLD above are important because they form a basis for inclusion criteria in trials testing interventions, and they provide an idea of the natural history of the diseases, for patients seen in the clinic. However, it is important to note that for a significant proportion of the general population as well as for patients attending primary/secondary care clinics, such definitions can be misleading. For example, some patients may be classified as having either AFLD or NAFLD, particularly if they fit the criteria for NAFLD and their alcohol consumption has on occasion been above the threshold for defining AFLD.

2. NAFLD and AFLD as Multisystem Diseases

Both AFLD and NAFLD are associated with an increased risk for progression to advanced liver fibrosis and cirrhosis, leading to complications such as hepatocellular carcinoma and decompensated liver diseases. The growing prevalence of severe liver disease attributable to NASH was demonstrated in a retrospective cohort study of 182,368 new liver transplant registrants in the United States.[10] The investigators analysed the United Network for Organ Sharing (UNOS) database and found that there was a 170% rise in NASH liver transplant registrants between 2005-2015. Among NASH registrants with HCC, 36% were females. Among NASH registrants without HCC, 51% were females. The number of liver transplant registrants was also examined by birth cohort. There was a steep increase in number of liver transplant registrants from younger birth cohorts. This increase in the number of younger registrants suggests that the burden of NASH is still growing.[10] UNOS did not code for NASH prior to 2004, but it did code for cryptogenic cirrhosis (CC). It has been proposed for a number of years that many CC cases could well have been burnt out

NASH.[11] Trends in CC liver transplant registrants before 2004 and then NASH liver transplant registrants after 2004 support the observation that NASH has been growing in prevalence.[12] With regards to AFLD, another study of the UNOS registry data showed that the number of liver transplant registrants with alcohol related liver disease (ArLD) has also risen. ArLD liver transplant registrant numbers rose from 433/1791 (24.2%) in 2002 to 1253/3419 (36.7%) in 2016.[13] The majority of liver transplant registrants with ArLD were male (76.2%).

In addition to the potential for liver-related complications, NAFLD is also associated with significant burden of cardiometabolic complications such as cardiovascular disease and type 2 diabetes[14–17] making NAFLD a multisystem disease[18] with ramifications extending beyond the liver.

3. Liver-related Mortality associated with NAFLD and AFLD

3.1 Fibrosis / Cirrhosis

AFLD is well established as one of the commonest causes of liver cirrhosis in the Western world. Despite this, there are relatively few studies on the natural history of histological change which occur in AFLD and ASH. Progression of fibrosis has been described in a retrospective study of patients who were acutely admitted to two French hospitals with alcohol excess and underwent liver biopsy.[19] 193 patients in this study had a repeat biopsy after 4 years. Simple hepatic steatosis attributable to alcohol progressed to cirrhosis in 11% of patients. Alcoholic hepatitis progressed to cirrhosis in 39% of patients.[19] In a Danish study of biopsy proven simple steatosis due to alcohol there was progression to cirrhosis in 6.9% after 5 years, compared to 16.0% of patients with alcoholic steatohepatitis.[20] The 5 year mortality risks were 16.7% and 25.1% respectively.[20]

One of the first studies to examine mortality outcomes in patients with fatty liver disease was the Danish National Registry of Patients.[21] The majority of patients in the study were labelled as AFLD (76%). Overall mortality was increased 5.4-fold (95% CI 5.2-5.6) in patients with AFLD, and 2.6-fold (95% CI 2.4-2.9) in patients with what was termed 'non-alcoholic or unspecified fatty liver'.[21]

A recent systematic review by Parker et al described the findings in 37 studies of >7,000 participants with histologically proven alcohol-related liver disease.[22] Amongst hazardous drinkers, 15% of specimens demonstrated normal histological appearance, 27% demonstrated hepatic steatosis, 24% demonstrated steatohepatitis and 26% demonstrated cirrhosis. For participants with simple steatosis the annual mortality rate was approximately 6%, whilst for participants with steatohepatitis it was 14.8%.[22] The annual mortality rate for ASH is low compared to data from the more recent STOPAH study in which 90-day mortality was ~30%.[23] This reflects the heterogeneity of the studies analysed, particularly when comparing older studies in which individuals with milder disease were biopsied.

In contrast to AFLD, the histological progression of NAFLD has been much more systematically studied in recent years. There is a wide spectrum of disease severity encountered in NAFLD and progression of disease is also slow compared to AFLD. A Danish study with a follow-up of 20 years showed that for patients with simple steatosis on biopsy, 1.2% of NAFLD and 22% with AFLD progressed to cirrhosis.[24]

The slow rate of disease progression in NASH has driven the need for robust endpoints to predict clinical outcomes. The US Food & Drug Administration (FDA) currently requires liver histological improvements to be demonstrated for any therapeutics to be granted accelerated approval.[25] One of the first long-term outcome studies to examine mortality data based on histology was a retrospective cohort study of 173 patients with at least 5 years of follow-up since biopsy.[26] The NAFL group (n=101) and NASH group (n=72) were matched with the exception that there were significantly more women in the NASH group. This study demonstrated that participants with biopsy proven NASH had an increased liver-related mortality. Both NASH and T2DM were independent predictors of liver-related mortality in this study. However, it is important to note that the most common causes of death in both groups was coronary artery disease, followed by malignancy.[26]

[Figure 1]

NASH is recognised as the progressive form of NAFLD. However, within the broad category of NASH, it is the presence of fibrosis which is the strongest predictor of liver-related mortality (see **Figure 1**). Furthermore, patients with the subset of advanced fibrosis are at particularly increased risk of liver as well as non-liver related mortality.[27–30] As fibrosis

stage increases from stage 2 to 3 to 4 (see **Box 1**)[31] it is associated with an increasing mortality.[27–29]

[Box 1]

Although it has been shown that fibrosis may sometimes spontaneously regress in a small proportion of individuals (e.g. 18% [32]), fibrosis is still the strongest predictor of disease-specific mortality.[28,33,34] Hagstrom et al performed a retrospective study of 646 biopsy proven NAFLD cases and found that fibrosis stage was the only independent predictor of clinical outcomes.[34] The defined clinical outcomes in the study were all cases of severe liver disease, including oesophageal variceal bleeding, ascites, hepatorenal syndrome, hepatic encephalopathy, (acute) liver failure, HCC and portal hypertension. In this study, multivariate analyses with models to account for different covariates were used to conclude that fibrosis stage superseded NASH as an independent predictor and that adding NASH to fibrosis stage did not improve the model.[34] However, it seems logical that NASH is driving fibrogenesis and so NASH and fibrosis are not independent risk factors. Consequently, the use of multivariable regression analyses to show an association between NASH and hepatic outcomes that is independent of fibrosis is potentially flawed because of high levels of co-linearity between NASH and fibrosis.

One issue with establishing a diagnosis of NASH and monitoring regression or progression of disease is that there is greater inter-observer variability between reporting pathologists than there is for either steatosis or fibrosis severity.[35] Therefore it has been advocated to use the presence of 'steatofibrosis' (the presence of steatosis and fibrosis) rather than NASH.[36] 'Steatofibrosis' is independently associated with liver-related mortality like NASH, but unlike NASH it also is independently associated with all-cause mortality (aHR, 1.76; 95% CI, 1.02-3.05; P = 0.043).[36]

There is varied presence of fibrosis with NASH. For example, 35% of specimens with stage 0 fibrosis show NASH, compared to 94% of specimens with cirrhosis (which show NASH).[34] After 15 years of follow-up, liver cirrhosis is more prevalent in those with NASH compared to bland/simple steatosis (10.8% vs 0.7%).[37]. This reinforces the point that there is co-linearity between NASH and fibrosis. However, since there is greater imprecision in establishing a diagnosis of NASH, than with liver fibrosis, stronger independent associations with outcomes might be expected with liver fibrosis than with NASH. That said, along with

age, NASH is an independent predictor of progression to fibrosis.[38] It is analogous to hepatitis C virus (HCV) for which the enormously successful treatments have been those treatments that directly target the virus and not those treatments that target anti-fibrogenic mechanisms.[39]

There appears to be no significant difference in survival between AFLD and NAFLD after liver transplantation.[40]. The outcomes of patients with AFLD or NAFLD who undergo liver transplant are beyond the scope of this review. However, it is of interest that cardiovascular disease (CVD) mortality appears to be more common in NAFLD patients post-transplantation (26% vs 7%, p=0.21) and malignancy-related mortality is more common in AFLD patients post-transplantation (29% vs 0%, p=0.024).[40] Interestingly, although post-transplant CVD mortality is higher for patients with NAFLD related cirrhosis, after adjustment for pre-transplantation T2DM, renal function and CVD, this association was no longer significant.[41]

4. Cardiometabolic complications in NAFLD and AFLD

4.1 Cardiovascular disease (CVD)

 The 2009 study by Rafiq, mentioned in *Section 3.1*.[26] did not compare CVD in NAFLD with a control group. However, this study showed that in both groups, those with NAFLD and those with NASH, the primary cause of mortality was coronary artery disease.[26]

NAFLD is associated with a number of metabolic comorbidities, including obesity (51.3%), T2DM (22.5%), hyperlipidaemia (69.1%), hypertension (39.3%) and the metabolic syndrome (MetS) (42.5%).[8] In view of the presence of these established risk factors for CVD, it is rational to expect CVD to be one of the leading causes of mortality in patients with NAFLD. However, a recent a meta-analysis concluded that NAFLD is associated with all-cause mortality but not specifically CVD mortality.[42]

It is important to recognise that the risk of CVD outcomes is positively associated with severity of disease.**16*** CVD outcomes are more common with bridging fibrosis (F3 fibrosis) than with cirrhosis (F4 fibrosis), at which point liver-related death is more common.[43] However, even simple steatosis, in the form of both AFL and NAFL, was associated with increased all-cause mortality compared to mortality in the general population

in a 28 year follow-up study in Sweden.[44] Cardiovascular events were the most common cause of death.[44] Data from the Third National Health and Nutrition Examination Survey (NHANES III) showed that for 186 patients with AFLD/ASH in a population of 8,306 there was an increased risk of liver-related mortality but no increase in overall mortality or cardiovascular mortality.[45] In contrast, a southern Chinese study found that there was increased all-cause mortality as well as CVD mortality compared to controls.[46]

These studies suggest any association with increased risk of CVD mortality remains a point for debate in NAFLD. However, there seems little doubt that NAFLD is a risk factor for incident CVD. A 2017 meta-analysis of patients with NAFLD has demonstrated an increased risk of incident CVD, consistent for subgroups with coronary artery disease and ischaemic stroke.[47] The risk of CVD mortality was also increased in this systematic review (RR 1.46, 95% CI 1.31–1.64, p < 0.001).[47] Patients with more severe NAFLD are more likely to develop both fatal and non-fatal CVD events.[48]. Although as discussed below, T2DM is very common in patients with NAFLD, the relationship between NAFLD and CVD is not confounded by the presence of T2DM. In a recent study undertaken in a large national database in Scotland of patients with T2DM, there was the same independent association between NAFLD and incident CVD[49], and thus, the strength of the association between NAFLD and CVD seems remarkably similar, regardless of whether subjects have T2DM or not.

The presence of coronary artery calcium can be used as a proxy indicator of sub-clinical coronary artery disease. Both AFLD and NAFLD were positively associated with coronary artery calcification in a Korean cohort.[50] In another study which recruited 360 patients admitted with a ST elevation myocardial infarction, the patients were classified according to grade of steatosis using ultrasonography (grades 0, 1, 2, 3).[51] In-hospital mortality for grades 0, 1, 2, and 3 were 4.7%, 8.3%, 11.3%, and 33.9%, respectively. Three-year mortality for grades 0, 1, 2, and 3 were 5.6%, 7.8%, 9.5%, and 33.3%, respectively. The presence of NAFLD was associated with mortality in patient with STEMI.[51]

NAFLD is associated with several different cardiovascular risk factors. However, treating dyslipidaemia with lipid lowering agents has not been demonstrated to reduce cardiovascular mortality in a retrospective cohort study.[52] In patients admitted with acute heart failure both the in-patient mortality and post-discharge mortality were higher in patients

with concurrent NAFLD.[53] NAFLD is also associated with an increased risk of atrial fibrillation in middle-aged and elderly individuals (especially in those with type 2 diabetes).[54] However, an association between AF and mortality has not been demonstrated so far.

There is an increased risk of stroke in patients with NAFLD, adjusted for other variables including ethnicity. This is increased for ischaemic and haemorrhagic stroke.[55] Although there is a suggestion that patients with NAFLD may have more severe ischaemic stroke, it not yet established whether there is an increased risk of fatal stroke in NAFLD.[56]

4.2 Type 2 Diabetes Mellitus (T2DM)

The prevalence of NAFLD in patients with T2DM ranges widely (from 45% to 75%) in large hospital-based studies and (from 30% to 70%) in population-based studies, reflecting demographic differences between studies and differences in diagnostic criteria for defining NAFLD.[57]

T2DM is an independent predictor of liver-related and overall mortality in NAFLD.[58,59] Furthermore, T2DM is a risk factor for the development of a severe liver disease due to any aetiology compared to non-diabetic controls (hazard ratio, 2.28; 95% CI, 2.21–2.36).[60] Higher age, male sex, hypertension, higher body mass index, lower glomerular filtration rate, microalbuminuria, and smoking were risk factors associated with severe liver disease in patients with T2DM.[60]

It is important to note that there is a bidirectional relationship between NAFLD and T2DM. Although the MetS is predictive of NAFLD and progression[61,62], there is also evidence that development of hepatic steatosis is associated with incident T2DM,[63] and that resolution of NAFLD is associated with attenuation of the increased risk of developing T2DM.[64] Furthermore, NAFLD is also an independent risk factor for T2DM in non-obese, and non-central obese patients [65] suggesting that NAFLD is contributing to increase the risk of T2DM, regardless of the presence of excess body fat.

In a national retrospective cohort study in Scotland of patients with chronic liver disease (CLD) among patients without T2DM the most common cause of CLD was AFLD but among

patients with T2DM the most common cause of CLD was NAFLD. T2DM was associated with an increased risk of hospital admission or death for all common aetiologies of CLD.[66]

Therefore, T2DM is an important risk factor for liver specialists treating patients with any aetiology of liver disease, not just fatty liver. The bidirectional relationship between T2DM and NAFLD also has implications for the care of patients with diabetes, as the presence of NAFLD and T2DM together increases the risk of complications from diabetes [67].

4.3 Chronic kidney disease (CKD)

NAFLD is independently associated with an increased risk of incident CKD.[68] There is a ~40% long term increased risk of incident CKD in NAFLD.[68] The prevalence of NAFLD in CKD is 17.9%.[69] Although patients with CKD are already known to have an increased CVD risk, the presence of NAFLD in patients with CKD independently increases this risk further (hazard ratio 2.95; 95% CI 1.31–6.60; p = 0.01). This same study did not demonstrate an association with all-cause mortality or CKD progression.[69]

In NAFLD, the presence of NAFLD was shown to be associated with an increase in overall mortality rate in a Swedish study of 120 patients with biopsy-proven NAFLD.[70] However, the increase in mortality rate may be explained by the increased prevalence of metabolic comorbidities such as T2DM during the mean 19.5 years of follow up.

[Figure 2]

5. Malignancy associated with NAFLD and AFLD

5.1 Hepatocellular carcinoma (HCC)

Patients with NAFLD are at an increased risk of developing HCC[14] and this increased risk occurs even in the absence of cirrhosis.[71] In the United States NAFLD has become the most common risk factor for HCC which continues to increase in prevalence over time.[72] Furthermore NAFLD-HCC (along with HCV-HCC) is associated with an increased mortality compared to HCC occurring with other liver pathologies.[72]

T2DM is independently associated with both poorer overall survival and poorer disease-free survival in HCC patients [73] and both T2DM and the MetS are independent risk factors for the development of HCC.[74] Although the risk of HCC is higher in patients with NAFLD than

in the general clinical population, most cases of HCC in NAFLD develop in patients with cirrhosis.[74,75] In patients with NAFLD and cirrhosis T2DM is associated with an increased risk of HCC.[76] For patients with cirrhosis, the mean annualised incidence of HCC in NAFLD is 1.56% and incidence of HCC in AFLD is 1.44%.[77]

5.2 Extra-hepatic malignancy

In patients with biopsy-proven NAFLD it has been demonstrated that liver and non-liver related malignancy was the second most common cause of mortality.[26] NAFLD is independently associated with a higher risk of colorectal adenomas and colorectal carcinoma[78] as noted in a meta-analysis of nine observational studies. In this analysis an increase in NAFLD severity was associated with increased risk of colorectal cancer (HR 2.12, 95% CI: 1.56–2.88).[78] However, the observational nature of these studies preclude making any conclusions about causality.

There are a number of proposed mechanisms linking development of GI cancers and NAFLD and in particular these focus on changes in adipose tissue function. Proposed mechanisms include increased insulin resistance with subsequent hyperinsulinaemia, insulin-like growth factor 1 (IGF-1) which can promote cellular proliferation via activation of mitogen-activated protein kinase (MAPK) and phosphoinositide (PI3K) pathways in addition to the consideration of adipose tissue-derived inflammation (i.e. obesity is chronic inflammatory state) with release of pro-inflammatory cytokines tumour necrosis factor (TNF), interleukin-1β (IL-1β) and interleukin-6 (IL-6).[79]

A study of malignancy in NAFLD has also demonstrated an increased incidence rate of breast cancer in NAFLD (IRR 1.77, 95% CI 1.15-2.74, p=0.01).[80] In the same study there was also a trend towards an association with bladder cancer (IRR 1.93, 95% CI 0.94-3.95, p=0.07), kidney and renal pelvis cancer (IRR 1.76, 95% CI 0.96-3.22, p=0.07) and stomach cancer (IRR 1.36, 95% CI 1.00-1.86, p=0.053).[80]

The presence of malignancy also needs to be strongly considered in patients with AFLD because of the established association between alcohol excess and a number of cancers.[81,82] Alcohol excess is associated with cancer of the oral cavity and pharynx, oesophageal squamous cell carcinoma, breast cancer and colorectal cancer.[83]

6. Risk Factors for Mortality in NAFLD and AFLD

6.1 Age

Age is a risk factor for liver fibrosis in NAFLD, and liver fibrosis is an independent risk factor for liver-related mortality.[84] Age is also an independent risk factor for both increased cardiovascular mortality and liver-related mortality in NAFLD.[85] Thus, it is possible that aging may confound any independent association between liver fibrosis and mortality outcomes. This possibility has been demonstrated in a recent study which analysed 3,271 NHANES-III participants representative of the US population.[86] The presence of NAFLD in participants was confirmed by a United States-Fatty Liver Index score $\geq$ 30. The prevalence rates of NAFLD were 40.3% (95% CI: 37.2-43.5%) and 39.2% (95% CI: 34.4-44.0%) among 60-74 and > 74 years old respectively. Among aged 60-74 years, the risks for 5-year and 10-year all-cause mortality were associated with presence of NAFLD [adjusted hazard ratios: 1.60 (95% CI: 1.24-1.96) for 5-year and 1.22 (95%CI: 1.01-1.49) for 10-year]. cardiovascular mortality was higher in this group were (aHR: 2.12 (95% CI: 1.20-3.75) for 5-year and 1.06 (95%CI: 0.73-1.52) for 10-year]. In contrast, in individuals > 74 years, diagnosis of NAFLD was not associated with all-cause or CVD mortality.[86]

6.2 Sex

In a retrospective cohort study of more than 300,000 Koreans, male sex was not associated with an increased risk of mortality due to NAFLD. Furthermore, in this study male sex and NAFLD was surprisingly associated with a decreased rate of malignancy-associated mortality. However, in woman NAFLD was independently associated with death from all causes, including malignancy, cardiovascular disease and liver disease.[87] That said, is important to interpret these findings with caution. Overall mortality was low (0.51%) and the follow-up may be too short at 5-7 years, or the population studied too healthy, to achieve reliable estimates of the strength of the associations. The women were also 7 years older than the men.

There is a strong biological explanation for an association between sex and clinically relevant outcomes in NAFLD based on age. Men are at a higher risk of having more severe fibrosis compared to women before menopause, while post-menopausal women have a similar

severity of liver fibrosis compared to men. These findings may be explained by the protective effects of oestrogen against fibrogenesis and the lack of the protective effects of oestrogen post-menopause on cardiovascular and metabolic risk factors, contributing to the development of the MetS.[88,89] In a Japanese study age was shown to be a risk factor for NAFLD, with men presenting at age 40-49 years, and women presenting at age 60-69 years.[90] Overall, men are more commonly affected by NAFLD than woman.[91]

6.3 Adiposity

The growing prevalence of NAFLD has paralleled the increasing prevalence of obesity in recent years. The age-standardised prevalence of obesity increased from 3·2% in 1975 to 10·8% in 2014 in men, and from 6·4% to 14·9% in women. In 2014, the global prevalence of severe obesity (BMI ≥35 kg/m$^{2)}$ was 2·3% in men and 5·0% in women. In 2014, the global prevalence of morbid obesity (BMI ≥40 kg/m^2) was 0·64% in men and 1·6% in women.[92]

However, as demonstrated by Younossi et al[8], obesity (defined by BMI) may only be associated with NAFLD in ~50% of patients. A Finnish study in the general population demonstrated that BMI was not associated with incident liver disease. However, waist circumference/BMI was strongly associated with incident liver disease, reinforcing the importance of using more specific measurements of regional adiposity and visceral adiposity than BMI alone.[93]

It should also be noted that a non-obese (or 'lean') NAFLD phenotype exists, which is associated with female sex, younger age, insulin resistance and hypertension.[94] The majority of non-obese patients with NAFLD have insulin resistance but only a minority have manifestations of the MetS.[95] Up to 18% of patients with NAFLD in the United States are non-obese.[94] That said, lifestyle measures, both exercise and weight loss, remain the recommendation of choice for patients with non-obese NAFLD.[96]

Guidelines issued by EASL, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) recommend weight loss of 7-10% based on improvement in histology.[97] However, the impact weight loss on liver-related mortality is uncertain. Non-obese patients with NAFLD seem to have less severe disease and experience fewer complications than obese patients with NAFLD.[98] However, the study which demonstrated this had a relatively short follow-up and only 27% of the cohort

had follow-up biopsies. Importantly, prevalence of advanced fibrosis was not significantly different in obese patients with NASH than non-obese patients with NASH. Another study similarly found that patients with NASH, despite those with lower waist circumference having milder metabolic alterations, had similar rates of fibrosis ≥ F2.[99] Therefore, once NASH is established it may be NASH, rather than obesity, that is the key 'driver' of fibrogenesis and liver-related outcomes.

6.4 Ethnicity and genetics

In the United States, African-Americans have the lowest prevalence of NAFLD despite having higher prevalence rates of risk factors associated with NAFLD such as T2DM, obesity and hypertension.[100] Furthermore, the prevalence of advanced fibrosis in NAFLD appears to vary with ethnicity. [101]

Hispanic populations have a significantly higher prevalence of NAFLD compared to non-Hispanic white or non-Hispanic black populations. This is despite the higher prevalence of obesity in non-Hispanic blacks.[102] Although a systematic review and meta-analysis has demonstrated disparities in NAFLD prevalence amongst different ethnic populations (with the highest prevalence in Hispanics and lowest prevalence in African-Americans), no differences in outcomes in patients with NAFLD were observed.[103]

There is evidence of ethnic variation in the prevalence of alcohol related cirrhosis prevalence as well, such as the disproportionately higher prevalence of alcohol related cirrhosis in Asian men compared to the prevalence in Afro-Caribbean men in a British population.[104]

Sociocultural factors undoubtedly have a bearing on these observed difference in prevalence between ethnic groups. However, genetic susceptibility to liver disease is also a likely factor. The rs738409 G allele of the PNPLA3 gene has a strong association with hepatic steatosis.[105] In addition to sociocultural differences this genotype may be one of the factors accounting for variation in prevalence of NAFLD globally, with higher prevalence rates in South America, where the PNPLA3 rs738409 G allele is more prevalent as well.[105]

PNPLA3 rs738409 and TM6SF2 rs58542926 genotypes have been found to be associated with increased utilization of health services [106], although these genotypes have not been

demonstrated to be associated with increased mortality in NAFLD. There is evidence that the rs738409 G allele also plays role in the risk of developing alcohol-related cirrhosis as well as NAFLD.[107] In patients with severe alcoholic hepatitis homozygosity the rs738409 G allele is associated with an increased risk of medium-term mortality.[108]

6.5 Caffeine

Caffeine intake is not associated with prevalence of NAFLD or fibrosis. However, subgroup analysis has suggested that increased coffee intake is associated with reduced hepatic fibrosis.[109]

6.6 Smoking

Smoking is associated with NAFLD.[110] Mortality is increased two-fold by smoking in the US population.[111] However, there is not significant difference in mortality risk for patients with NAFLD who smoke versus patients without NAFLD who smoke.[111]

6.7 Alcohol

Although it has been suggested that modest amounts of alcohol is beneficial for CVD risk in the general population, there is a linear relationship between alcohol intake and other cardiac events/outcomes including stroke, heart failure, fatal hypertensive disease and fatal aortic aneurysm.[112] In patients with the MetS, alcohol consumption (below the limit required for AFLD) is associated with an increased risk of severe liver disease.[113]

In patients with NAFLD, the data is less clear as to whether modest alcohol intake confers any increase in mortality. In a study of participants representative of the general population and enrolled to NHANES, it was demonstrated that for participants with NAFLD who drank modest amounts of alcohol (0.5–1.5 drinks/day) there was an associated decrease in all-cause mortality.[114] High alcohol consumption in participants with NAFLD was associated with increased all-cause mortality.[114] Another study of participants enrolled in NHANES III, analysed the effect of alcohol consumption on mortality in the presence of NAFLD and the MetS.[115] This study found an association between increased alcohol consumption (>3 drinks/day for men and >1.5 drinks/day for women) and mortality for participants with NAFLD and MetS. This association was not evident for lower amounts of alcohol.[115] The J curve often seen in population studies of alcohol effect needs to be interpreted carefully given the possibility of reverse causality or unaccounted confounders in teetotal participants.

7. Biomarkers of disease severity in NAFLD and AFLD

7.1 Transaminases

In NAFLD, diabetes and obesity (and low initial fibrosis stage) have been shown to be predictors of fibrosis progression, but interestingly aminotransferases do not correlate well with histological changes over time.[116] However, higher ALT is associated with increased liver-related mortality[42] and GGT is associated with all-cause mortality.[42,117]

7.2 NAFLD Fibrosis Score / FIB-4 / APRI / Fatty liver index

In patients with biopsy-proven NAFLD, the NAFLD Fibrosis Score (NFS) and FIB-4 were predictive of all-cause mortality.[118] The same study found an association between higher FIB-4 score and higher NAFLD fibrosis score in patients with NAFLD who developed malignancy. A Japanese study of patients with biopsy-proven NAFLD similarly found that FIB-4 was strongly associated with HCC and liver cirrhosis complications (HR 26.6, 95% CI 3.3-212.5).[119] A systematic review with meta-analysis found that NFS was predictive of all-cause mortality.[120] In this study FIB-4 and APRI were not predictive of all-cause mortality.

In a Chinese study of 180 patients with ultrasound defined NAFLD (with -ve HBsAg and low alcohol intake) NFS as a continuous variable was identified as the only predictor of all-cause mortality over a follow-up of 6.6 years (HR 2.74, 1.67-4.50).[121]

In a retrospective analysis of 646 patients with biopsy proven NAFLD, FIB-4 and NFS performed best in terms of predicting mortality or severe liver disease. However, neither FIB-4 nor NFS performed well enough to be useful in clinical practice.[122] For example, for mortality, AUROC curve values were: NFS 0.72 (95% CI, 0.68–0.76); FIB-4, 0.72 (95% CI, 0.68–0.76). For severe liver disease AUROC curve values were: NFS, 0.72 (95% CI, 0.66–0.78); FIB-4, 0.72 (95% CI, 0.66–0.79).

The value of these scores may extend beyond prediction of liver-related outcomes. NFS and FIB-4 scores are also association with increased HRs for cardiovascular mortality in patients >65 years with NAFLD.[123] NFS is independently associated with impaired eGFR.[124]

and fatty Liver Index (FLI) ≥ 30 is associated with an increased risk of colorectal adenoma.[125], both of which could contribute to increased mortality.

Munteanu et al recently provided evidence to suggest that the FibroTest score provides long-term (10 year) prognostic value for mortality in NAFLD populations, with a high AUROC of 0.941 compared to 0.875 for the comparator control group of patients with chronic hepatitis C (CHC). [126] The Fibrotest score was best at predicting survival without liver-related deaths, but also had prognostic value for predicting cardiovascular death and, to a lesser extent, overall mortality.[126]

8. Current pharmaceutical approaches in NAFLD and AFLD[*]

We have described above that there are a range of risk factors which appear to mediate the multisystemic outcomes associated with both NAFLD and AFLD. To date there is no pharmacological agent that confers a clear survival benefit for either of these complex conditions. However, herein we outline a selection of the agents which are either available or which have shown promise in recent clinical trials.

8.1 Pharmaceutical approaches in NAFLD[†]

There is no pharmacological agent that is currently licensed for the treatment of NAFLD. As mentioned (in Section 3.1), based on the association between histological evidence of fibrosis and/or NASH and mortality, the FDA will offer accelerated approval to agents which demonstrate improvement in fibrosis and/or NASH.[25] There is a large number of therapeutic agents in development for NASH with a selection of agents in registered phase II/III trials.[127] One promising agent is obeticholic acid (OCA) which is a farnesoid-X-receptor (FXR) agonist. The FLINT study was a previously conducted phase II multi-centre, double-blind, randomised, placebo-controlled trial of OCA in patients with NASH.[128] In FLINT, patients who received OCA achieved the primary outcome of improvement in the NAFLD Activity Score (NAS) with no worsening in fibrosis more frequently than those randomised to placebo (51% vs 21%).[128]The REGENERATE study is the currently recruiting phase III multi-centre, double-blind, randomised, placebo-controlled trial of OCA in patients with NASH. The investigators of REGENERATE reported the interim analysis

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[*] *New section added to address comments by Reviewer 2*
[†] *New section added to address comments by Reviewer 2*

results in abstract form at EASL International Liver Congress 2019.[129] The interim analysis found that REGENERATE was currently meeting its primary outcome of improvement in fibrosis ≥1 stage with no worsening in NASH. However, unlike FLINT, in REGENERATE there was no demonstrable improvement in NAS. Similar to FLINT, the most common adverse event in REGENERATE was pruritus, which affected a considerable 51% of patients on OCA 25mg vs 19% of patients on placebo.

It is notable that OCA has been associated with an increase in serum LDL-C and serum triglycerides in both the FLINT and REGENERATE studies. This deterioration in the lipid profile was ameliorated with concurrent lipid lowering therapy. Nonetheless, this observed side effect is not ideal given the increased cardiometabolic risk and associated CVD-mortality in patients with NAFLD. It is important that future therapeutic regimens for NAFLD carefully take CVD risk into account. Pioglitazone and liraglutide are two such agents which reduce CVD risk, are already available and also lead to resolution of NASH in up to 50% of patients.[130,131] Furthermore, the consideration of pioglitazone in NASH is recommended in international guidelines on the management of NAFLD.[97,132,133]

With regards to the other major cause of mortality in NAFLD, i.e. malignancy, it is unclear yet whether any agents ameliorate this risk. However, there is some evidence to suggest that metformin is associated with a lower risk of HCC in patients with NASH.[134] Furthermore, there is biological plausibility in an animal model that metformin alters the gut microbiota with reduction in oxidative stress and downregulation of hepatocarcinogenesis.[135] Given the fact that T2DM increases risk of HCC in patients with NASH who have developed liver cirrhosis[76], there is a need for more prospective studies to examine the relationship between hypoglycaemic agents and HCC risk in patients with NAFLD and T2DM.

8.2 Pharmaceutical approaches in AFLD[‡]

There remains a paucity of pharmacological agents for AFLD despite the risk of both liver-related and all-cause mortality that we have discussed above. One major reason for the lack of a pharmacological 'silver bullet' in AFLD is that the predominant aetiological risk factor,

[‡] New section added to address comments by Reviewer 2

namely hazardous alcohol consumption, is the result of a complex interplay of socioeconomic, demographic, genetic and biological factors.[136] Nonetheless, there are pharmacological agents which are broadly available for patients with alcohol use disorder (AUD) and these agents may have particular benefit in selected individuals with AFLD which include the acetaldehyde dehydrogenase inhibitor disulfiram, the μ- and k-opioid receptor antagonist naltrexone, and the N-metil-D-aspartate receptor antagonist acamprosate.[137] Both disulfiram and naltrexone undergo hepatic metabolism and the manufacturers recommend against their use in patients with hepatic impairment. Acamprosate may be a safer option for patients with cirrhosis given that acamprosate undergoes minimal hepatic metabolism and a previous meta-analysis demonstrated no significant difference between acamprosate and naltrexone.[138] However, the $GABA_B$-receptor agonist, baclofen, remains the only anti-craving medication recommended for continue use in end-stage liver disease.[139]

With regards to the lack of agents which directly target histopathological changes in AFLD this may well be due to the lack of understanding of the pathogenesis of AFLD. The most studied subgroup of patients with AFLD in recent years is the subgroup of patients who present with severe alcoholic hepatitis. In 2015, Thursz et al published findings of a multi-centre, double-blind, randomised, placebo-controlled trial of prednisolone vs pentoxifylline vs placebo in patients with severe alcoholic hepatitis. Although prednisolone demonstrated a trend towards reduction in 28-day mortality, there was no difference in outcomes at 90 days or 1 year.[23] There are a number of registered clinical trials which are recruiting, or not yet recruiting, for severe alcoholic hepatitis, which include infusion of the small investigational molecule DUR-928 (NCT03917407), hepatic artery injection of autologous human bone marrow-derived mesenchymal stem cells (Cellgram™) (NCT03838250), administration of omega 5 fatty acid as an adjuvant to corticosteroids (NCT03732586), administration of granulocyte colony stimulating factor (G-CSF) monotherapy (NCT02776059, NCT03703674, NCT02442180), corticosteroid monotherapy vs corticosteroid and G-CSF combination therapy (NCT04066179) and Anakinra (plus zinc) vs steroids vs G-CSF (NCT04072822).

There are currently no pharmacological agents which improve histopathological changes in patients with AFLD at an earlier, less severe stage of disease. A broad mechanistic strategy which could be developed in future could be targeting of the gut microbiota in patients with

AFLD.[140] *There appears to be some similarities between AFLD and NAFLD in this regard, particularly with the respect to the translocation of endotoxins such as lipopolysaccharide (LPS), activation of Toll-like receptors and alteration of ostensibly important gut bacteria such as Akkermansia muciniphila.*[135,141,142] *However, at present there are only two registered trials of agents which target the gut microbiota in patients with AFLD, one study in which Profermin® (consists of fermented oats, Lactobacillus plantarum 299v, barley malt, lecithin and water) is administered to participants with AFLD (NCT03863730) and a study of S-Adenosyl methionine and choline supplementation in AFLD (NCT03938662).*

9. Conclusion

Fatty liver disease is a multisystem disease that is associated with increased mortality independent of its associated co-morbidities. The predominant causes of mortality are cardiometabolic and liver-related. However, fatty liver disease is also associated with increased risk of malignancy. Currently the strongest predictor of mortality is fibrosis stage and the gold standard for assessing the stage of liver fibrosis in both NAFLD and AFLD remains histological examination of liver tissue.

Although there are not currently any licensed treatments for NAFLD, this is likely to change soon. However, in view of the mortality risks described above, amelioration of cardiometabolic risk factors will be equally as important as anti-fibrogenic therapies. Furthermore, although AFLD and NAFLD are distinctly separated in clinical trials, in clinical practice there is considerable overlap between both conditions, and both diseases are not mutually exclusive.

Disclosure Statement

No conflicts of interest to disclose.

ABBREVIATIONS

AASLD, American Association for the Study of Liver Diseases

AFLD, alcohol related fatty liver disease

ALT, alanine aminotransferase

APRI, AST to platelet ratio score

ASH, alcoholic steatohepatitis

AST, aspartate transaminase

AUD, alcohol use disorder

AUROC, area under the receiver operating characteristics

BMI, body mass index

CC, cryptogenic cirrhosis

CI, confidence interval

CKD, chronic kidney disease

CVD, cardiovascular disease

EASL, European Association for the Study of the Liver

G-CSF, granulocyte colony stimulating factor

GGT, glutamyl transpeptidase

HBsAg, hepatitis B surface antigen

HCC, hepatocellular carcinoma

HDL-C, high density lipoprotein C

HTN, hypertension

IGF-1, insulin-like growth factor 1

IL-1β / -6, interleukin-1β / -6

MAPK, mitogen-activated protein kinase

MetS, metabolic syndrome

NAFLD, non-alcoholic fatty liver disease

NASH, non-alcoholic steatohepatitis

NFS, NAFLD Fibrosis Score

NHANES, National Health and Nutrition Examination Survey

PI3K, phosphoinositide

PNPLA3, patatin-like phospholipase domain-containing protein 3

STOPAH, steroids or pentoxifylline for alcoholic hepatitis (trial)

STEMI, ST elevation myocardial infarction

T2DM, type 2 diabetes mellitus

TM6SF2, transmembrane 6 superfamily member 2

TNF, tumour necrosis factor

UNOS, United Network for Organ Sharing

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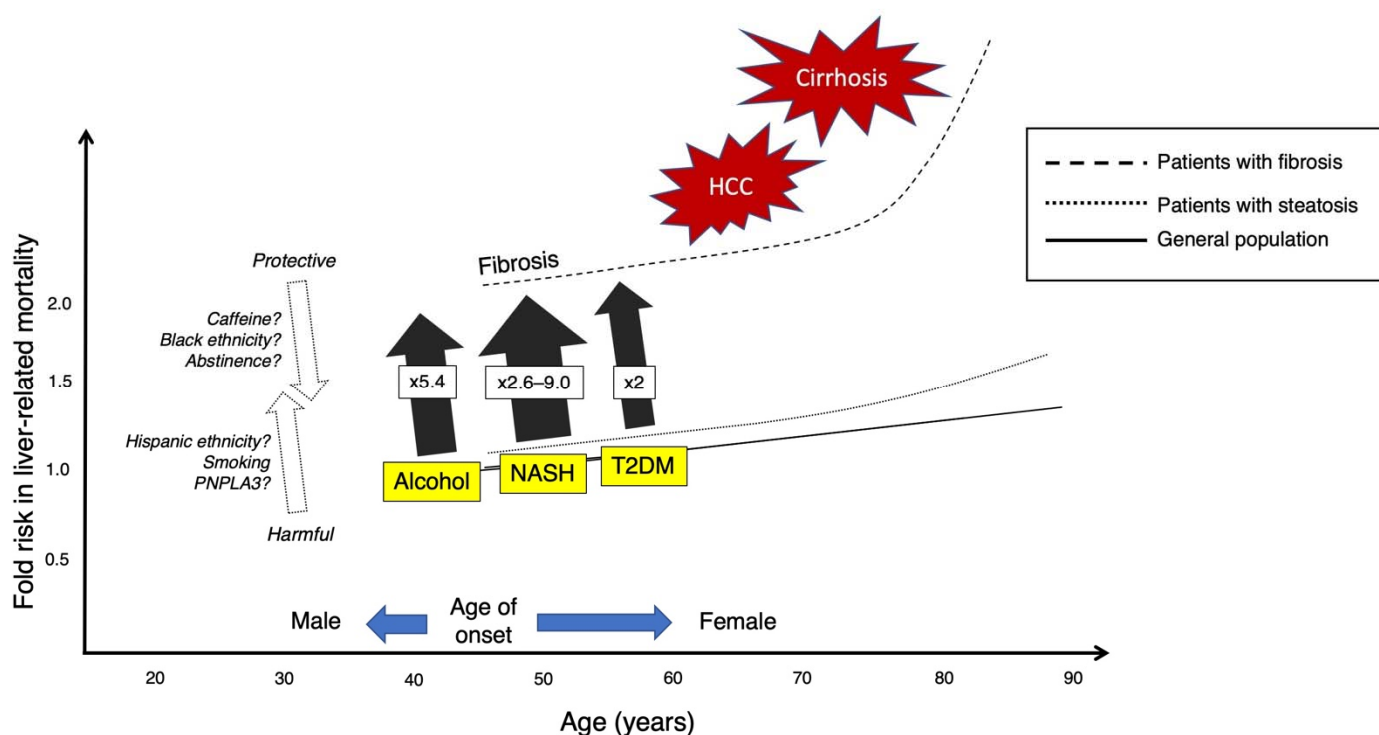
Figure 1. Fibrosis is the strongest predictor of progressive liver disease and associated liver-related mortality. Although sex is not associated with increased mortality, males with NAFLD present at an earlier age than females. Both NASH and T2DM are independently associated with increased liver-related mortality. Depending on alcohol consumption, AFLD/ASH has been associated with a 5.4-fold increase in liver related mortality.[21] (AFLD, alcoholic fatty liver disease; ASH, alcoholic steatohepatitis; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing protein 3; T2DM, type 2 diabetes.)
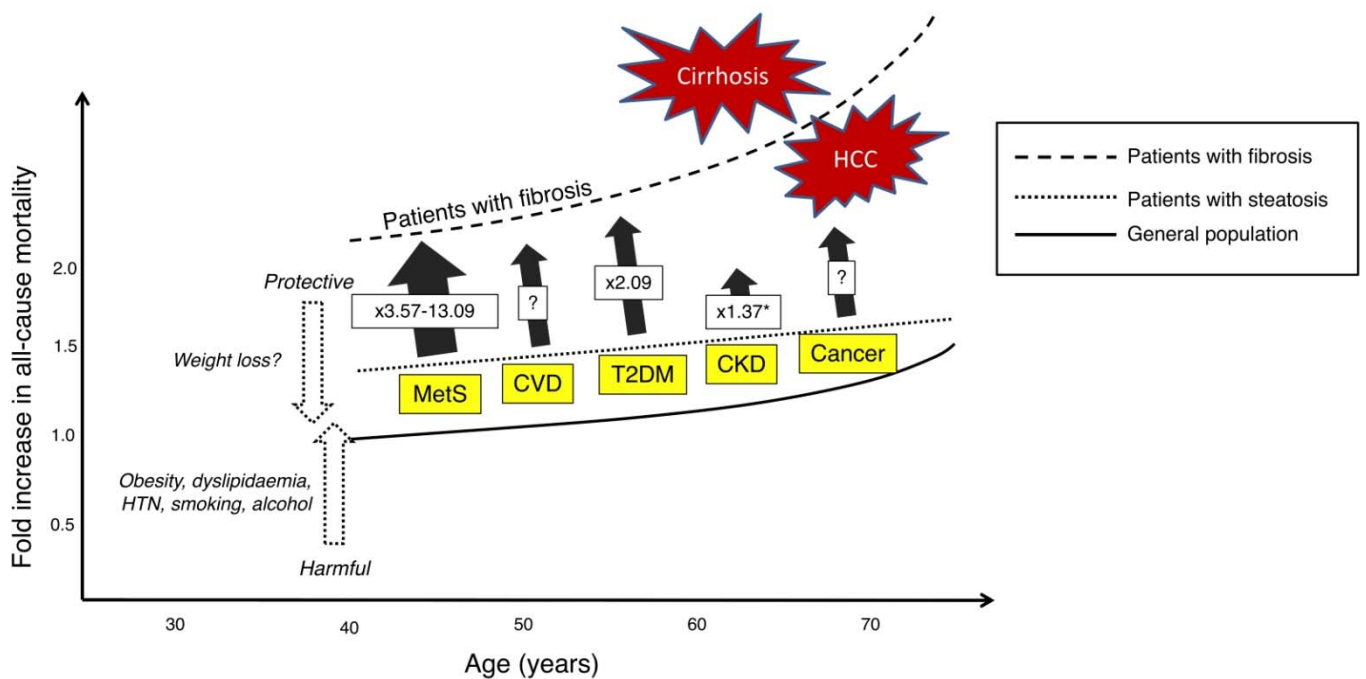
*CKD increases cardiovascular mortality, not all-cause mortality

Figure 2. Fibrosis is a predictor of all-cause mortality in patients with NAFLD. The presence of NAFLD is an independent predictor of increased all-cause mortality. The increased all-cause mortality risk compared to the general population becomes less significant with increasing age. The presence of components of the MetS in NAFLD increases all-cause mortality. The magnitude of this effect on all-cause mortality increases with the number of components of the MetS include increased fasting plasma glucose or T2DM, hypertriglyceridaemia low high-density lipoprotein level, increased waist circumference, and hypertension. CKD increases cardiovascular mortality in NAFLD. The most common causes of death in NAFLD are cancer and CVD. *(CKD, chronic kidney disease; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; HTN, hypertension; NAFLD, non-alcoholic fatty liver disease; PNPLA3, patatin-like phospholipase domain-containing protein 3; T2DM, type 2 diabetes.)*

Box 1	Staging classification for fibrosis in NASH[31]

Stage 1	Zone 3 perisinusoidal/pericellular fibrosis; focally or extensively present.
Stage 2	Zone 3 perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis
Stage 3	Zone 3 perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis.
Stage 4	Cirrhosis.

Table 1 Multivariable-adjusted Hazard Ratios for Mortality in Patients with AFLD and NAFLD

Variable	Adjustments	Adjusted HR (95% Confidence Interval)		Reference
All-cause mortality				
Older age in NAFLD	Demographics, comorbidities	**1.07 (1.05-1.11)**[58]	1.0	NAFLD[b]
T2DM in NAFLD	Demographics, comorbidities	**2.09 (1.39–3.14)**[58]	1.0	NAFLD[b] without T2DM
AFLD[††]	Age, sex, socioeconomic status, smoking status, HTN, T2DM, dyslipidaemia, CVD.	**4.85 (4.49-5.23)**[49]	1.0	No chronic liver disease
NAFLD	Age, sex, municipality	1.14 (0.99-1.32)[34]	1.0	No NAFLD
	Age, sex, race, education, income, T2DM, HTN, CVD, lipid-lowering medication, smoking status, waist circumference, alcohol consumption, caffeine consumption, total cholesterol, HDL-C, trans%, CRP	0.89 (0.78-1.02)[30]	1.0	No NAFLD
[5yr mortality][†]	Age, sex, race, smoking status, presence of MetS	**1.60 (1.24-1.96)**[86]	1.0	No NAFLD
[10yr mortality][†]		**1.22 (1.01-1.49)**[86]	1.0	No NAFLD
NASH	Demographics, comorbidities	1.13 (0.74-1.71)[58]	1.0	NAFL[b]
Fibrosis[*]	Age, sex	**2.44 (1.45-4.08)**[70]	1.0	NAFLD[b] without fibrosis
	Age, sex, race, BMI, T2DM, HTN, statin use, smoking, study centre	**F1 1.82 (1.18-2.81)**[28] **F2 1.91 (1.20-3.03)** **F3 1.90 (1.16-3.12)** **F4 6.35 (3.35-12.04)**	1.0	NAFLD[b] without fibrosis
'Steatofibrosis'	Age, sex, obesity, T2DM	**1.76 (1.02-3.05)**[36]	1.0	NAFL[b]
Smoking	Age, sex, race, comorbidities	**1.65 (1.31–2.07)**[85]	1.0	NAFLD non-smoker
	Age, sex, race/ethnicity, smoking history, obesity, diabetes/ insulin resistance and hypertension.	**2.09 (1.72-2.53)**[45]	1.0	AFLD non-smoker

Cardiovascular mortality					
Older age in NAFLD	Demographics, comorbidities	**1.12 (1.08-1.18)**[58]	1.0	NAFL[b]
AFLD[††]	Age, sex, socioeconomic status, smoking status, HTN, T2DM, dyslipidaemia, CVD.	**2.05 (1.63-2.58)**[49]		No chronic liver disease
NAFLD	Age, sex, race, education, income, T2DM, HTN, CVD, lipid-lowering medication, smoking status, waist circumference, alcohol consumption, caffeine consumption, total cholesterol, HDL-C, trans%, CRP	0.75 (0.56-1.01)[30]	1.0	No chronic liver disease
NASH	Demographics, comorbidities	0.51 (0.23–1.10)[58]	1.0	NAFL[b]
CKD in NAFLD	Age, sex	**2.07 (1.03-4.14)**[70]	1.0	Matched controlled without
	Age, sex, T2DM, HTN, fibrosis	0.79 (0.39-1.61)[70]	1.0	known NAFLD

Liver-related Mortality					
Older age in NAFLD	Demographics, comorbidities	**1.06 (1.02-1.10)**[58]		
NAFLD	Age, sex, race, education, income, T2DM, HTN, CVD, lipid-lowering medication, smoking status, waist circumference, alcohol consumption, caffeine consumption, total cholesterol, HDL-C, trans%, CRP	1.90 (0.57-6.35)[30]	1.0	No chronic liver disease
NASH	Demographics, comorbidities	**9.16 (2.10–9.88)**[58]	1.0	NAFL[b]
	Age, sex, obesity, T2DM	**9.9 (1.3-74.9)**[36]	1.0	NAFL[b]
'Steatofibrosis'	Age, sex, obesity, T2DM	**6.7 (1.5-29.8)**[36]	1.0	NAFL[b]
T2DM in NAFLD	Age, sex, race, history of T2DM, presence of obesity, hyperglycaemia, hyperlipidaemia	**2.19 (1.00–4.81)**[58]	1.0	NAFLD[b] without T2DM
AFLD	Age, sex, race/ethnicity, smoking history, obesity, diabetes/ insulin resistance and hypertension	**7.06 (2.09–23.79)**[45]	1.0	No AFLD

[b]Biopsy proven NAFLD
[*]Fibrosis stage 2-4
[†]In study of patients > 60 years old
[††]Patients with a hospital admission diagnosis of AFLD based on ICD-9 and ICD-10 codes
(AFLD, alcohol related fatty liver disease; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; HDL-C, high density lipoprotein C; HTN, hypertension; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.)