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# Alcoholic liver disease

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Abstract | Alcoholic liver disease (ALD) is the most prevalent type of chronic liver disease worldwide. ALD can progress from alcoholic fatty liver (AFL) to alcoholic steatohepatitis (ASH), which is characterized by hepatic inflammation. Chronic ASH can eventually lead to fibrosis and cirrhosis and in some cases hepatocellular cancer (HCC). In addition, severe ASH (with or without cirrhosis) can lead to alcoholic hepatitis, which is an acute clinical presentation of ALD that is associated with liver failure and high mortality. Most individuals consuming >40 g of alcohol per day develop AFL; however, only a subset of individuals will develop more advanced disease. Genetic, epigenetic and non-genetic factors might explain the considerable interindividual variation in ALD phenotype. The pathogenesis of ALD includes hepatic steatosis, oxidative stress, acetaldehyde-mediated toxicity and cytokine and chemokine-induced inflammation. Diagnosis of ALD involves assessing patients for alcohol use disorder and signs of advanced liver disease. The degree of AFL and liver fibrosis can be determined by ultrasonography, transient elastography, MRI, measurement of serum biomarkers and liver biopsy histology. Alcohol abstinence achieved by psychosomatic intervention is the best treatment for all stages of ALD. In the case of advanced disease such as cirrhosis or HCC, liver transplantation may be required. Thus, new therapies are urgently needed.

Alcoholic liver disease (ALD) is one of the most prevalent liver diseases in Europe and the United States[1–3]. The disease can be caused by the chronic consumption of alcohol exceeding a certain daily amount, which varies considerably between individuals. Chronic, heavy alcohol consumption, which is classified in this Primer as the consumption of >40 g of pure alcohol per day (equating to 375 ml of 13 vol% wine or >1 litre of 5 vol% beer) over a sustained period of time (years) leads to the highest risk of ALD[4,5]. However, a recent meta-analysis has shown that even the chronic consumption of 12–24 g of alcohol per day has an increased risk of cirrhosis (a late stage of ALD) as compared with non-drinking[4]. According to these data, the threshold level of chronic alcohol consumption that increases the risk of ALD may be rather low and therefore may be difficult to detect. No data exist regarding threshold levels of binge drinking that increase ALD risk. Unquestionably, the risk of cirrhosis correlates to the length of time over which alcohol has been consumed.

ALD follows a well-recognized pattern of disease progression (FIG. 1; BOX 1). The spectrum of ALD begins with alcoholic fatty liver (AFL), which is characterized by hepatic steatosis (an accumulation of triglycerides in hepatocytes). Some individuals will progress and develop hepatic inflammation, hepatocyte injury and ballooning, which is histologically defined as alcoholic steatohepatitis (ASH). ASH may progress slowly, with continual chronic liver injury and inflammation eventually leading to progressive fibrosis and cirrhosis, which ultimately may drive the development of hepatocellular carcinoma (HCC). In addition to this slow chronic progression, individuals with ALD (with or without cirrhosis) with rapidly progressing ASH may present with an acute clinical syndrome called alcoholic hepatitis, which is associated with poor prognosis[6] (FIG. 1; BOX 1). Alcoholic hepatitis in the presence of cirrhosis is referred to as acute-on-chronic disease. Prevention and treatment of ALD needs a multidisciplinary approach to manage alcohol use disorder (AUD) as well as nutritional, pharmacological and surgical interventions for decompensated (symptomatic) liver disease; clinical guidelines have been published by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL)[6–8].

In this Primer, epidemiology, pathophysiology, diagnosis and management of ALD are discussed and an outlook for future therapeutic possibilities is given.

## Epidemiology

### *Incidence and mortality*

ALD is associated with substantial morbidity and mortality that is largely preventable, mostly through political measures that decrease the availability of alcohol. Harmful alcohol consumption, defined by the WHO as

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drinking that causes detrimental health and social consequences for individuals, their friends and families and society at large (as well as the patterns of drinking that are associated with increased risk of adverse health outcomes), causes ~3.3 million deaths every year (5.9% of all deaths) owing to a large number of alcohol-associated diseases in different organs (BOX 2) as well as injuries caused by traffic accidents and violence[4]. The proportion of global deaths attributable to alcohol is 7.6% among men and 4.0% among women[9]. Additionally, the harmful effects of alcohol particularly affect those of working age, with 139 million disability-adjusted life years lost, or 5.1% of the total global burden of disease, attributable to alcohol consumption. Moreover, alcohol-related morbidity and mortality closely correlate with the amount of alcohol consumption.

A large variation in alcohol consumption and related morbidity and mortality exists worldwide, with the WHO European Region having the highest alcohol consumption and the highest incidence of ALD[9]. Globally, the mean pure alcohol consumption (in individuals aged >15 years) is 6.2 litres per person per year, whereas consumption in the WHO European Region is 10.9 litres per person per year (FIG. 2). Interestingly, a decrease in alcohol consumption has been observed between 1990 and 2014 in the WHO European Region, which is associated with decreases in consumption in the central and western European Union and Mediterranean countries; however, there have been simultaneous increases in consumption in eastern and southeastern parts of the WHO European Region. This increase in consumption was tightly associated with an increase in mortality due to liver cirrhosis in these areas[10].

Liver disease can be associated with many different causative factors. Recent data have shown that the relative contribution of different aetiologies follows a geographical pattern, with alcohol being a predominant cause of liver disease in Western European countries and viral hepatitis B and C being more prevalent in Eastern European countries. In Central European countries, alcohol and viral infections contribute equally[11]. When all WHO regions are considered, adult per capita alcohol consumption increased ~10% in the past 25 years, mostly owing to marked increases in consumption in Asia (mostly China and India) and in Africa, whereas in North and South America and in Europe consumption decreased by 1% and 10%, respectively[10]; however, no clear information exists regarding the effect on mortality from liver cirrhosis.

The Global Burden of Disease (GBD) project estimated that there were 1,256,900 deaths in 2016 due to cirrhosis and chronic liver disease. Among those, 334,900 (27%) were attributable to alcohol[12]. In addition, there were 245,000 deaths caused by HCC associated with alcohol, representing 30% of all HCC deaths[13]. The data from GBD 2010 have been modelled based on the alcohol-attributable fraction (the contribution alcohol has as a risk factor to disease or death) for different regions; this analysis found that alcohol-attributable liver cirrhosis represented 47.9% of all liver cirrhosis deaths[3]. The prevalence of ALD reflects the levels of consumption in different regions; therefore, there is evidence that alcohol-related harm, in addition to being dose related at an individual level, is also dose related at a population level. Furthermore, changes in consumption are accompanied by changes in the prevalence of ALD[14]. One of the best examples of this is France, where from 1970 to 2018 there has been a reduction of alcohol consumption that is associated with a 3.5-fold reduction in liver-related mortality.

Alcoholic hepatitis is a major cause of mortality and morbidity in Europe and North America[15,16]. Among patients with ALD who have heavy alcohol consumption, those who develop alcoholic hepatitis have the fastest progression of fibrosis[17], which partially explains the increased risk of mortality described in patients with alcoholic hepatitis. There were 56,809 hospital admissions for alcoholic hepatitis in the United States in 2007, with a median length of stay of 6.5 days, which accounted for 0.7% of the total hospital admissions[16] with in-hospital mortality at 6.8%. In Denmark, from 1999 to 2011, the annual incidence rate of alcoholic hepatitis increased from 37 to 46 cases per million individuals for men and from 24 to 34 cases per million individuals for women, although consumption remained stably high[15].

### *Liver transplantation*

The analysis of the number of patients who have undergone or who are awaiting for liver transplantation can highlight the burden of ALD, as this is the only long-term management option for decompensated liver cirrhosis. Transplantation for alcoholic hepatitis is generally not accepted as a suitable treatment everywhere because in many countries patients are required to abstain from alcohol consumption for 6 months before surgery (BOX 1). In the United States, according to the Health Core Integrated Research Database, there were 44,064 patients on the liver transplantation waiting lists between 2006 and 2014. Among these patients, 12,506 (28.4%) were secondary to ALD[18]. Using the United Network for Organ Sharing and Organ Procurement and

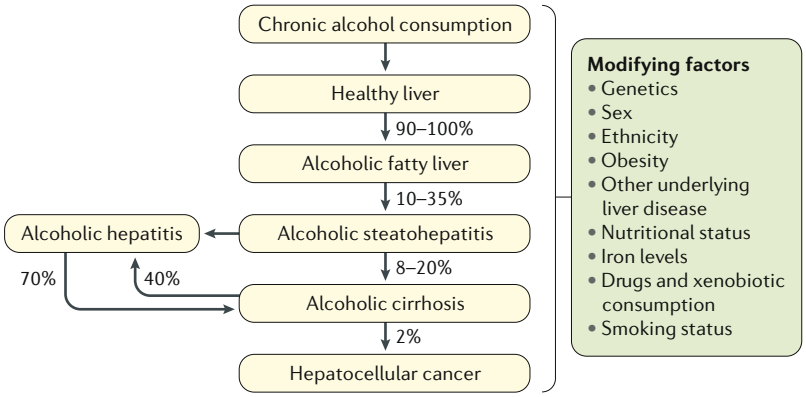


Fig. 1 | **The natural disease course of alcoholic liver disease.** Chronic heavy (>40 g of alcohol per day) alcohol consumption over a sustained period (months or years) will result in 90–100% of individuals developing alcoholic fatty liver. Only 10–35% of individuals with alcoholic fatty liver who continue with chronic heavy alcohol consumption will develop alcoholic steatohepatitis, which is inflammation of the liver characterized by specific histological features. Furthermore, only 8–20% of chronic heavy drinkers will develop alcoholic liver cirrhosis. Of these patients with cirrhosis, ~2% per year develop hepatocellular cancer. Patients with severe alcoholic steatohepatitis may develop the acute clinical entity of alcoholic hepatitis, a disease characterized by jaundice and liver failure. Of the patients who survive alcoholic hepatitis, 70% will develop cirrhosis. By contrast, 40% of patients with alcoholic liver cirrhosis may also develop alcoholic hepatitis (acute-on-chronic disease), with very high mortality rates. The natural course of alcoholic liver disease is modified by various factors (right-hand box). Figure adapted from REF.[46], Springer Nature Limited.

Transplantation 2003–2014 database, the number of liver transplantations secondary to ALD accounted for 17.2% of all liver transplantations in the United States in the year 2014 (REF.[19]). In Europe between 1988 and 2016, according to the European Liver Transplantation Registry, among 71,007 liver transplantations performed for cirrhosis, 24,380 (34.3%) were secondary to alcohol, which was the second indication for liver transplantation in cirrhosis after viral-related disease[20]. These data may substantially underestimate the number of individuals with end-stage ALD because evidence exists that as many as 90–95% of patients with alcohol-related end-stage liver disease are never formally evaluated for liver transplantation[21].

### *Risk factors*

A relationship exists between the amount of alcohol consumed and the risk of developing ALD[22]. The vast majority (90–100%) of chronic heavy drinkers develop AFL. However, only 10–20% of chronic heavy drinkers develop advanced ALD; therefore, additional factors may modify the course of the disease (FIG. 1). Genetics are of major importance, as discussed below. Sex is also a factor, as women are more sensitive towards alcohol and develop ALD at a lower dose and in less time than men[23]. The mechanisms may involve a lower total body water content in women, lower gastric alcohol metabolism in women and alcohol-mediated increases in serum oestrogens[24].

The presence of other underlying liver diseases is also associated with an increased risk of developing ALD. These diseases include hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, hereditary haemochromatosis (characterized by iron overload), α1-antitrypsin deficiency (that is, individuals who are heterozygous) and non-alcoholic steatohepatitis (NASH)[25–30]. The risk to develop HCC in HBV and HCV infection as well as in NASH is substantially elevated by alcohol consumption[31,32]. Overweight and obese individuals are also more prone to the toxic effects of alcohol on the liver[33] (BOX 3). The intake of certain drugs or vitamins (for example, paracetamol (otherwise known as acetaminophen), isoniazid and methotrexate as well as β-carotene or vitamin A) together with alcohol potentiate hepatic injury[34]. Finally, smoking increases the risk of ALD threefold[35].

## Mechanisms/pathophysiology

As mentioned above, various host factors including genetics modify the risk of ALD. Although metabolic alterations are responsible for AFL, epigenetic changes, oxidative stress and inflammation contribute to ALD by affecting primarily hepatocytes but also hepatic stellate cells (HSCs).

### *Genetics*

Evidence suggests that individual susceptibility to develop ALD after chronic alcohol consumption is influenced by genetic factors[36]. In addition, genetic factors may predispose to both AUD and the development of ALD. For example, a number of patients with severe ALD (alcoholic cirrhosis) have a family history of AUD and ALD[37]. Moreover, monozygotic twins have a higher concordance rate for alcohol-related cirrhosis than dizygotic twins[37]. Genes influencing the susceptibility to AUD include modifiers of neurotransmission such as GABA and modifiers of alcohol metabolism[38]. The role of these genes in the progression of ALD is unclear.

Several large studies, including a 2015 genome-wide association study, revealed that patatinlike phospholipase domain-containing protein 3 (*PNPLA3*) and, to a lesser extent, transmembrane 6 superfamily member 2 (*TM6SF2*) and membrane-bound *O*-acyltransferase domain-containing protein 7 (*MBOAT7*) are important genetic determinants of risk and severity of ALD[39–41]. *PNPLA3* is closely involved with lipid metabolism and is a risk factor for non-alcoholic fatty liver disease (NAFLD) and HCC, suggesting that it plays an integral role in maintaining liver health[42]. The mechanisms by which *PNPLA3* influences the development of ALD are unclear. By contrast, mutation in *TM6SF2* can result in hepatic fat accumulation owing to a defect in the secretion of very-low-density lipoproteins, and mutation in *MBOAT7* can cause a disturbance in the acetylation of phosphatidylinositol, but it is not clear whether this results in hepatic fat accumulation.

A group of genes involved in inflammation may influence the development and progression of ALD through different mechanisms involving liver fibrosis, alcoholic hepatitis severity and development of HCC. Small candidate gene studies initially suggested a role for polymorphisms in genes encoding inflammatory mediators (such as tumour necrosis factor (TNF) and IL-1 receptor antagonist), genes involved in the endotoxin response (such as CD14 endotoxin receptor and cytotoxic T lymphocyte antigen 4) and genes involved in oxidative stress (such as glutathione-*S*-transferase and manganese superoxide dismutase)[43]. However, the importance of these genes for the development of ALD

has been questioned owing to the lack of large studies and some studies that show no link to ALD[36].

### *Acetaldehyde and oxidative stress*

Alcohol is oxidized by alcohol dehydrogenase in hepatocytes to acetaldehyde, which is then further metabolized to acetate. In addition, cytochrome P450 2E1 (CYP2E1), which is an enzyme found in both the endoplasmic reticulum (ER) and mitochondria of hepatocytes, metabolizes alcohol to acetaldehyde in the presence of oxygen and NADPH[44]. CYP2E1-mediated alcohol metabolism is an alternative pathway for alcohol oxidation and is induced by chronic alcohol consumption (FIG. 3). Acetaldehyde, which is a product of both metabolic pathways, is extremely toxic and carcinogenic; it binds to proteins, leading to structural and functional alterations (for example, of mitochondria and microtubules), and induces the formation of neoantigens (host antigens that have been altered enough to generate an immune response)[45]. Structural mitochondrial alterations caused by acetaldehyde lead to functional impairment, including decreased ATP generation via the respiratory chain, the production of reactive oxygen species (ROS) and a decrease in acetaldehyde dehydrogenase activity, an enzyme located in mitochondria that is responsible for the metabolism of acetaldehyde to acetate[46].

Box 1 | **Key terms in ALD**

- Alcoholic liver disease (ALD) comprises a spectrum of conditions arising from excessive alcohol intake, from reversible fatty liver to acute alcoholic hepatitis, chronic fibrosis and cirrhosis and hepatocellular cancer (HCC).
- Alcoholic fatty liver is diagnosed when chronic or acute alcohol consumption results in hepatic fat (triglycerides) accounting for >5–10% of the weight of the liver.
- Alcoholic steatohepatitis (ASH) is inflammation of the liver that is characterized by specific histological features (fat, ballooning of hepatocytes and infiltration of neutrophils) caused by chronic alcohol consumption.
- Severe ASH can lead to alcoholic hepatitis, which is a distinct acute clinical entity characterized by abrupt jaundice and clinical decompensation and a high short-term mortality ranging from 20% to 50%. Alcoholic hepatitis can also occur as an acute-on-chronic disease within alcoholic cirrhosis.
- Alcoholic liver fibrosis is the excessive accumulation of extracellular matrix protein including collagen, which is caused by chronic liver inflammation associated with long-term alcohol consumption.
- Alcoholic liver cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic alcohol consumption.
- HCC is a primary tumour of the liver that develops most frequently in a cirrhotic liver.
- The definition of heavy alcohol consumption differs worldwide but generally includes binge drinking (see below) as well as chronic alcohol consumption of >40 g per day.
- According to various public health guidelines, moderate alcohol drinking is up to one drink per day for women and up to two drinks per day for men.
- Binge drinking is defined by the National Institute on Alcohol Abuse and Alcoholism as a pattern of drinking that brings blood alcohol concentration levels to 0.08 g $dl^{-1}$. This level typically occurs after four drinks for women and five drinks for men consumed over a 2-hour period.
- Alcohol use disorder is a chronic relapsing psychiatric disorder characterized by compulsive alcohol consumption, loss of control over alcohol intake and a negative emotional state when not using alcohol (withdrawal syndrome).
- Acute-on-chronic liver failure is a clinical entity encompassing an acute deterioration of liver function in patients with cirrhosis, which results in failure of one or more organs and high short-term mortality.

In addition to the direct toxic effects of acetaldehyde production, alcohol consumption can cause oxidative stress, which is mediated through the generation of ROS. ROS can bind to proteins, changing their functional and structural properties, and generate neoantigens[47]. In addition, ROS bind directly to and damage DNA, or lead to lipid peroxidation, with the generation of lipid peroxidation products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). These lipid peroxidation products then bind to DNA bases and generate highly carcinogenic exocyclic etheno–DNA adducts[48–50] (FIG. 3).

Alcohol-mediated ROS formation is triggered by two mechanisms: CYP2E1 induction by chronic alcohol consumption[48,51,52] or alcohol-induced inflammation (such as alcoholic hepatitis, discussed below)[53]. CYP2E1 has a high rate of NADPH oxidase activity; therefore, CYP2E1 induction can stimulate the transport of reduced NADH into mitochondria, which is associated with increased electron leakage from the hepatocyte mitochondrial respiratory chain and ROS production[54]. In alcohol-induced inflammation, TNF production can facilitate an interaction between *N*-acetyl-sphingosine and mitochondria, which also results in ROS production[55]. In addition, nitrosative stress (the production of reactive nitrogen species) is also increased by alcohol. In rats, alcohol stimulates inducible nitric oxide synthase, which results in the formation of highly reactive peroxynitrite[56].

CYP2E1 is upregulated by chronic heavy alcohol consumption; its activity is even upregulated after 1 week of heavy alcohol consumption (BOX 1) of 40 g of alcohol per day[57]. The induction of CYP2E1 differs between individuals and depends on dietary factors such as the chain length of dietary triglycerides[58]. Moreover, alcohol and iron can act synergistically to produce ROS and oxidative stress and potentiate progressive liver damage. Chronic alcohol consumption increases hepatic iron through an increased absorption from the duodenum mediated by decreased hepcidin concentrations[59].

The importance of CYP2E1-mediated hepatic injury has been convincingly demonstrated in mouse models of ALD[60–62]; the severity of ALD was increased in CYP2E1-overexpressing mice or reduced in CYP2E1-deficient mice. Interestingly, a pharmacological inhibitor of CYP2E1 (chlormethiazole, which is a drug used for alcohol detoxification therapy in Europe) improves ALD and carcinogenesis in experimental animals[63,64]. In patients with ALD, hepatic CYP2E1 expression correlates significantly with the level of etheno–DNA adducts and with the severity of fibrosis[50].

In addition to the generation of oxidative stress, the activity of the antioxidant defence system is low in individuals with chronic heavy alcohol consumption[65], partly owing to an acetaldehyde-mediated decrease of glutathione, which is responsible for the detoxification of ROS. However, the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2; also known as Nfe2l2), which regulates the expression of important cytoprotective enzymes, is upregulated following chronic alcohol exposure as an adaptive response against oxidative stress caused by CYP2E1 induction in an in vitro cellular assay[66].

Box 2 | **Other diseases associated with alcohol abuse**

Alcohol is responsible for 200 different diseases[229]. Patients with alcohol-associated liver injury may also present with other alcohol-associated gastrointestinal diseases such as acute or chronic pancreatitis and various types of cancer (in particular, cancers of the oropharynx, larynx, oesophagus, colorectum and female breast). In addition, central nervous system disorders (for example, cognitive dysfunction), peripheral polyneuropathy, myopathy, immunoglobulin A (IgA) nephritis and alcoholic cardiomyopathy may occur. In patients with cirrhosis, an assessment of cardiac function is often necessary because of the frequent presence of ascites and peripheral oedema, which can also result from heart failure. Patients with cognitive dysfunction should be assessed for the presence of Wernicke encephalopathy, characterized by encephalopathy, oculomotor dysfunction and gait ataxia. Finally, malnutrition is common in the setting of alcohol use disorder and cirrhosis and should be thoroughly assessed in patients with alcoholic liver disease. Furthermore, chronic pancreatitis can exacerbate nutritional deficiencies through exocrine insufficiency and malabsorption and, if present, should be addressed with pancreatic enzyme supplementation.

### *Epigenetics*

Alcohol-induced epigenetic changes in the liver can lead to dysregulated hepatocyte and immune cell functions. Histone modifications can occur via alcohol-induced oxidative stress. Epigenetic changes include acetylation and phosphorylation as well as hypomethylation of DNA and alterations of microRNAs (miRNAs)[67]. Alcohol modulates the acetylation of histone H3 via increased histone acetyltransferase (HAT) activity and histone deacetylase (HDAC) inhibition[68]. Expression of the class III HDAC, NAD-dependent protein deacetylase sirtuin 1 (SIRT1), is reduced in alcohol-exposed hepatocytes; this results in the upregulation of sterol regulatory element-binding protein 1 (SREBP1) and a subsequent decrease in hepatic lipid metabolism leading to fatty liver (discussed below)[69]. DNA hypomethylation in ALD can lead to transcriptional activation, which may alter cellular function. The predominant methyl donor in DNA methylation, *S*-adenosyl-methionine (SAMe), is depleted in alcoholic rat livers, and DNA methylation is decreased by 40% in rats after intragastric alcohol feeding[70]. Alcohol-related epigenetic regulation also alters immune cell functions. In macrophages, alcohol increases the activity of HDAC11, a regulator of IL-10, resulting in decreased production of the anti-inflammatory cytokine IL-10 (REF.[71]).

### *Hepatic steatosis*

An early pathophysiological response to chronic alcohol consumption is the accumulation of fat (mainly triglycerides, phospholipids and cholesterol esters) in hepatocytes (hepatic steatosis), which can lead to AFL. Alcohol and its metabolite acetaldehyde do not directly contribute to fatty acid synthesis, whereas acetate, the metabolite of acetaldehyde (FIG. 3), can be converted to acetyl-CoA, which does contribute to fatty acid synthesis. However, acetate generated from alcohol metabolism in hepatocytes is rapidly secreted into the circulation. Thus, acetate may have a minimal direct contribution to fatty acid synthesis in AFL.

Alcohol consumption can induce fat accumulation in the liver via alterations to fat metabolism by several mechanisms[72]. First, alcohol consumption elevates the ratio of reduced NAD/oxidized NAD ($NADH/NAD^+$) in hepatocytes, which interrupts mitochondrial β-oxidation of fatty acids and results in steatosis[73]. Second, alcohol consumption can upregulate hepatic expression of SREBP1c, a transcription factor that stimulates expression of lipogenic genes[74], which results in increased fatty acid synthesis. Third, alcohol inactivates peroxisome proliferator-activated receptor-α (PPARα), a nuclear hormone receptor that upregulates expression of many genes involved in free fatty acid transport and oxidation[75]. Evidence suggests that alcohol is able to directly alter transcription of *SREBF1* (encoding SREBP1c) and *PPARA* (encoding PPARα) via the metabolite acetaldehyde or indirectly control the expression of these genes via the regulation of multiple factors (for example, bacterial translocation of pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), 2-arachidonoylglycerol, complement activation, ER stress, increases in adenosine, decreases in adiponectin, decreased signal transducer and activator of transcription 3 (STAT3) activation and dysregulated zinc homeostasis) that affect their expression and activation[72] (FIGS 3,4). Fourth, alcohol can inhibit 5′-AMP-activated protein kinase (AMPK) and subsequently inhibit fatty acid synthesis but promote fatty acid oxidation via the dysregulation of acetyl-CoA carboxylase (ACC), carnitine *O*-palmitoyltransferase 1, liver isoform (CPT1) and SREBP[76].

In addition to alteration of fat metabolism, alcohol consumption can affect fatty acid mobilization and clearance. Alcohol consumption induces lipolysis (the breakdown of fats into fatty acids and other products) and adipocyte death, resulting in elevation of circulating fatty acids and their subsequent hepatic accumulation[77–79]. Alcohol consumption can also increase the supply of lipids to the liver from the small intestine[73]. Notably, autophagy has a critical role in clearing lipid droplets in hepatocytes, and chronic alcohol consumption inhibits autophagy, thereby reducing lipid clearance[80]. By contrast, acute alcohol intake may activate autophagy, which may play a compensatory role in preventing the development of AFL during the early stages of alcoholic liver injury[81].

### *Hepatic inflammation*

AFL may progress to inflammation, which is a prerequisite for the development of fibrosis, cirrhosis and HCC. Hepatic inflammation, histologically defined as ASH, is primarily triggered by gut-derived PAMPs with the release of cytokines and chemokines from Kupffer cells and damage-associated molecular patterns (DAMPs) released by dying hepatocytes (BOX 4). In addition, an increase in adaptive immune responses induced by neoantigens (protein adducts with acetaldehyde and ROS) may further contribute to inflammation. ASH can be mild, leading slowly to fibrosis and cirrhosis, or it can be severe, resulting in acute alcoholic hepatitis with poor prognosis.

***Pro-inflammatory cytokines.*** In ALD, PAMPs derived from the gut microbiota (BOX 4) and DAMPs that are released from stressed or damaged cells are recognized by different Toll-like receptors (TLRs) and NOD-like receptors (NLRs) that are expressed on immune cells as

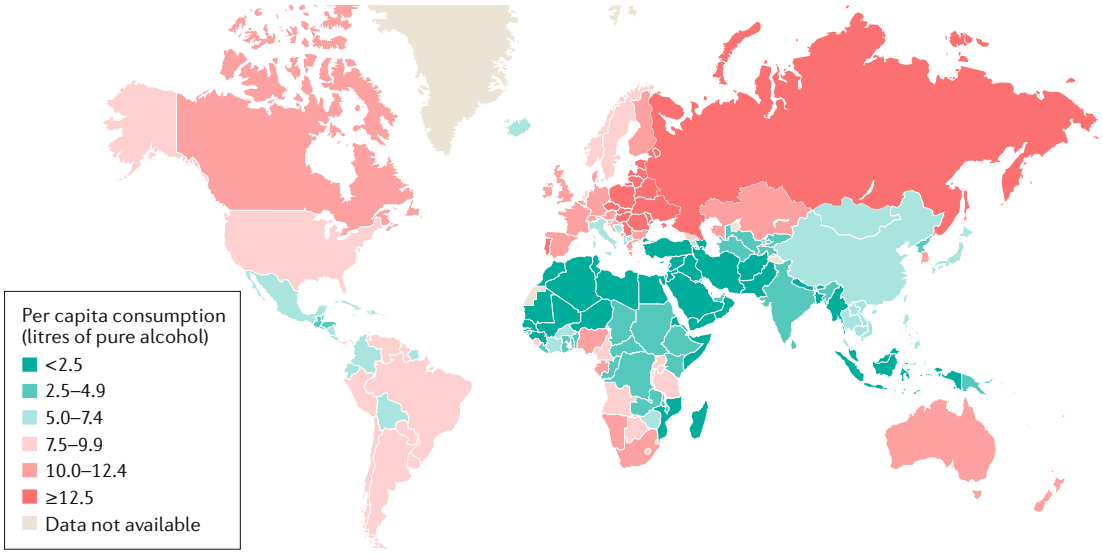


Fig. 2 | **Global total alcohol per capita consumption.** A map showing the total alcohol per capita consumption by region in individuals >15 years of age in 2010. Data from the global WHO report 2014 (REF.[9]).

well as parenchymal cells in the liver[82]. This recognition can lead to alcoholic liver inflammation (FIG. 5).

For example, a gut-derived PAMP, LPS is sensed by TLR4, leading to the activation of nuclear factor-κB (NF-κB) and the production of pro-inflammatory chemokines and cytokines. Of those, CC-chemokine ligand 2 (CCL2) and IL-8 are chemokines that recruit macrophages and neutrophils to the liver, respectively. In addition, TLR4-mediated NF-κB activation induces the production and release of the pro-inflammatory cytokines TNF and IL-6, which are increased both in animal models and in human liver biopsy samples after chronic alcohol consumption. More importantly, both TNF and IL-6 are substantially increased in the circulation of patients with acute alcoholic hepatitis and have been shown in some patients to contribute to disease severity and multiorgan failure.

Another pro-inflammatory cytokine, IL-1β, is also induced via TLR4–NF-κB activation in a pro-IL-1β form; the active form is released only after cleavage by caspase 1 (REF.[83]). This process requires activation of the intracellular multiprotein complex, the inflammasome. In ALD, increased uric acid and ATP levels in the liver can activate the NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome in liver macrophages, which leads to caspase 1 activation and active IL-1β release[84,85]. IL-1β has multiple pathogenetic effects in ALD: first, it amplifies pro-inflammatory cytokine production via autocrine IL-1β and TNF induction; second, IL-1β sensitizes hepatocytes to death signals; third, IL-1β induces hepatic steatosis by upregulating fatty acid synthesis[86]; and, fourth, IL-1β promotes liver fibrosis (see below). Interestingly, inhibiting IL-1 signalling with a recombinant IL-1 receptor antagonist (anakinra) attenuated ALD and promoted liver regeneration in mice[87]. Finally, studies showed that pro-inflammatory cytokine induction and hepatocyte steatosis are mediated via activation of the spleen tyrosine kinase (SYK) in inflammatory liver mononuclear cells and hepatocytes after chronic alcohol feeding in mice. Moreover, activated SYK kinases are found in liver biopsy samples from patients with ALD[88].

***MicroRNAs.*** miRNAs are small non-coding RNAs that have an intracellular role in the post-transcriptional regulation of their target genes[67]. In addition, miRNAs are also found in the circulation. Interestingly, the expression of specific miRNAs is increased whereas others are decreased in ALD[67,89]. For example, miRNA-155, a key regulator of inflammation, is increased in the liver and circulation in a mouse model of ALD and in patients with alcoholic hepatitis. Chronic alcohol consumption increases the expression of miRNA-155 in Kupffer cells (specialized liver macrophages) via NF-κB-mediated transcriptional regulation; increased miR-155 contributes to increased LPS-triggered TNF production, thereby augmenting the activation of the alcohol-induced inflammatory cascade in the liver[90]. A mouse model deficient in miR-155 showed attenuated intestinal inflammation, a lack of serum increases in LPS (a marker of bacterial translocation), decreased pro-inflammatory cytokines and attenuated liver damage and fibrosis after chronic alcohol administration[91]. Alcohol-related LPS hyper-responsiveness in macrophages was associated with miR-155-mediated decreases in the expression of negative regulators of TLR signalling, such as IL-1 receptor-associated kinase M (IRAKM; also known as IRAK3), SH2 domain-containing inositol 5′-phosphatase 1 (SHIP1; also known as INPP5D) and transcription factor PU.1 (REF.[92]).

In hepatocytes, miR-122 is an abundant miRNA that regulates lipid metabolism[67]. Chronic alcohol consumption increases the serum levels of miR-122 in humans and in mice; however, chronic alcohol consumption has a direct inhibitory effect on the transcriptional regulation of miR-122 (REF.[93]). Evidence suggests that hepatocyte-specific inhibition of miR-122 is associated with features of ALD in mice, and a combination of alcohol feeding

and miR-122 inhibition accelerates alcohol-induced liver injury, steatosis, inflammation and fibrosis[94]. Restoration of miR-122 levels in alcoholic livers via a gene therapy approach ameliorated alcohol-induced liver injury in the mice[94]. Importantly, chronic heavy alcohol consumption can impair liver regeneration. In rodents, alcohol attenuates the regeneration of hepatocytes following partial hepatectomy[95]. This deleterious effect of alcohol is related to miRNA reprogramming[96], although the role of alcohol on liver regeneration in patients is unclear.

***Inhibition of the ubiquitin–proteasome pathway.*** Another mechanism by which alcohol may contribute to ASH is by inhibiting the ubiquitin–proteasome pathway. The ubiquitin–proteasome pathway regulates protein digestion within the cell. Many liver cell functions are regulated by this pathway, including cell cycle checkpoints and activation of transcription factors (for example, NF-κB and hypoxia-inducible factor 1α (HIF1α))[97]. The loss of proteasomes or the inhibition of this pathway may lead to cellular injury, proliferation, apoptosis and hepatic inclusion of aggregated cytokeratins. Hepatic gene expression, which depends on transcription factor activation by proteasomes, can inhibit the hepatic inflammatory response and the response to hypoxic injury. Alcohol can stabilize proteins that are normally degraded by proteasomes, meaning that pro-inflammatory proteins such as NF-κB, HIF1α and CYP2E1 can increase in abundance when exposed to alcohol, and their toxicity becomes increased[97].

***Apoptosis and cell regeneration.*** Alcohol induces both cell death and an adaptive cell survival response in the liver, and the balance between the two processes determines the rate of disease progression and the onset of liver failure. Alcohol induces apoptosis of hepatocytes; the mechanisms of alcohol-induced hepatocyte apoptosis include activation of the mitochondrial (intrinsic) apoptotic pathway, caspase-dependent and caspase-independent apoptotic pathways and ER stress[98]. For example, in ALD, alcohol-related intracellular activation of interferon regulatory factor 3 (IRF3) induces hepatocyte apoptosis[99]. Alcohol-induced ER stress causes the stimulator of interferon genes protein (STING) to trigger TANK-binding kinase (TBK)-mediated phosphorylation of IRF3, which interacts with the mitochondrial apoptotic machinery in hepatocytes[100]. Although the role of apoptosis in early phases of ALD is uncertain, severe hepatocyte cell death due to apoptosis is a prominent feature of alcoholic hepatitis[101].

### *Progression*

A subset of patients with ALF will progress to develop ASH and then fibrosis if they continue to consume alcohol heavily (BOX 1). Although the exact driving forces for this progression are not well known, modifying factors stimulating specific pathogenesis as described above are of major importance. The link between NASH, obesity and ALD is described in BOX 3.

***Fibrosis and cirrhosis.*** Fibrogenesis is the prerequisite for the development of liver cirrhosis. Liver fibrosis is a wound-healing response to chronic liver damage, including hepatic inflammation induced by chronic alcohol exposure. In the later stages, ALD is characterized by a marked fibrotic response and the development of advanced fibrosis, which is associated with early mortality[102]. Extracellular matrix production by activated HSCs is the key event in hepatic fibrogenesis (FIG. 6). In addition, to a lesser extent, other cells such as portal fibroblasts as well as bone-marrow-derived myofibroblasts are involved in hepatic fibrogenesis[103]. The pattern of fibrosis in ALD is characterized by pericellular and perisinusoidal (terminal small blood vessels with fenestrated discontinuous epithelium in the liver) matrix accumulation with a 'chicken-wire' appearance.

Persistent alcohol intake activates Kupffer cells through gut-derived endotoxins and promotes hepatic inflammation that further activates neighbouring Kupffer cells that in turn activate HSCs[104–107]. Moreover, alcohol, acetaldehyde and ROS (FIG. 3) can promote liver fibrogenesis by directly activating HSCs and by stimulating immune cells to produce pro-fibrogenic mediators. In addition, alcohol-mediated inhibition of several anti-fibrotic pathways may further contribute to hepatic fibrosis. Importantly, natural killer (NK) cells can kill activated HSCs or produce IFNγ that induces HSC death and cell cycle arrest[108], both mechanisms that inhibit hepatic fibrogenesis[108,109]. However, alcohol can inhibit this process. If the process of fibrogenesis

Box 3 | **ALD, obesity and NAFLD**

Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) share similarities in hepatic morphology and pathogenesis, and both diseases include fatty liver as a prerequisite. The histological features of alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH) appear similar, which suggests similar pathogenetic mechanisms in the generation of hepatic inflammation. However, the mechanisms for non-alcoholic and alcoholic fatty liver (AFL) are somehow different. As alcohol consumption and an excess of dietary caloric intake may occur together, the effect of chronic alcohol consumption on patients with obesity and patients with NAFLD is of special interest. Various epidemiological studies report that >40 g of alcohol per day and even moderate (20–40 g of alcohol per day) alcohol consumption can increase hepatic steatosis, inflammation, fibrosis and cirrhosis in patients who are overweight or obese[5,33,230–234]. Unquestionably, obesity is a risk factor for ALD.

By contrast, epidemiological studies from Japan and Europe suggest that moderate alcohol consumption improves hepatic steatosis compared with no alcohol consumption owing to an improvement of peripheral insulin[29] resistance. Furthermore, various cross-sectional studies on NAFLD report a beneficial effect of alcohol consumption (>40 g per day) on hepatic fat[30]. In addition, some studies examining the effect of alcohol on histopathologically diagnosed NAFLD had controversial findings. Although in some studies moderate alcohol intake in patients with NAFLD resulted in an accelerated progression of fibrosis[233] and in an elevation of serum transaminase activities[234], other studies (some in morbidly obese patients) did not confirm this finding[30]. However, these studies are small, and most of them do not account for various confounding factors. Thus, on the basis of currently available data, it may be difficult to determine the role of moderate alcohol consumption on NAFLD progression. Moreover, results may also vary depending on whether alcohol is consumed in patients with pure fatty liver or in patients with NASH.

By contrast, the data on alcohol and the development of hepatocellular carcinoma (HCC) in patients who are overweight or obese, and in patients with NAFLD, are more clear. Almost all retrospective studies report an increased risk with alcohol consumption at any level for the development of HCC in patients with NASH[29,30,32,235].

In conclusion, in clinical practice, it seems wise to recommend that at least patients with NASH should refrain from any amount of alcohol consumption[29,236].

continues, hepatic architecture will be severely affected. When fibrosis becomes advanced, the liver becomes cirrhotic and consists predominantly of fibrotic tissue, which leads to a major disturbance of hepatic blood flow by a narrowing of vascular structures within the hepatic lobule, including the sinusoids. As a result, portal hypertension may occur with other complications, including ascites and oesophageal varices. In addition, the function of the liver decreases owing to the loss of hepatocytes.

***HCC.*** Alcoholic beverages are group 1 carcinogens (known to be carcinogenic to humans) per classification by the International Agency for Research on Cancer[110] (BOX 2). Alcohol is a procarcinogen that requires its bioconversion to a primary carcinogenic metabolite, acetaldehyde. Individuals with the *ALDH2*2* (which encodes aldehyde dehydrogenase) loss-of-function mutation have an increased risk of oesophageal cancer, which serves to convincingly link acetaldehyde to cancer[111,112]. Acetaldehyde is electrophilic and, as mentioned previously, forms an adduct with DNA and interstrand crosslinks[113,114]. DNA mutations can result if DNA repair is insufficient, particularly for homologous recombination repair[114]. Acetaldehyde also inhibits the activity of the DNA repair enzyme $O^6$-methylguanine DNA methyltransferase[115], causing both genotoxicity and DNA repair failure.

As mentioned above, ROS generated by alcohol-associated CYP2E1 induction generates aldehydic lipid metabolites such as 4-HNE and MDA. The presence of MDA increases acetaldehyde adduct formation by ~10–30-fold, synergizing the formation of a highly reactive, hybrid MDA–acetaldehyde adduct[116]. These aldehydes modify proteins (generating neoantigens) and DNA (causing mutations) while depleting reduced glutathione, amplifying oxidant stress and cytotoxicity. Induced CYP2E1 also converts other procarcinogens to active carcinogens, including nitrosamines[117] (FIGS 3,7).

Epigenetic changes induced by chronic heavy alcohol consumption can lead to chromosomal instability[118]. Hypomethylation of promoters for oncogenes (for example, *SERPINB5* and *IGF2*) causes their aberrant activation and loss of imprinting (loss of the normal expression pattern), whereas hypermethylation of promoters of genes involved in cellular differentiation or DNA repair (for example, *MLH1* and *MGMT*) promotes transformation.

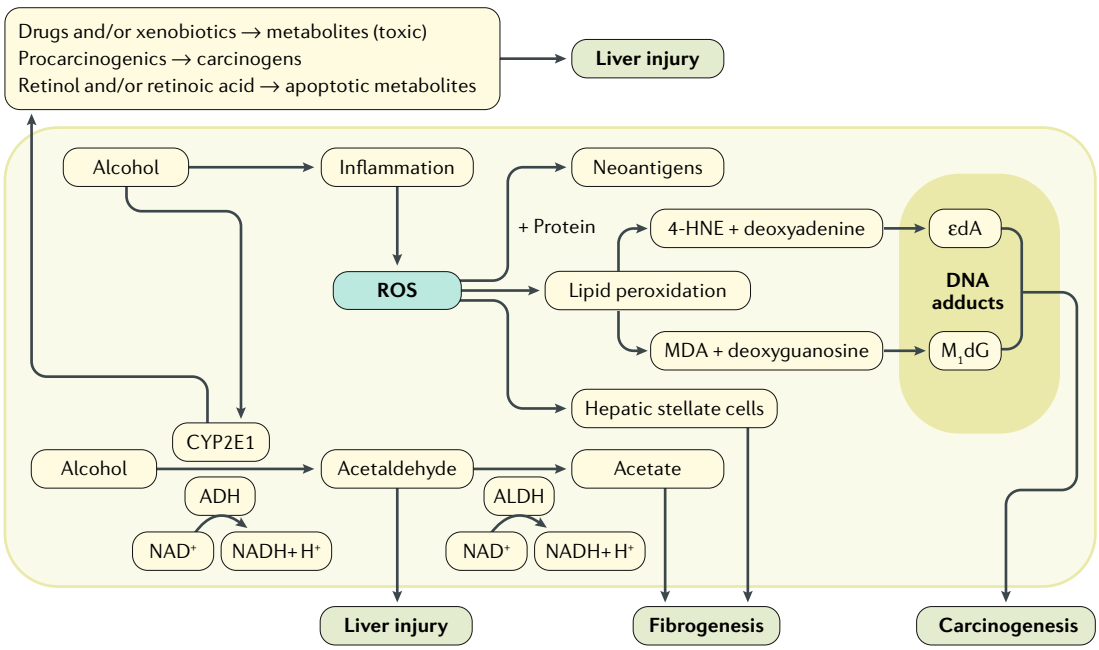


Fig. 3 | **Metabolic pathways related to alcohol.** In hepatocytes, alcohol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH), and acetaldehyde is further metabolized to acetate by acetaldehyde dehydrogenase (ALDH). Acetaldehyde is both toxic and carcinogenic. In addition, chronic alcohol consumption results in the induction of cytochrome P450 2E1 (CYP2E1), which also metabolizes alcohol to acetaldehyde. Reactive oxygen species (ROS) are produced as a by-product of CYP2E1 activity. ROS are also generated through inflammation; for example, ROS are generated in alcoholic hepatitis. CYP2E1 also metabolizes some drugs (such as paracetamol or isoniazid) to toxic metabolites, activates procarcinogens to form carcinogens (such as nitrosamines) and degrades retinol and retinoic acid to apoptotic polar intermediates, which can induce hepatic cell death. All these pathways may further contribute to liver injury. In addition, ROS may bind to proteins and generate neoantigens, which are modified host proteins that induce a host immune response. ROS can also lead to lipid peroxidation with the generation of lipid peroxidation products such as 4-hydroxynonenal (4-HNE) or malondialdehyde (MDA). Both compounds can bind to DNA bases with the formation of carcinogenic exocyclic etheno–DNA adducts. ROS can also stimulate hepatic stellate cells, which results in fibrogenesis. Thus, alcohol-generated ROS are responsible for a cascade of negative events that can contribute to the development of alcoholic liver disease. εdA, 1,$N^6$-etheno-2′-deoxyadenosine; $M_1$dG, 3-(2-deoxy-β-D-erythro-pentofuranosyl)pyrimido(1,2-α)purin-10(3H)-one.

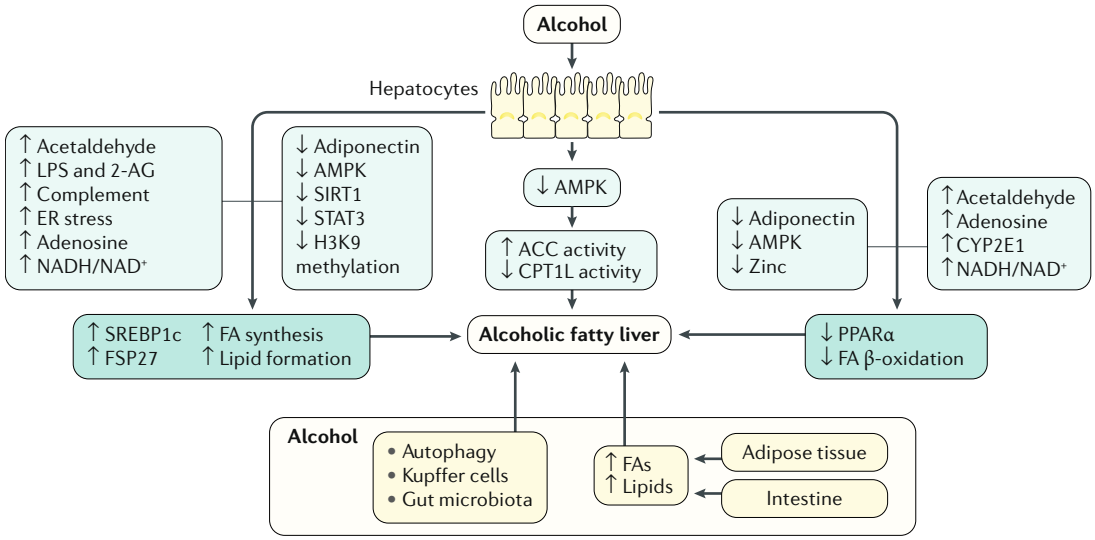


Fig. 4 | **Mechanisms involved in alcoholic fatty liver.** Mechanisms involved in the formation of alcoholic fatty liver. First, alcohol increases fatty acid (FA) synthesis via the upregulation of sterol regulatory element-binding protein 1c (SREBP1c) and downstream lipogenic genes. For example, alcohol activates SREBP1c by increasing acetaldehyde, lipopolysaccharide (LPS), 2-arachidonoylglycerol (2-AG), complement, endoplasmic reticulum (ER) stress, adenosine and NADH/NAD$^+$ or via the inhibition of adiponectin, 5′-AMP-activated protein kinase (AMPK), NAD-dependent protein deacetylase sirtuin 1 (SIRT1), signal transducer and activator of transcription 3 (STAT3) and H3K9 (trimethylation of lysine 9 of histone 3) methylation. Second, alcohol inhibits FA β-oxidation via the inactivation of peroxisome proliferator-activated receptor-α (PPARα) and downstream β-oxidation genes via the modulation of several factors. For example, alcohol suppresses PPARα via the elevation of acetaldehyde, adenosine, cytochrome P450 2E1 (CYP2E1) and NADH/NAD$^+$ or via the inhibition of adiponectin, AMPK and zinc levels. Third, alcohol inhibits AMPK and subsequently elevates acetyl-CoA carboxylase (ACC) activity but inhibits carnitine *O*-palmitoyltransferase 1, liver isoform (CPT1) activity. Fourth, alcohol promotes mobilization of FA and lipids from adipose tissue and intestine to the liver. Lastly, alcohol can also alter autophagy, Kupffer cells and gut microbiota, thereby regulating hepatic steatosis. For example, alcohol consumption activates Kupffer cells to release pro-inflammatory cytokines (for example, tumour necrosis factor) that promote fat accumulation in the liver. Alcohol consumption also induces gut bacterial overgrowth and dysbiosis, which cause elevation of pathogen-associated molecular patterns that promote inflammation and Kupffer cell activation, thereby inducing steatosis. FSP27, fat-specific protein FSP27 homologue (also known as CIDEC).

Alcohol-induced hepatic inflammation and the oxidative stress associated with such inflammation causes hepatocellular DNA damage and contributes to tumour initiation[119]. Tumour-associated M2-polarized macrophages support tumour promotion, in part by activating HSCs. Ectopic expression of TLR4 in hepatocytes and its activation by LPS induces HCC[120] via generation of TLR4 and homeobox protein Nanog-dependent liver tumour-initiating stem-cell-like cells (TICs)[121]. In addition to promoting fibrosis, activated HSCs also promote HCC formation via production of matrix or soluble factors that support tumour cell survival and growth[122]. Activated HSCs also promote TIC-mediated liver tumorigenesis and liver tumour formation induced by a hepatotoxin, diethylnitrosamine, and promoted by alcohol[123]. The two major drivers of alcohol-associated tumour initiation, CYP2E1 in hepatocytes[49,124] (FIG. 3), and LPS from gut dysbiosis[125] (BOX 4), also activate HSCs and promote tumour development (FIG. 5). The role of the senescence-associated secretory phenotype of HSCs may be important in HCC promotion, as shown in obesity-associated HCC[126].

Alcohol-promoted hepatocarcinogenesis is associated with activation of the canonical WNT–β-catenin pathway[127], which may allow β-catenin-dependent tumour growth and stimulate *CYP2E1* transcription[128]. Finally, alcohol consumption promotes HCC development via immunosuppression, with decreased numbers of antitumour CD8$^+$ cells[129], and by loss of miR-122, which upregulates HIF1α, a tumour-promoting transcription factor[130]. In summary, chronic heavy alcohol consumption supports both tumour initiation and promotion by the generation of carcinogenic aldehydes, ROS, DAMPs and PAMPs that also cause inflammation, the genesis of TICs, activation of HSCs and immunosuppression[45] (FIG. 7).

## Diagnosis, screening and prevention

### *Clinical diagnosis*

Before patients with ALD undergo laboratory or sonographical evaluation, a clinical diagnosis is needed, which includes the search for signs of AUD. A major problem exists in the clinical diagnosis of ALD, which is that patients often appear asymptomatic until they develop serious and advanced disease. AUDs, which put individuals at high risk of developing ALD, are highly prevalent but poorly identified[131]; heavy alcohol consumption is difficult to detect, but it is important to identify in patients with suspected ALD as it can substantially worsen the course of disease. Patients

Box 4 | **The effect of alcohol consumption on the microbiota**

Acute as well as chronic alcohol consumption injures the mucosa of the small intestine, which can result in maldigestion and malabsorption of nutrients, vitamin and trace element deficiencies and weight loss. The toxic effect of alcohol consumption has been observed in the colon of experimental animals[237] and in patients with alcohol use disorder[238] and is induced primarily by the metabolic product of alcohol — acetaldehyde[237,239]. The concentration of pure alcohol in the colon after drinking correlates with blood alcohol concentration. Furthermore, various colonic bacteria are capable of metabolizing alcohol to produce high acetaldehyde concentrations, which lead to cellular damage of colonic mucosa cells. Chronic alcohol consumption can induce dysbiosis of the microbiota by increasing the total intestinal bacterial load[240] and by changing the composition and the prevalence of specific taxa in the microbiota. In addition, alcohol consumption can affect intestinal motility, pH of the gut lumen and bile flow, all factors that affect intestinal flora and vice versa[240].

Colonic acetaldehyde that is generated by the microbiota can damage tight junction and adherens junction proteins that maintain the epithelial barrier. Furthermore, acetaldehyde is associated with further intestinal barrier dysfunction caused by oxidative stress-mediated phosphorylation of the epithelial-to-mesenchymal transition protein snail homologue 1 (also known as zinc-finger protein SNAI1)[241]. Acetaldehyde is toxic and leads to cellular damage and inflammation. Consequently, individuals who have chronic heavy levels of alcohol consumption may develop a 'leaky' gut, resulting in the translocation of endotoxins (bacterial products and lipopolysaccharide) into the portal vein and to the liver[240,242]. This translocation is a major mechanism that triggers hepatic inflammation in alcoholic liver disease. Indeed, it has been shown that modification of the intestinal microbiota by antibiotics or an inhibition of endotoxin binding to Kupffer cells reduces alcoholic liver disease in animal experiments[243,244]. Furthermore, a reduction of endotoxins in the blood translocalized from the gut (by blocking with antibodies) may have a beneficial effect in humans[245].

with early ALD, such as AFL, or low to moderate ASH (BOX 1) may not show any clinical symptoms, and ALD may be detected during a routine follow-up. Patients with advanced ALD may present with signs of cirrhosis with hepatic decompensation. In addition, patients with both AUD and ALD may present to clinicians with the clinical signs of AUD (BOX 5). Patients with alcoholic hepatitis present with jaundice, fever, elevated leukocytes and signs of liver decompensation such as ascites and hepatic encephalopathy. In contrast to cirrhotics, they are typically younger and have a heavy but shorter drinking history.

One important issue in clinical diagnosis is that as patients with AUD are generally treated by psychiatrists, hepatic evaluation is often not performed and vice versa. The sensitivity and specificity of biological markers of alcohol use are low and do not allow them to be used as screening or diagnostic tools[132], although they may be useful in the management of ALD. The diagnosis of AUD is based on the presence of 2 or more of 11 diagnostic criteria in the past 12 months (BOX 5). Depending on the number of criteria met, the disorder may be classified as mild, moderate or severe[133]. Part of the diagnosis of AUD should be the assessment of alcohol-related comorbidity. Patients with AUD very often experience hepatic and neurological problems, accidents, injuries and comorbid psychiatric conditions such as anxiety and depression.

***Alcoholic fatty liver.*** Patients with AUD and individuals who declare that they consume >40 g pure alcohol per day should be screened for fatty liver, particularly individuals who are overweight (BOX 3). AFL is present in 90–100% of individuals who have chronic heavy alcohol consumption (FIG. 1), and the prevalence of AFL is strongly modulated by the presence of obesity (BOX 3). Simple abdominal ultrasonography using bright echo pattern can be used to screen for AFL, but it has only moderate sensitivity and specificity[134]. By contrast, ultrasonography techniques based on attenuation of shear waves such as controlled attenuation parameter (CAP) run on commercially available platforms and are more accurate for the quantification of AFL in patients with ALD. CAP diagnosed severe steatosis with good accuracy (area under the curve (AUC) score = 0.82; CI = 0.75–0.88) and was superior to bright liver echo pattern by regular ultrasonography[135]. Moreover, in patients who are not obese, CAP could be used to monitor the rapid decrease of steatosis occurring during alcohol withdrawal[135]. CAP has a good diagnostic accuracy for diagnosing severe AFL and can be used to detect steatosis of any degree. Another technique that can be used to detect AFL is MRI, which has an excellent accuracy for detecting liver fat and is superior to CAP and ultrasonography; however, appropriate software platforms are not available in all centres and it is too expensive for population-level screening[136,137]. Differential diagnosis of AFL is NAFLD (BOX 3), which cannot be discriminated by the techniques described above.

***Inflammation.*** Inflammation is a key mechanism in the pathophysiology of ASH, fibrosis, cirrhosis and HCC; therefore, an accurate diagnosis of liver inflammation is important when ALD is suspected. Characteristic laboratory findings may help to identify ALD[138]. Most frequently, an elevation of serum γ-glutamyltransferase (GGT; a biomarker from bile ducts but also other tissues) activity is observed with values up to 3,000 U per litre. If GGT activity is elevated without elevation of serum transaminase (biomarker of liver cellular integrity) activities, the combined sensitivity and specificity for alcohol-associated hepatic inflammation is >70%[139]. However, elevated serum GGT activity can also be found in other situations, such as cholestatic liver disease, cardiac insufficiency, drug-induced liver injury and many more, which reduces the specificity of this test for advanced stages of ALD[46,140]. Furthermore, in almost all stages of ALD, the ratio of the serum activities of aspartate transaminase (AST; a marker of liver damage but also of damage to other tissues) to alanine aminotransferase (ALT; a more specific marker of liver injury) is typically >1, and in 70% of patients with ALD it is >2 (REF.[141]). Serum AST activities >300 U per litre are rarely observed in all patients with ALD, and in patients with cirrhosis serum transaminase activities may normalize whereas serum AST activity may continuously increase even in the absence of alcohol intake[142]. Novel markers such as caspase-cleaved cytokeratin 18 (CK18; also known as KRT18) fragments M30 and M65 are more sensitive than transaminases and more specifically detect apoptotic death of hepatocytes[143]. Notably, and in contrast to M65 and AST levels, M30 levels significantly increase during alcohol withdrawal, which highlights the specific role of apoptosis in ALD[143]. Accordingly, alcohol seems to block hepatocyte apoptosis as

measured by M30 levels, and this process is unchained during alcohol withdrawal.

***Alcoholic hepatitis.*** Patients with heavy chronic alcohol consumption and severe ASH or advanced fibrosis and/or cirrhosis may present with sudden jaundice, fever, abdominal pain, anorexia, weight loss and signs of hepatic failure and portal hypertension. This clinical syndrome, which is caused by severe ASH with or without cirrhosis (BOX 1), is called alcoholic hepatitis and has a poor prognosis of 20–50% mortality within 3 months[144]. Alcoholic hepatitis can occur as the first manifestation of clinically silent ALD, or in acute-on-chronic disease it occurs as an exacerbation of pre-existing cirrhosis. Alcoholic hepatitis must be distinguished from early ASH (BOX 1) in fully compensated patients. Differential diagnosis may include severe sepsis, biliary obstruction, diffuse HCC, drug-induced liver injury and ischaemic hepatitis (that is, due to massive bleeding or cocaine use)[145]. Thus, not all episodes of jaundice in patients with underlying ALD should be attributed to alcoholic hepatitis. Transjugular liver biopsy is recommended to confirm alcoholic hepatitis and to rule out other causes of jaundice as suggested in a recent expert conference organized by the National Institute on Alcohol Abuse and Alcoholism (NIAAA)[146].

***Fibrosis and cirrhosis.*** Liver fibrosis is graded in five histological stages, with F0 representing no fibrosis and F4 representing the most severe stage with cirrhosis. The measurement of liver stiffness by non-invasive elastographic techniques such as transient elastography has drastically improved the diagnosis of all fibrosis stages ranging from F0 to F4. One such technique, fibroscan, has been approved clinically worldwide. Other competing bedside technologies are continuously being developed (for example, acoustic radiation force impulse imaging elastography and shear wave elastography). In addition, magnetic resonance elastography is a promising tool for the 3D assessment of liver stiffness but is currently available only in a few centres.

Liver stiffness values highly correlate with histological fibrosis stage (namely, advanced alcoholic fibrosis (F3) and cirrhosis (F4)) in ALD. A liver stiffness scale with cut-off values for the various fibrosis stages in ALD is shown in FIG. 8. Liver stiffness values <6 kPa are generally considered as normal and exclude even mild fibrosis (histological fibrosis stages F1–F2) (FIG. 8). Although severe hepatic fat deposition may affect liver stiffness, steatosis rarely has an impact on fibrosis stage determined by liver stiffness. Owing to the rather small inconclusive 'grey range' from 6 to 8 kPa and potential interferences (positioning, breathing or eating), an exact

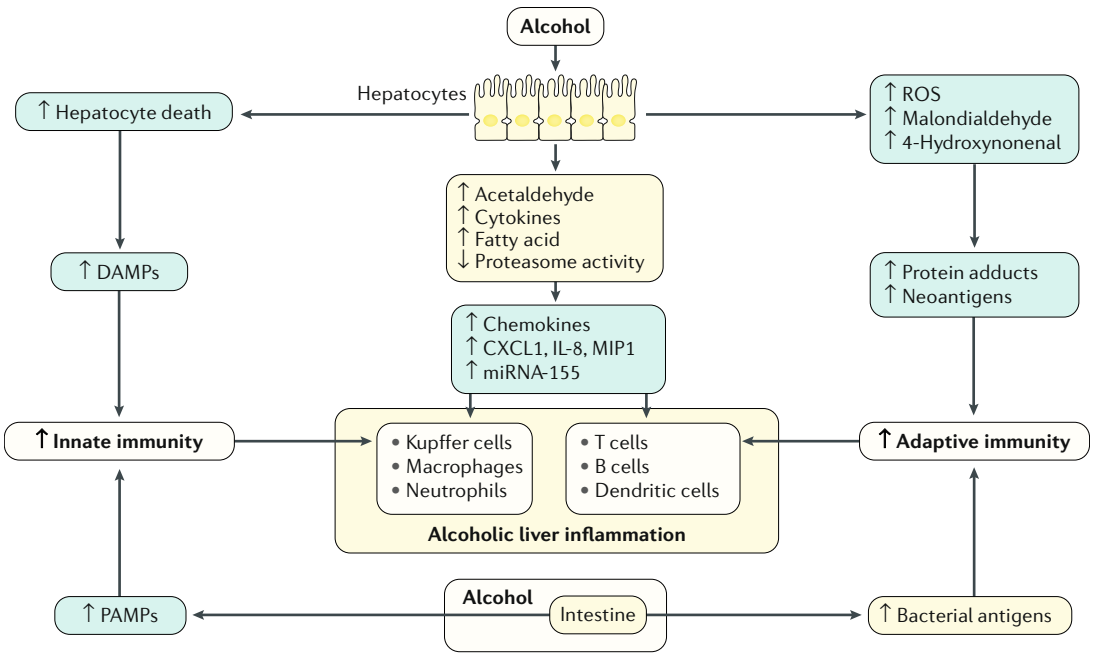


Fig. 5 | **Mechanisms involved in alcoholic liver inflammation.** Multiple mechanisms are involved in the development of alcoholic liver inflammation. Alcohol consumption causes hepatocyte death, followed by a release of damage-associated molecular patterns (DAMPs; for example, mitochondrial DNA and high-mobility group box 1 protein). Alcohol intake also increases gut bacterial overgrowth and dysbiosis, resulting in elevation of pathogen-associated molecular patterns (PAMPs; for example, lipopolysaccharide (LPS) and bacterial DNA). DAMPs and PAMPs strongly activate innate immunity (for example, inducing the production of inflammatory cytokines, activation of Kupffer cells, macrophages and neutrophils). Alcohol consumption can also activate adaptive immunity by reactive oxygen species (ROS) mediating the generation of protein adducts and neoantigens and by increasing translocation of bacterial antigens. Finally, alcohol consumption promotes hepatocytes to produce a variety of chemokines that induce hepatic infiltration of inflammatory cells. Alcohol increases the expression of microRNA (miRNA)-155 in Kupffer cells via nuclear factor-κB-mediated transcriptional regulation, which stimulates LPS-triggered tumour necrosis factor production from Kupffer cells, thereby contributing to inflammation. CXCL1, CXC-chemokine ligand 1; MIP1, macrophage inflammatory protein 1.

discrimination between early stages of fibrosis (F1 and F2) is not recommended for clinical diagnosis. Finally, liver stiffness values highly correlate with complications of liver disease (for example, portal hypertension and oesophageal varices) and HCC and are likely to be >20 kPa. Additional stiffness measurements of the spleen may improve the detection of portal hypertension.

Liver stiffness is affected not only by fibrosis stage but also by inflammation, hepatic perfusion and hepatocyte ballooning, which are all negative predictors of disease progression. Liver stiffness should be interpreted in the context of imaging, laboratory and clinical findings as the above-mentioned conditions may be present in patients with ALD. For more accurate fibrosis assessment, two algorithms can be used: either patients withdraw from alcohol for 1–2 weeks and liver stiffness is re-determined after the normalization of transaminase activities (FIG. 8a) or inflammation-adapted cut-off values are used as shown in FIG. 8b[142].

With regard to fibrosis assessment in ALD, serum markers are inferior to liver stiffness measurement; however, they remain an option when elastography is not accessible or cannot be performed[138]. TABLE 1 shows important serum fibrosis markers and their outcome in ALD studies[147–155]. Generally, serum markers can well differentiate between mild fibrosis and advanced fibrosis stages. In addition, no specific equipment is needed to perform these tests; therefore, they are useful in resource-limited settings. Fibrotest (a score calculated from the results of a six-parameter blood rest combined with patient age and sex) has been evaluated in ALD and has fairly good diagnostic accuracy (AUC = 0.8)[156]. The enhanced liver fibrosis (ELF) test (serum levels of hyaluronic acid, procollagen III peptide and tissue inhibitor of metalloproteinases 1 (TIMP1)) or levels of CK18 (M30) have also been recommended as fibrosis markers (TABLE 2). However, hyaluronic acid (a component of extracellular matrix) seems to perform best in comparative studies with histology[148,153].

It is possible to diagnose alcoholic cirrhosis before the onset of symptoms through transient elastography and the combination of serum biochemistry tests (for example, elevated bilirubin, which is a marker of jaundice, and international normalized ratio (INR), which is a measure for blood coagulation, low serum albumin and low platelet count) and serum fibrosis markers (TABLE 1). However, most patients with alcoholic cirrhosis are diagnosed when they develop clinical decompensation such as jaundice or ascites, often in the setting of a superimposed acute alcoholic hepatitis. Patients with cirrhosis may present with spider angiomas (small arteriovenous shunts on the skin of 1–10 mm in diameter, mostly occurring on the head, neck and upper thorax), palmar erythema (a red palm of the hand) and gynaecomastia (enlargement of the breasts in men). In addition, sarcopenia (muscle wasting) and malnutrition may occur. The clinical consequences of cirrhosis may depend on the pattern of ongoing alcohol consumption. For instance, heavy alcohol consumption can result in acute alcoholic hepatitis, which may precipitate clinical decompensation in the setting of stable compensated cirrhosis. By contrast, patients with decompensated cirrhosis may have improvements in liver function and portal hypertension with prolonged abstinence. AUD is associated with several extrahepatic diseases that should be investigated in the setting of alcoholic cirrhosis[157] (BOX 2).

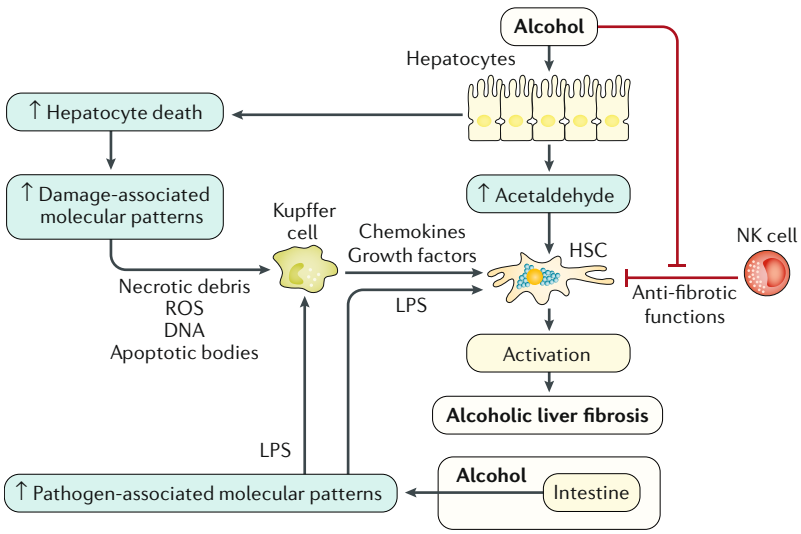


Fig. 6 | **Mechanisms involved in alcoholic liver fibrosis.** Multiple mechanisms are involved in the development of alcoholic liver fibrosis. Alcohol-induced hepatic inflammation activates Kupffer cells, which produce a large number of cytokines and growth factors that promote hepatic stellate cell (HSC) activation and liver fibrosis. In addition, acetaldehyde, the first alcohol metabolite, can directly induce HSC activation. Last, natural killer (NK) cells play an important role in suppressing liver fibrosis by directly killing activated HSCs and producing IFNγ. Chronic heavy alcohol consumption abolishes the anti-fibrotic functions of NK cells. LPS, lipopolysaccharide; ROS, reactive oxygen species.

***HCC.*** Cirrhosis of any aetiology including alcohol is a strong risk factor for the development of HCC. The reported 5-year incidence of HCC in patients with alcoholic cirrhosis ranges from 1% to 16%[158]. Because the incidence in many reports is >1.5% per year (which has been identified as the threshold for surveillance cost-effectiveness), ultrasonography surveillance for HCC at 6-month intervals of patients with alcoholic cirrhosis is recommended in clinical practice guidelines[159].

### *Confirmation of the diagnosis*

The use of liver biopsy for the diagnosis of ALD remains a debated issue. Liver biopsy is not without complications such as hepatic bleeding, with a potential morbidity rate of approximately 2%; therefore, this risk must be weighed against the benefit of information gained that may guide treatment decisions (risk–benefit relationship)[160]. A liver biopsy may be required in settings of diagnostic uncertainty and/or concurrent liver disease to determine the exact staging of ALD and may help to evaluate the prognosis in alcoholic hepatitis[145,146]. Another advantage of liver biopsy and histology is that some of the morphological features of ALD are associated with prognostic utility (see below).

In patients with underlying ALD and heavy chronic alcohol consumption, alcoholic hepatitis may develop[17,160]. In these patients, the clinical diagnosis of alcoholic hepatitis cannot be confirmed by histology

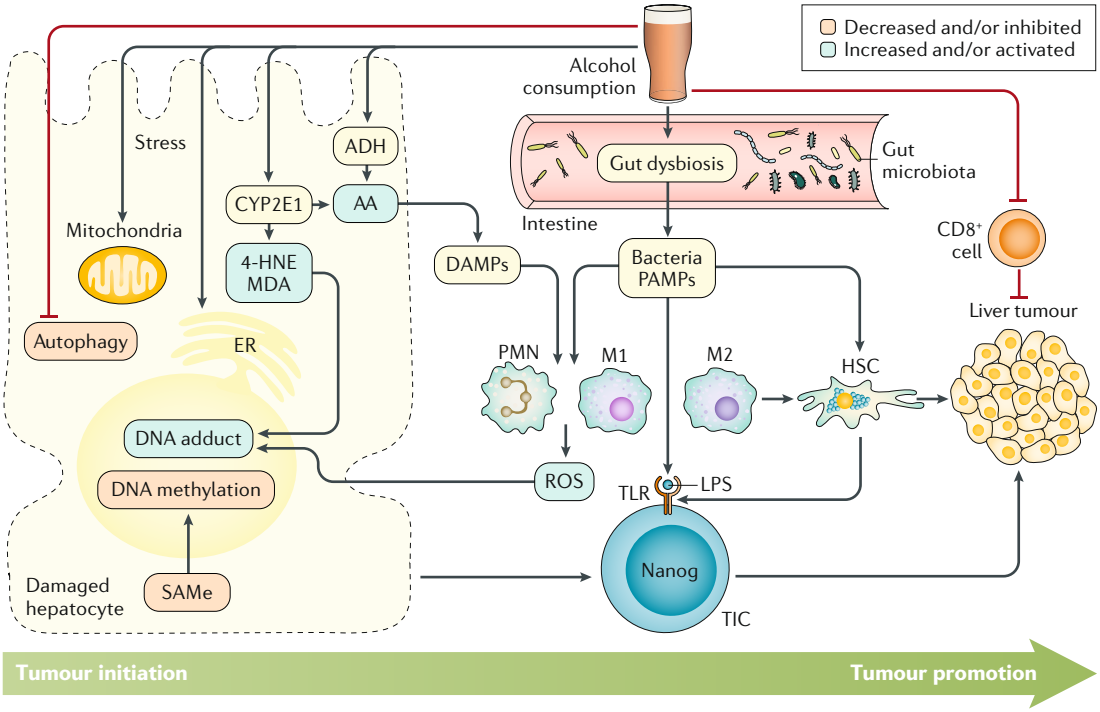


Fig. 7 | **Mechanisms of alcohol-mediated liver tumour initiation and promotion.** Alcohol metabolism by alcohol dehydrogenase (ADH) or cytochrome P450 2E1 (CYP2E1) generates an electrophilic metabolite, acetaldehyde (AA), which forms protein adducts causing cellular dysfunction and death. Reactive oxygen species (ROS) generated by induced CYP2E1 promote lipid peroxidation, which generates aldehydic metabolites such as malondialdehyde (MDA) or 4-hydroxynonenal (4-HNE). These aldehydes form adducts with DNA, leading to genotoxicity if DNA repair is compromised. Excessive alcohol consumption also induces stress in the endoplasmic reticulum (ER) and mitochondria and damages these organelles, which are usually cleared by autophagy. However, alcohol also suppresses autophagy, leading to accumulation of damaged organelles and dysplastic hepatocytes. Aberrant DNA methylation also occurs owing to a reduced pool of methyl donor, S-adenosyl-methionine (SAMe), which may be associated with tumour initiation. Alcohol also causes intestinal dysbiosis and translocation of gut bacteria and pathogen-associated molecular patterns (PAMPs), which along with damage-associated molecular patterns (DAMPs) released from injured hepatocytes stimulate innate immunity and inflammation: pro-inflammatory M1-activated macrophages are followed by tissue-restorative M2-activated macrophages; and infiltration of polymorphonuclear cells (PMNs). ROS generated by these inflammatory cells further damage hepatocytes. A very small fraction of dysplastic hepatocytes may acquire ectopic Toll-like receptor 4 (TLR4) expression, and activation of this receptor with endotoxin (lipopolysaccharide (LPS)) induces the pluripotency transcription factor Nanog, leading to the genesis of tumour-initiating stem-cell-like cells (TICs). Inflammation and PAMPs activate hepatic stellate cells (HSCs), which also increases TICs' tumour-initiating activity and promotes tumorigenesis. Alcohol also causes immunosuppression, particularly of $CD8^+$ T cells, leading to tumour promotion.

in 10–50% of cases[161–164]. In patients with a clinical suspicion of ALD, another liver disease or a concurrent liver disease may be present in up to 20%[165,166]. In these patients, confirmation of the clinical diagnosis is important, particularly in patients for whom steroid treatment is indicated, such as patients with severe alcoholic hepatitis, because unnecessary steroid treatment should be avoided owing to potentially life-threatening immunosuppressive side effects. Therefore, the risk–benefit relationship is in favour of liver biopsy in these patients.

The histological diagnoses in ALD comprise AFL, ASH, alcoholic fibrosis and/or cirrhosis and HCC (BOX 1; FIG. 9). In AFL, hepatocytes contain large lipid droplets displacing the nucleus towards the plasma membrane (macrovesicular steatosis) (FIG. 9b). Typical morphological features of ASH include hepatocellular injury, ballooning and Mallory–Denk bodies, necrosis, lobular inflammation with mononuclear and neutrophilic granulocytes and variable macrovesicular steatosis in hepatocytes[167,168] (FIG. 9c). In severe cases of ASH, bile pigment is seen in hepatocytes, canaliculi (FIG. 9c) and/or ductular reaction (hepatocellular, canalicular and ductular cholestasis, respectively). ASH is a potent driver of fibrosis. In most patients with precirrhotic fibrosis, collagen fibres may first extend along sinusoids and surround centrilobular hepatocytes (pericellular fibrosis) (FIG. 9d), and then fibres extend into the lobular parenchyma, often in septal configuration, linking central veins and portal tracts. Perivenular fibrosis and fibro-obliterative changes of venous vessels are typical features of alcoholic liver fibrosis. Progression of liver fibrosis paves the way for the development of cirrhosis (FIG. 9e), which may lead to the development of HCC (FIG. 9f). Most patients with advanced ALD have histological signs of septal fibrosis and cirrhosis, whereas ~50% of patients with early-compensated ALD have septal fibrosis or cirrhosis[7]. The morphological features of ALD may be also seen in NAFLD. However,

Box 5 | **Criteria for AUD**

Alcohol use disorder (AUD) is diagnosed and classified according to the number of the below criteria met by the patient. Mild AUD is diagnosed if two to three criteria are met, moderate AUD if four to five criteria are met and severe AUD if six or more criteria are met.

- Tolerance: markedly increased amounts of alcohol are needed to achieve intoxication or the desired effect, or continued use of the same amount of alcohol achieves a markedly diminished effect
- Withdrawal: the appearance of clinical symptoms when alcohol consumption suddenly stops. These include anxiety, insomnia, nausea (associated with cardiovascular reactions) and occasionally delirium tremens (hallucinations, fever, seizures and agitation)
- Heavier alcohol consumption or consumption for longer periods than is considered normal according to government guidelines
- Persistent desire or failure to reduce or control consumption
- Considerable time spent consuming alcohol
- Social activities given up because of alcohol consumption
- Continued consumption despite causing (or exacerbating) physical or psychological problems
- Consumption results in failures to fulfil major role obligations
- Alcohol consumption in situations that are physically hazardous
- Continued consumption despite causing (or exacerbating) interpersonal problems
- Craving

extensive microvesicular steatosis, cholestasis and fibro-obliterative damage of venous vessels of the liver have not been reported in NAFLD.

As mentioned above, prognostic utility has been described for several histological findings of ALD. In the setting of alcoholic hepatitis, ductular and/or canalicular cholestasis are independent risk factors for short-term mortality[169] and have also been correlated with risk of death in the early and compensated stages of ALD[102]. Morphological cholestasis may be a sign of subclinical developing sepsis[162,169]. The stage of fibrosis is a major predictor of prognosis in ALD. As non-invasive fibrosis tests (serum biomarkers and elastography-based fibrosis measurements) are not reliable in the presence of ASH, liver biopsy may be important for histological assessment of fibrosis stage, because patients without cirrhosis have much better outcome[162,169,170]. Furthermore, pericellular fibrosis in decompensated ALD may be associated with improved prognosis[102,145].

### *Screening and prevention*

In order to facilitate early detection of alcohol-related disease, alcohol consumption should be assessed routinely in all patients presenting with medical conditions that might be alcohol related (BOX 2). If risky alcohol drinking is identified (BOX 1), laboratory tests for markers of liver damage such as serum transaminase activity and GGT activity, as well as tests reflecting liver function (blood coagulation, serum albumin and bilirubin) should be performed, and the patient should be seen either by a psychiatrist or a gastroenterologist or ideally both. An exact assessment of alcohol use should preferably be performed with a validated tool. The Alcohol Use Disorders Identification Test (AUDIT) questionnaire was developed by the WHO, and a shortened version has been compiled for use as a screening tool[171,172]. Given the social stigma associated with AUD, clinicians should be very careful to conduct the interview with a professional, empathic and non-judgemental attitude.

General preventive measures should aim to decrease alcohol consumption by pricing-based policy (for example, increased taxation and higher prices for alcoholic beverages), reduced availability for alcohol by restrictions on the number of vendors, banning the advertising of alcohol and making care facilities for managing AUDs widely available[172–174].

Liver stiffness measurements enable the monitoring of drinking activity and fibrotic ALD progression, even in the presence of inflammation when corrected for the severity of inflammation determined by serum transaminase activities[175,176]. Liver stiffness improved shortly after alcohol withdrawal in >80% of individuals with heavy alcohol consumption presenting for alcohol detoxification[176]. In addition to the good diagnostic performance of elastography for the screening of fibrosis, non-invasive tests may be useful in predicting liver-related mortality; in an 8-year survey of patients with ALD, survival was correlated with the baseline non-invasive fibrosis score[156]. Outcome may also be predicted by the ELF test (TABLE 1) in patients with chronic liver disease[177], but its efficacy needs further evaluation in larger cohorts of patients with ALD.

## Management

### *Alcohol use disorder*

Contrary to common beliefs, the integrated treatment (psychosocial and pharmacological) of AUDs is effective, with rates of good clinical outcome (abstinence or moderate drinking without problems) >70% at 4 months after intervention[178]. Although in recent years it has been well established that the reduction of alcohol use is a suitable goal for some patients[179], those with ALD should always aim for alcohol abstinence to reduce the risk of disease progression. The basic pillars of the medical management of AUD are patient-centred care; an integrated clinical decision-making approach; a motivational style of clinician–patient communication; careful monitoring of abstinence, including self-reports (such as Timeline Followback)[180]; and the regular use of biological markers of alcohol use (such as ethyl glucuronide or phosphatidyl alcohol)[181].

Patients with heavy chronic alcohol consumption or those who have previously experienced an alcohol withdrawal syndrome (characterized by fever, vomiting, anxiety, seizures and psychosis, among other symptoms) will need an initial detoxification period[182]. Diazepam in a tapering dose is commonly used; however, any benzodiazepine can be used to counteract withdrawal symptoms with their sedative, anxiolytic and anticonvulsive effects. In the presence of hepatic damage, lorazepam is recommended[183]. Many individuals with AUD, especially those who drink intermittently, do not require a detoxification period and directly start a psychosocial rehabilitation process that may also include pharmacological support. Several drugs are approved by the US FDA and the European Medicines Agency (EMA) for the treatment of AUD; these are disulfiram, naltrexone and acamprosate. In addition, nalmefene has been

approved by the EMA, and sodium oxybate is approved only in Italy and Austria (TABLE 2).

Alcohol abstinence has a statistically significant impact on survival. Continuous chronic heavy drinking is associated with a 4-year survival for patients with AFL of 70%, for patients with alcoholic hepatitis of 58%, for patients with cirrhosis of 49% and for patients with alcoholic hepatitis and underlying cirrhosis of 35%[184]. In a Danish population-based study with a cohort of 446 patients with alcoholic cirrhosis, the risk of developing complications of cirrhosis (ascites, variceal bleeding or hepatic encephalopathy) was ~25% after 1 year and ~50% after 5 years[185]. With abstinence, the expected 5-year transplant-free survival following the development of hepatic decompensation is 60% versus 30% for those who continued to drink alcohol[186].

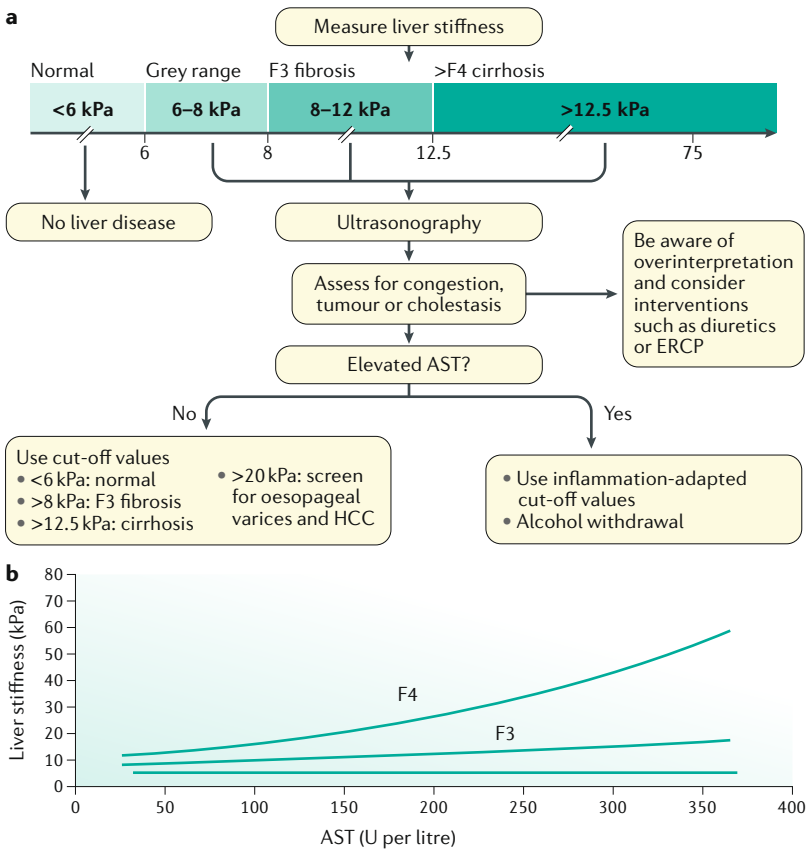


Fig. 8 | **Clinical interpretation of liver stiffness in alcoholic liver disease. a** | Algorithm for clinical interpretation of liver stiffness in patients with alcoholic liver disease (based on data from REF.[138]). A normal liver stiffness (<6 kPa) rules out any chronic liver disease with a high negative predictive value; however, caution is required to directly interpret an elevated liver stiffness with regard to fibrosis stage. Thus, additional ultrasonography imaging should be performed to rule out potential other confounders such as congestion, liver nodules and biliary obstructions. In addition, serum aspartate transaminase (AST) activities should be obtained to assess the impact of liver inflammation on elevated liver stiffness. Finally, interventions should be considered, such as treatment with diuretics to ameliorate congestion, an endoscopic retrograde cholangiopancreatography (ERCP) to remove mechanic cholestasis or an alcohol withdrawal therapy to resolve liver inflammation. After these interventions, liver stiffness can be assessed again and fibrosis stage can be determined more accurately according to the depicted cut-off values. **b** | AST-adapted cut-off values of liver stiffness for immediate assessment of fibrosis stage (adapted from REF.[142]). This graph enables the immediate readout of fibrosis stage in the case of elevated liver stiffness values and elevated AST levels. It is important to conceive that cut-off values are also aetiology-dependent and other cut-off values should be used, for example, for hepatitis C virus infection. HCC, hepatocellular carcinoma.

### *Alcoholic hepatitis*

***Assessing disease severity.*** The severity of alcoholic hepatitis was previously classified on the basis of the evaluation of the risk of 1-month mortality, which can be assessed using a discriminant-function score[144,187,188]. The discriminant-function score can be calculated using serum liver function test parameters ($4.6 \times$ (*prothrombin time of the patient – control prothrombin time* [in seconds]) + *serum bilirubin* [in mg $dl^{-1}$]). Episodes of alcoholic hepatitis were defined as severe for patients with a discriminant-function score ≥32, in whom the risk of 1-month mortality exceeds 20–30%. As a consequence, clinicians gave priority to the treatment of severe forms of alcoholic hepatitis[144] and recommended the threshold of a discriminant-function score of 32 to indicate the need for initiating specific therapy in patients with severe alcoholic hepatitis. In 2018, the modified Maddrey's discriminant-function score[144,188], MELD (Model for End-stage Liver Disease)[189], ABIC (Age, Bilirubin, INR and Creatinine)[190] and Glasgow[191] alcoholic hepatitis scores are accurate in predicting short-term mortality.

The strong association between the early evolution of liver function parameters and short-term mortality led to the development of the Lille model[192], a dynamic score that permits the identification of patterns of complete, partial and null response to treatment, with each response being associated with a particular risk of 1-month mortality[193]. Combining results from static (Maddrey's discriminant-function score, MELD and ABIC) and dynamic (Lille) scoring systems for liver disease is the most efficient approach to better predict the outcomes of patients with alcoholic hepatitis compared with static or dynamic models alone[194]. Using a combination of basic and dynamic scores will enable clinicians to tailor therapeutic management according to the magnitude of risk of mortality and may be employed in the future evaluation of new molecules. Furthermore, the prediction of a continuum of risk of mortality may enable the accurate selection of suitable candidates for early liver transplantation. In addition, patients with a low competitive risk of mortality identified with this combinative scoring approach may be considered as the optimal candidates for phase I or II clinical studies that require a sufficient time of exposure to evaluate the pharmacological effects. Thus, combination of basic and dynamic scores may be efficient to improve patient management.

***Management.*** Cessation of alcohol consumption is the most important prerequisite of therapy for alcoholic hepatitis regardless of disease severity. A daily energy intake of 35–40 kcal per kg of body weight and a daily protein intake of 1.2–1.5 g per kg of body weight has been recommended in patients with alcoholic hepatitis. For patients unable to maintain adequate oral intake, tube feeding is recommended[7]. The therapeutic guidelines of EASL recommend corticosteroids to reduce hepatic inflammation for patients with severe

Table 1 | **Serum biomarkers of alcoholic liver fibrosis**

| Serum marker | Serum marker normal function | Outcome | Refs |
|---|---|---|---|
| ApoAI | A component of high-density lipoprotein | Correlation with fibrosis ($r=-0.70$; $P\leq0.001$) | Bedossa et al.[147] |
| HA and PIIINP | Components of extracellular matrix (connective tissue) | AUROC[a] for PIIINP 0.867 ± 0.054 | Pares et al.[148] |
| HA and PT | HA is a glycosaminoglycan, a component of connective tissue and part of the extracellular matrix. PT is a protein produced by the liver that is important in blood coagulation | Accuracy for cirrhosis diagnosis from 89.5% to 95% | Oberti et al.[149] |
| HA | See above | Significant correlation ($P<0.01$) between HA and serum markers of liver function (albumin, platelets and bilirubin) but not with ALT | Plevris et al.[150] |
| Type VI and type XIV collagens | Part of connective tissue | Sensitive markers of fibrosis progression in patients with ALD | Stickel et al.[155] |
| PT | See above | Correlation between serum PT and fibrosis score (determined by liver biopsy histology); $r=-0.70$, $P<0.0001$ | Croquet et al.[151] |
| YKL40 and PIIINP | YKL40 is a chitinase-like protein produced in the liver involved in remodelling of the extracellular matrix; see above for PIIINP | Serum levels of YKL40 and PIIINP are elevated in alcoholic patients and correlate with level of fibrosis | Nøjgaard et al.[152] |
| HA | See above | Correlation between serum HA and the histological stage of alcoholic liver disease ($r=0.54$, $P<0.0001$); AUROC for HA and fibrosis 0.76 | Stickel et al.[153] |
| ELF panel | ELF panel, consisting HA, PIIINP and TIMP1, is relevant in fibrolysis | Elevated ELF panel markers are predictive of fibrosis stage; AUROC 0.94 ± 0.056 | Rosenberg et al.[154] |

ALT, alanine aminotransferase; ALD, alcoholic liver disease; ApoAI, apolipoprotein AI; ELF, enhanced liver fibrosis; HA, hyaluronic acid; PIIINP, procollagen III N-terminal propeptide; PT, prothrombin; TIMP1, tissue inhibitor of metalloproteinases 1; YKL40, also known as chitinase 3-like protein 1 (CHI3L1). [a]Area under the receiver operating characteristic curve (AUROC) is a measure for sensitivity; values >0.9 are excellent and those between 0.8 and 0.9 are good.

alcoholic hepatitis to reduce 28-day mortality[7]. Since the publication of EASL guidelines, a randomized study of 1,103 patients with severe alcoholic hepatitis has confirmed the effectiveness of corticosteroids. The study observed using a 2-by-2 factorial design that the odds ratio for 28-day mortality (adjusted for prognostic variables) was 0.61 in patients treated with corticosteroids as compared with those who did not receive corticosteroids, whereas pentoxifylline, a TNF inhibitor, did not improve 28-day mortality[195]. Moreover, a meta-analysis confirmed the reduction in 28-day mortality in patients treated with corticosteroids[196]. However, neither treatment with corticosteroids or pentoxifylline decreased the risk of 6-month mortality[195,196]. A randomized controlled trial testing the combination of pentoxifylline and corticosteroids did not show any benefit in 1-month survival compared with prednisolone (a corticosteroid) alone[197]. By contrast, a combination of corticosteroids and *N*-acetyl cysteine, an antioxidant, may be considered as an attractive therapeutic approach to induce early improvement in liver function and decrease short-term mortality[198].

Tailoring corticosteroid therapy according to treatment response is required in the management of patients with alcoholic hepatitis. Patients with a Lille score ≥0.45 after 7 days of corticosteroid treatment are considered as non-responders. Response to therapy may classified in three groups according to Lille score: complete response (Lille score ≤0.16; 91% survival at 28 days); partial response (Lille score between 0.16 and 0.56; 79% survival at 28 days); and null response (Lille score >0.56; 53% survival at 28 days)[193]. EASL guidelines recommend considering the cessation of corticosteroids in non-responders, particularly in those classified as null responders. Corticosteroids are sufficient in complete responders, and novel pharmacological therapies may be required in intermediate responders and null responders.

Infection is observed in ~25% of patients with severe alcoholic hepatitis and is major factor contributing to death[199,200]. The level of circulating serum bacterial DNA before treatment could identify patients who are at high risk of infection if given immunosuppressive prednisolone; therefore, this parameter has been proposed to determine the optimal candidates for treatment with corticosteroids[200]. An early improvement in liver function is the most important factor contributing to decreased risk of infection, as shown by the

Table 2 | **Drugs for the treatment of alcohol dependency**

| Drug | Main mechanism of action | Frequent adverse effects | Strength of evidence | Comments |
|---|---|---|---|---|
| Disulfiram | Inhibits acetaldehyde dehydrogenase, producing high levels of acetaldehyde if alcohol is consumed | Skin rash, garlic taste and headache | Small for abstinence; very old studies | Used under supervision, outcomes improve. Approved in the United States and European Union |
| Naltrexone | Antagonist of opioid receptors, reducing the release of dopamine in the reward system produced by alcohol | Diarrhoea, abdominal cramping and hepatotoxicity | Small to moderate in reduction of heavy drinking days | Approved in the United States and European Union |
| Acamprosate | Counteracts hyperglutamatergic states | Diarrhoea, nausea and headache | Small to moderate in abstinence | Approved in the United States and European Union |
| Nalmefene | Antagonist of opioid receptors, reducing dopamine release in the reward system produced by alcohol | Nausea, dizziness, insomnia and headache | Small to moderate in reduction of heavy drinking days | Approved in the European Union |
| Topiramate | Antagonist of glutamate receptors | Cognitive impairment, drowsiness and dizziness | Small to moderate in reduction and abstinence | Off-label use |
| Baclofen | Unknown | Fatigue, sleepiness and drowsiness | Inconclusive | Used mostly in France and the United Kingdom; controversial |
| Sodium oxybate | Agonistic action in GABA receptors | Vertigo, dizziness and risk of abuse | Small in abstinence | Marketed in Italy and Austria |
| Gabapentin | Inhibits presynaptic sodium and calcium channels | Dizziness, fatigue, drowsiness, ataxia and peripheral oedema | Small in reduction of heavy drinking days | Off-label use |
| Varenicline | Partial agonist of nicotinic receptors | Nausea, headache, difficulty sleeping and nightmares | Small in reduction of heavy drinking days | Off-label use |

low incidence of infection in treatment responders as compared with non-responders[199].

***Liver transplantation.*** The poor outcome of non-responders to medical therapy stresses the need to evaluate early liver transplantation in these patients. A pilot study was used to evaluate liver transplantation in a group of highly selected patients with severe alcoholic hepatitis who failed to respond to medical therapy and were undergoing their first episode of liver disease[201]. The failure of medical therapy was identified using a Lille score ≥0.45 or worsening of liver function by day 7. This case–control study showed an unequivocal improvement of survival in patients who received early transplantation[201]. These favourable results have been recently confirmed by two American studies[202,203]. Importantly, the rate of alcohol relapse was similar in those highly selected patients undergoing early liver transplantation to transplanted patients who were selected after a period of abstinence[202,203]. Some experts fear that the practice of early liver transplantation in severe, non-treatment-responsive alcoholic hepatitis may decrease public willingness to donate. However, this fear is not supported by evidence, as the results of a questionnaire sent to a representative sample of US donors showed that 82% of them were neutral about the early liver transplantation programme for alcoholic hepatitis[204].

### *Alcoholic cirrhosis and HCC*

As in cirrhosis of other aetiologies, patients with alcoholic cirrhosis are at risk of complications such as ascites, hepatic encephalopathy, hepatorenal syndrome variceal haemorrhage, liver failure and HCC. These complications of cirrhosis need to be treated according to the guidelines for cirrhosis therapy[205] or guidelines for HCC[206].

In Child–Pugh score class C cirrhosis (the most severe stage of cirrhosis), liver transplantation is the treatment of choice with excellent results[207]. In Europe, >30% of all liver transplantations are performed for ALD[1]. Although in many countries liver transplantations are performed only following 6 months of alcohol abstinence (6-month rule), this criterion to prevent relapse into alcohol dependency after liver transplantation is questionable because it is based on the observation of 11 patients[208]. Indeed, it was found that 6-month abstinence is a good inclusion criterion but a poor exclusion criterion as a predictive value for post-transplant relapse[209,210].

The diagnosis of HCC is typically delayed in patients with ALD-associated cirrhosis owing to lack of

surveillance and poor patient compliance[211]. This delay results in increased tumour size at diagnosis and poorer outcomes. The management of HCC in patients with ALD does not differ from patients with HCC due to other aetiologies[206,212]. Patients are strongly encouraged to stop drinking and smoking. The principles of HCC management include surgery, radiofrequency ablation, chemoembolization and chemotherapy[206].

### Quality of life

Quality of life reflects the positive and negative aspects of life and is extended upon by health-related quality of life (HRQoL), which addresses how health influences the well-being of patients. In patients with ALD, HRQoL may be impaired owing to the presence of an AUD or to complications of the liver disease. In the early or compensated phases of disease, there are usually few symptoms. However, as disease progresses into decompensated cirrhosis, the increase in portal pressure and reduction of liver function triggers the appearance of symptoms and signs that severely affect the well-being of patients. The symptoms may include abdominal distension and discomfort associated with ascites, changes in sleep patterns that may be associated with early stages of hepatic encephalopathy, muscle cramps associated with electrolyte disturbances, fatigue, impaired mobility, breathlessness, gastrointestinal symptoms and change of body image associated with the presence of ascites, lower leg oedema and the presence of jaundice. In addition, the stigma associated with ALD may negatively affect HRQoL. A recent survey among 149 patients with cirrhosis associated with a variety of aetiologies observed that 89% felt stigmatized in at least one aspect of their lives. Moreover, alcohol as the aetiology of liver disease was one of the more perceived stigmas on multivariable linear regression ($P = 0.01$)[213].

In addition, it has been shown that patients who have undergone liver transplantation or who have a previous history of ALD had twice as many deaths by suicide or caused by social problems when compared with patients with liver disease associated with a viral aetiology[214]. After liver transplantation, no difference was found in drug compliance, adherence to check-ups or incidence of graft rejection when comparing patients who had relapsed with patients who were non-relapsers[215]. Evidence exists that patients with ALD tend to lead active and productive lives after liver transplantation, with a similar capacity for work and physical activity to those transplanted for non-alcohol-related causes[216,217].

Regarding costs, it is difficult to know the exact costs arising from ALD, but it was calculated that harmful alcohol consumption resulted in estimated costs of €125 billion, equivalent to 1.3% of gross domestic product (GDP), in the European Union in 2003 (REF.[218]).

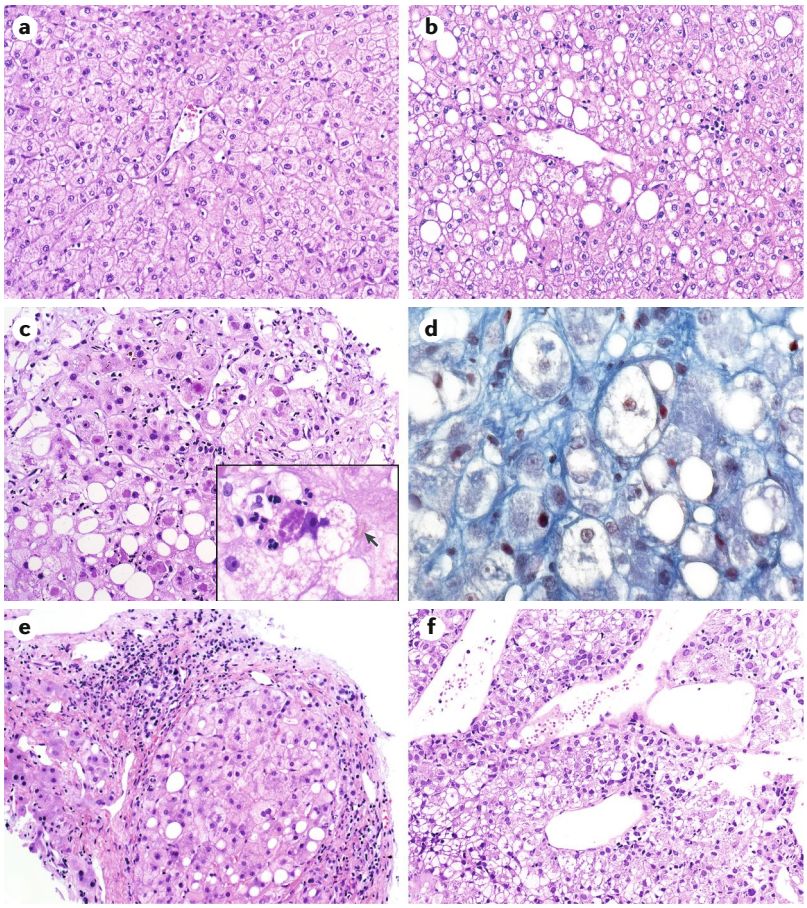


Fig. 9 | **Liver biopsy diagnosis of alcoholic liver disease. a** | (Haematoxylin & eosin; 200×). Histology sample of healthy liver tissue. Hepatocytes are arranged in one-cell-thick trabeculae separated by sinusoids converging at the central vein in normal liver. **b** | (Haematoxylin & eosin; 200×). Many hepatocytes containing lipid droplets (macrovesicular steatosis) in a case of alcoholic fatty liver. **c** | (Haematoxylin & eosin; 200×). A case of alcoholic steatohepatitis. In addition to steatotic hepatocytes (lower corner on the left), there are numerous enlarged hepatocytes with rounded cell shape (ballooned hepatocytes) containing large eosinophilic cytoplasmic inclusions (Mallory–Denk bodies (MDBs)). Between the hepatocytes, a mononuclear inflammatory infiltrate with admixed neutrophils is seen. The inset shows an enlargement of a ballooned hepatocyte with MDBs surrounded by neutrophils (satellitosis). The arrow indicates bile pigment in a dilated canaliculus. **d** | (chromotrope aniline blue; 600×). An example of pericellular fibrosis. Hepatocellular ballooning is often associated with deposition of collagen fibres in a pericellular fashion. **e** | (Haematoxylin & eosin; 200×). Alcoholic micronodular cirrhosis with small parenchymal nodules surrounded by fibrous septa. **f** | (Haematoxylin & eosin; 200×). Hepatocellular carcinoma with several-cell-thick trabeculae lined by endothelial cells.

### Outlook

ALD is a leading type of chronic liver disease and the main cause of liver-related mortality worldwide[3,219]. Since the 1970s, substantial progress has been made in understanding the pathogenesis of ALD, and genetic and epigenetic mechanisms have been uncovered. Moreover, novel non-invasive diagnostic methods such as elastography have been developed. The efficacy of public health policies to reduce the burden of ALD is limited, although three important public health approaches have been shown to decrease alcohol consumption in a population. These include increases in price (including higher taxation), limitations in availability and advertising bans on alcoholic beverages[220].

Therapy for alcoholic hepatitis has not evolved in the past decades, suggesting that future research should be focused in this direction. However, achieving permanent abstinence from alcohol is the best therapeutic strategy for all stages of ALD. Patients with ALD should be managed by a multidisciplinary clinical team, including addiction therapists and hepatologists. Moreover, there

exists a need for hepatologists to be trained in the diagnosis and management of AUD. The use of motivational interviewing and pharmacological agents to treat AUD in the setting of ALD is not well known and deserves to be the subject of future studies.

Inflammation is considered as a critical factor for causing liver damage in alcoholic hepatitis; many drugs that target inflammation are currently in clinical trials for the treatment of alcoholic hepatitis, including IL-1 inhibitors, apoptosis signal-regulating kinase 1 (ASK1; also known as MAP3K5) inhibitors, LPS blockers and probiotics (to modulate the microbiota)[221]. Another approach includes the inhibition of CYP2E1 to decrease oxidative stress and the generation of ROS[50].

Alcoholic hepatitis is associated not only with hepatocellular injury but also with the impairment of liver regeneration. The application of hepatoprotective agents may provide some benefits in therapy for ALD to protect against hepatocellular damage and promote liver regeneration. For example, the hepatoprotective cytokine IL-22 is currently in clinical trials for the treatment of alcoholic hepatitis. By targeting hepatocytes, IL-22 plays an important role in ameliorating hepatocellular damage, promoting liver regeneration and alleviating liver fibrosis[222]. In addition, IL-22 treatment may effectively impede bacterial infection and ameliorate kidney injury, two deleterious conditions that often contribute to death of patients with alcoholic hepatitis. IL-22 therapy is currently being tested in clinical trials for the treatment of patients with severe alcoholic hepatitis[223]. Granulocyte colony-stimulating factor (GCSF) is also currently also being tested for the treatment of patients with alcohol hepatitis[224–226].

Novel manoeuvres aimed at promoting hepatocellular growth, such as bone marrow cell transplantation, may improve the outcome of patients[227]. In addition, clinical trials of extracorporeal cell therapy (in which the patient's blood cells are separated from plasma and then incubated extracorporally with C3A cells (an immortalized liver cell line) that express anti-inflammatory proteins and growth factors, then injected back into the patient) for severe alcoholic hepatitis are also currently ongoing[228]. Thus, we might see these new treatments in the future for the treatment of severe alcoholic hepatitis. With increasing interest from pharmaceutical companies and from funding agencies (such as NIAAA, NIH and the EASL Study of Alcoholic Liver Disease in Europe), these clinical trials will likely move forward faster; novel targeted therapies from these clinical trials are expected to emerge within the next 5 years.

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