JAMA | Review

Alcohol-Related Liver Disease
A Review

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IMPORTANCE Alcohol-related liver disease (ALD) is the leading cause of liver-related morbidity and mortality, and the most common indication for liver transplant in Europe and the US. In the US, ALD-related mortality increased from 6.7 deaths per 100 000 people in 1999 to 12.5 deaths per 100 000 people in 2022.

OBSERVATIONS ALD can develop with long-term daily alcohol consumption of more than 20 g per day for women (1.4 standard drinks/d) and more than 30 g per day for men (2.1 standard drinks/d), with 1 standard drink containing 14 g of ethanol, equivalent to approximately 12 oz of beer, 5 oz of wine, or 1.5 oz of distilled spirits. ALD encompasses reversible steatosis; steatohepatitis, which can cause alcohol-associated hepatitis; and fibrosis, which can cause cirrhosis, portal hypertension, hepatic decompensation, and hepatocellular carcinoma. Risk factors for ALD progression include increased quantity and duration of alcohol use, female sex, older age, obesity, type 2 diabetes, metabolic syndrome, smoking, viral hepatitis, and specific genetic variants. Most patients with ALD (90%) are asymptomatic or have nonspecific symptoms, such as fatigue. Alcohol-associated hepatitis often causes fever, anorexia, nausea, vomiting, abdominal pain, and jaundice. Individuals with decompensated cirrhosis typically have ascites, variceal bleeding, jaundice, and/or hepatic encephalopathy. Noninvasive liver fibrosis tests, such as the Fibrosis-4 score (which includes alanine transaminase, aspartate aminotransferase, platelet count, and age), and more specific second-line tests, including liver stiffness measurement (vibration-controlled transient elastography) and blood-based fibrosis markers such as the enhanced liver fibrosis test and N-terminal propeptide of type III collagen, provide early diagnosis of ALD and assess liver fibrosis severity, which is the strongest predictor of liver-related outcomes. Alcohol cessation interventions such as motivational enhancement therapy, cognitive behavioral therapy, and pharmacologic therapy (eg, baclofen, naltrexone) are recommended to prevent disease progression. Because alcohol consumption is often underreported, screening tools, such as the Alcohol Use Disorders Identification Test, and sensitive biomarkers of recent alcohol intake (eg, blood phosphatidylethanol) may improve clinical accuracy. Sustained abstinence from alcohol is the primary treatment for ALD. Among patients with alcohol-related cirrhosis, alcohol abstinence over a median follow-up of 36 months was associated with reduced risk of liver-related mortality (adjusted hazard ratio, 0.43 [95% CI, 0.26-0.70]) and all-cause mortality (adjusted hazard ratio, 0.45 [95% CI, 0.30-0.67]). Liver transplant evaluation should be considered for patients with severe alcohol-associated hepatitis or decompensated cirrhosis.

CONCLUSIONS AND RELEVANCE People with chronic daily heavy alcohol consumption should be assessed for ALD with noninvasive testing. The primary treatment goal is alcohol cessation. Patients with severe alcohol-associated hepatitis or decompensated cirrhosis should be considered for liver transplant.

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Alcohol-related liver disease (ALD) is defined by hepatic steatosis and/or significant liver fibrosis with alcohol intake above 20 g per day for women and above 30 g per day for men.[1] Based on a modeling study of global data from 2000 to 2020, alcohol use caused 2.6 million premature deaths and 4.7% of all global deaths annually.[2] In the US, heavy drinking (≥5 drinks on any day or ≥15 drinks per week for men and ≥4 drinks on any day or ≥8 drinks per week for women) increased from 5.10% in 2018 to 6.13% in 2020, with the greatest increases in young adults (aged 25-44 years) and women.[3-5] This pattern was sustained even after the COVID-19 pandemic (2022).[3,6] ALD is the leading cause of liver-related morbidity, mortality, and liver transplant in Europe and the US, and ALD mortality in the US has increased from 6.7 to 12.5 deaths per 100 000 persons from 1999 to 2022.[3,7] However, ALD is underdiagnosed and undertreated; in a multinational cross-sectional study from 17 countries including 3453 consecutive patients, ALD accounted for only 3.8% of early-stage but 29% of advanced-stage liver disease in gastroenterology units.[8,9] The recently introduced term *steatotic liver disease* includes ALD and metabolic dysfunction and ALD,[1] a subcategory of ALD that includes patients with hepatic steatosis and/or significant fibrosis (fibrosis stage 2-4), at least 1 cardiometabolic risk factor, and alcohol intake of 20 to 50 g per day for women and 30 to 60 g per day for men.[1] Individuals with heavy alcohol use frequently have obesity, type 2 diabetes, and other cardiometabolic risk factors, which substantially increase the risk of cirrhosis, liver cancer, and cardiovascular disease.[10-15] Additionally, alcohol consumption can accelerate progression of other liver diseases such as metabolic dysfunction–associated steatotic liver disease (MASLD)[13,16] and chronic hepatitis B and C.[17] This review focuses on the epidemiology, diagnosis, and treatment of ALD (**Box**).

Box. Commonly Asked Questions About Alcohol-Related Liver Disease (ALD)

What individuals are at risk of ALD?
Individuals at risk of ALD are those with long-term daily alcohol consumption of more than 20 g/d for women (1.4 standard drinks/d) and more than 30 g/d for men (2.1 standard drinks/d), with 1 standard drink containing 14 g of ethanol, equivalent to approximately 12 oz of beer, 5 oz of wine, or 1.5 oz of distilled spirits.

What is the clinical value of identifying ALD in individuals with harmful alcohol intake?
Identification of ALD is important because alcohol cessation or decreased use is associated with reduced risk of liver-related complications and decreased mortality. Additionally, knowledge about advanced liver disease can motivate patients to reduce or avoid alcohol intake.

What interventions should be offered to individuals with ALD?
All patients with ALD who are currently consuming alcohol should be offered behavioral therapy and/or medications to reduce alcohol intake. Depending on success of initial treatment and presence of alcohol use disorder, referral to an addiction specialist should be considered if available.

Methods

We conducted a PubMed search for observational studies, clinical trials, reviews, and meta-analyses on the pathophysiology, epidemiology, diagnosis, treatment, and prognosis of ALD published from January 1, 2015, through May 30, 2026, using the terms ("alcohol*") and ("liver" or "cirrhosis" or "fibrosis").

Of 3129 identified articles, 2394 were excluded because they focused exclusively on MASLD. The 735 remaining articles underwent manual screening of titles, abstracts, and full text. In addition, select landmark studies published prior to 2015 were included. A total of 114 articles were included, comprising 61 observational studies, 9 randomized clinical trials, 11 systematic reviews or meta-analyses, 23 narrative reviews, 6 guideline recommendations, 1 consensus statement, and 3 commission reports.

Discussion

Pathophysiology

Alcohol can cause hepatic damage that induces accumulation of scar tissue in the liver (fibrosis) both from direct liver toxicity and indirectly from increased gut permeability that allows bacterial-produced molecules such as lipopolysaccharides, peptidoglycans, and bacterial DNA to enter portal circulation and cause release of proinflammatory cytokines such as tumor necrosis factor, IL-1β, and IL-6, leading to inflammation and fibrosis and changes in lipid and glucose metabolism (**Figure 1**).[18]

The metabolism of alcohol through alcohol dehydrogenase and CYP2E1 produces acetaldehyde, reactive oxygen species, lipid peroxidation products, and a disturbed NAD^+/NADH balance, which contribute to hepatocellular injury and cell death, leading to hepatic inflammation.[19] Alcohol metabolism also leads to reduced beta oxidation (fatty acid breakdown) and accumulation of lipids within hepatocytes,[20] which is exacerbated by the increased release of free fatty acids from peripheral adipose tissue during alcohol-induced lipolysis.[21]

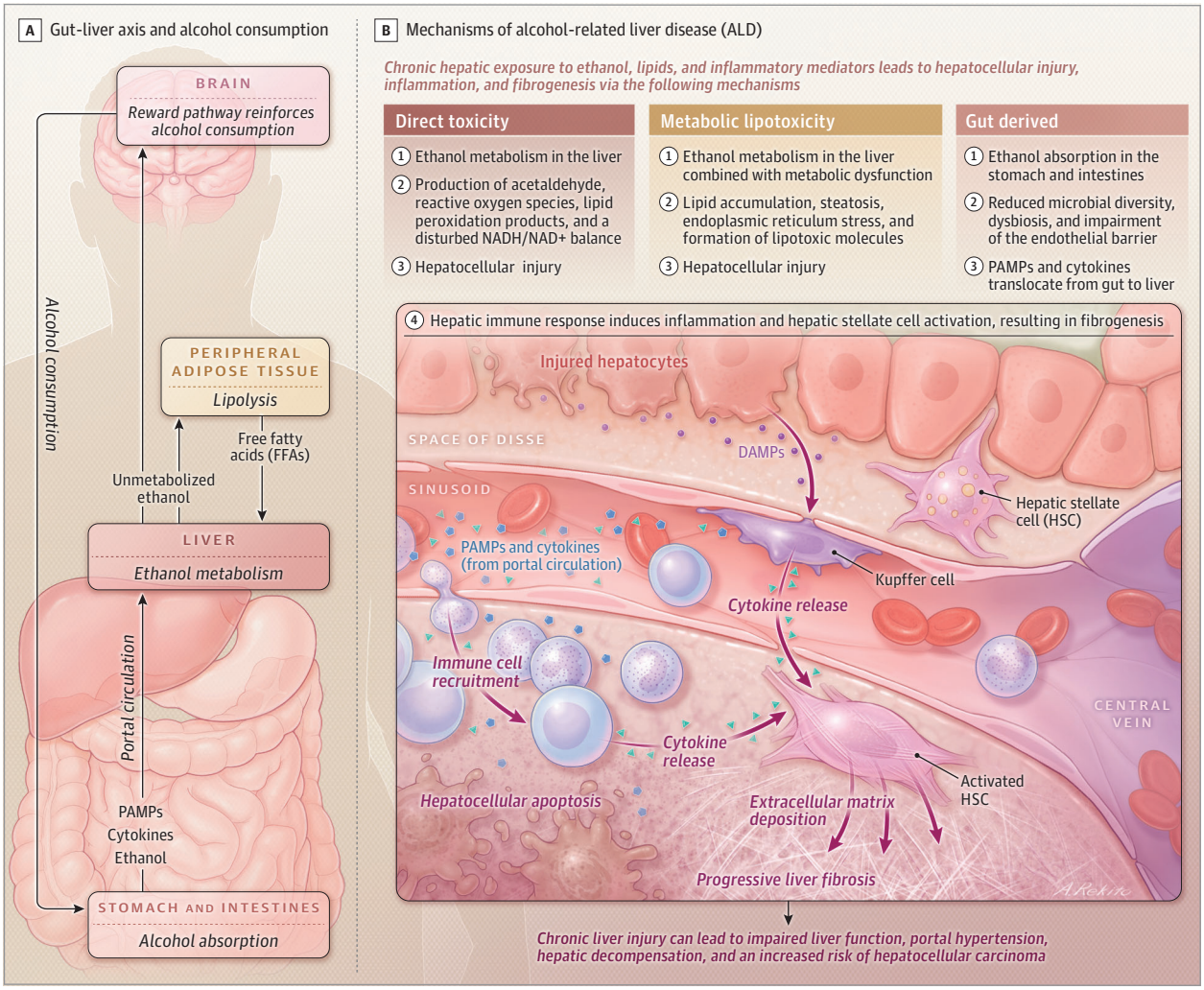
Metabolic dysfunction, including adiposity and insulin resistance, combined with alcohol use substantially increases the risk of developing decompensated cirrhosis (defined as portal hypertensive complications including ascites, variceal bleeding, or hepatic encephalopathy),[22,23] likely through steatosis, hepatocellular injury, inflammation, and fibrosis.[24] Genetic variations such as in *PNPLA3*, *HSD17B13*, and *TM6SF2*, which impair hepatic lipid handling, can further potentiate these pathways.[25,26] The alcohol-induced metabolic shift and potential underlying metabolic dysfunction promote lipid accumulation (steatosis), endoplasmic reticulum stress due to accumulation of misfolded proteins, and formation of lipotoxic molecules, resulting in hepatocyte injury and inflammation. In response to hepatocyte injury and inflammation, liver-specific fibroblasts (stellate cells) secrete extracellular matrix, which appears as fibrosis on histology.[18,27] Fibrosis replaces hepatocytes, and progressive fibrosis causes impaired liver function and can lead to portal hypertension and hepatic decompensation,[28] which predisposes to carcinogenesis and increased risk of hepatocellular carcinoma (HCC).[29]

Epidemiology

Based on 2017-2020 National Health and Nutrition Examination Survey (NHANES) data, reported prevalence estimates without

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Figure 1. Illustration of the Pathophysiology of Alcohol-Related Liver Disease



A, Following alcohol intake, ethanol is absorbed from the stomach and intestine into the blood together with gut derived microbial products (pathogen associated molecular patterns [PAMPs]). Ethanol and PAMPs reach the liver predominantly via the portal vein. The ethanol that is not metabolized in the first pass of the liver, reaching the adipose tissue, results in lipolysis and increased delivery of free fatty acids to the liver. In parallel, ethanol acts on the central nervous system reward pathways, reinforcing repeated alcohol consumption. The combined effects lead to chronic hepatic exposure to ethanol, lipids, and inflammatory mediators, thereby predisposing to hepatocellular injury and fibrogenesis. Ethanol exposure alters the gut microbiome, leading to reduced microbial diversity and dysbiosis, as well as directly impairs intestinal barrier integrity. This activates the immune system leading to local inflammation with releases of cytokines. These mechanisms lead to translocation of microbial products (PAMPs) and cytokines via the portal venous system to the liver. Here they activate a hepatic immune response and contribute to hepatic inflammation, which in turn promotes stellate cell activation and fibrogenesis. B, Hepatic injury occurs through several pathways. The first pathway is the direct hepatotoxicity, in which ethanol metabolism via alcohol dehydrogenase and CYP2E1 generates acetaldehyde, reactive oxygen species, lipid peroxidation products and a disturbed NADH/NAD^+ balance, leading to hepatocyte injury, cell death, and release of damage associated molecular patterns (DAMPs), thereby triggering immune cells leading to inflammation and activation of hepatic stellate cells with extracellular matrix deposition. The second pathway is the metabolic lipotoxicity, whereby ethanol induces a metabolic shift including reduced beta oxidation that promotes lipid accumulation, steatosis, endoplasmic reticulum stress, and formation of lipotoxic species, resulting in hepatocyte injury and inflammation. This pathway may be exacerbated by underlying metabolic dysfunction, including insulin resistance and overweight. Genetic susceptibility shared between metabolic dysfunction–associated steatotic liver disease (MASLD) and ALD is also thought to relate to this pathway, as most identified risk variants affect hepatic lipid handling (PNPLA3, HSD17B13, and TM6SF2), independent of insulin resistance or overweight. The third pathway is gut derived, in which ethanol induced dysbiosis and barrier dysfunction lead to increased translocation of microbial products to the liver, activation of hepatic immune responses, stellate cell activation, and extracellular matrix deposition. All 3 pathways lead to progression of liver fibrosis, which ultimately disrupts liver architecture and predisposes to decompensation and hepatocellular carcinoma.

correction for underreporting of alcohol use were 2.0% for metabolic dysfunction and ALD, 0.7% for ALD, and 31.3% for MASLD.[13] However, in an analysis of NHANES data from 2021 to 2023, prevalence estimates corrected for underreporting of alcohol use were 4.10% for metabolic dysfunction and ALD, 4.59% for ALD, and 28.16% for MASLD.[30] The lower reported prevalence of ALD compared with MASLD is likely multifactorial,[31] including underreporting of alcohol use because of stigma, culture, religion, difficulty recalling quantity or standard drink sizes, or having reduced or stopped drinking in the preceding year.[31-33]

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A systematic review and meta-analysis of 35 prospective or retrospective cohort studies involving 513 278 individuals in 15 countries undergoing evaluation for ALD with biochemistry, imaging (including vibration-controlled transient elastography), and liver biopsy reported an ALD prevalence of 3.5% in the general population, 26.0% among those with hazardous drinking (study-specific definitions), and 55.1% among those with alcohol use disorder (AUD).[34] A meta-analysis of 38 observational cohort studies of 120 928 individuals with alcohol-related health problems reported incidence of alcohol-related cirrhosis of 7% to 16% after 8 to 12 years.[35] Based on NHANES data, the prevalence of advanced liver disease (defined as FIB-4 score >2.67) among individuals in the US with heavy alcohol use and metabolic syndrome increased from 3.0% in 1999 to 10.8% in 2018.[36]

Risk Factors

The primary risk factors for ALD are high levels of alcohol consumption and prolonged duration of alcohol use,[37,38] including both daily alcohol consumption[39,40] and heavy episodic drinking (≥4 drinks for women and ≥5 for men on a single occasion).[41] Alcohol-induced steatosis develops within a few weeks in 90% of individuals consuming more than 60 g per day of ethanol, whereas cirrhosis usually develops only after decades of chronic alcohol use.[42] Although ALD is commonly defined by long-term intake of alcohol exceeding 20 g per day in women and 30 g per day in men, no safe limit of alcohol intake has been established, and individual susceptibility to ALD varies. Reports of lower ALD risk with wine than with beer or spirits may reflect confounding because wine consumption is associated with higher socioeconomic status and fewer comorbidities.[39,43]

Other risk factors for ALD include older age, female sex, obesity, type 2 diabetes, coexisting liver disease such as chronic viral hepatitis B and C, and genetic variants involved in hepatic fat accumulation (eg, *PNPLA3, TM6SF2, HSD17B13*).[12,22,44,45] Women generally have greater susceptibility to ALD than men at any alcohol consumption level, owing in part to lower body water and reduced first-pass alcohol metabolism.[46]

Tobacco smoking is also associated with ALD progression and increased risk of HCC.[47] In contrast, a healthy diet (assessed by multiple-item dietary scores such as the Healthy Eating Index), regular physical activity (defined as 150 minutes/week), and coffee consumption are associated with lower ALD-related morbidity and mortality.[48-50]

Clinical Presentation

Most patients (90%) with ALD without alcohol-associated hepatitis or cirrhosis are asymptomatic[51] and have normal or mildly elevated liver function test results (aspartate aminotransferase, alanine transaminase, and gamma-glutamyl transferase) and/or hepatic steatosis on imaging (abdominal ultrasonography, computed tomography, magnetic resonance imaging). Patients with alcohol-associated hepatitis typically present with fever, anorexia, nausea, vomiting, abdominal pain, and jaundice.[12]

In contrast, up to 70% of patients with ALD and compensated cirrhosis are asymptomatic, and the remainder experience fatigue or occasional abdominal pain.[51] Patients with ALD and decompensated cirrhosis may present with ascites, gastrointestinal bleeding, jaundice, and/or hepatic encephalopathy.[28] Physical examination findings with high specificity for cirrhosis include jaundice (0.93), spider angiomas (0.89), ascites (0.95), splenomegaly (0.90), and palmar erythema (0.91), but sensitivity is low (0.28, 0.46, 0.35, 0.34, and 0.46, respectively).[52] Patients with clinical signs of cirrhosis should be referred to a hepatologist.

Assessment and Diagnosis

Clinicians should consider the diagnosis of ALD in patients with a history of harmful alcohol intake (exceeding 20 g/d in women and 30 g/d in men), prolonged abnormal liver enzymes (>6 months), and/or hepatic steatosis on imaging (**Figure 2**).[42,53] Patients with prolonged abnormal or very elevated liver enzymes should undergo testing for viral hepatitis (hepatitis B and C), autoimmune conditions (eg, autoimmune hepatitis, primary biliary cholangitis), and hereditary liver diseases (eg, hereditary hemochromatosis, Wilson disease, alpha 1 antitrypsin deficiency). Clinicians should routinely assess for alcohol use in individuals with type 2 diabetes and obesity because a substantial proportion may have concomitant alcohol use that can contribute to liver disease (Figure 2). More than 95% of patients with ALD have at least 1 cardiometabolic risk factor[10,13] and approximately one-quarter meet criteria for metabolic syndrome.[44,54] If heavy alcohol consumption is not recognized, these patients may be misclassified as having MASLD[55-57] (Figure 2).

Assessment of Alcohol Use in Patients With ALD

The assessment of alcohol intake and AUD should be approached in a structured, nonjudgmental manner to ensure an accurate and clinically relevant evaluation. Clinicians should quantify alcohol consumption (eg, mean grams per day or drinks per week) and use validated screening tools such as the Alcohol Use Disorders Identification Test to identify AUD.[58]

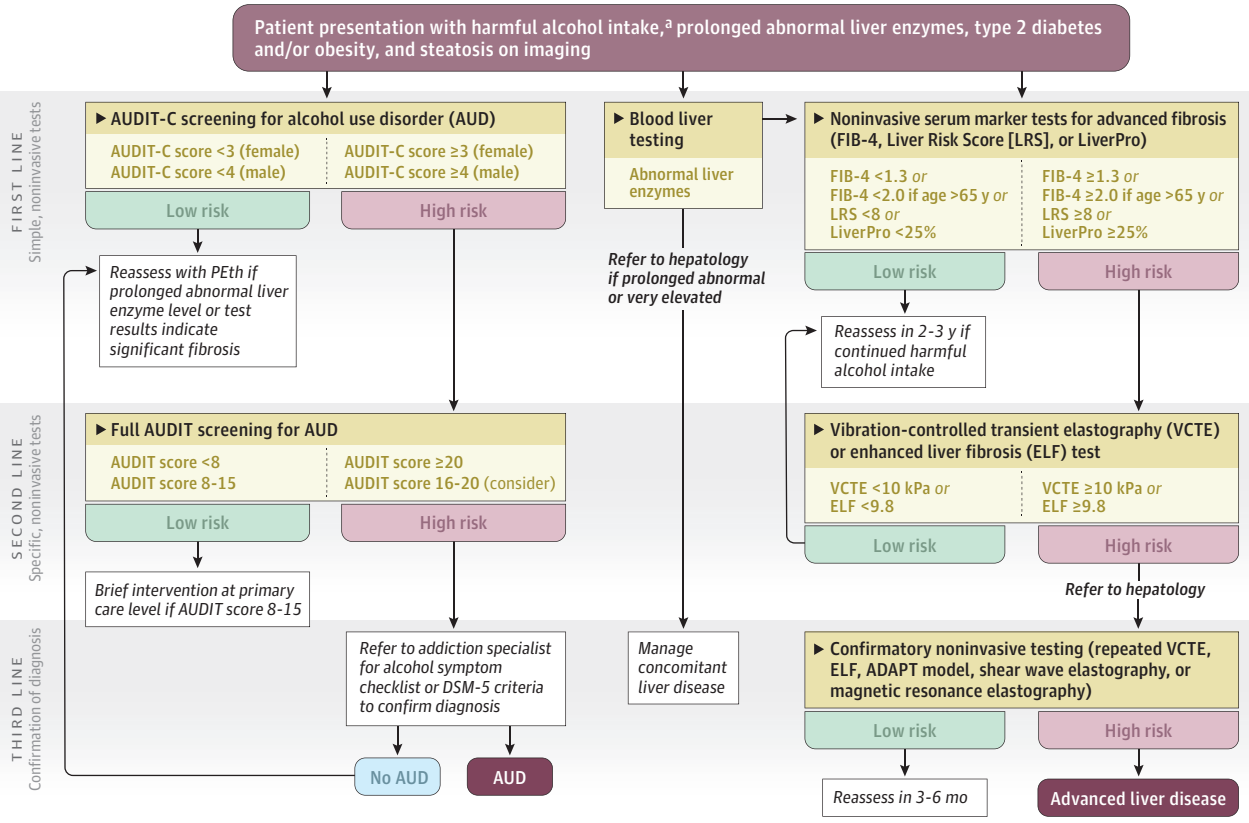
Direct ethanol metabolites such as phosphatidylethanol[59] and ethyl glucuronide are biomarkers that detect recent alcohol consumption (within the prior 3 to 4 weeks for phosphatidylethanol and within the prior 5 days for ethyl glucuronide).[32] These biomarkers can be ordered by generalists and gastroenterologists and are highly accurate for detecting recent alcohol consumption within their respective detection windows,[32] but do not provide precise quantification of the amount consumed.[60] Before ordering these tests, clinicians should explain to patients that alcohol biomarkers are useful to help detect alcohol consumption that may be difficult to discuss and may be helpful for making decisions about treatment.[61] Current clinical guidelines recommend use of alcohol biomarkers as adjuncts to clinical interview and surveys among patients with liver disease who do not self-report active heavy drinking, with the choice of test guided by when alcohol was thought to have been last consumed.[62] Among patients with steatotic liver disease, higher phosphatidylethanol levels correlate with more advanced stages of liver disease and fibrosis progression and greater risk of cirrhosis, liver decompensation events, need for liver transplant, and liver-related mortality[63-65] (**Figure 3**; eTable 1 in the Supplement).

Assessment of Liver Fibrosis in Patients With ALD

Based on guidelines from the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, first-line testing for assessment of liver fibrosis is performed

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Figure 2. Diagnostic Pathway for Assessment of Alcohol Use Disorder and Liver Fibrosis in Individuals at Risk of Steatotic Liver Disease (SLD)



The figure illustrates a parallel, stepwise diagnostic approach integrating evaluation of alcohol use disorder and liver fibrosis in individuals at risk of SLD. Individuals are considered at risk of SLD if 1 or more of the following criteria are present: harmful alcohol intake (defined as >30 g/d in men and >20 g/d in women), prolonged abnormal liver enzymes (defined as persistently elevated liver biochemistry for ≥6 months), hepatic steatosis detected on imaging, or presence of type 2 diabetes or obesity. Individuals with obesity and type 2 diabetes undergoing assessment for liver fibrosis should also be systematically assessed for alcohol intake, as a substantial proportion may have concomitant alcohol use that would otherwise remain unrecognized and may contribute to liver disease. ADAPT, algorithm including age, presence of diabetes, PRO-C3, and platelet count; AUDIT, alcohol use disorders identification test; AUDIT-C, Alcohol Use Disorders Identification Test–Consumption; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; FIB-4, Fibrosis-4 Index; LRS, liver risk score; MRE, magnetic resonance elastography; NIT, noninvasive test; PEth, phosphatidylethanol.

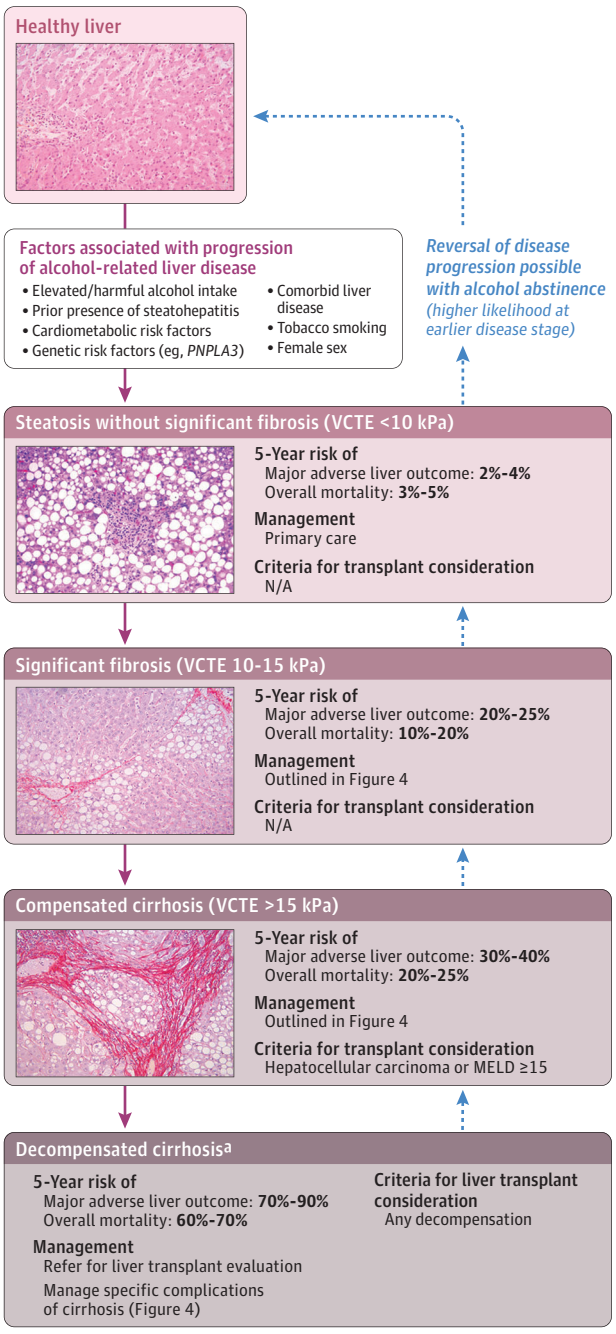
[a]Given the modest sensitivity of FIB-4, some guidelines, including the American Gastroenterological Association guidelines on metabolic dysfunction–associated steatotic liver disease, recommend direct second-tier testing in high-risk groups (eg, type 2 diabetes); this may also be considered in prolonged harmful alcohol intake, although evidence is limited.

with noninvasive tests such as the Fibrosis-4 (FIB-4) score (calculated using alanine transaminase, aspartate aminotransferase, platelet count, and age) (eTable 2 in the Supplement).[70,71] The FIB-4 score, which can be calculated by generalists, is useful as an initial screening test due to its high negative predictive value for ALD (0.83), but its sensitivity is only 0.70 in low-prevalence settings.[72] Patients with FIB-4 score greater than or equal to 1.3 should proceed to secondary testing, which includes vibration-controlled transient elastography (VCTE), an ultrasound imaging method that quantifies liver stiffness and hepatic steatosis using the controlled attenuation parameter, or proprietary blood tests such as Enhanced Liver Fibrosis (ELF) score or N-terminal propeptide of type III collagen, which measures circulating biomarkers, including type III collagen fragments. For patients with FIB-4 scores greater than 2.67, secondary testing results suggesting stage 2 or higher liver fibrosis, or persistently elevated liver enzymes with unclear cause, referral to a gastroenterologist or hepatologist for further assessment is recommended. Other recently developed models (eTable 2 in the Supplement),[73-75] which use standard laboratory parameters, have higher diagnostic accuracy for identification of liver fibrosis and prognostic discrimination, but have not been evaluated for inclusion in current clinical guidelines.[76,77]

Current European Association for the Study of the Liver and American Association for the Study of Liver Diseases guidelines[76,77] recommend that individuals at low risk of liver fibrosis based on first-line noninvasive test results should be rescreened after 2 to 3 years, particularly if they continue to consume alcohol. For patients with noninvasive test results indicating intermediate or high risk of liver fibrosis, second-line noninvasive tests (eg, VCTE, ELF test) provide information about fibrosis severity and help stratify the risk of developing liver-related complications. A screening study of 953 patients with ALD reported that use of FIB-4 followed by an ELF test correctly classified patients as having normal or elevated liver stiffness (measured by VCTE) in approximately 85% of patients compared with approximately 60% with FIB-4 alone.[78] A study of 462 patients with ALD reported that only 3% to 5% of patients

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Figure 3. Graphical Timeline of the Natural History of Alcohol-Related Liver Disease Including Prognosis



Estimated risk of liver related events and mortality based on observational studies (eTable 4 in the Supplement).[66-68] Major adverse liver outcome defined as a composite of decompensation (hepatic encephalopathy, bleeding esophageal varices, ascites), hepatocellular carcinoma, liver transplant, or liver-related death. Histology images were adapted from the review by Singal and Mathurin.[69] MELD indicates Model for End-Stage Liver Disease; N/A, not applicable; VCTE, vibration-controlled transient elastography.

[a]Presence of ascites, hepatic encephalopathy, or variceal bleeding.

with low-risk noninvasive test results (VCTE <10 kPa or ELF <9.8) developed liver-related complications within 5 years vs 53% to 54% of those with high-risk noninvasive test results (VCTE >15 kPa or ELF >10.5) (hazard ratio [HR], 28.0 [95% CI, 13.8%-56.8%]).[66] N-terminal propeptide of type III collagen achieved similar accuracy for prognostic discrimination and diagnosing advanced fibrosis[67] (Figure 2).

However, second-line noninvasive tests may produce false-positive results. For example, among 1491 participants who had elevated liver stiffness values (>8 kPa), based on screening VCTE, 715 (48%) had VCTE values below this threshold at the subsequent hepatology assessment.[79] Third-line testing, which may be performed to confirm an elevated second-line testing result, includes specialized modalities such as shear-wave elastography integrated into standard ultrasonography and magnetic resonance–based elastography, which are typically only available at tertiary referral centers.

Liver biopsy is rarely required for the diagnosis, staging, or management of ALD, and is generally only indicated if concomitant liver diseases are suspected, such as autoimmune liver disease, hereditary liver disease, or viral hepatitis if serology results are not diagnostic.[42] Liver biopsy may also be considered for patients with suspected alcohol-associated hepatitis if the diagnosis is unclear or may be used in research settings.

Prospective studies suggest that detection of liver fibrosis can serve as a behavioral motivator. In a prospective cohort study of 1850 Danish individuals with a history of harmful alcohol intake who underwent noninvasive liver fibrosis assessment, excessive drinking declined from 46% at baseline to 32% after 6 months.[80] A positive fibrosis screen result (transient elastography ≥8 kPa) was associated with abstinence or reduced alcohol use at 6 months (odds ratio [OR], 2.45 [95% CI, 1.32-4.57]) and 2 years (OR, 1.84 [95% CI, 1.09-3.11]).[80] In a prospective cohort study of 334 individuals in Spain with AUD undergoing noninvasive liver fibrosis assessment, 149 of 334 (45%) were abstinent at 6 months vs 40 of 137 (29%) in the matched control cohort who did not undergo noninvasive liver fibrosis assessment.[81] Similarly, a trial of 184 participants in the UK with AUD were randomized 1:1 to undergo usual care plus transient elastography-based fibrosis assessment with tailored feedback or usual care alone. Among the 52 participants who underwent fibrosis assessment, 67.3% (35 of 52) reduced or stopped drinking, compared with 43.9% of controls, and median daily alcohol intake decreased by 22.5 units vs 17.5 units in controls.[82]

Treatment

Patient-centered, holistic management of alcohol-related liver disease requires stage-adapted care that evolves from compensated to decompensated liver disease together with ongoing assessment and treatment of alcohol use and general medical care, including cardiometabolic risk reduction (**Figure 4**).

The goal of treatment for ALD is to achieve alcohol abstinence, and it may involve behavioral therapy and/or medication-assisted treatment. Choice of therapy depends on the amount of alcohol consumption and the presence and severity of AUD, which is characterized by inability to stop or decrease alcohol use despite negative effects on health or on social or occupational functioning and is diagnosed as mild, moderate, or severe.[83]

Behavioral Therapy to Promote Alcohol Cessation

A systematic review of 10 randomized trials that included 1519 participants with AUD and ALD[84] reported increased alcohol abstinence

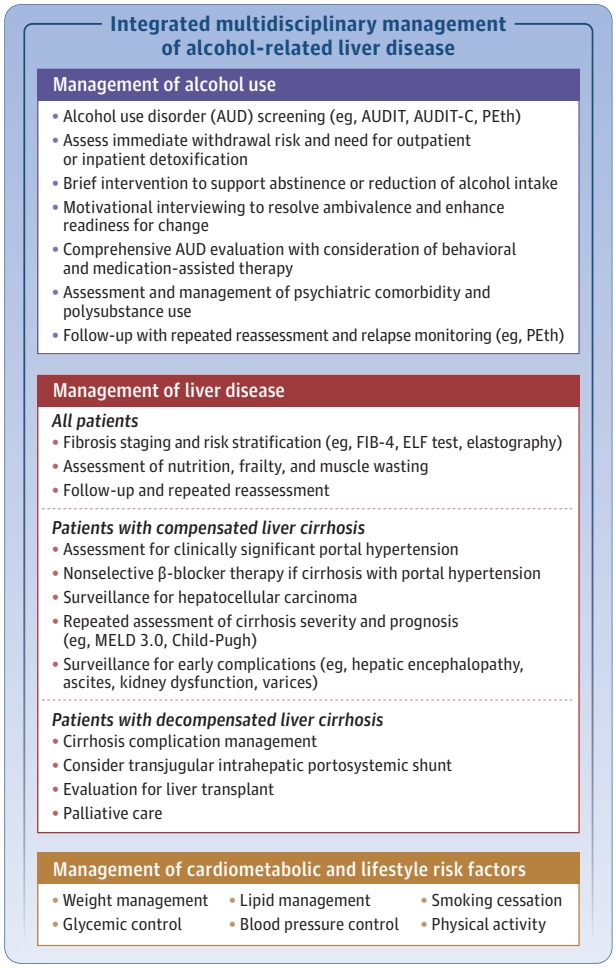
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with motivational enhancement therapy (MET), a 4-session, counselor-delivered motivational intervention with liver health feedback and specific counseling on alcohol's effect on liver health (percentage of days abstinent at 6 months, 73.1% with MET vs 59.5% with control; $P < .02$),[85] and cognitive behavioral therapy (CBT) with MET (percentage of days abstinent at 2 years, 74% with CBT and MET vs 48% with control; $P = .02$).[86] More severe AUD may require residential inpatient treatment and/or intensive outpatient programs followed by individual or group therapy.[87] A 2025 meta-analysis of 9 randomized and 16 nonrandomized studies reported lower mortality for 1623 patients with ALD in pre– and post–liver transplant phases of care who received integrated alcohol care, which involved alcohol and medical care provided in the same clinical setting (adjusted hazard ratio, 0.44 [95% CI, 0.28-0.68]; $P < .001$; absolute rates not available).[88]

Medication-Assisted Treatment to Promote Alcohol Cessation

There are 3 US Food and Drug Administration (FDA)–approved medications (naltrexone, acamprosate, disulfiram) and several off-label medications (gabapentin, baclofen, topiramate) for treatment of AUD (eTable 3 in the Supplement). However, baclofen is the only medication tested in randomized clinical trials in patients with ALD and cirrhosis. In a trial of 84 patients with ALD cirrhosis, abstinence from alcohol at 12 weeks was higher among patients randomized to receive baclofen (10 mg 3 times daily) (30 of 42 [71%]) vs placebo (12 of 42 [29%]) (OR, 6.3 [95% CI, 2.4-16.1]; $P < .001$).[89] In a randomized clinical trial of 104 patients with AUD, 58 (56%) had ALD, of whom 45 (43% of the total cohort) had cirrhosis. A significant treatment effect of baclofen was observed for percentage days abstinent from alcohol: 69% with baclofen 30 mg daily, 65% with baclofen 75 mg daily, and 43% with placebo ($P < .05$).[90] However, the proportion of patients who remained continuously abstinent throughout the 12 week follow-up (7 of 33 [21%] with baclofen 30 mg daily, 7 of 31 [23%] with baclofen 75 mg daily, and 3 of 31 [10%] with placebo) was low and did not differ significantly between the groups ($P = .15$).[90] Baclofen has low addictive potential. Case reports have shown severe adverse events with abrupt withdrawal of baclofen, and the FDA label includes a warning to avoid abrupt discontinuation.[91] Patients should be counseled to avoid abrupt discontinuation due to the potential for severe adverse reactions with sudden withdrawal of the medication. Naltrexone, a μ-opioid receptor antagonist, is safe to use in patients without cirrhosis or alcohol-associated hepatitis, but should be used with caution in patients with decompensated cirrhosis or alcohol-associated hepatitis. In a retrospective cohort study of 9635 patients with AUD, pharmacotherapy for AUD was associated with lower incidence of liver decompensation in patients with cirrhosis (adjusted OR, 0.35 [95% CI, 0.23-0.53]), including naltrexone (adjusted OR, 0.27 [95% CI, 0.10-0.64]) and gabapentin (adjusted OR, 0.36 [95% CI, 0.23-0.56]) (absolute rates not available).[92] Although disulfiram is FDA approved for AUD, it is not recommended in patients with ALD due to the risk of hepatotoxicity.[42] A randomized, double-blind, placebo-controlled trial of 108 patients with obesity and AUD reported a significantly greater reduction in heavy drinking days at 26 weeks compared with baseline in those assigned to receive a glucagon-like peptide-1 receptor agonist (2.4 mg of semaglutide subcutaneously weekly) vs placebo (−41.1% [95% CI, −48.7 to −33.5] vs −26.4 [95% CI, −34.1 to −18.6]; estimated treatment difference, −13.7% [95% CI, −22.0% to −5.4%]; $P = .0015$).[93]

Figure 4. Patient-Centered, Holistic Management of Alcohol-Related Liver Disease



A surrounding societal context strongly influences access to care, continuity of treatment, and clinical outcomes but is often beyond the direct control of clinicians. AUD indicates alcohol use disorder; AUDIT-C, Alcohol Use Disorders Identification Test–Consumption; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4 Index; MELD, Model for End-Stage Liver Disease; PEth, phosphatidylethanol.

Medications for ALD

There are currently no FDA-approved medications for ALD, though several phase 2 clinical trials are ongoing (eTable 5 in the Supplement). Recommended treatment for acute alcohol-associated hepatitis is use of prednisolone, 40 mg daily for 7 days with continuation for 28 days if improvement is noted, in patients without infection, active gastrointestinal bleeding, or hepatorenal syndrome who have severe disease (Maddrey discriminant function ≥32 or Model for End-stage Liver Disease [MELD] 3.0 score ≥21).[69] Complications of ALD cirrhosis (variceal bleeding, ascites and acute kidney injury, spontaneous bacterial peritonitis, and hepatic encephalopathy) should be treated similarly to cirrhosis of other etiologies and is beyond the scope of this review.[28,83]

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Liver Transplant

In the US in 2023, a total of 3505 liver transplants were performed for patients with alcohol-associated cirrhosis and 658 were performed for patients with alcohol-associated hepatitis.[94] ALD is currently the most common indication for liver transplant in the US, increasing from 17% of total liver transplants in 2012 to 41% in 2023.[95,96] The MELD 3.0 score, which incorporates plasma bilirubin, creatinine, international normalized ratio, sodium, albumin, and sex, can be used to evaluate the need for and urgency of liver transplant. The MELD score ranges from 6 to 40, with higher scores indicating greater risk of mortality. Patients with a MELD score of 10 or higher should generally undergo referral for liver transplant evaluation.[42]

A survey published in 2024 reported that 97% of US centers currently offer early liver transplant (with less than 6 months of alcohol abstinence) for carefully selected patients with ALD.[97] Prior to 2011, 6 months of sustained abstinence from alcohol was generally mandated in the US prior to consideration for liver transplant. The first US multicenter study in early liver transplant for alcohol-associated hepatitis was published in 2018.[98] Across 12 US centers, 147 patients carefully selected for strong social support, favorable psychosocial profile, first decompensation of liver disease, and commitment to lifelong alcohol abstinence underwent liver transplant for acute alcohol-associated hepatitis without 6 months of prior abstinence from alcohol.[99] Posttransplant survival was 94% (95% CI, 89%-97%) at 1 year and 84% (95% CI, 75%-90%) at 3 years, compared with a predicted 6-month survival of less than 20% based on a median MELDNa and Lille model scores.[98] In this study, sustained alcohol use was 10% (95% CI, 6%-18%) at 1 year post transplant and 17% (95% CI, 10%-27%) at 3 years post transplant; sustained alcohol use was the strongest risk factor for posttransplant death (HR, 4.59; $P = .01$).[99]

A trial of patients with severe alcohol-associated hepatitis reported similar 2-year posttransplant survival for 61 of 68 early liver transplant recipients (90%) compared with 81 of 93 patients (87%) who underwent liver transplant after 6 months of abstinence. However, the early transplant group had non–statistically significant higher alcohol relapse rates at 2 years compared with those who underwent transplant after 6 months of abstinence from alcohol (34% vs 25%; relative risk, 1.45 [95% CI, 0.82-2.60]).[100]

Treatment of Cardiometabolic Risk Factors

Among patients with ALD, diagnosis and treatment of cardiometabolic risk factors such as diabetes and obesity is recommended by guidelines to decrease the risk of liver-related[42] and cardiovascular-related events (eTable 4 in the Supplement).[14-16,101] Lifestyle modification, including smoking cessation, increased exercise (at least 150 minutes of moderate-intensity activity, minimize sedentary time), improved diet quality (increased fiber, vegetables, and fruits and reduced sugar-sweetened beverages, ultraprocessed food, and processed meat), and medications such as statins for dyslipidemia and glucagon-like peptide-1 receptor agonists for obesity and diabetes, have demonstrated safety and efficacy among patients who have minimal to advanced stages of liver fibrosis (**Table**).[96,102-110]

Prognosis

ALD prognosis depends on liver fibrosis stage and continuation of alcohol use.[4,66] Reductions in alcohol use, alcohol cessation, and AUD treatment engagement are associated with longer-term survival.[68,88,111] In patients with steatosis without liver fibrosis, liver injury is reversible within weeks of alcohol abstinence and can lead to complete resolution of ALD.[112] In a prospective cohort study of 446 patients with a history of excessive alcohol use, compared with patients without steatotic liver disease, those with ALD had increased overall mortality (HR, 3.57 [95% CI, 1.64-7.80]) after adjustment for disease severity at diagnosis (absolute rates not available).[10] In a single-center prospective observational study of 320 patients with ALD cirrhosis, over a median follow-up of 36 months, 241 patients (75.3%) remained abstinent and 79 (24.7%) continued alcohol consumption. Alcohol abstinence was associated with reduced risk of liver-related mortality (median survival, 97.9 [95% CI, 62.0-133.8] months vs 52.8 [95% CI, 35.4-70.2] months; $P < .001$; adjusted HR, 0.43 [95% CI, 0.26-0.72]) and all-cause mortality (adjusted HR, 0.45 [95% CI, 0.30-0.69]).[111]

In a US Department of Veteran Affairs study, among a subgroup of 129 642 patients with baseline high-risk alcohol use (defined as Alcohol Use Disorders Identification Test–Consumption score ≥3 for women and ≥4 for men), those reporting decreased alcohol use during median follow-up of 9.1 years had a reduced incidence of cirrhosis compared with those who did not decrease alcohol use (0.52 vs 0.77 per 100 person-years; HR, 0.61 [95% CI, 0.45-0.83]). However, many studies have reported that continued use of alcohol at low levels (1-6 drinks/week), particularly in patients with cirrhosis, is associated with increased morbidity and development of ascites, hepatic encephalopathy, variceal bleeding, and mortality.[37,68,113]

ALD prognosis may also be affected by access to specialist care. For example, in a study examining ALD-related deaths between 2010 and 2019 in the US, increased state-level density of gastroenterologists was associated with lower ALD-related mortality, with 9.0 (95% CI, 1.3-16.7) fewer ALD-related deaths per 1 000 000 population for each additional gastroenterologist per 100 000 population.

In the US in 2023, ALD caused 28 632 deaths from alcohol-associated cirrhosis, accounting for 50.3% of all deaths from cirrhosis.[114] In a US national analysis, ALD-related mortality increased from 6.71 (95% CI, 6.59-6.83) deaths per 100 000 in 1999 to 12.53 (95% CI, 12.38-12.67) per 100 000 in 2022, with a significant acceleration from 2018 and 2022 (annual percentage change, 8.94% [95% CI, 6.27%-14.51%]).[3]

A study of 23 385 patients with incident ALD in Denmark reported 1-, 5-, and 15-year mortality rates of 26%, 53%, and 81%, respectively. The 5-year risk of liver-related mortality after ALD diagnosis was 25.8% (95% CI, 25.3%-26.4%), whereas cancer, cardiovascular disease, and AUD were predominant causes of death after 5 years.[8] Hepatocellular carcinoma was the most common cause of cancer-related death, and 10-year risk of death from hepatocellular carcinoma was 2.5% (95% CI, 2.3%-2.7%).[8] In a prospective cohort study of 192 patients with liver biopsy–proven ALD, 77 (40%) died from liver-related complications and 11 (5.7) died from non–liver-related causes over a median follow-up of 4.1 years.[115]

In a 2023 nationwide analysis from Sweden, among 22 658 patients with ALD cirrhosis, the mean loss in life expectancy matched to patients in the general population for age, sex, and calendar year of diagnosis was 14.3 years for men and 15.8 years for women, with life-years lost exceeding 25 years among patients aged 18 to 49 years.[116]

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Table. Use of Medications to Treat Cardiometabolic Risk Factors in Chronic Liver Disease

	GLP-1 RA	SGLT2 inhibitor	Pioglitazone	Metformin	Statins	ACE inhibitor/ARB
Primary cardiometabolic indication	Type 2 diabetes, obesity, MASH	Type 2 diabetes, heart failure, chronic kidney disease, ASCVD risk in type 2 diabetes	Type 2 diabetes	Type 2 diabetes	Dyslipidemia ASCVD risk	Arterial hypertension
Liver benefits in prospective studies	Decreased steatosis, steatohepatitis, and fibrosis ESSENCE (wk 72; n = 800): MASH resolution, 62.9% vs 34.3% with placebo (difference, 28.7%); fibrosis improvement, 36.8% vs 22.4% (difference, 14.4%); both $P < .001$ Semaglutide FDA-approved for MASH F2-F3 (noncirrhotic)[102]	Decreased steatosis; limited biopsy data (MRI-PDFF end points) Empagliflozin 10 mg for 52 wk: median PDFF, −2.49% vs −1.43% with placebo ($P = .025$); steatosis resolution, 44.9% vs 28.6% (NS)[103]	Decreased steatosis and individual steatohepatitis features; fibrosis effect uncertain Cusi et al[104] (45 mg): NASH and prediabetes or type 2 diabetes: NASH resolution, 51% vs 19% (difference, 32%); ≥2-pt NAS reduction, 58% (difference, 41%); $P < .001$ PIVENS (30 mg): histologic improvement, 34% vs 19% placebo ($P = .04$; NS at prespecified threshold); no fibrosis benefit[105]	Histology neutral TONIC RCT: no ALT superiority vs placebo; NASH resolution, 41% vs 28% with placebo ($P = .23$, NS)[96]	Decreased portal hypertension: simvastatin (20 to 40 mg) lowered HVPG −8.3% vs no change with placebo (1-mo study); durability and clinical significance unclear[106]	No RCT data for histology Observational data suggests association with decreased liver related events[107]
Suitability of use in liver cirrhosis						
Compensated[a]	Yes (limited long-term data)	Yes (limited long-term data)	Yes	Yes	Yes	Yes
Decompensated[a]	Limited data	Child-Pugh B only	Not recommended	Not recommended	Limited data in Child-Pugh C[b]	Avoid if ascites
Practical considerations	Gastrointestinal adverse effects (nausea, diarrhea, constipation) common; careful titration and monitoring May reduce alcohol craving and consumption (phase 2 AUD RCT) Caution in sarcopenia[108]	Genital mycotic infections; can worsen hypovolemia; rare diabetic ketoacidosis	Edema, weight gain (approximate gain of 2.5 kg vs placebo in study by Cusi et al[104]), fracture risk Caution in heart failure Weight gain possibly mitigated by lower dosing or combination with GLP-1 RA or SGLT2 inhibitor	Risk for lactic acidosis Avoid when eGFR<30 mL/min Contrast agent or acute illness precautions	Lower doses in Child-Pugh B-C (eg, simvastatin maximum 20 mg/d) Monitor for muscle and liver toxicity Transient transaminase elevation common, but DILI uncommon; generally safe in compensated cirrhosis	Monitor kidney function and potassium

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine transaminase; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; AUD, alcohol use disorder; DILI, drug-induced liver injury; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HVPG, hepatic venous pressure gradient; MASH, metabolic dysfunction–associated steatohepatitis; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, Nonalcoholic Fatty Liver Disease Activity Score; NASH, nonalcoholic steatohepatitis; NS, not significant; SGLT2, sodium–glucose cotransporter 2; RCT, randomized clinical trial.

[a] Among patients with cirrhosis, decompensated refers to the presence of either ascites, hepatic encephalopathy, or variceal bleeding; compensated refers to their absence.

[b] Can be considered in select patients by experts.

Practical Considerations

Delayed diagnosis of ALD is common and associated with increased risk of liver complications and death. A registry-based study in Denmark reported that 40% of 7719 patients with ALD cirrhosis had at least 1 prior inpatient admission, outpatient visit, or emergency department visit related to alcohol problems, and 15% had more than 5 medical encounters prior to diagnosis of ALD.[117] Reasons for late diagnosis may include internalized shame, negative societal attitudes toward ALD/AUD, and institutional and certain governmental rules, policies, and practices such as inadequate insurance coverage, limited reimbursement for alcohol-related treatment, clinician shortages, and restricted access to evidence-based addiction services.[118,119]

The most effective public health and policy interventions to reduce population-level alcohol use and ALD include increased pricing and marketing and access restrictions.[120] In Scotland and Ireland, implementation of a fixed lower limit on the price of a unit of alcohol for sale on May 1, 2018, was associated with a 12% reduction in alcohol-attributable deaths, including those related to ALD and cirrhosis, and a 10% reduction in ALD-related hospitalizations over the next 32 months.[99,121]

Limitations

This review has several limitations. First, study quality was not formally assessed. Second, most evidence on ALD is based on self-reported alcohol intake, which may be inaccurate due to recall bias, underreporting, stigma, and social desirability bias. Third, acute alcohol-associated hepatitis was not discussed in detail. Fourth, relevant articles may have been missed.

Conclusions

People with chronic daily heavy alcohol consumption should be assessed for ALD with noninvasive testing to enable timely diagnosis and intervention. The primary goal is alcohol cessation. Patients with severe alcohol-associated hepatitis or decompensated should be considered for liver transplant.

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