

Alcohol-Associated Liver Disease and Alcoholic Hepatitis: Pathophysiology and therapeutic strategies.

Jebastin Jacob I¹, Chinnakkaruppan C¹, Mrs. R. Rajakumari¹,

¹Associate Professor, Department of Pharmaceutical Biotechnology, PPG College of Pharmacy, Coimbatore, Tamil Nadu, India

Corresponding author: jebastinjacob10@gmail.com

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Abstract

Alcohol-associated liver disease (ALD) remains a primary driver of global hepatology-related mortality, presenting a progressive pathological continuum that terminates in cirrhosis and hepatocellular carcinoma. Within this spectrum, alcoholic hepatitis (AH) represents a critical, acute inflammatory crisis that carries an alarmingly high short-term mortality rate and demands immediate clinical intervention. This comprehensive review examines the multifaceted pathogenesis driving AH, focusing on the interplay between CYP2E1-mediated oxidative stress, toxic acetaldehyde accumulation, and gut dysbiosis-induced macrophage activation. Given the rising burden of chronic liver disease in India—where shifting lifestyles and metabolic factors increasingly intersect with heavy alcohol use—we highlight the evolving epidemiological landscape and existing public health gaps. We evaluate current diagnostic paradigms, assessing the clinical utility of traditional markers alongside emerging non-invasive indicators like cytokeratin-18. Finally, we scrutinize modern therapeutic strategies; while absolute abstinence and nutritional rehabilitation form the bedrock of management, we deliberate on the limits of standard corticosteroid regimens and explore the clinical horizons of gut-microbiota modulation and mesenchymal stem cell therapies.

Key words:

Alcohol-associated liver disease (ALD), alcoholic hepatitis, gut-liver axis, oxidative stress, cytokeratin-18, corticosteroids, liver transplantation, mesenchymal stem cells, clinical biomarkers, public health burden (India).

Introduction

The clinical spectrum of alcohol-associated liver disease (ALD) represents a profound global health crisis and a primary driver of chronic hepatic morbidity worldwide. Prolonged ethanol consumption initiates a progressive pathological cascade within the hepatic parenchyma. This continuum typically originates as simple, reversible hepatic steatosis before advancing into alcoholic steatohepatitis (ASH), accelerated fibrogenesis, irreversible cirrhosis, and ultimately, hepatocellular carcinoma (HCC). While baseline steatosis frequently resolves with abstinence, continued metabolic insult triggers persistent inflammation and profound cellular injury. This chronic damage often precipitates an acute, life-threatening clinical crisis: alcoholic hepatitis (AH). Clinically, AH is characterized by the abrupt onset of profound icterus, systemic malaise, low-grade pyrexia, tender hepatomegaly, and rapidly escalating hepatic decompensation. Because severe presentations carry an alarmingly high short-term mortality rate, expedited diagnosis and immediate, targeted therapeutic interventions are critical.

The underlying pathogenesis of AH is dictated by a complex, multi-hit mechanism involving direct, metabolite-mediated hepatocyte damage and a hyper-activated systemic immune response. At the cellular level, this destructive process is driven by:

- * Severe CYP2E1-mediated oxidative stress and the accumulation of cytotoxic acetaldehyde adducts.
- * Profound mitochondrial dysfunction and energy failure.
- * Distinct disruption of the gut-liver axis, allowing the translocation of gut-derived endotoxins (lipopolysaccharides) into the portal circulation.
- * Activation of Toll-like receptors on resident Kupffer cells, fueling an unmitigated release of pro-inflammatory cytokines.

Beyond localized hepatic destruction, chronic heavy alcohol consumption severely disrupts systemic homeostasis. It frequently induces severe protein-energy malnutrition and escalates the risk for multi-organ complications, including cardiovascular instability, neurological degradation, chronic pancreatitis, and gastrointestinal dysmotility. Yet, despite substantial strides in unravelling the molecular and genetic pathways governing ALD, current pharmacological options remain limited. Standard-of-care regimens centred on systemic corticosteroids yield only modest, short-term survival benefits in strictly selected subsets of patients, while definitive options like orthotopic liver transplantation remain restricted by organ scarcity and rigorous psychosocial selection criteria.

Compounding these clinical challenges, the global epidemiological burden of ALD is expanding at an alarming rate, heavily exacerbated by shifting sociocultural drinking patterns, rising metabolic comorbidities, and delayed clinical presentations. This upward trajectory places an immense structural and economic strain on healthcare infrastructures,

underscoring an urgent need to refine preventive frameworks, optimize early screening methodologies, and pioneer targeted molecular therapies.

To address these challenges, this comprehensive review dissects the current clinical landscape of alcoholic hepatitis. We evaluate its global and regional epidemiology, predisposing risk factors, intricate pathophysiological mechanisms, and evolving diagnostic criteria. Furthermore, we critically analyse established treatment modalities alongside emerging therapeutic frontiers—such as mesenchymal stem cell transplantation and gut-microbiota modulation—underscoring the vital synergy between early clinical intervention and multidisciplinary abstinence strategies in transforming long-term patient outcomes.

Epidemiology of Alcoholic Liver Disease (ALD)

To map the precise etiological landscape of hepatic cirrhosis within the Indian population, a landmark systematic review and meta-analysis synthesized data spanning up to January 2023. Evaluating a robust cohort of 158 distinct studies comprising 41,432 adult and 977 paediatric patients, the pooled estimates reveal a stark reality: alcohol consumption stands as the uncontested primary driver of liver cirrhosis across the nation, accounting for a massive ****43.2%**** of all cases (95% CI: 39.8–46.6%). In comparison, non-alcoholic fatty liver disease (NAFLD) and cryptogenic causes constitute 14.4% (95% CI: 11.7–17.3%), followed closely by viral hepatitis B (HBV) at 11.5% (95% CI: 9.8–13.3%) and hepatitis C (HCV) at 6.2% (95% CI: 4.8–7.8%).

Regional Variation and Temporal Trends

Granular analysis of the pooled data reveals distinct geographic and chronological shifts that reflect evolving regional habits and healthcare interventions:

Zonal Heterogeneity: While alcohol remains the leading cause of adult cirrhosis globally across the subcontinent, its prevalence peaks sharply in the Western and Southern zones of India, approaching or exceeding 50% of the local cirrhosis burden. Conversely, viral etiologies like HBV maintain a disproportionately higher footprint in the Central and Southern cohorts compared to the rest of the country.

The Post-2005 Chronological Surge: Historical timeline analysis demonstrates a profound macroeconomic shift in disease etiology. Prior to 2005, alcohol accounted for a relatively modest 20% of documented cirrhosis cases, with viral hepatitis (particularly HBV) serving as a dominant clinical challenge. However, in the blocks spanning 2005–2015 and 2015–2022, alcohol-related cirrhosis exploded, expanding to over 40% and nearly 48% of the total caseload respectively.

The Rise of Metabolic Co-factors: Paralleling the surge in alcohol consumption, NAFLD/Cryptogenic cirrhosis has experienced a steady climb over the last two decades, driven by rising national rates of obesity and type 2 diabetes.

Concurrently, due to successful universal infant immunization mandates and targeted antiviral therapies, the relative proportion of viral hepatitis-related cirrhosis has entered a steep, steady decline.

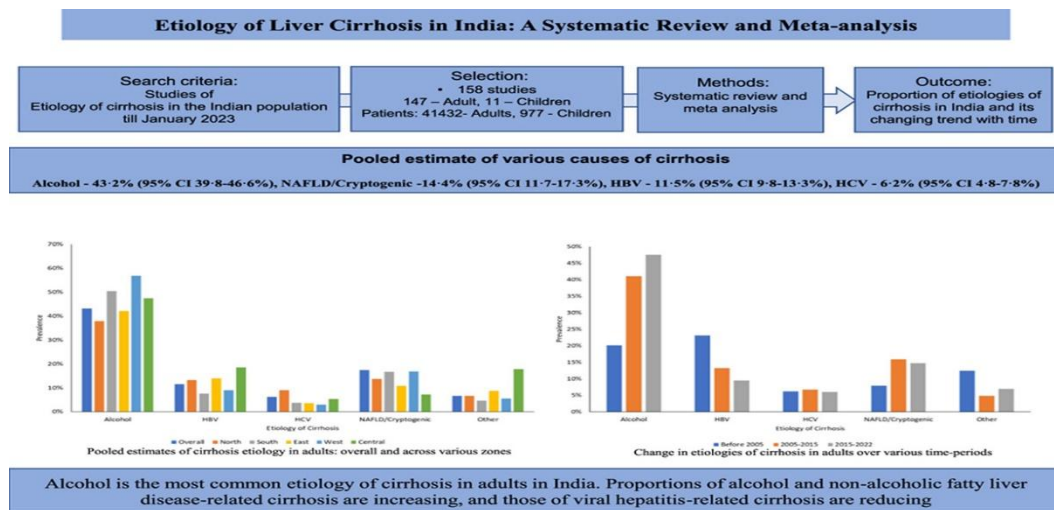


Figure 1: Etiology of liver cirrhosis in India and its shifting trends over time. Adapted from “Epidemiology of Liver Diseases in India,” by D. Mondal, K. Das, and A. Chowdhury, 2022, Clinical Liver Disease, 19(1), p. 115. Copyright 2021 by the American Association for the Study of Liver Diseases.

Risk factors

Table 1:

Risk Factor	Mechanism	Clinical Impact
Chronic heavy alcohol use	Acetaldehyde and ROS cause oxidative stress and hepatocyte injury.	Primary cause of alcoholic hepatitis.
Binge drinking	Triggers inflammatory cytokines (TNF- α , IL-6).	Increase liver disease severity
Female sex	Lower alcohol metabolism and higher blood alcohol levels	Greater susceptibility to liver damage.
Genetic factors	PNPLA3, TM6SF2, MBOAT7 variants increase liver injury.	Accelerates fibrosis and cirrhosis.
Obesity/Metabolic syndrome	Promotes steatosis and inflammation.	Worsens disease progression.
Hepatitis B/C co-infection	Enhances hepatic inflammation and fibrosis.	Higher risk of cirrhosis and HCC.

Gut dysbiosis	LPS activates Kupffer cells via TLR4.	Promotes hepatic inflammation.
Malnutrition	Vitamin and protein deficiencies impair liver repair.	Poor prognosis.

Pathophysiology of Alcoholic Hepatitis

Pathophysiology of Alcohol-Associated Liver Injury

Ethanol clearance is a compartmentalized process orchestrated primarily within the hepatic parenchyma, with minor metabolic contributions from the gastrointestinal tract. Under baseline physiological conditions, alcohol elimination relies almost exclusively on cytosolic alcohol dehydrogenase (ADH), which oxidizes ethanol into acetaldehyde—a volatile, cytotoxic intermediate. Acetaldehyde is rapidly sequestered into mitochondria, where aldehyde dehydrogenase (ALDH) converts it into inert acetate.

However, chronic, high-volume alcohol exposure triggers a profound metabolic shift, upregulating the microsomal ethanol-oxidizing system (MEOS) via cytochrome P450 2E1 (CYP2E1). While catalase provides an ancillary pathway, its contribution to hepatic clearance remains negligible. Sustained CYP2E1 induction creates a major metabolic bottleneck: it accelerates ethanol oxidation but generates an unmitigated flux of reactive oxygen species (ROS) that overwhelms endogenous antioxidant defences.

The downstream pathobiology of this metabolic insult unfolds across four distinct cellular phases:

1. Redox Imbalance and Steatosis

The overproduction of reducing equivalents severely skews the intracellular NAD⁺/NADH redox balance. This altered ratio suppresses mitochondrial beta-oxidation of fatty acids and halts gluconeogenesis, while simultaneously channelling substrates into *de novo* lipogenesis and triglyceride hoarding. At the transcriptional level, ethanol exposure reinforces this process by upregulating sterol regulatory element-binding protein-1c (SREBP-1c) and blunting peroxisome proliferator-activated receptor-alpha (PPAR-alpha) signalling, driving the rapid development of diffuse hepatic steatosis.

2. Cellular Cytotoxicity and Adduct Formation

Persistent CYP2E1-mediated ROS generation triggers extensive lipid peroxidation, destabilizing mitochondrial membranes, inducing structural DNA damage, and driving hepatocytes toward apoptosis. Concurrently, highly reactive acetaldehyde modifies structural proteins to form stable, antigenic malondialdehyde-acetaldehyde (MAA) adducts. These adducts impair vital intracellular machinery and act as neoantigens, provoking an autoimmune-like lymphocytic attack against host hepatocytes.

3. Gut-Liver Axis Disruption and Acute Inflammation

Chronic ethanol consumption compromises the structural integrity of intestinal tight junctions, driving hyper-permeability and the translocation of gut-derived lipopolysaccharides (LPS) into the portal circulation. Upon reaching hepatic sinusoids, LPS binds Toll-like receptor 4 (TLR4) on resident Kupffer cells. This ligation initiates an aggressive inflammatory cascade, triggering the unmitigated release of potent pro-inflammatory cytokines, including:

- * Tumour necrosis factor-alpha (TNF-alpha)
- * Interleukin-1 (IL-1) and Interleukin-6 (IL-6)
- * Interferons and Transforming growth factor-beta (TGF-beta)

These signalling molecules recruit a massive influx of polymorphonuclear neutrophils into the parenchyma, manifesting as the classic histological hallmarks of acute alcoholic hepatitis: intense lobular inflammation, Mallory–Denk bodies, and hepatocyte ballooning necrosis.

4. Fibrogenesis and Malignant Transformation

The chronic intersection of inflammatory signalling and oxidative stress activates quiescent hepatic stellate cells (Ito cells) into proliferative, contractile, myofibroblastic phenotypes. Driven by sustained exposure to TGF-beta, platelet-derived growth factor (PDGF), and damage-associated molecular patterns (DAMPs) shed from necrotic hepatocytes, these activated stellate cells orchestrate an unregulated deposition of Type I and III collagens.

This fibrotic matrix begins in a perisinusoidal "chicken-wire" pattern around central veins before forming dense bridging scars. Over time, this progressive deposition chokes vascular flow, distorts hepatic architecture, and culminates in cirrhosis, severe portal hypertension, and a microenvironment highly primed for transformation into hepatocellular carcinoma (HCC).

Progression of Alcohol-Associated Liver Disease (ALD)

Alcohol-associated liver disease (ALD) progresses through a well-defined spectrum of pathological changes, beginning with alcoholic fatty liver (steatosis) and advancing to alcoholic steatohepatitis (ASH)/alcoholic hepatitis (AH), fibrosis, cirrhosis, and finally hepatocellular carcinoma (HCC). The progression is influenced by the quantity and duration of alcohol consumption, genetic susceptibility, nutritional status, obesity, and coexisting liver diseases. Although not all heavy drinkers progress through every stage, persistent alcohol intake markedly increases the risk of irreversible liver damage.

1. Alcoholic Fatty Liver (Steatosis)

Alcoholic fatty liver is the earliest and most common manifestation of ALD. Hepatic fat accumulation results from disturbances in lipid metabolism, including increased fatty acid synthesis (de novo lipogenesis), triglyceride accumulation, enhanced influx of free fatty acids from extrahepatic tissues, reduced export of triglycerides from the

liver, and impaired mitochondrial fatty acid oxidation. During alcohol metabolism, excessive production of NADH disrupts the normal NAD^+/NADH redox balance, suppressing β -oxidation of fatty acids while promoting lipogenesis.

Alcohol also increases the expression of sterol regulatory element-binding protein-1c (SREBP-1c), a major regulator of lipogenic genes, and decreases the expression of peroxisome proliferator-activated receptor- α (PPAR- α), which normally stimulates fatty acid oxidation. Downregulation of AMP-activated protein kinase (AMPK) together with endoplasmic reticulum stress and reactive oxygen species (ROS) accumulation further aggravates lipid accumulation. Collectively, these alterations lead to triglyceride deposition within hepatocytes, resulting in hepatic steatosis. This stage is generally reversible with complete alcohol abstinence.

2. Alcoholic Steatohepatitis (ASH)/Alcoholic Hepatitis (AH)

Continued alcohol consumption promotes progression from steatosis to alcoholic steatohepatitis or alcoholic hepatitis. Persistent oxidative stress, inflammatory cytokine production, and hepatocellular injury trigger a marked inflammatory response. Histologically, alcoholic steatohepatitis is characterized by hepatocyte ballooning degeneration, Mallory–Denk bodies (aggregated cytokeratin inclusions), and infiltration of polymorphonuclear neutrophils.

Chronic alcohol intake also increases intestinal permeability, allowing lipopolysaccharides (LPS) from gut bacteria to enter the portal circulation. LPS activates Toll-like receptors (TLRs) on Kupffer cells, resulting in the release of pro-inflammatory cytokines and amplification of hepatic inflammation. Reactive oxygen species generated through CYP2E1, NADPH oxidases, endoplasmic reticulum stress, and mitochondrial dysfunction further damage hepatocytes. Cellular injury leads to the release of damage-associated molecular patterns (DAMPs), which perpetuate immune activation and inflammation.

Clinically, alcoholic hepatitis presents with abrupt jaundice, impaired liver function, severe inflammatory response, and a poor prognosis, with reported mortality of 20–50% within three months in severe cases.

3. Fibrosis and Cirrhosis

Persistent alcohol consumption and recurrent hepatocellular injury initiate repeated wound-healing responses that ultimately result in fibrosis. The principal mediators of fibrosis are hepatic stellate cells (HSCs), which become activated by alcohol, acetaldehyde, ROS, and fibrogenic mediators such as transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF), and inflammatory cytokines released from damaged hepatocytes, activated Kupffer cells, and infiltrating immune cells.

Activated HSCs transform into collagen-producing myofibroblasts, leading to excessive extracellular matrix deposition, particularly around the pericentral and perisinusoidal regions, producing the characteristic “chicken-wire” fibrosis. Alcohol also suppresses the clearance of activated stellate cells by natural killer (NK) cells, further promoting fibrogenesis.

With continued collagen accumulation, hepatic architecture becomes progressively distorted, leading to the formation of regenerative nodules and cirrhosis. Advanced cirrhosis is associated with narrowing of the hepatic vasculature, portal hypertension, ascites, hepatic encephalopathy, variceal bleeding, and liver failure.

4. Hepatocellular Carcinoma (HCC)

In advanced ALD, persistent inflammation, oxidative stress, repeated hepatocyte injury, and cirrhosis markedly increase the risk of hepatocellular carcinoma (HCC). Progressive genomic instability, impaired hepatocyte regeneration, and chronic inflammatory signalling contribute to malignant transformation, making HCC one of the most serious long-term complications of alcohol-associated liver disease.

Diagnosis

Alcoholic hepatitis (AH) has a broad spectrum of clinical presentations, ranging from asymptomatic disease with mild laboratory abnormalities to severe liver failure. Since there is no single clinical feature that reliably distinguishes alcohol-associated liver disease (ALD) from other liver disorders, diagnosis relies on a combination of drinking history, clinical features, laboratory findings, imaging studies, and histopathological examination. Because alcohol consumption is often underreported, clinicians should maintain a high index of suspicion for alcohol use disorder (AUD), particularly in patients presenting with nonspecific symptoms.

Clinical Features

Patients with AH may present with fatigue, abdominal pain, jaundice, weight loss, confusion, hepatomegaly, ascites, muscle wasting, and signs of hepatic encephalopathy. Physical examination may reveal spider angiomas, palmar erythema, icteric sclera, splenomegaly, gynecomastia, and Dupuytren's contracture.

Laboratory Findings

Elevated aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) are useful indicators of recent excessive alcohol consumption. However, laboratory findings alone are insufficient to establish the diagnosis.

Imaging Studies

Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) can detect hepatic steatosis. MRI provides the most accurate assessment of hepatic fat content. Transient elastography and serum fibrosis markers may help evaluate liver fibrosis but are not yet validated for routine diagnosis of AH.

Liver Biopsy

Liver biopsy is not routinely required. It is recommended when the diagnosis is uncertain or to distinguish definite, probable, and possible alcoholic hepatitis according to the 2016 consensus criteria. Histological features include neutrophilic lobular inflammation, hepatocyte ballooning, Mallory–Denk bodies, steatosis, and pericellular fibrosis.

Emerging Biomarkers

Circulating fragments of cytokeratin-18 (CK-18; M30 and M65) have shown promising diagnostic performance for alcoholic hepatitis. Other non-invasive biomarkers and breath analysis techniques are under investigation, although none have been sufficiently validated for routine clinical use.

Biomarkers

Table 2:

Biomarker	Clinical Significance
Cytokeratin-18 (M30/M65)	Predicts hepatocyte injury, disease severity, and prognosis
CD163	Marker of Kupffer cell activation; correlates with disease severity
ST2 receptor	Indicates ongoing inflammation and fibrosis
Immunoglobulins (IgA, IgG, IgM)	Elevated in AH; reflects immune activation
SCD1	Early metabolic biomarker of ALD
Magnesium	Low levels are associated with disease progression
miR-155, miR-223	Predict disease severity and have therapeutic potential
Uric acid	Associated with inflammation and disease severity

Treatment of Alcohol-Associated Liver Disease (ALD)

The primary goals of ALD treatment are to prevent further liver injury, reduce inflammation, improve liver function, correct nutritional deficiencies, manage complications, and prevent progression to cirrhosis and liver failure. Complete abstinence from alcohol remains the cornerstone of therapy, while pharmacological and supportive treatments are selected according to disease severity.

Alcohol Abstinence

Alcohol abstinence remains the cornerstone of treatment for all stages of alcohol-associated liver disease and is the only intervention proven to slow disease progression and improve long-term survival. Continued alcohol consumption accelerates hepatic steatosis, inflammation, fibrosis, and cirrhosis, whereas complete abstinence promotes hepatic regeneration, improves liver function, and decreases the risk of complications, including portal hypertension and hepatocellular carcinoma. Long-term abstinence is best achieved through a multidisciplinary approach combining behavioural counselling, psychosocial support, and pharmacological therapy. Medications such as baclofen, acamprosate, and naltrexone may be used in selected patients to reduce alcohol craving and prevent relapse, although their use should be individualized according to liver function and patient characteristics.

Nutritional Therapy

Malnutrition is highly prevalent in patients with alcohol-associated liver disease, particularly in alcoholic hepatitis, and is associated with increased morbidity and mortality. Poor dietary intake, anorexia, vomiting, malabsorption, and metabolic disturbances contribute to protein-energy malnutrition. Nutritional support improves clinical outcomes by correcting nutritional deficiencies, promoting hepatocyte regeneration, preserving muscle mass, and reducing complications such as hepatic encephalopathy and infections. Current recommendations include an energy intake of 35–40 kcal/kg/day and protein intake of 1.2–1.5 g/kg/day unless contraindicated. Supplementation with vitamins, particularly thiamine (vitamin B1), folic acid, vitamin B12, vitamin D, pyridoxine, and trace elements such as zinc, magnesium, and selenium is frequently required. Whenever feasible, enteral nutrition is preferred over parenteral nutrition because it maintains intestinal mucosal integrity, reduces bacterial translocation, lowers the risk of sepsis, and is associated with better clinical outcomes.

Corticosteroid Therapy

Corticosteroids remain the standard pharmacological treatment for patients with severe alcoholic hepatitis. Prednisolone at a dose of 40 mg daily for 28 days, followed by gradual tapering, is recommended for patients with severe disease, typically defined by a Maddrey Discriminant Function score of ≥ 32 or the presence of hepatic encephalopathy. Corticosteroids suppress hepatic inflammation by inhibiting the production of pro-inflammatory cytokines, particularly tumour necrosis factor- α (TNF- α) and interleukin-8 (IL-8). Although randomized clinical trials and meta-analyses have demonstrated short-term survival benefits, approximately 40% of patients fail to respond to therapy. Treatment response should therefore be reassessed after seven days using the Lille score. Patients with a Lille score greater than 0.45 are considered non-responders, and corticosteroid therapy is generally discontinued because the risks of infection outweigh potential benefits.

Pentoxifylline

Pentoxifylline has been investigated as an alternative therapy for patients in whom corticosteroids are contraindicated. It acts by inhibiting phosphodiesterase activity, increasing intracellular cyclic AMP concentrations, and reducing macrophage-mediated production of inflammatory cytokines, particularly TNF- α . Earlier studies suggested that pentoxifylline might reduce the incidence of hepatorenal syndrome; however, subsequent randomized trials and meta-analyses failed to demonstrate consistent improvements in overall survival. Consequently, pentoxifylline is no longer recommended as routine therapy, although it may occasionally be considered when corticosteroid treatment cannot be administered.

Anti-TNF Therapy

Since TNF- α plays a central role in the inflammatory response of alcoholic hepatitis, biological agents such as infliximab and etanercept have been evaluated as potential therapeutic options. Although early experimental studies demonstrated reductions in inflammatory activity, larger clinical trials reported an increased incidence of severe

infections and higher mortality without significant survival benefit. Based on current evidence, anti-TNF biological therapies are not recommended for the routine management of alcoholic hepatitis.

Antioxidant Therapy

Oxidative stress is an important contributor to hepatocyte injury in alcohol-associated liver disease, making antioxidant therapy an attractive therapeutic strategy. N-acetylcysteine (NAC) replenishes intracellular glutathione stores and reduces oxidative damage. When administered in combination with prednisolone, NAC has been shown to improve short-term survival and decrease infectious complications in patients with severe alcoholic hepatitis; however, convincing long-term survival benefits have not yet been established. Metadoxine has also demonstrated improvement in liver function tests and reduction of hepatic steatosis in some clinical studies, but current evidence remains insufficient to support its routine clinical use.

Miscellaneous Pharmacological Agents

Several other drugs have been investigated, although none has become standard therapy.

Propylthiouracil (PTU)

PTU was evaluated because of its ability to reduce hypermetabolism during acute alcoholic hepatitis. However, meta-analysis failed to demonstrate significant improvement in liver histology or overall mortality.

Colchicine

Colchicine inhibits collagen synthesis, enhances collagen degradation, and interferes with hepatic fibrogenesis. Although early studies suggested antifibrotic effects and possible survival benefit, later controlled trials produced conflicting results.

Polyunsaturated Lecithin (PPC)

PPC stabilizes hepatocyte membranes and may reduce activation of hepatic stellate cells.

Despite favourable experimental findings, clinical trials have not consistently demonstrated prevention of liver fibrosis.

Angiotensin II Receptor Blockers (ARBs)

ARBs have shown potential antifibrotic activity.

Some studies reported improved liver histology when combined with ursodeoxycholic acid; however, larger clinical trials are required before routine recommendation.

Silymarin

Silymarin possesses antioxidant, anti-inflammatory, and antifibrotic properties.

Although experimental studies are promising, clinical evidence remains insufficient to support routine therapeutic use.

Liver Transplantation

Liver transplantation (LT) is the definitive treatment for patients with end-stage alcohol-associated liver disease (ALD) and for carefully selected patients with severe alcoholic hepatitis who fail to respond to optimal medical therapy. It is indicated in patients with decompensated cirrhosis presenting with complications such as refractory ascites, recurrent variceal haemorrhage, hepatic encephalopathy, hepatorenal syndrome, or progressive liver failure despite complete alcohol abstinence and standard medical management. In patients with severe alcoholic hepatitis, liver transplantation may also be considered when corticosteroid therapy is ineffective or contraindicated and the predicted mortality remains extremely high.

The decision to perform liver transplantation requires a comprehensive multidisciplinary evaluation involving hepatologists, transplant surgeons, psychiatrists, addiction specialists, psychologists, and social workers. Candidate selection is based not only on the severity of liver disease, commonly assessed using the Model for End-Stage Liver Disease (MELD) score and Child–Pugh classification, but also on the patient’s psychosocial stability, commitment to lifelong alcohol abstinence, family support, nutritional status, and risk of alcohol relapse after transplantation. Although many transplant centres have traditionally required at least six months of documented abstinence before listing patients for transplantation, recent evidence suggests that carefully selected patients with severe alcoholic hepatitis who are unlikely to survive six months may benefit from early liver transplantation without compromising long-term outcomes.

Liver transplantation provides excellent long-term survival in patients with ALD. One-year survival rates exceed 85–90%, while five-year survival rates are comparable to those achieved in patients transplanted for other chronic liver diseases. Restoration of normal liver function significantly improves nutritional status, quality of life, physical performance, and overall survival. However, long-term success depends heavily on sustained alcohol abstinence after transplantation. Relapse to harmful alcohol consumption is associated with recurrent steatosis, fibrosis, graft dysfunction, cardiovascular complications, de novo malignancies, and reduced patient survival. Therefore, lifelong follow-up with regular psychological assessment, addiction counselling, and medical monitoring is essential to minimize relapse and optimize graft function.

Despite remarkable advances in transplantation, organ shortage remains a major limitation, emphasizing the importance of careful recipient selection and effective prevention strategies for alcohol-associated liver disease. Ongoing research continues to refine selection criteria, identify predictors of post-transplant alcohol relapse, and improve long-term outcomes through individualized psychosocial interventions and multidisciplinary care.

Stem Cell Therapy

Mesenchymal stem cell (MSC) transplantation has emerged as a highly compelling, innovative experimental frontier for patients with advanced, non-responsive ALD. Owing to their distinct immunomodulatory and regenerative profiles, MSCs actively home to damaged hepatic tissues where they exert a potent, multi-pronged therapeutic effect. Clinical and preclinical models demonstrate that these stem cells effectively dampen acute intrahepatic inflammation, directly inhibit the fibrogenic activation of hepatic stellate cells, and release critical trophic factors that stimulate

endogenous hepatocyte proliferation. Early-phase clinical pilots have reported highly encouraging outcomes, including measurable improvements in serum albumin, stabilization of Child-Pugh scores, and notable histological reductions in collagen deposition. Despite this immense clinical promise, MSC therapy is currently classified as strictly investigational; establishing standardized protocols regarding optimal cell sources, precise dosing regimens, ideal delivery routes, and long-term oncogenic safety remains an absolute prerequisite before wide-scale clinical adoption can occur.

Emerging Therapies

Novel therapeutic approaches are currently under investigation to improve outcomes in alcohol-associated liver disease. Mesenchymal stem cell therapy has demonstrated anti-inflammatory, antifibrotic, and regenerative properties in early clinical studies, leading to improvements in liver function and histological findings. Other emerging strategies include modulation of the gut microbiota using probiotics, prebiotics, antibiotics, and fecal microbiota transplantation, as well as therapies targeting inflammatory cytokines, chemokine pathways, lipopolysaccharide-mediated signalling, complement activation, and endocannabinoid pathways. Although these approaches show considerable promise, additional large-scale clinical trials are required before they can be incorporated into routine clinical practice.

Conclusion

Alcohol-associated liver disease remains a significant global health challenge because of its increasing prevalence, progressive nature, and high mortality in advanced stages. Alcoholic hepatitis represents a severe inflammatory manifestation of ALD resulting from complex interactions among alcohol metabolism, oxidative stress, immune activation, gut-derived endotoxins, and hepatic fibrosis. Early recognition, accurate diagnosis, and complete alcohol abstinence are essential for improving clinical outcomes. Current management combines nutritional support, corticosteroid therapy in selected patients, and liver transplantation for advanced disease, while several novel therapeutic strategies, including stem cell therapy and gut microbiota modulation, are under active investigation. Continued research into disease mechanisms, biomarkers, and targeted therapies is expected to improve future prevention, diagnosis, and treatment of alcoholic hepatitis, ultimately reducing the burden of alcohol-related liver disease.

References :

1. Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and treatment of alcohol-associated liver diseases: 2019 Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2020;71(1):306-333.
2. Shah NJ, Royer A, John S. Alcohol-Associated Hepatitis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026.
3. Single AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG Clinical Guideline: Alcoholic Liver Disease. *Am J Gastroenterol*. 2018;113:175-194.
4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. *J Hepatol*. 2018;69:154-181.

5. Gao B, Bataller R. Alcoholic liver disease: Pathogenesis and new therapeutic targets. *Gastroenterology*. 2011;141:1572-1585.
6. Seitz HK, Bataller R, Cortez-Pinto H, et al. Alcoholic liver disease. *Nat Rev Dis Primers*. 2018;4:16.
7. Louvet A, Mathurin P. Alcoholic liver disease: Mechanisms of injury and targeted treatment. *Nat Rev Gastroenterol Hepatol*. 2015;12:231-242.
8. Mathurin P, Lucey MR. Management of alcoholic hepatitis. *J Hepatol*. 2012;56(Suppl 1):S39-S45.
9. O'Shea RS, Dasarthy S, McCullough AJ. Alcoholic liver disease. *Hepatology*. 2010;51:307-328.
10. Gao B, Ahmad MF, Nagy LE, Tsukamoto H. Inflammatory pathways in alcoholic liver disease. *J Hepatol*. 2019;70:249-259.
11. Tsukamoto H, Lu SC. Current concepts in alcoholic liver disease. *F1000Res*. 2018;7:F1000 Faculty Rev-1267.
12. Lackner C, Tiniakos D. Fibrosis and alcoholic liver disease. *Histopathology*. 2019;74:197-210.
13. Bataller R, Brenner DA. Liver fibrosis. *J Clin Invest*. 2005;115:209-218.
14. Nagy LE. The role of innate immunity in alcoholic liver disease. *Alcohol Res*. 2015;37:237-250.
15. World Health Organization. Global Status Report on Alcohol and Health 2024. Geneva: World Health Organization; 2024.
16. Rehm J, Shield KD. Global burden of alcohol-associated liver disease. *J Hepatol*. 2019;70:151-161.
17. Cleveland Clinic. Alcoholic liver disease. Cleveland Clinic. Available at: <https://my.clevelandclinic.org/departments/digestive/medical-professionals/hepatology/alcoholic-liver-disease>. Accessed July 2026.
18. PathologyOutlines.com. Alcoholic hepatitis. PathologyOutlines.com. Available at: <https://www.pathologyoutlines.com/topic/liveralcoholichep.html>. Accessed July 2026.
19. Alcoholic liver disease: Epidemiology, pathogenesis and management. *J Clin Exp Hepatol*. 2023.
20. Alcohol-associated liver disease: Current concepts and emerging therapeutic strategies. *Clin Liver Dis*. 2025.
21. Pathophysiology of alcohol-associated liver disease. *Clin Mol Hepatol*. 2021.
22. Kumar P, et al. Alcoholic liver disease: Pathogenesis, biomarkers and therapeutic strategies. *World J Hepatol*. 2022;14. Available at: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9599689/>.
23. Singal AK, Shah VH. Current trials and future therapies in alcoholic hepatitis. *Clin Liver Dis*. 2016;20:607-620.
24. Louvet A, Labreuche J, Artru F, et al. Main drivers of outcome differ between short-term and long-term survival in severe alcoholic hepatitis. *Hepatology*. 2017;66:1464-1473.
25. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med*. 2011;365:1790-1800.
26. Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis (STOPAH trial). *N Engl J Med*. 2015;372:1619-1628.
27. Lucey MR. Alcohol-associated liver disease. *Clin Liver Dis*. 2019;23:1-11.

28. Nagy LE, Ding WX, Cresci G, Saikia P, Shah VH. Linking pathogenic mechanisms of alcoholic liver disease with clinical phenotypes. *Gastroenterology*. 2016;150:1756-1768.
29. Mann RE, Smart RG, Govoni R. The epidemiology of alcoholic liver disease. *Alcohol Res Health*. 2003;27:209-219.
30. Alcoholic liver disease: Recent advances in pathogenesis and management. *World J Hepatol*. 2011;3:114-128.
31. Gao B. Alcoholic liver disease: Mechanisms and therapeutic opportunities. *Nat Rev Gastroenterol Hepatol*. 2022.
32. Osna NA, Donohue TM Jr, Kharbanda KK. Alcoholic liver disease: Pathogenesis and current management. *Alcohol Res*. 2017;38:147-161.
33. Ceni E, Mello T, Galli A. Pathogenesis of alcoholic liver disease. *World J Gastroenterol*. 2014;20:17756-17772.
34. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. *J Hepatol*. 2013;59:160-168.
35. National Institute on Alcohol Abuse and Alcoholism. *Alcohol Facts and Statistics*. Bethesda (MD): National Institute on Alcohol Abuse and Alcoholism; 2024.