OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article **Pharmacy**

Liver Cirrhosis: Contemporary Insights into Pathogenesis, Evidence-Based Management, and Emerging Therapeutic Strategies

Ayisha Mohamed Hanifa[1], Safrin Fathima Saifudeen[1], Hariprasad Murugesan[1], Shalini Sivadasan[2]*, Karthick Murugesan[3]

[1]Pharm D Intern, Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore 641-048, Tamil Nadu, India
[2]Professor, Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore 641-048, Tamil Nadu, India
[3]Assistant Professor, Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore 641 048, Tamil Nadu, India

DOI: https://doi.org/10.36348/sjmps.2025.v11i04.017 | **Received:** 17.03.2025 | **Accepted:** 23.04.2025 | **Published:** 29.04.2025

***Corresponding author:** Shalini Sivadasan
Professor, Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore 641-048, Tamil Nadu, India

Abstract

Liver cirrhosis is the end stage of chronic liver disease, characterized by progressive fibrosis, architectural distortion, and impaired hepatic function. It arises from diverse etiologies including viral hepatitis, alcohol-associated liver disease, non-alcoholic fatty liver disease, autoimmune hepatitis, and cholestatic disorders. Complications such as portal hypertension, hepatic encephalopathy, ascites, and hepatocellular carcinoma significantly impact morbidity and mortality, particularly in decompensated stages. Early identification and etiology-specific treatment, including antiviral therapy, alcohol cessation, and metabolic management, are essential to slow progression. Multidisciplinary care, nutritional optimization, infection prophylaxis, and regular surveillance for hepatocellular carcinoma are key components of effective management. Liver transplantation remains the definitive therapy for selected patients with advanced disease. As global prevalence increases, there is an urgent need for integrated care models, improved access to treatment, and innovations in antifibrotic therapies. This review highlights current strategies and future directions in the comprehensive management of liver cirrhosis.

Keywords: Liver Cirrhosis, Liver Failure, Chronic, Portal Hypertension, Hepatocellular Carcinoma, Multidisciplinary Care Team.

INTRODUCTION

Liver cirrhosis is the final stage of chronic liver injury, marked by progressive fibrosis, architectural distortion, and regenerative nodule formation. It is a significant global health concern, ranking as the 11th leading cause of death and responsible for approximately 2 million deaths annually [1, 2]. Causes include chronic hepatitis B and C, alcohol-related liver disease, and increasingly, non-alcoholic fatty liver disease (NAFLD), which is now a leading contributor worldwide [3, 4].

Cirrhosis is classified into compensated and decompensated stages. In the compensated stage, liver function is preserved and symptoms may be minimal. Decompensated cirrhosis, however, presents with complications such as ascites, variceal bleeding, hepatic encephalopathy, and jaundice, and is associated with a median survival of under two years without transplantation [5, 6].

The disease process is driven by chronic hepatocyte injury, inflammation, and activation of hepatic stellate cells, which stimulate fibrosis. This cascade involves complex molecular and immune pathways, presenting opportunities for targeted antifibrotic therapies [7]. Non-invasive tools like transient elastography and serum fibrosis markers have transformed the diagnosis and monitoring of liver fibrosis, reducing the need for liver biopsy [8].

Despite improvements in managing underlying liver diseases and complications, cirrhosis remains a progressive and often fatal condition. Optimal care requires a multidisciplinary approach involving hepatologists, nutritionists, addiction specialists, and transplant teams. This coordinated strategy is essential to address the complexities of cirrhosis and improve patient outcomes. Ongoing research continues to explore new diagnostic markers and therapeutic targets, with the aim

of slowing disease progression and enhancing long-term survival.

Alcohol-Associated Liver Cirrhosis

Alcohol-associated liver cirrhosis (ALC) remains a major global health issue, contributing to about 25% of all cirrhosis-related deaths in 2019. The global age-standardized death rate (ASDR) was 4.5 per 100,000, highest in Africa and lowest in the Western Pacific. While ASDR for alcohol-related cirrhosis has declined slightly, deaths from alcohol-related liver cancer are increasing. Without effective intervention, cirrhosis- and cancer-related deaths due to alcohol are expected to rise, especially among men [9, 10].

Pathogenesis

ALC develops through hepatocyte injury, inflammation, and fibrosis. Ethanol is primarily metabolized in the liver, producing acetaldehyde—a toxic compound that damages cell and promotes oxidative stress. This process generates reactive oxygen species (ROS), disrupts mitochondria, and depletes antioxidants. Damaged cells activate Kupffer cells (liver macrophages), which release inflammatory cytokines like TNF-α, recruiting immune cells and worsening injury. These signals also activate hepatic stellate cells, which deposit extracellular matrix proteins, especially collagen, leading to fibrosis and structural distortion [11-14].

Integrated Management Approach

Early alcohol abstinence can reverse hepatic steatosis and slow disease progression. A multidisciplinary, integrated care model (ICM) involving hepatologists, addiction psychiatrists, counselors, nurses, and social workers has proven effective in managing both alcohol use disorder (AUD) and ALC. However, barriers such as stigma, training gaps, and healthcare disparities hinder widespread implementation.

Nutritional Support

Nutritional therapy is essential, with recommendations of 1.2–1.5 g protein/kg/day and 35 kcal/kg/day. Nighttime feeding has shown benefits in cirrhosis, and biomarkers like myostatin (high in severe disease) and decorin (low in severe disease) correlate with muscle loss and poor outcomes. Combining decorin levels with MELD scores improves mortality prediction [15].

A personalized, holistic strategy that integrates medical, psychological, and nutritional support is critical for improving outcomes in patients with advanced alcohol-associated cirrhosis.

Non-Alcoholic Fatty Liver Disease and Its Progression to Liver Cirrhosis

NAFLD is the most prevalent chronic liver disease globally, affecting 25–30% of the population [16]. It includes a spectrum from simple steatosis to non-alcoholic steatohepatitis (NASH), the latter involving liver inflammation and damage that can lead to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), even without alcohol consumption [8].

Pathogenesis and Progression

NAFLD is driven by insulin resistance, oxidative stress, adipose dysfunction, and chronic inflammation. It is closely linked with obesity, type 2 diabetes, and metabolic syndrome [17]. While many with steatosis remain stable, about 20% develop NASH, and of those, up to 25% may progress to cirrhosis [18]. NAFLD-related cirrhosis is often silent until complications such as ascites, encephalopathy, or variceal bleeding occur. HCC can also develop without cirrhosis, especially in NASH patients.

Epidemiology and Burden

As obesity and diabetes rise, so does NAFLD. It is now the second leading cause of liver transplant in the U.S. and is expected to become the first. NAFLD is also a growing cause of HCC, often diagnosed late due to its silent progression [18].

Diagnosis and Risk Stratification

Although biopsy remains the gold standard, non-invasive tools like FIB-4, NAFLD Fibrosis Score, and FibroScan are commonly used to assess fibrosis and guide referrals [8]. HCC surveillance with ultrasound ± AFP every six months is recommended for cirrhotic patients.

Management

Lifestyle change, especially 7–10% weight loss, is key for improving liver health. A Mediterranean diet and regular exercise are advised. No approved drugs exist, but pioglitazone and GLP-1 receptor agonists (e.g., semaglutide) show promise. For advanced disease, standard cirrhosis care and liver transplantation may be necessary. A multidisciplinary approach and early detection in high-risk populations are essential to reduce NAFLD-related complications.

Viral Hepatitis and Its Progression to Liver Cirrhosis

Hepatitis B (HBV) and hepatitis C (HCV) remain major causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) worldwide. Over 296 million people live with chronic HBV and 58 million with chronic HCV [19]. Persistent infection triggers inflammation and fibrosis, leading to progressive liver damage [20].

HBV is a DNA virus capable of integrating into the host genome, often establishing chronic infection when acquired early in life. Chronic HBV causes immune-mediated liver injury, driving fibrosis and cirrhosis. Without treatment, 15–40% of chronic HBV patients may develop cirrhosis, particularly those with high viral loads and liver inflammation [21]. While

antivirals suppress HBV replication and slow disease progression, cirrhosis and HCC remain prevalent in endemic areas.

HCV, an RNA virus, becomes chronic in 75–85% of cases post-infection. Ongoing hepatic inflammation and stellate cell activation lead to fibrosis. Around 20–30% of chronic HCV patients develop cirrhosis within two decades, with risk factors including HIV co-infection, alcohol, male sex, metabolic syndrome, and older age at infection (Thomas, 2019). The introduction of direct-acting antivirals (DAAs) has transformed HCV management, achieving cure rates over 95% and significantly reducing liver-related complications [22].

HDV, which co-infects or superinfects HBV patients, accelerates liver damage and increases the risk of cirrhosis and HCC [23]. HEV, typically self-limiting, can become chronic and cause cirrhosis in immunocompromised individuals.

Cirrhosis develops gradually through fibrosis, septa formation, and regenerative nodules. This process is often silent until complications arise [6]. While liver biopsy is the diagnostic gold standard, non-invasive tools like FibroScan, APRI, and FIB-4 are commonly used [8].

Despite treatment, cirrhotic patients remain at lifelong risk for HCC. Global strategies—vaccination, early diagnosis, treatment access, and harm reduction—aim to eliminate HBV and HCV as public health threats by 2030.

Primary Sclerosing Cholangitis and Its Progression to Liver Cirrhosis

PSC is a chronic, progressive liver disorder marked by inflammation and fibrosis of the intrahepatic and/or extrahepatic bile ducts. This leads to cholestasis, biliary cirrhosis, and eventually end-stage liver disease. Though its exact cause is unknown, PSC is believed to have an immune-mediated origin, influenced by genetic and environmental factors. Notably, 70–80% of PSC patients also have inflammatory bowel disease (IBD), particularly ulcerative colitis, indicating a gut-liver connection [24].

The clinical course of PSC varies widely. Some individuals remain stable for years, while others quickly progress to cirrhosis and its complications. It often presents subtly, discovered incidentally via abnormal liver tests or imaging. Disease progression involves bile duct obstruction and fibrosis, leading to hepatic damage and architectural distortion. Histologically, periductal "onion-skin" fibrosis may be observed but is not always present [25].

PSC can range from asymptomatic to decompensated cirrhosis. Median survival from diagnosis to death or liver transplant is 12–18 years [26]. Complications like dominant strictures, recurrent cholangitis, or cholangiocarcinoma—common in PSC—can hasten progression.

Magnetic resonance cholangiopancreatography (MRCP) is the preferred diagnostic tool, showing bile duct narrowing and beading. Liver biopsy is reserved for unclear cases or suspected overlap syndromes.

No approved medical cure exists. Ursodeoxycholic acid (UDCA) shows no survival benefit at high doses and may be harmful [27]. Liver transplant is the only effective treatment for end-stage disease, though recurrence occurs in 10–30% of cases [28]. Even in early stages, patients may suffer from cholangitis, fatigue, and pruritus, requiring multidisciplinary care. Ongoing research into the gut microbiome, immune pathways, and bile acid regulation offers promise for future therapies [29].

Primary Biliary Cholangitis and Its Progression to Liver Cirrhosis

Primary biliary cholangitis (PBC) is an autoimmune liver disease marked by the destruction of intrahepatic bile ducts, primarily affecting middle-aged women. This condition results in bile flow impairment, cholestasis, hepatocellular damage, and potential fibrosis or cirrhosis. The prevalence of PBC is estimated between 1.9 and 40.2 per 100,000 globally, with a significant female predominance [30].

The diagnosis of PBC is often confirmed by the presence of anti-mitochondrial antibodies (AMAs) and elevated alkaline phosphatase (ALP) levels. Histopathological examination reveals nonsuppurative granulomatous cholangitis and accompanying periportal inflammation and fibrosis [31].

PBC progresses through four histological stages, from portal inflammation to cirrhosis, with untreated patients having a 50% chance of progressing to cirrhosis within 15-20 years. Symptoms such as pruritus and fatigue may appear before the onset of complications like portal hypertension and HCC [32, 33].

Ursodeoxycholic acid (UDCA) is the primary therapeutic agent for PBC, improving clinical outcomes and delaying disease progression when administered early. However, 30-40% of patients do not respond adequately to UDCA, necessitating second-line treatments like obeticholic acid and fibrates to manage cholestasis [30-35].

Cirrhosis progression in PBC entails significant health risks, prompting the development of prognostic models like the GLOBE and UK-PBC risk scores for predicting patient outcomes. For those with severe cirrhosis or significant symptoms, liver transplantation provides a curative approach, achieving over 75% 10-year survival rates [36, 37].

Despite effective therapies, early diagnosis and risk assessment are essential, as complications from cirrhosis still affect many patients. Research focusing on the immunopathogenesis of PBC is ongoing, potentially leading to new therapeutic interventions to enhance patient outcomes.

Autoimmune Hepatitis and Its Progression to Liver Cirrhosis

Autoimmune hepatitis (AIH) is a chronic liver disorder marked by immune-mediated inflammation, interface hepatitis, autoantibodies, and elevated IgG levels. Its etiology is unclear but involves genetic and environmental factors leading to immune tolerance breakdown and autoimmunity [38].

AIH affects all demographics, predominantly females, with a 3:1 female-to-male ratio. Clinical manifestations vary from asymptomatic transaminase elevation to severe hepatic failure, often diagnosed post liver dysfunction or cirrhosis. Histologically, it features interface hepatitis, plasma cell infiltration, and fibrosis [39].

Untreated, AIH can lead to fibrosis and cirrhosis within years, with 40% of patients showing cirrhosis at diagnosis [40]. Progression risk correlates with disease severity, diagnosis delay, and treatment response, with persistent inflammation causing hepatocyte necrosis and complications like cirrhosis, portal hypertension, and hepatocellular carcinoma [41].

Immunosuppressive therapy is fundamental in AIH management, markedly enhancing long-term outcomes. First-line treatments include corticosteroids, with azathioprine as needed, achieving remission in over 80% of cases if started early [42]. However, incomplete responses or late-stage disease may lead to continued progression despite treatment.

Cirrhosis development in AIH correlates with poorer prognosis, with decompensated cirrhosis showing lower transplant-free survival. Patients with cirrhosis require vigilant monitoring for complications, and liver transplantation is the definitive treatment in advanced cases, yielding over 85% five-year survival, though graft recurrence occurs in up to 30% [43].

Monitoring disease activity and fibrosis is crucial throughout AIH progression. Non-invasive markers like APRI, FIB-4, and transient elastography are utilized to assess fibrosis without liver biopsies. Long-term follow-up also includes monitoring treatment side effects, remission assessment, and early cirrhosis complication detection.

Despite advancements in diagnosis and therapy, challenges persist in early detection and managing atypical cases. Ongoing research into pathogenesis, including regulatory T cells, HLA polymorphisms, and gut-liver interactions, may identify new therapeutic targets and enhance outcomes for at-risk patients.

Drug-Induced Liver Cirrhosis

Drug-induced liver injury (DILI) is a significant contributor to acute liver failure and can lead to chronic liver disease and cirrhosis when exposure to the causative agent persists. Although most DILI cases resolve after drug cessation, some may progress to drug-induced liver cirrhosis, a rare yet severe complication [44].

DILI may present as hepatocellular, cholestatic, or mixed injury, classified into intrinsic (predictable) or idiosyncratic (unpredictable) types [45]. Cirrhosis typically develops from chronic DILI due to recurrent hepatocyte damage, inflammation, and fibrogenesis.

Chronic liver injury with fibrotic progression can be caused by various medications, including: Methotrexate, commonly used in rheumatology and oncology, has been linked to hepatic fibrosis and cirrhosis, particularly in patients with metabolic risk factors [46]. Amiodarone can induce phospholipidosis and mitochondrial dysfunction, resulting in steatohepatitis and cirrhosis with prolonged use. Isoniazid may lead to a hepatocellular injury pattern that can occasionally progress to chronic hepatitis and fibrosis. Leflunomide and nitrofurantoin, associated with autoimmune-like hepatitis, can also result in cirrhosis if not promptly identified and discontinued [47].

Histologically, drug-induced cirrhosis is indistinguishable from cirrhosis of other origins, characterized by bridging fibrosis, regenerative nodules, and distorted liver architecture. Diagnosis relies on thorough clinical history, exclusion of other causes, and sometimes liver biopsy, with non-invasive assessments like transient elastography and serum fibrosis markers aiding in fibrotic detection.

Management of drug-induced cirrhosis involves stopping the offending drug, monitoring progression, and providing supportive care. Established cirrhosis patients require standard management for complications such as portal hypertension, varices, and hepatic encephalopathy, with liver transplantation considered for decompensated cirrhosis, yielding outcomes comparable to other causes [48].

Prevention is crucial through risk stratification, liver function monitoring, and prompt identification of hepatic adverse effects in at-risk individuals. The advancement of predictive models and pharmacogenomic screening tools may further improve early detection and mitigate the impact of drug-induced cirrhosis in clinical settings.

Complications of Cirrhosis

Cirrhosis marks the final stage of chronic liver disease, defined by extensive fibrosis, regenerative nodules, and liver structural distortion. As liver function deteriorates and intrahepatic pressure rises, life-threatening complications may develop, broadly divided into those related to portal hypertension and liver failure [49].

Portal Hypertension and Complications

Portal hypertension, identified by a hepatic venous pressure gradient over 5 mmHg, is a key factor in cirrhosis complications. Pressures above 10–12 mmHg heighten the risk of decompensation [50].

- Variceal bleeding, affecting up to 30% of those with esophageal varices, has high mortality, especially in decompensated patients [51].
- Ascites is the most common complication and a sign of poor prognosis, with 1-year mortality nearing 50% [52].
- Spontaneous bacterial peritonitis (SBP) occurs in 10–30% of hospitalized cirrhotic patients and requires urgent antibiotic treatment [53].
- Hepatic encephalopathy (HE) results from ammonia buildup, leading to cognitive issues or coma [54].
- Hepatorenal syndrome (HRS), particularly HRS-AKI, reflects severe renal dysfunction with poor outcomes [55].

Liver Failure-Related Effects

Declining liver function leads to:

- Coagulopathy, due to reduced clotting factor production [56]
- Jaundice, hypoalbuminemia, and hyponatremia, indicating worsening liver function and circulatory imbalance [57]
- Hepatocellular carcinoma (HCC), requiring regular surveillance [58]

Other Issues

Acute-on-chronic liver failure (ACLF) involves rapid decompensation with multi-organ failure, often triggered by infection or bleeding [59[. Cirrhosis also raises risks for infections, malnutrition, sarcopenia, osteoporosis, and hormonal imbalances, especially in cholestatic diseases like PBC and PSC.

Effective Management of Liver Cirrhosis

Managing cirrhosis requires a comprehensive approach focused on halting disease progression, preventing complications, and enhancing survival. Since cirrhosis can remain compensated for years, early detection and intervention are crucial.

1. Treating the Underlying Cause

Addressing the root cause is key. Antivirals such as DAAs for hepatitis C and entecavir or tenofovir for hepatitis B improve liver outcomes and reduce complications [60]. In ALD, sustained alcohol abstinence, along with psychosocial support, significantly improves survival [61]. For NAFLD-related cirrhosis, lifestyle changes, weight loss, and cardiovascular risk management are essential. Autoimmune liver diseases are managed with immunosuppressants or bile acid therapy [30].

2. Managing Complications

- **Portal hypertension**: Use non-selective beta-blockers or EVL to prevent variceal bleeding.
- **Ascites**: Managed through sodium restriction, diuretics, and paracentesis; TIPS may be needed in refractory cases [38].
- **SBP**: Treated with antibiotics and albumin; prophylaxis in high-risk patients is recommended [62].
- **HE**: Lactulose and rifaximin are standard, with attention to triggers [63].
- **HRS**: Managed with vasoconstrictors and albumin; TIPS or transplant may be needed [52].

2. Nutrition and Supportive Care

Addressing malnutrition with high-protein, calorie-rich diets and late-night snacks is vital. BCAAs may help in select cases [53].

3. HCC Surveillance

Biannual ultrasound ± AFP is advised for early cancer detection [56].

4. Preventive Care

Vaccinations (HAV, HBV, influenza, pneumococcus, COVID-19) and education on avoiding hepatotoxic drugs are essential [49].

5. Liver Transplantation

Indicated in advanced cases (MELD ≥15), with high success rates post-transplant [64].

6. Multidisciplinary Care

A coordinated team approach improves outcomes, especially in complex cases [65].

CONCLUSION

Liver cirrhosis is a critical, irreversible chronic liver disease with various causes and significant health implications. Its progression to advanced stages increases morbidity and mortality due to complications like portal hypertension and hepatocellular carcinoma. Effective cirrhosis management relies on early detection, removal of causes, and preventive measures against complications. Key strategies include antiviral treatment, alcohol cessation, and metabolic disease management, alongside multidisciplinary approaches to enhance patient outcomes. Innovative strategies, including integrated care and precision medicine, promise personalized treatment options, especially for patients with coexisting conditions. Nevertheless, access to liver transplantation remains limited, highlighting the necessity for improved health system preparedness. As

our comprehension of cirrhosis advances, future initiatives should focus on early intervention, health equity, and novel therapies to reverse fibrosis and enhance patient quality of life.

REFERENCE

1. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019 Jan;70(1):151-171. doi: 10.1016/j.jhep.2018.09.014. Epub 2018 Sep 26. PMID: 30266282.
2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020 Oct 17;396(10258):1204-1222. doi: 10.1016/S0140-6736(20)30925-9. Erratum in: Lancet. 2020 Nov 14;396(10262):1562. doi: 10.1016/S0140-6736(20)32226-1. PMID: 33069326; PMCID: PMC7567026.
3. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016 Jul;64(1):73-84. doi: 10.1002/hep.28431. Epub 2016 Feb 22. PMID: 26707365.
4. Marcellin P, Kutala BK. Liver diseases: A major, neglected global public health problem requiring urgent actions and large-scale screening. Liver Int. 2018 Feb;38 Suppl 1:2-6. doi: 10.1111/liv.13682. PMID: 29427496.
5. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006 Jan;44(1):217-31. doi: 10.1016/j.jhep.2005.10.013. Epub 2005 Nov 9. PMID: 16298014.
6. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014 May 17;383(9930):1749-61. doi: 10.1016/S0140-6736(14)60121-5. Epub 2014 Jan 28. PMID: 24480518.
7. Hernandez-Gea V, Friedman SL. Pathogenesis of liver fibrosis. Annu Rev Pathol. 2011;6:425-56. doi: 10.1146/annurev-pathol-011110-130246. PMID: 21073339.
8. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021 Sep;75(3):659-689. doi: 10.1016/j.jhep.2021.05.025. Epub 2021 Jun 21. PMID: 34166721.
9. Huang DQ, Mathurin P, Cortez-Pinto H, Loomba R. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. Nat Rev Gastroenterol Hepatol. 2023 Jan;20(1):37-49. doi: 10.1038/s41575-022-00688-6. Epub 2022 Oct 18. PMID: 36258033; PMCID: PMC9579565.
10. Liu, Y., Sun, Z., Wang, Q. *et al.* Contribution of alcohol use to the global burden of cirrhosis and liver cancer from 1990 to 2019 and projections to 2044. *Hepatol Int* 17, 1028–1044 (2023). https://doi.org/10.1007/s12072-023-10503-2.
11. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011 Nov;141(5):1572-85. doi: 10.1053/j.gastro.2011.09.002. Epub 2011 Sep 12. PMID: 21920463; PMCID: PMC3214974.
12. Orman, E. S., Odena, G., & Bataller, R. Alcoholic liver disease: Pathogenesis, management, and novel targets for therapy. Journal of Gastroenterology and Hepatology, 2013, 28, 77-84. https://doi.org/10.1111/jgh.12030.
13. Osna NA, Donohue TM Jr, Kharbanda KK. Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol Res. 2017;38(2):147-161. PMID: 28988570; PMCID: PMC5513682.
14. Neuman MG. Cytokines--central factors in alcoholic liver disease. Alcohol Res Health. 2003;27(4):307-16. PMID: 15540802; PMCID: PMC6668870.
15. Ahmad Anouti, Thomas A Kerr, Mack C Mitchell, Thomas G Cotter, Advances in the management of alcohol-associated liver disease, Gastroenterology Report, Volume 12, 2024, goae097, https://doi.org/10.1093/gastro/goae097.
16. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023 Apr 1;77(4):1335-1347. doi: 10.1097/HEP.0000000000000004. Epub 2023 Jan 3. PMID: 36626630; PMCID: PMC10026948.
17. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018 Jul;24(7):908-922. doi: 10.1038/s41591-018-0104-9. Epub 2018 Jul 2. PMID: 29967350; PMCID: PMC6553468.
18. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE, Loomba R. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023 May 1;77(5):1797-1835. doi: 10.1097/HEP.0000000000000323. Epub 2023 Mar 17. PMID: 36727674; PMCID: PMC10735173.
19. World Health Organization (WHO). (2021). Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Retrieved from https://www.who.int
20. Thomas DL. Global Elimination of Chronic Hepatitis. N Engl J Med. 2019 May 23;380(21):2041-2050. doi: 10.1056/NEJMra1810477. PMID: 31116920.
21. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and

treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560-1599. doi: 10.1002/hep.29800. PMID: 29405329; PMCID: PMC5975958.

22. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014 May 15;370(20):1889-98. doi: 10.1056/NEJMoa1402454. Epub 2014 Apr 11. PMID: 24725239.
23. Rizzetto M. Hepatitis D Virus: Introduction and Epidemiology. Cold Spring Harb Perspect Med. 2015 Jul 1;5(7):a021576. doi: 10.1101/cshperspect.a021576. PMID: 26134842; PMCID: PMC4484953.
24. Karlsen TH, Folseraas T, Thorburn D, Vesterhus M. Primary sclerosing cholangitis - a comprehensive review. J Hepatol. 2017 Dec;67(6):1298-1323. doi: 10.1016/j.jhep.2017.07.022. Epub 2017 Aug 10. PMID: 28802875.
25. Lindor KD, Kowdley KV, Harrison ME; American College of Gastroenterology. ACG Clinical Guideline: Primary Sclerosing Cholangitis. Am J Gastroenterol. 2015 May;110(5):646-59; quiz 660. doi: 10.1038/ajg.2015.112. Epub 2015 Apr 14. PMID: 25869391.
26. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol. 2012 May;56(5):1181-1188. doi: 10.1016/j.jhep.2011.10.025. Epub 2012 Jan 13. PMID: 22245904.
27. Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, Harnois D, Jorgensen R, Petz J, Keach J, Mooney J, Sargeant C, Braaten J, Bernard T, King D, Miceli E, Schmoll J, Hoskin T, Thapa P, Enders F. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology. 2009 Sep;50(3):808-14. doi: 10.1002/hep.23082. PMID: 19585548; PMCID: PMC2758780.
28. Graziadei IW, Wiesner RH, Batts KP, Marotta PJ, LaRusso NF, Porayko MK, Hay JE, Gores GJ, Charlton MR, Ludwig J, Poterucha JJ, Steers JL, Krom RA. Recurrence of primary sclerosing cholangitis following liver transplantation. Hepatology. 1999 Apr;29(4):1050-6. doi: 10.1002/hep.510290427. PMID: 10094945.
29. Eaton JE, Talwalkar JA, Lazaridis KN, Gores GJ, Lindor KD. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. Gastroenterology. 2013 Sep;145(3):521-36. doi: 10.1053/j.gastro.2013.06.052. Epub 2013 Jul 1. PMID: 23827861; PMCID: PMC3815445.
30. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology. 2019 Jan;69(1):394-419. doi: 10.1002/hep.30145. Epub 2018 Nov 6. PMID: 30070375.
31. Selmi C, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. Lancet. 2011 May 7;377(9777):1600-9. doi: 10.1016/S0140-6736(10)61965-4. Epub 2011 Apr 28. PMID: 21529926.
32. Scheuer P. Primary biliary cirrhosis. Proc R Soc Med. 1967 Dec;60(12):1257-60. doi: 10.1177/003591576706001205. PMID: 6066569; PMCID: PMC1901478.
33. Poupon R. Primary biliary cirrhosis: a 2010 update. J Hepatol. 2010 May;52(5):745-58. doi: 10.1016/j.jhep.2009.11.027. Epub 2010 Feb 18. PMID: 20347176.
34. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, Drenth JP, Pockros PJ, Regula J, Beuers U, Trauner M, Jones DE, Floreani A, Hohenester S, Luketic V, Shiffman M, van Erpecum KJ, Vargas V, Vincent C, Hirschfield GM, Shah H, Hansen B, Lindor KD, Marschall HU, Kowdley KV, Hooshmand-Rad R, Marmon T, Sheeron S, Pencek R, MacConell L, Pruzanski M, Shapiro D; POISE Study Group. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med. 2016 Aug 18;375(7):631-43. doi: 10.1056/NEJMoa1509840. PMID: 27532829.
35. Corpechot C, Chazouillères O, Rousseau A, Le Gruyer A, Habersetzer F, Mathurin P, Goria O, Potier P, Minello A, Silvain C, Abergel A, Debette-Gratien M, Larrey D, Roux O, Bronowicki JP, Boursier J, de Ledinghen V, Heurgue-Berlot A, Nguyen-Khac E, Zoulim F, Ollivier-Hourmand I, Zarski JP, Nkontchou G, Lemoinne S, Humbert L, Rainteau D, Lefèvre G, de Chaisemartin L, Chollet-Martin S, Gaouar F, Admane FH, Simon T, Poupon R. A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis. N Engl J Med. 2018 Jun 7;378(23):2171-2181. doi: 10.1056/NEJMoa1714519. PMID: 29874528.
36. Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HL, Floreani A, Ponsioen CY, Mayo MJ, Invernizzi P, Battezzati PM, Parés A, Burroughs AK, Mason AL, Kowdley KV, Kumagi T, Harms MH, Trivedi PJ, Poupon R, Cheung A, Lleo A, Caballeria L, Hansen BE, van Buuren HR; Global PBC Study Group. Development and Validation of a Scoring System to Predict Outcomes of Patients With Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy. Gastroenterology. 2015 Dec;149(7):1804-1812.e4. doi: 10.1053/j.gastro.2015.07.061. Epub 2015 Aug 7. PMID: 26261009.
37. Akamatsu N, Sugawara Y. Primary biliary cirrhosis and liver transplantation. Intractable Rare Dis Res.

2012 May;1(2):66-80. doi: 10.5582/irdr.2012.v1.2.66. PMID: 25343075; PMCID: PMC4204562.
38. Manns, M. P., Lohse, A. W., & Vergani, D. (2015). Autoimmune hepatitis—Update 2015. *Journal of Hepatology*, 62(1), S100–S111. https://doi.org/10.1016/j.jhep.2015.03.005
39. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, Bianchi FB, Shibata M, Schramm C, Eisenmann de Torres B, Galle PR, McFarlane I, Dienes HP, Lohse AW; International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008 Jul;48(1):169-76. doi: 10.1002/hep.22322. PMID: 18537184.
40. Gleeson D, Heneghan MA; British Society of Gastroenterology. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut. 2011 Dec;60(12):1611-29. doi: 10.1136/gut.2010.235259. Epub 2011 Jul 13. PMID: 21757447.
41. Zachou K, Muratori P, Koukoulis GK, Granito A, Gatselis N, Fabbri A, Dalekos GN, Muratori L. Review article: autoimmune hepatitis -- current management and challenges. Aliment Pharmacol Ther. 2013 Oct;38(8):887-913. doi: 10.1111/apt.12470. Epub 2013 Sep 8. PMID: 24010812.
42. Montano-Loza AJ, Carpenter HA, Czaja AJ. Predictive factors for hepatocellular carcinoma in type 1 autoimmune hepatitis. Am J Gastroenterol. 2008 Aug;103(8):1944-51. doi: 10.1111/j.1572-0241.2008.01922.x. Epub 2008 Jun 28. PMID: 18564111.
43. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019 Jun;70(6):1222-1261. doi: 10.1016/j.jhep.2019.02.014. Epub 2019 Mar 27. PMID: 30926241.
44. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR; Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. Am J Gastroenterol. 2021 May 1;116(5):878-898. doi: 10.14309/ajg.0000000000001259. PMID: 33929376.
45. Conway R, Carey JJ. Risk of liver disease in methotrexate treated patients. World J Hepatol. 2017 Sep 18;9(26):1092-1100. doi: 10.4254/wjh.v9.i26.1092. PMID: 28989565; PMCID: PMC5612840.
46. Björnsson ES. Drug-induced liver injury: an overview over the most critical compounds. Arch Toxicol. 2015 Mar;89(3):327-34. doi: 10.1007/s00204-015-1456-2. Epub 2015 Jan 25. PMID: 25618544.
47. Mindikoglu AL, Magder LS, Regev A. Outcome of liver transplantation for drug-induced acute liver failure in the United States: analysis of the United Network for Organ Sharing database. Liver Transpl. 2009 Jul;15(7):719-29. doi: 10.1002/lt.21692. Erratum in: Liver Transpl. 2010 Dec;16(12):1446. PMID: 19562705.
48. European Association for the Study of the Liver (EASL). (2018). EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *Journal of Hepatology*, 69(2), 406–460. https://doi.org/10.1016/j.jhep.2018.03.024
49. Bosch J, Iwakiri Y. The portal hypertension syndrome: etiology, classification, relevance, and animal models. Hepatol Int. 2018 Feb;12(Suppl 1):1-10. doi: 10.1007/s12072-017-9827-9. Epub 2017 Oct 24. PMID: 29064029.
50. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding--unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference. Hepatology. 2008 May;47(5):1764-72. doi: 10.1002/hep.22273. PMID: 18435460.
51. Runyon BA; AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009 Jun;49(6):2087-107. doi: 10.1002/hep.22853. PMID: 19475696.
52. Arroyo V, Angeli P, Moreau R, Jalan R, Clària J, Trebicka J, Fernández J, Gustot T, Caraceni P, Bernardi M; investigators from the EASL-CLIF Consortium, Grifols Chair and European Foundation for the Study of Chronic Liver Failure (EF-Clif). The systemic inflammation hypothesis: Towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. J Hepatol. 2021 Mar;74(3):670-685. doi: 10.1016/j.jhep.2020.11.048. Epub 2020 Dec 7. PMID: 33301825.
53. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K, Wong P. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014 Aug;60(2):715-35. doi: 10.1002/hep.27210. Epub 2014 Jul 8. PMID: 25042402.
54. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S, Moore K, Lee SS, Durand F, Salerno F, Caraceni P, Kim WR, Arroyo V, Garcia-Tsao G; International Club of Ascites. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut. 2015 Apr;64(4):531-7. doi: 10.1136/gutjnl-2014-308874. Epub 2015 Jan 28. PMID: 25631669.
55. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011 Jul

14;365(2):147-56. doi: 10.1056/NEJMra1011170. PMID: 21751907.

56. Ginès, P., Solà, E., Angeli, P. *et al.* Hepatorenal syndrome. *Nat Rev Dis Primers* **4**, 23 (2018). https://doi.org/10.1038/s41572-018-0022-7
57. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J, Finn RS. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021 Jan 21;7(1):6. doi: 10.1038/s41572-020-00240-3. Erratum in: Nat Rev Dis Primers. 2024 Feb 12;10(1):10. doi: 10.1038/s41572-024-00500-6. PMID: 33479224.
58. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013 Jun;144(7):1426-37, 1437.e1-9. doi: 10.1053/j.gastro.2013.02.042. Epub 2013 Mar 6. PMID: 23474284.
59. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Aguilar Schall R, Bornstein JD, Kitrinos KM, Subramanian GM, McHutchison JG, Heathcote EJ. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet. 2013 Feb 9;381(9865):468-75. doi: 10.1016/S0140-6736(12)61425-1. Epub 2012 Dec 10. PMID: 23234725.
60. Papatheodoridi M, Papatheodoridis G. Finite therapy of chronic hepatitis B infection: Pros. Clin Liver Dis (Hoboken). 2024 May 3;23(1):e0148. doi: 10.1097/CLD.0000000000000148. PMID: 38707241; PMCID: PMC11068136.
61. Lieber CS. Alcoholic liver disease: new insights in pathogenesis lead to new treatments. J Hepatol. 2000;32(1 Suppl):113-28. doi: 10.1016/s0168-8278(00)80420-1. PMID: 10728799.
62. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017 Jan;65(1):310-335. doi: 10.1002/hep.28906. Epub 2016 Dec 1. Erratum in: Hepatology. 2017 Jul;66(1):304. doi: 10.1002/hep.29169. PMID: 27786365.
63. Sundaram V, Manne V, Al-Osaimi AM. Ascites and spontaneous bacterial peritonitis: recommendations from two United States centers. Saudi J Gastroenterol. 2014 Sep-Oct;20(5):279-87. doi: 10.4103/1319-3767.141686. PMID: 25253362; PMCID: PMC4196342.
64. Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J; DGEM (German Society for Nutritional Medicine); Ferenci P, Holm E, Vom Dahl S, Müller MJ, Nolte W; ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin Nutr. 2006 Apr;25(2):285-94. doi: 10.1016/j.clnu.2006.01.018. Epub 2006 May 16. PMID: 16707194.
65. Manns, M. P Kwong AJ, Ebel NH, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Foutz J, Gauntt K, Cafarella M, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2020 Annual Data Report: Liver. Am J Transplant. 2022 Mar;22 Suppl 2:204-309. doi: 10.1111/ajt.16978. PMID: 35266621.