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Review

# Recent Advances in the Diagnosis and Treatment of Liver Cirrhosis

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**Abstract**

The liver is an essential organ that carries out metabolism, detoxification, and processing of nutrients. Liver cirrhosis occurs when prolonged injury results in the replacement of normal liver tissue with scar tissue (fibrosis), which interferes with the function of the liver. The most frequent causes are chronic hepatitis C virus (HCV) infection and alcohol abuse. As cirrhosis advances, it becomes more challenging to diagnose and treat, hence posing a serious global health issue. Multiple etiologies are responsible for the causation of cirrhosis, such as alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and chronic viral hepatitis. The diagnosis is made with a combination of imaging studies and laboratory tests like magnetic resonance imaging (MRI) and ultrasound to determine liver damage. Cirrhosis was thought to be a irreversible condition previously, but current evidence indicates that advanced liver disease in some cases can be reversed. This has resulted in a change of nomenclature, with "advanced chronic liver disease" being used instead of "cirrhosis" to describe this changing concept. Treatment of chronic liver disease involves an extensive clinical evaluation, including symptoms, physical findings, medical history, and histological examination through biopsies or other investigations. Novel therapeutic strategies, such as gene therapy, stem cell therapy, and immunotherapy, are being investigated as novel avenues to enhance outcomes in patients. This research intends to integrate existing knowledge and new developments in hepatology, with observations that can guide future studies and improve clinical practice in the management of liver disease.

**Keywords**: Hepatic fibrosis, Alcoholic liver disease (ALD), Non-alcoholic fatty liver disease (NAFLD), Chronic hepatitis C virus (HCV), Wilson's Disease, Magnetic resonance imaging (MRI).



## 1. Introduction

The term "cirrhosis," derived from the Greek word "κίρρος" (kirrhos) meaning tawny, historically denoted individuals with chronic "burned out" liver disease characterized by solid, noduled livers. These diseases underscore the end-stage nature of the process and the associated low survival rate (1). Sheila Sherlock's definition of liver cirrhosis hinges on a diffuse process of fibrosis and nodule formation, grounded in morphology. Extensive fibrosis and vascular architecture lead to liver dysfunction and increasing portal hypertension. Cirrhosis of the liver has been recognized since ancient times. Egyptians, Greeks, and Romans were among the earliest to

document the symptoms of liver illness. Hippocrates emphasized the liver's critical role in the body's operation. However, therapies remained rudimentary throughout the Middle Ages due to limited medical knowledge. Advances in anatomy and pathology during the 17th century spurred improved understanding of liver illnesses. In the 19th century, René Laënnec coined the term "cirrhosis" and linked it to alcohol addiction. Significant progress was made in the 20th century with the identification of hepatitis viruses and the subsequent development of vaccines and antiviral medications. Non-alcoholic steatohepatitis was also recognized as a significant contributor to cirrhosis. As of 2024, cirrhosis has emerged as a major health burden worldwide. Cirrhosis, along with other chronic liver illnesses, accounts for a tremendous mortality rate, with over 0.8 million deaths occurring annually (2). Affecting more than 160 million individuals globally, it stands as one of the leading causes of death associated with heavy alcohol consumption and non-alcoholic steatohepatitis in numerous countries. Significant case variation in cirrhosis arises from diverse etiologies and geographic distribution variables. Alcohol consumption has the highest impact in the US and Europe, while HBV and HCV have played important roles in most Asian and African countries. According to recent estimates, liver cirrhosis causes 1.3 million deaths yearly worldwide, making it a leading cause of death with immense public health implications. Liver cirrhosis patients may present in several unusual ways. Diagnoses are made through screening programs (such as those for hepatitis C in blood donors) or routine medical checkups. Individuals might experience non-specific symptoms, such as lethargy, malaise, and abdominal discomfort, or symptoms more specific to liver illness, such as jaundice, pruritus, pigmentation, or ascites. Spider naevi, palmar erythema, gynecomastia, splenomegaly, a flapping tremor, and xanthelasma are among the symptoms that may indicate chronic liver illness. The condition arises when scar tissue replaces healthy liver tissues. Treatment and diagnostic approaches for liver illnesses are continuously improving, benefiting patients. Cirrhosis can be diagnosed and addressed with remarkable effects. Novel non-invasive imaging types, such as MRIs and elastography, are utilized by doctors to evaluate liver diseases. Further biomarkers and genetic testing are being employed to diagnose conditions and determine clinical outcomes. Liver transplantation treatment has improved survival rates. Liver cirrhosis remains a major global health concern. Prevention strategies include promoting healthy lifestyles, reducing alcohol consumption, and boosting immunity. In treatment, antiviral drugs reduce the rate at which patients with viral hepatitis progress to cirrhosis. New treatments targeting the mechanisms leading to liver scarring are under development, including medications aimed at reversing fibrosis. Improved organ preservation methods and the utilization of more donors in liver transplantation are innovations that have improved outcomes for patients with severe liver disease. Patients with chronic liver disease should receive advanced treatment based on clinical linkages, such as symptoms, physical exam results, medical history, and pathologic findings from biopsies, autopsies, and other tissue examinations (1).

**2.Pathophysiology and Mechanism of liver cirrhosis**

Liver cirrhosis is causing sickness and death worldwide. In the natural history of this disease, which is progressive and dynamic, an advanced stage of compensated cirrhosis develops (3). Care units are being called upon to help manage patients with end-stage liver disease or life-threatening consequences due to the rising incidence of alcohol- and obesity-related liver diseases, and the rising prevalence of viral hepatitis (3,4). The main key factor or liver cirrhosis is Portal Hypertension (PH), and primary source of this problem is varices, ascites, renal failure, hepatic encephalopathy (HE), hyperdynamic circulation, and cardiomyopathy. The few more syndrome of liver cirrhosis are acute-on-chronic liver failure (ACLF) also characterized as decline in liver function, Non-alcoholic fatty liver disease (NAFLD) also known as fatty liver related liver disease and Alcoholic liver disease (ALD) also known for alcoholism (5). The diagram explains the mechanism of liver cirrhosis in Fig.1, in this cirrhosis the resistance to blood flow within the liver when increases, it also causes portal hypertension. They are the structural changes and functional alterations in the liver, which raise the blood pressure within the portal vein. As a result, blood faces increased pressure when trying to flow through the liver, creating collateral blood vessels to bypass the resistance. This generates further

complications, like varices and hepatic encephalopathy. Along with an increased portal inflow, there is splanchnic vasodilation—dilation of the blood vessels in the abdomen, leading to hypovolemia—a perceived lack of effective blood volume. These will trigger compensatory mechanisms like the Renin-Angiotensin-Aldosterone System and the Sympathetic Nervous System, which retain sodium and water, increasing blood volume. However, these very mechanisms can again lead to other complications like sodium retention, fluid accumulation in the body, hypervolemia, ascites—fluid accumulation in the abdomen, hepatorenal syndrome—kidney dysfunction, cardiomyopathy (6,7).

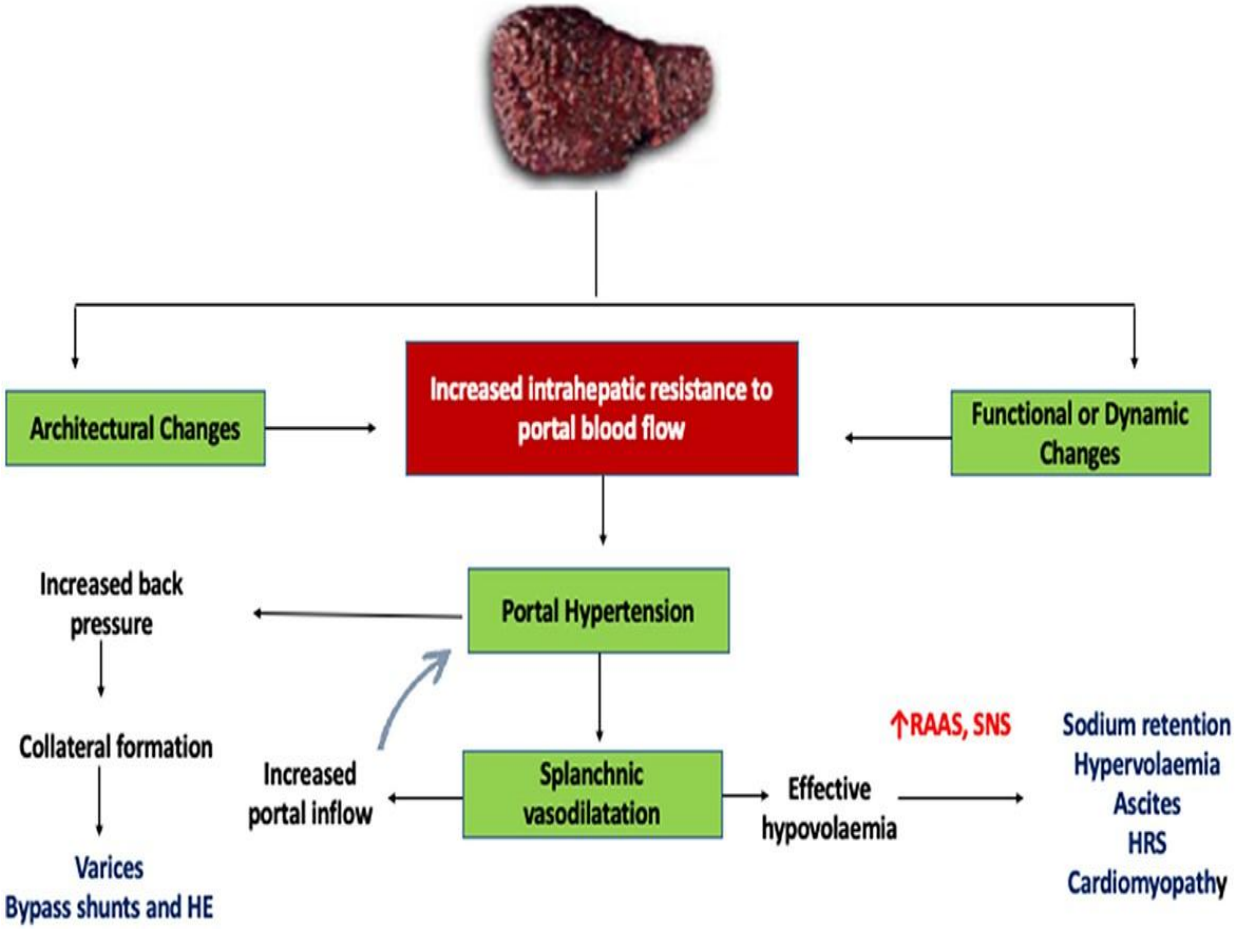


Fig.1 Detailed description of Mechanism of action in Liver Cirrhosis (6).

**Portal Hypertension**

Portal Hypertension explains how blood flow and resistance combine to determine blood pressure. As a result, portal hypertension develops when there is an increase in blood flow or resistance (8). It is caused by both static and dynamic factors. Increasing portal pressure causes the intestinal microcirculation to release nitric oxide and other vasodilators in the splanchnic arterioles, which also affects the blood nearby. The vessel in the splanchnic circulation, leading to a rise in blood flow into the portal system and splanchnic arterial vasodilation. Blood collecting in the splanchnic circulation lowers the systemic circulation's effective blood volume, which activates neurohumoral systems such the antidiuretic hormones and the renin-angiotensin-aldosterone system. This causes retention of water and sodium, growth of the plasma volume which increases the output (9). Due to this there is an increase in blood flow and perpetuates the higher portal pressure.

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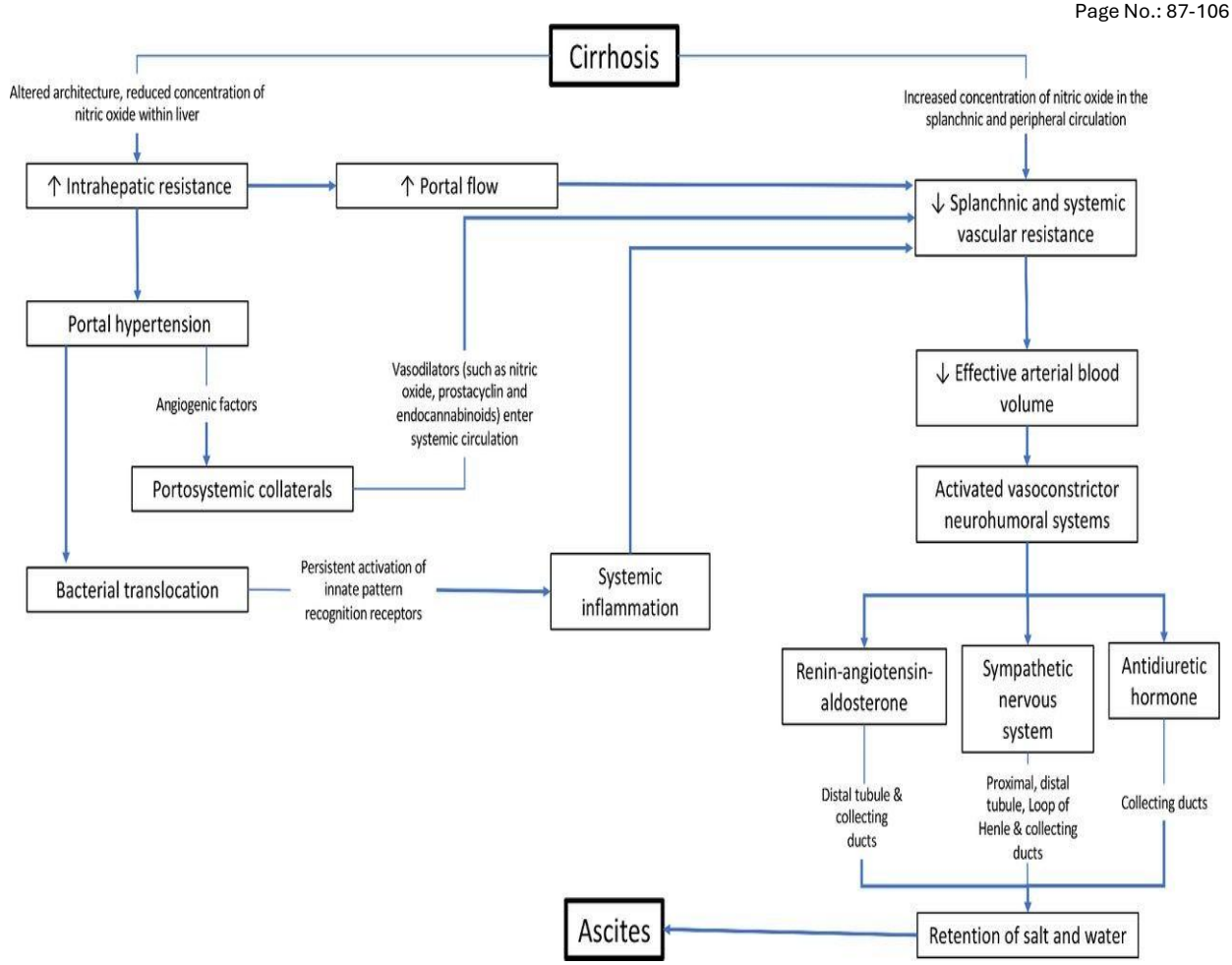


Fig.2 Pathogenies of Portal Hypertension. (8)

**Hepatocyte Damage**

Hepatocytes, or liver cells, eventually die from chronic liver injury. When there is continuing damage, the liver attempts to repair the injured cells, but this process can often be uneven and inefficient. The mechanisms of hepatocyte damage in cirrhosis vary depending on the underlying etiology. In ALD, chronic alcohol consumption leads to the accumulation of fat in hepatocytes (steatosis), inflammation, and oxidative stress, resulting in hepatocyte necrosis and apoptosis. In viral hepatitis, the hepatitis viruses directly infect and damage hepatocytes, triggering an immune response that contributes to further liver injury. In NAFLD, metabolic syndrome and glucose resistance lead to steatosis, inflammation, and oxidative stress, ultimately resulting in hepatocyte damage and fibrosis.Many forms of liver damage cause ploidy changes in hepatocytes in the adult liver. In nonalcoholic fatty liver disease and human chronic viral hepatitis, polyploidization has been shown to be enhanced. Hepatocyte polyploidization has also been shown to be caused in several animal models of liver damage, including those linked to tyrosinemia, iron buildup, copper accumulation, and total hepatectomy. Age-related hepatocyte alterations such as the buildup of DNA damage and malfunctioning mitochondria can cause pathological polyploidization, which is difficult to distinguish from healthy polyploidization. Polyploid hepatocytes also accumulate in elderly livers (10,11). The consequences of hepatocyte damage extend beyond the direct loss of liver function. In order to activate hepatic stellate cells and encourage fibrogenesis, damaged hepatocytes emit pro-inflammatory cytokines and chemokines. They also have a role in the development of hypertension in the portal vein and the disturbance of liver architecture.

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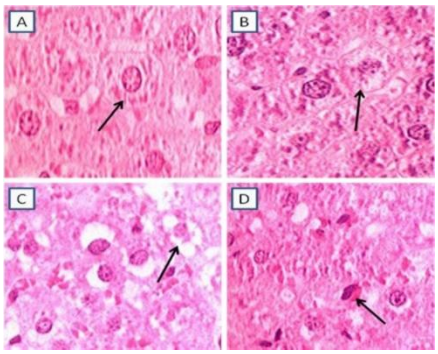


Fig.3 Hepatocyte damage of different grades, Arrows' heads show hepatocytes. A) normal, B) mild C) Moderate, D) severe (8).

**Ascites**

The main consequences of liver cirrhosis are ascites, which has a poor result. So, for direct therapy for patients with noncirrhotic ascites, it is important to differentiate between cirrhotic and noncirrhotic causes of ascites. (12) For the treatment of mild to moderate ascites diuretic and salt reduction are used. (8) Ascites fluid analysis, such as serum-ascites albumin gradient (SAAG) measurement, is advised to distinguish ascites from other potential causes. Ascites caused by PH have a 97% sensitivity when the SAAG levels are ≥ 1.1 g/dL. To reduce post-paracentesis circulatory failure and the condition hepatorenal syndrome (HRS), the large-volume paracentesis (LVP) should be carried out if the ascites becomes tight and covered with IV albumin replacement (20 g/2.5 liters) (13,14).

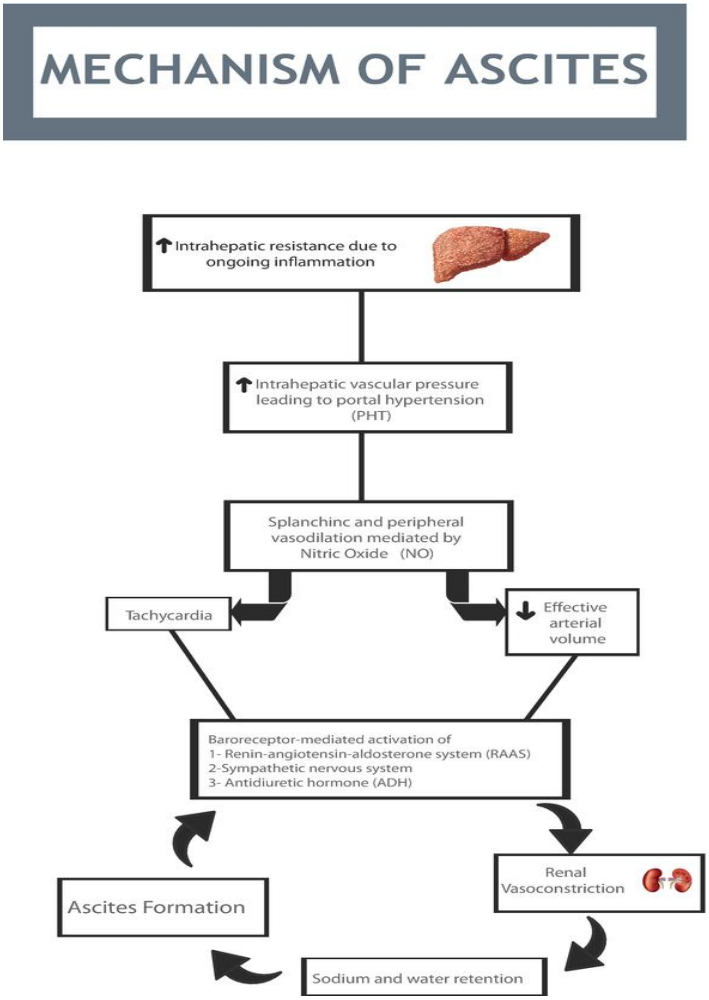


Fig.4 Mechanism of Ascites explained in a flowchart

**Varices**

In liver cirrhosis, varices are dilated veins that develop in the stomach or lower esophagus due to portal hypertension. The liver develops fibroses and scars from cirrhosis, which prevents blood flow through it. Pressure in the veins that empty into the portal vein

rises due to which the blood starts backing up in the vein and result to the increased resistance. To control the extra pressure, esophageal varices, or expanded veins in the esophagus, or gastric varices, or swollen veins in the stomach, swell and become engorged. Due to their weakness, these veins might rupture at any time (77).

**Renal dysfunctions**

There are several reasons for renal failure in cirrhosis. While ascites and hepatorenal syndrome patients have well-established therapies, for acute kidney damage (AKI) in cirrhosis, which are well known these days. The pathogenesis of renal failure and the production of ascites in cirrhosis is dependent on the loss in centrally effective blood volume. Therefore, every recommendation promotes albumin infusion after large volume paracentesis. Trans jugular intrahepatic portosystemic shunt improves survival and offers effective ascites control in certain individuals (15).

**Acute-on-Chronic Liver Failure (ACLF)**

Individuals suffering from cirrhosis may move from stage A to stage C in the Child stage depending upon the kind and amount of decompensation. It is a dynamic process with an acute event such as an infection, treatment toxicity, or gastrointestinal bleeding, ACLF is the sudden decompensation of chronic liver disease, typically cirrhosis. ACLF increases the risk of decline in the liver functions due to chronic hepatic damage. Fibrosis and metabolic dysfunction are inflammatory responses due to acute trigger (8). This causes systemic inflammation and liver failure, eventually resulting in multiple organ failure. Other problems like variceal hemorrhage could result from the elevated portal pressure (16). Microcirculatory dysfunction and systemic inflammatory response syndrome cause multiorgan failure and due to chronic damage, the liver is not able to recover from ACLF.

**Non-alcoholic fatty liver disease (NAFLD)**

NAFLD is a global health concern due to rising cases of people suffering from it. The NAFLD causes abnormal lipid deposition within liver cells due to which glucose resistance, a condition in which the body's cells become less responsive to insulin, increasing blood glucose levels, and thereby raising the amount of fat deposited in the liver. Reactive oxygen species produced by stored fat causes oxidative stress, which damages liver cells (17). The generated inflammatory response following the hepatic parenchymal injury may precipitate nonalcoholic steatohepatitis, a severe variant of NAFLD marked by hepatic cell damage and inflammation (18). Fibrogenesis, or the breakdown of liver scar tissue, is the result of persistent inflammation and cellular damage. Cirrhosis gradually impairs the liver's ability to function. Environmental factors such as poor food, lack of exercise, and the genetic predispositions that promote NAFDL also lead to increased insulin and fat accumulation, which causes liver fibrosis.

**Alcoholic liver disease (ALD)**

Steatosis is the term used to signify the accumulation of fat (triglyceride, cholesterol and phospholipid) in the hepatocytes, which is the consequence of alcohol misuse. According to preliminary research, excessive consumption of alcohol ultimately results in hepatocytes' ratio of reduced to oxidized nicotinamide adenine dinucleotide to rise. This imbalance impairs mitochondrial β-oxidation of fatty acids, leading to steatosis. It has also been demonstrated that drinking alcohol increases the amount of lipids that enter the liver from the small intestine, which facilitates the liver's uptake of fatty acids and the mobilization of fatty acids from adipose tissue. Further research is necessary to determine the precise role that these systems play in the development of steatosis following prolonged alcohol use. Liver disease, which results from alcohol use, is a product of a series of interlinked pathologic processes (19). Continual alcohol use can progress from fatty liver to alcoholic hepatitis, marked by prominent inflammation with hepatocyte injury, which in turn then activates hepatic stellate cells and promotes fibrosis. In those cases where the condition worsens, fibrosis may progress to cirrhosis—a well-defined pathological state characterized by significant scarring, poor liver function, and increased portal pressure. This increased portal pressure in the portal vein causes complications like ascites and variceal bleeding. Advanced liver disease impairs detoxification to the toxic accumulation of hepatic encephalopathy, reveling in neurological conditions. The overall pathophysiology of alcohol-induced liver disease is complex interaction of metabolic disturbances, oxidative stress, inflammation, and fibrosis that end up causing severe liver dysfunction (20)

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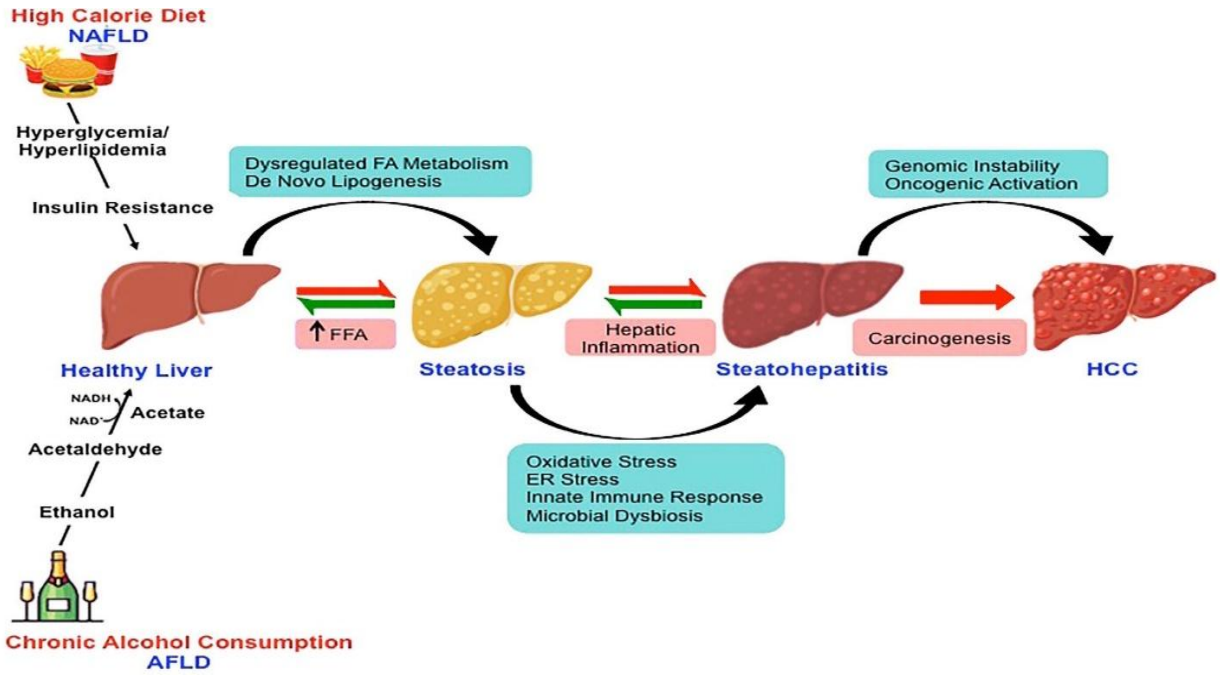


Fig.7. Pathophysiology of Alcoholic Liver Disease (ALD)

**3. Etiology of Liver Cirrhosis**

Cirrhosis results in an immunopathological or autoimmune, vascular, exogenous or toxic, infectious, toxic, or allergic or a genetic metabolic mistake. Several long-term illnesses and other factors that lead to increasing liver damage and fibrosis can culminate in cirrhosis. Chronic viral hepatitis, especially from the hepatitis B and C viruses, is one of the most frequent causes(21). Due to this condition liver causes chronic liver inflammation and scarring. ALD is another significant factor caused by high alcohol intake. This leads to damage to the liver by causing cirrhosis and fibrosis. The NAFLD is also a factor that leads to liver inflammation, which is due to intake of fatty food which leads to fat accumulations. NAFLD, also includes its more complex variant known as non-alcoholic steatohepatitis (NASH), is hepatic fat accumulation which are unrelated to alcohol consumption and is frequently linked to obesity and metabolic syndrome. There are few causes of liver cirrhosis are listed:

**Chronic Viral Hepatitis**

**Hepatitis B:** According to studies it has being proven that HBV replication causes an increase in risk of HCC (Hepatocellular carcinoma). Recent studies, mostly in Asia, demonstrate that entecavir and tenofovir treatment reduces the risk of HCC in cirrhosis by 30% and in non-cirrhosis individuals by 80%, even though the current lack of data in Western patients .Notably, even very low viral loads (< 2,000 IU/mL) in cirrhosis individuals raise the risk of HCC vs to patients with undetectable HBV. This suggests that the risk of HCC is not entirely reduced by current HBV antivirals. PAGE-B score has been verified in the Caucasian population undergoing antiviral medication. Prolonged infection with these viruses causes inflammation and liver damage. It makes liver damage worse ( 22).

**Hepatitis C:** A significant cause of chronic liver disease is hepatitis B and C, with hepatitis C being a higher risk of developing cirrhosis if left undiagnosed. Due to the immense genetic variety of viruses, the development of a preventive vaccination as primary prophylaxis remains challenging, despite encouraging developments. Thus, the primary objective of prevention is to prevent transmission, especially parenterally, through contaminated needles or blood products in transfusions. No matter how much the patient's liver disease has fibrosed, those who achieve sustained viral response (SVR) after infection have a decreased risk of developing HCC, complications, and mortality related to the development of cirrhosis ( 22,33).

**Alcoholic Liver Disease:** Alcoholic liver disease occurs as most people who overuse alcohol for days eventually acquire fatty liver. On the other hand, abstinence can completely reverse this disease, which is typically undiagnosed. While most people who abuse alcohol for a long time do not progress to the point where they have alcoholic liver disease, 15% to 20% of those who abuse alcohol also acquire cirrhosis and/or alcoholic hepatitis, which can occur simultaneously or consecutively. For the development of ALD, there is an amount of alcohol intake needed daily. It is likely that a daily alcohol intake of 80 g, or 6 to 8 drinks per day for years, leads to the development of several types of alcoholic liver disease. Since women consume more alcohol than men do, alcoholic liver disease is far more likely to develop at any given amount of alcohol consumption. Many other routes have been suggested, including the theory that women are more susceptible to alcohol-related liver impairment due to a decrease in stomach alcohol metabolism, which is linked to a drop-in gastric alcohol dehydrogenase activity. The necessary dosage for advanced alcoholic liver disease varies from patient to patient, and other reasons other than total alcohol intake play a major influence in determining whether alcoholic liver disease will develop or not. These results emphasize the importance of genetic factors that can predispose some individuals to alcohol-induced liver injury (24,25).

**Non-Alcoholic Fatty Liver Disease (NAFLD):** Type 2 diabetes and NAFLD are related which are all part of metabolic syndrome like obesity, insulin resistance, dyslipidemia. An important factor in the development of non-alcoholic fatty liver disease (NAFLD) is insulin resistance, which increases the hepatic fatty acid influx and lipolysis, both of which promote fat storage. It is obesity that leads to NAFLD. Insulin resistance develops from stomach fat increasing the liver's free fatty acid level (26) . The secretion of inflammatory cytokines by adipose tissue worsens fibrosis and liver inflammation. Nephropathy is due to insulin resistance, which is a type of type 2 diabetes. Blood glucose and insulin levels rise because of insulin resistance, which reduces cells' capacity to use glucose efficiently. By boosting the synthesis of new fat in the liver, high insulin levels increase the development of liver fat. In NAFLD, the main vital is diet. The hepatic fat accumulates due to increased consumption of fructose and saturated fats that results in a higher chance of hepatic fat buildup. Fructose is processed in the liver, where it can promote the formation of fat and lipogenesis. NAFLD is caused due to sedentary behavior and lack of physical activity. A lack of activity results in the increase of insulin resistance and adds to weight gain, these are the conditions that results in the non-alcoholic fatty liver disease (NAFLD) (27).

**Wilson's Disease:** Multiple motor or neuropsychiatric symptoms, as well as liver damage, are associated with Wilson's disease, an uncommon, autosomal recessive, genetic copper overload condition. The ATP7B gene is affected by several mutations, which is the result. Within the liver and brain's trans-Golgi network. They facilitate the secretion of excess copper into the bile. The excessive copper gets stored in the brain, liver, and tissues of body when it is not needed. In addition to lowering the cell's apoptotic threshold, free copper causes oxidative stress and lipid peroxidation. When an individual is afflicted, the symptoms might differ greatly and often manifest between the ages of 6 years and 2 years (76). However, there are other instances where the illness shows symptoms at a later age. We go over the factors to be considered when diagnosing, treating, and managing Wilson's illness in this overview. Furthermore, we showcase research endeavors aimed at investigating the pathophysiology of Wilson's illness in mice lacking ATP7B, innovative analytical methods that enhance the diagnosis during the first stages of the disease, and outcomes of copper-chelating drug treatment (28).

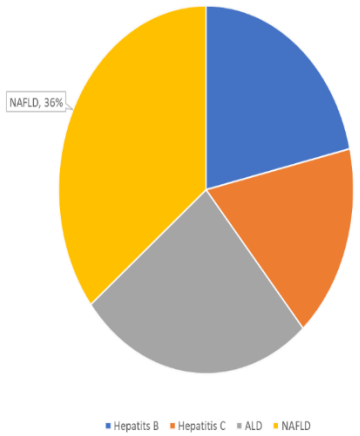


Fig.8. Distribution of etiologies of chronic liver diseases (29).

**4. Clinical Features:**

Table 1: The clinical features of liver cirrhosis (77):

| Symptoms | Physical Findings |
|---|---|
| Fatigue | Jaundice |
| Nausea and Vomiting | Ascites |
| Loss of Appetite | Edema |
| Abdominal Pain or Discomfort | Hepatomegaly |
| Itching (Pruritus) | Splenomegaly |
| Dark Urine | Spider Angiomas |
| Pale Stools | Palmar Erythema |
| Easy Bruising or Bleeding | Gynecomastia |
| Confusion or Cognitive Changes | Caput Medusae |
| Sleep Disturbances | Esophageal Varices |
| Muscle Cramps | Asterixis |
| Unexplained Weight Loss | Bruising and Petechiae |
| Menstrual Irregularities | Ascitic Fluid Wave |
| Gynecomastia | Dry Skin and Nails |

**5. Diagnosis of Liver Cirrhosis**

The primary cause of liver cirrhosis is nodules. Liver cirrhosis is a determined, chronic liver damage that leads to fibrosis. Cirrhosis, whether caused by problems, leads to a state of diminished liver function and is the most severe stage of liver disease. Liver cirrhosis, in 2023, is one of the global health concerns. It affects about 1-2% of the world's population, which is estimated to cause about 1.5 million deaths annually, thus serious in impact. Its prevalence with respect to cirrhosis varies by region: while it is related to non-alcoholic fatty liver disease and excessive use of alcohol in some countries, and some countries with, chronic viral hepatitis, mostly due to hepatitis B and C, dominates. Due to late diagnoses of cirrhosis, it becomes a source of expensive hospital stays. By treating cirrhosis before issues develop and a health crisis occurs, medical providers can frequently prevent decompensation ( 30).

Accurate diagnosis of cirrhosis is essential for managing individuals with chronic liver diseases. In a prospective multicenter trial, were studied in the diagnostic accuracy. For the diagnosis of cirrhosis, the fibro-scan was done to evaluate liver stiffness for 1,257 patients with various chronic liver conditions. They also discussed why liver histology and Fibro-scan differ from one another. 122 patients had inappropriate biopsy specimens, while 118 had unreliable liver stiffness evaluations. Analysis was performed on the diagnostic study of cirrhosis with the new 775 patients (31).

**Clinical Evaluation**

There was a thorough clinical evaluation. A traditional survey was used to document drug/herb intake and co-morbid disease. The body's physical measurements like body waist circumference, height of a patient and weight of the patient. The body mass index (BMI) used to clinical assessment and screen the health risk is calculated weight (kg) divided by height (m) squared. A tape is used to measure, placed horizontally across the body, and the waist circumference was measured halfway between the lower rib border and the cervical region. In the clinical evaluation medical history of all patients is also check like hepatitis infection, obesity, diabetes, and family history in case of liver cirrhosis (32).

**Laboratory Tests**

Liver Function Tests (LFTs) are very important in offering the general view of the health of the liver, mainly by assessing two enzymes: alanine aminotransferase and aspartate aminotransferase, whose values, if high, would indicate inflammation or damage of the liver. Prothrombin Time (PT) is a test that measures the liver's ability to synthesize blood-clotting proteins. Associated conditions like anemia and thrombocytopenia, both quite common in cirrhosis. Complete Blood Count (CBC)is a low hemoglobin, or hematocrit is an indicator of anemia, while low platelet count is usually caused by splenomegaly or decreased production in the liver. All these tests provide information about the liver condition; therefore, it will help in diagnosis and follow-up of the cirrhosis liver guiding the treatment (74).

**Imaging Studies**

**Ultrasound:** For the diagnosis of steatosis which affects more than 30% of the liver, ultrasound is the easiest method for the diagnosis. The symptoms of steatosis are seen in some people, some are heathy and till had steatosis they are more than 16%, non-obesity persons and over 95% of fatty people consume alcohol. The test is safe, affordable, and easily accessible. According to studies, there is a high correlation

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between the histological stage and the ultrasound classification. Moreover, the studies show that ultrasound has a 93% specificity and 89% sensitivity for steatosis identification. NASH and NFLD steatosis cannot be distinguished from one another (33).

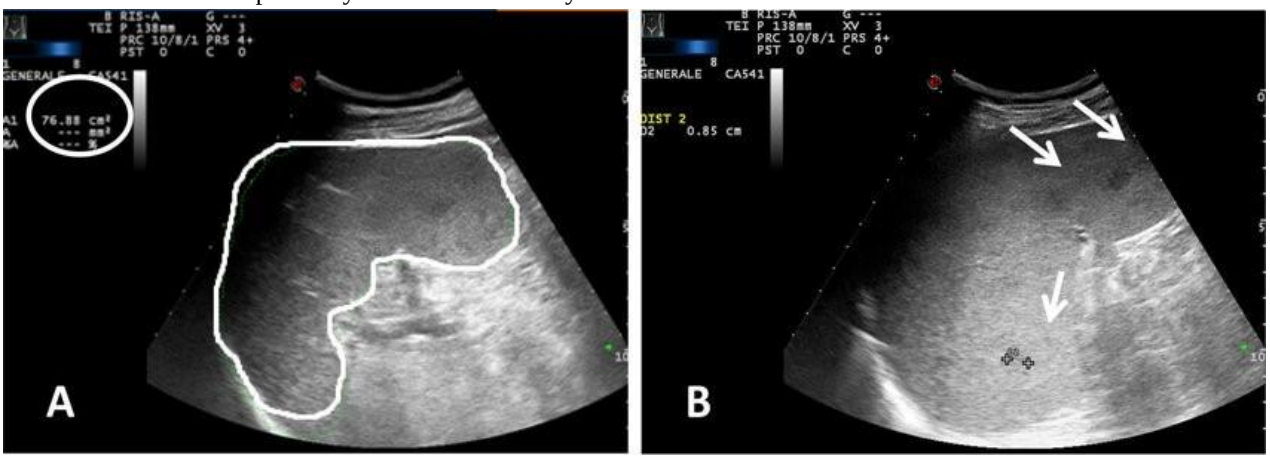


Fig .9. Ultrasound of Liver, A Normal liver; B Liver cirrhosis

**Magnetic Resonance Imaging (MRI):** Achieving precise staging of liver fibrosis is deemed essential for determining the prognosis of the disease and making management decisions. This is particularly important in the current global epidemic of NAFLD, which is linked to steatohepatitis and occasionally occurs spontaneously. Since early liver fibrosis can be diagnosed and easily treated and can be prevented by specific therapies (such as antiviral therapy in viral hepatitis), proper liver fibrosis staging is crucial, with significant benefits for the patients. Although liver fibrosis diagnosis and stages are currently mostly achieved through the histological study of core needle liver samples, this method is not perfect and has several disadvantages. First of all, a liver biopsy is an invasive procedure with a 1 in 10,000 chance of consequences, such as pain, bleeding, breathing difficulties, biliary tree punctures, and even death (34,35).

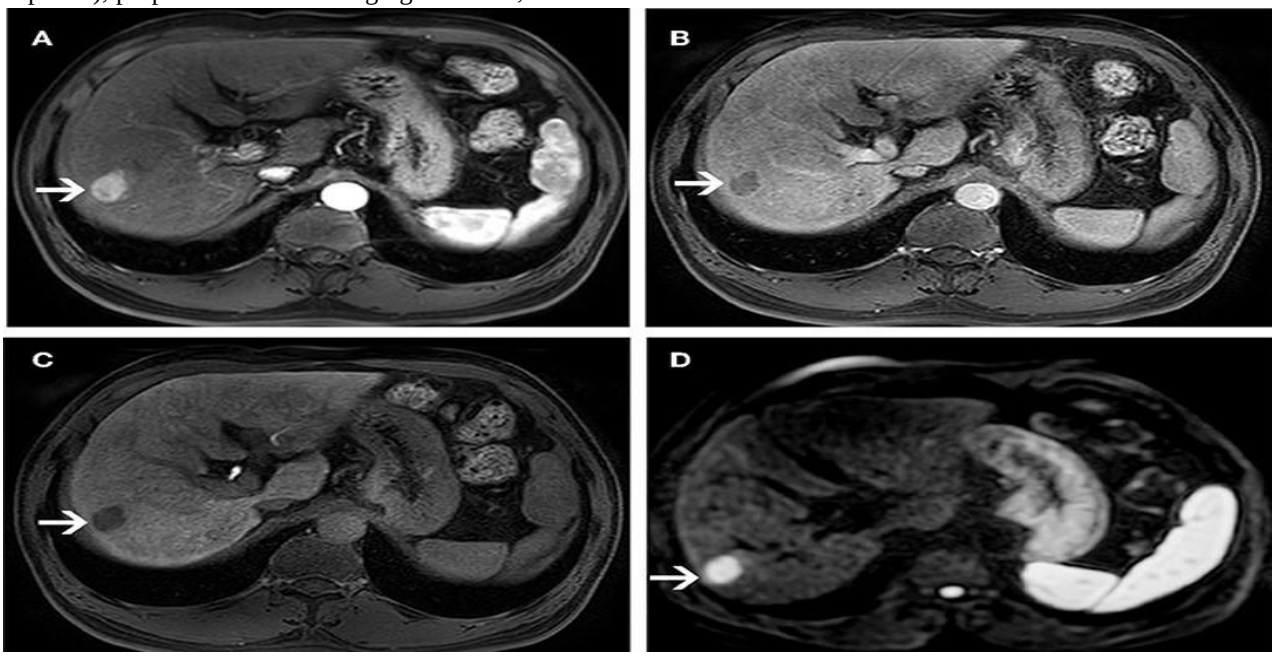


Fig.10. MRI of Liver Cirrhosis

**Elastography:** It is a helpful technique in the identification of preclinical ALD (Alcoholic Liver Disease) and has received widespread validation in the diagnosis of alcohol-associated fibrosis. Since past

few years many efforts have been made to create screening plans for the early identification of liver disease in those who consume alcohol at a high risk; these efforts have demonstrated the high performance of technique in identifying individuals with liver fibrosis within this demographic. However, a variety of factors that could influence the results must be considered, such as the presence of Alcohol-associated hepatitis (AH), cholestasis, recent alcohol use, and hypertransaminasemia linked to active alcohol intake. The higher cutoff values for advanced fibrosis in ALD than in other etiologies indicate that TE > 12–15 kPa is indicative of advanced fibrosis once the cofounders are eliminated (35).

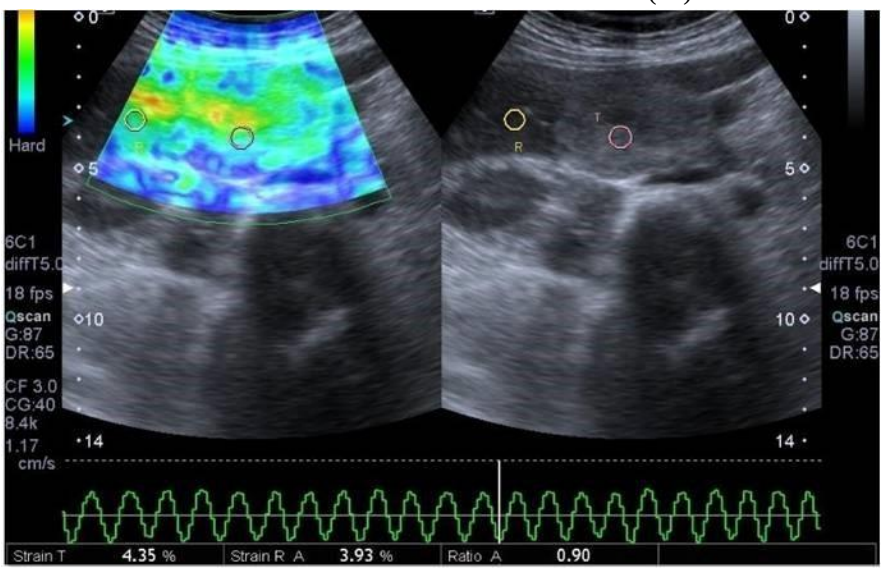


Fig.11. Elastography of Liver

**Liver Biopsy**

Still, a biopsy is important to confirm the Non-Alcoholic Steatohepatitis (NASH) diagnosis. It is important to consult each patient and determine whether to recommend a biopsy. Being over 45 years old, being obese or diabetic, and having an AST/ALT ratio > 1 are some of the clinical characteristics linked to it severe fibrosis and non-alcoholic steatohepatitis (NASH) in non-alcoholic fatty liver disease (NAFLD) patients that can support the indication of liver biopsy (33). During liver cirrhosis there are liver enzymes or fibrosis seen with steatosis (often observed in ultrasound) are the criteria for liver biopsy; additionally, liver biopsy is indicated to identify the predominant type of liver involvement in patients with concurrent illnesses. Despite being an intrusive and expensive technique, histological examination is still the most reliable diagnostic for assessing Alcoholic Fatty Liver Disease (ALD) (35).

**Artificial intelligence**

For decades, viral hepatitis was the leading cause of cirrhosis worldwide. However, Non-Alcoholic Steatohepatitis (NASH) and Alcoholic Fatty Liver Disease (AFLD) are poised to take the top spot. While cirrhosis secondary to Non-Alcoholic Fatty Liver Disease (NAFLD) is quite uncommon in the United States, occurring in only 1-2% of patients, screening patients at risk of NAFLD for chronic liver disease is still an integral part of Hepatocellular Carcinoma (HCC) surveillance programs. The American Gastroenterology Association (AGA) has published clinical guidelines and a technical review that emphasize the significance of elastography in identifying liver cirrhosis at an early stage. Non-invasive imaging methods are important in diagnosing AFLD, NAFLD, and chronic hepatitis B and C. Advanced imaging technologies like Magnetic Resonance Imaging (MRI) and Vibration-Controlled Transient Elastography (VCTE) are being given priority for assessing liver conditions. These techniques are of specific interest in determining liver stiffness cut-offs as a replacement for biopsies and informing clinical decision-making pathways for chronic liver disease management. Further, comparison between these imaging modalities and serum biomarkers of fibrosis is also under investigation to enhance the diagnosis of cirrhosis.Some well-proven non-invasive measures of

fibrosis and steatosis are being incorporated into decision-making algorithms. It has been suggested through recent studies to use standardized liver stiffness measurement (LSM) approaches such as the "rule of four" for Acoustic Radiation Force Impulse (ARFI)-derived methods and the "rule of five" for VCTE to discriminate among fibrosis phases. Additionally, Shear Wave Elastography (SWE) has shown promise as an indicator of the progression of the disease and death in cirrhotic patients. Research indicates that patients with advanced chronic liver disease are at increased risk of liver decompensation as liver stiffness values rise.Non-invasive screening methods, including VCTE and ARFI, have been found to be effective in identifying varices in high-risk patients. In addition, liver stiffness measurements have been included in predictive models to evaluate the risk of HCC development in patients with advanced chronic liver disease. (36,37,38).

**6. Recent Advance for Diagnosis**

**Non-Invasive Biomarker Panel**

Most chronic liver disorders have fibrosis as a common and potentially fatal effect. Hepatic fibrosis and cirrhosis are still being diagnosed via liver biopsy, which is still considered the gold standard. Yet, it is expensive, intrusive, and prone to significant sampling error. The invasive treatment of needle biopsy is being replaced or supplemented by the need for effective, liver-specific, non-invasive indicators of scarring and cirrhosis. Most class I biomarkers, or serum components that exhibit changes in the extracellular matrix (ECM) (fibrogenesis process and fibro lysis) and differences in fibrogenesis cells, originate from hepatic stellate cells, the most common profibrogenic cell type in the liver. During the development of cirrhosis or hepatic fibrosis, components of the hepatic extracellular matrix, including collagens like supplemental types I and III, basement membrane types IV, VI, and pericellular types V, and non-collagenous proteins such as laminin, fibronectin, and undulin, are synthesized more frequently, decreased less frequently, and possibly less efficiently than before (39). Panels of straightforward conventional laboratory procedures make up class II biomarkers. Class II biomarkers work upon algorithm assessment of frequently seen functioning abnormalities in the liver that may or may not be indicative of changes in fibrogenesis cells or ECM metabolism. The parameters, mainly standard laboratory tests and frequently multiparametric (panels), are provided as around 20 numerical scores or indices (40). These provide many criteria for fibrosis staging and detection, and for the grading of fibrogenesis activity. The combination of serum indicators for fibrosis that has been studied the most is the Fibro test. But many of these ratings still have little diagnostic utility, and assay standardization is still only partially achieved. Transient elastography, or Fibroscan, is an easy-to-use technique that uses ultrasound to quantify the stiffness of the liver as a proxy for fibrosis and cirrhosis. The variability between and among observers is minimal. To improve the diagnosis, one might mix the producers of liver fibrosis (39,41).

**Table 2: List of biomarkers with their functions and effectiveness (42):**

| Biomarker | Function | Effectiveness |
|---|---|---|
| ALT (Alanine Aminotransferase) | Indicates liver cell damage | AUC = 0.62; 75% specificity; 64% sensitivity; normal in 19% of NASH patients |
| AST (Aspartate Aminotransferase) | Reflects liver cell injury | 62% specificity; 77% sensitivity |
| CK-18 Fragments | Measures cell death and apoptosis | Sensitivity = 75%; specificity = 81%; AUC = 82%; >250 U/L linked to weight loss |
| Activated PAI-1 | Associated with reduced breakdown of fibrin; indicates fibrosis | Higher levels correlate with NASH; odds ratio = 1.20; $p < 0.001$ |
| OxNASH Panel | Includes age, BMI, AST, and specific fatty acids | 97% specificity for identifying NASH |
| FGF-21 | Boosts adiponectin and regulates lipid metabolism | Sensitivity = 92%; specificity = 85%; AUC = 0.94 |

| | | |
|---|---|---|
| PRO-C3 and FIBC3 | Measures a specific collagen marker for fibrosis | PRO-C3 > 14.5 ng/mL suggests NASH; FIBC3 shows 64% sensitivity and 77% accuracy |
| CK-18, Metabolic Syndrome, and NICE Model | Assesses indicators of cell death and metabolic issues | AUC = 0.83–0.88 |
| Adipocytokine and Apoptosis Indicators | Combines CK-18, adiponectin, and resistin | AUC = 0.91; 95% sensitivity; 70% specificity |
| HAIR Score | Measures liver injury and metabolic factors | Two or more indicators yield 80% sensitivity and 89% specificity |
| OWLiver® Test | Analyzes lipid profiles in serum | Sensitivity = 70%; specificity = 81%; AUC = 0.79 |
| 11,12-Dihydroxy[1]eicosatrienoic Acid | Indicates potential lipotoxicity | AUC = 1.0 for differentiating NASH from steatosis |

**Imaging Techniques for Liver Cirrhosis**

**Magnetic Resonance Elastography (MRE):** Magnetic resonance imaging scanners that are currently in use can be used for liver MRE. A connected passive driver part is placed on the liver, and an active compressor mechanical driver part placed outside the scanning room. Continuousory vibrations produced by the active compressor mechanical driver are transferred to the connected passive driver and then to the stomach, which includes the liver. Using MRE sequences as spreading shear waves, these waves cause microscopic shear displacement of tissues, which may be seen. After that, monochrome and colored stiffness maps, also called elastograms, are created. These comprise an image of magnitude that illustrates the upper stomach structure and an image of phase contrast that depicts shear waves at the same level. The ROI is then drawn inside the liver's confidence map by the readers, avoiding the edge, artifacts, fissures, fossa, and wave interference locations. ROIs on four slices are used to compute the mean liver stiffness value. The viscosity and elasticity of the tissue are both represented by the liver stiffness value, which is measured by MRE and expressed in kPa (43).

**Transient Elastography (FibroScan):** Fibro scan (Echosens, France) was used for TE, and its operators (Medical Physicist or Radiologic Technologist) were authorized by the manufacturer to quantify liver stiffness. With the patient's right arm completely extended and laying supine, TE was carried out. The medium (M) and extra-large (XL) probes were both employed. The manufacturer's recommendations were followed to evaluate. Each patient is validated with ten measurements for each examination for success scan (44).

**Molecular and Genetic Markers in Liver Cirrhosis:** The manufacturer's procedure was followed to extract miRNAs from the separated mononuclear cells using the miRNeasy Mini Kit (Qiagen, Germany). A NanoDropTM 2000 Spectrophotometer (ThermoFischer Scientific, USA) was used to measure its concentration and purity. ThermoFischer Scientific, USA's TaqMan MicroRNA Reverse Transcription Kit was used to execute reverse transcription operations in accordance with the manufacturer's instructions(45,46). ThermoFischer the USA scientist, was used to analyze the regulatory miRNAs expression in LCSCs. Ten microliters of the reaction were used to get the final volume of twenty milliliters. Because it has been shown that miR-1290 and miR-1825 are specific to CSCs and may have an impact on the initiation, progression, invasion, metastasis, chemoresistance, and recurrence of tumors, the study's finished goods were chosen for these assays (47).

**7.Treatment of Liver Cirrhosis**

Over the years, our doctors and investigators have been primarily responsible for preventing and treating a variety of clinically significant problems of liver cirrhosis, including variceal hemorrhage, ascites, hepatorenal disorder, and HE. A patient with liver cirrhosis's overall health, including whether they are malnourished, sarcopenic, or fragile, has received

more attention recently, except injuries to one or more organs. The fundamental reason for this is because accumulating data has made their effect on cirrhosis patients' lower survival rates clearer (48). It may be possible to minimize the number of liver disease-related deaths, the frequency of complications from advanced liver disease, and the associated healthcare costs by making investments in liver disease prevention, detection, and treatment. To find techniques that work for liver cirrhosis burden and to put cost-effective interventions into place, it is crucial to monitor changes in liver cancer(49).

**Chronic Hepatitis B and C Treatment**

**Antiviral Treatment:** In individuals with chronic hepatic B and C cirrhosis and liver fatigue, suppression of HBV and HCV replication has reduced hepatic damage and improved liver function. Any patient with congestive HBV-cirrhosis, regardless of HBV DNA levels, should be evaluated for antiviral therapy (50). For chronic Hepatitis B and C, two antiviral drugs that are commonly used are entecavir and tenofovir disoproxil fumarate (TDF). Drugs that lower viral loads and inflammation in the liver help to enhance liver function and slow the progression of the disease(51).

**Long-term outcome:** From the subset of patients who took antiviral medicine, ALT, quantitative HBsAg, qualitative HBeAg, and all relevant longitudinal HBV-DNA data were gathered. A year after the start of treatment, values were obtained. For the study, the values that were closest to the different dates of one, two, three, etc. years were considered; values that did not fall within the range of plus or minus three months were not (52).

**Alcohol-Related Liver Disease**

It's impossible to reverse ALD using approved pharmaceutical therapy. Coffee has been shown to slow the advancement of cirrhosis, according to observational evidence. As a result, management is centered on monitoring for consequences of cirrhosis, abstinence, and other lifestyle modifications such loss of weight and cooking changes. In a limited portion of individuals with end-stage illness, liver transplantation (LT) might be necessary. For individuals suffering from CC and liver fibrosis, abstinence from alcohol is essential to stopping the progression of their illness (53). Indeed, with appropriate lifestyle modifications, inflammation and fibrosis can still be reversed, even at an advanced level. Similarly, liver steatosis is thought to be reversible. Carbamazepine is not advised for patients with chronic cirrhosis of the liver and decreased synthetic function; instead, dosages of benzodiazepine medication should be lowered, and symptoms should be regularly and objectively monitored. In clinical practice, medications that lower hepatic metabolism, such as lorazepam or oxazepam, may be used. All patients undergoing alcohol withdrawal should receive parenteral thiamine treatment (often used together with other B vitamins) for three to five days until no symptoms (confusion, ataxia, ophthalmoplegia) remain, or treatment should be continued until no additional improvement in symptoms is observed, given the poor nutritional status of many patients (54).

**Non-Alcoholic Fatty Liver Disease (NAFLD)**

Lifestyle factors- Both the American and European associations suggest diet, reduction of weight and exercise as the primary components of any management for NAFLD studies. Steatosis of the liver and insulin resistance have been demonstrated to decrease with calorie intake reductions of at least fifty to one thousand kcal. At the end of the day, dieting causes weight loss, and overall weight loss has been strongly linked to improving liver anatomy and maybe curing cancer or NASH (nonalcoholic steatohepatitis). The prevalence of NAFLD and hepatic steatosis were significantly decreased in patients with type 2 diabetes throughout a 12-month lifestyle intervention program (55). Vitally, a study NAFLD patients who were managed with liver biopsies taken both before and after making lifestyle adjustments intended to cause weight loss.

**Table 3: List of drugs used are (56):**

| Drugs | Mechanism of Action | Recommendation of treat |
|---|---|---|
| Pioglitazone | PPARγ agonist | Yes |
| Vitamin E | Antioxidant | Yes |
| Statins | HMG Co reductase inhibitor | No (Only use in dyslipidemia) |
| Metformin | Reduced Insulin resistance | No |

**Liver Transplantation**

It has long been unknown whether orthotopic liver transplantation is beneficial in treating hepatocellular cancer. While patients with liver-confined cancers may benefit from liver replacement, prolonged consequences of liver transplantation for patients diagnosed with hepatocellular carcinoma have been disappointing, with a five-year survival rate. More recent years have allowed for more thorough, prospective evaluations of treatment in these patients because to modifications to the tumor–node–metastasis (TNM) classification system and other approaches for identifying the stage of hepatocellular carcinoma. According to studies, the rate of cancer recurrence following liver transplantation was directly correlated with the tumor stage prior to the transplant. Additionally, when hepatocellular cancer was detected in its early stages, liver transplantation was found to be more effective than resection(57) .

**8. Emerging Therapies for Liver Cirrhosis**

**Gene Therapy:**

Although transplanting a liver is thought to be the only viable therapy for end-stage liver fibrosis, there are drawbacks to this procedure, including poor outcome, immunological rejection, and difficulties obtaining a liver donor. These issues have been predicted to be resolved by gene therapy techniques such RNA interference, antisense oligonucleotide chains, and fake oligonucleotides over the few years. Several extracellular matrix proteins, such as collagen type I and type III, make up fibrous scars, forms during hepatic fibrogenesis. Hepatic- damage results from alcohol consumption, chemical assaults, viral hepatitis, or cholestatic damage and non-alcoholic steatohepatitis (NASH) are the main principal sclerosing cholangitis brought on by biliary cholangitis (PBC) (PSC) or biliary atresia are thought to be the two most common causes of liver the beginning of fibrosis(58) . It's crucial to note that a growing body of research indicates that effective treatment or the elimination of chronic damage factors might lead to a significant histological improvement in liver fibrosis. The required therapeutic target genes have also been identified through research on liver fibrosis patients or experimental models, and by employing the right gene carriers, rodent models of the disease have shown promising outcomes (59). MicroRNA (miRNA) therapy is an additional approach to treating liver fibrosis outside siRNA-based therapy. miRNA is a type of endogenous short RNA that is non-coding and

**Stem Therapy:**

Multiple researchers and medical studies have proven the positive effects of cell-based therapy with mesenchymal stem cells on liver fibrosis. Multipurpose stromal cells, also called MSCs, have minimal immunology and are extracted from various tissue sources and expanded in vitro. MSCs have several therapeutic benefits, including the capacity to self-renew, engraft, immunomodulate, differentiate into multiple lineages, and secrete trophic factors that aid in the regeneration and repair of injured tissue (61).Mammalian stem cells are the most used form of stem cells. They can be extracted from any adult or perinatal tissue, such as the liver, tooth, adipose tissue, umbilical cord, and common bone marrow. MSCs have been extracted from urine and other placenta sections in recent years (62).

**Table 4: Typical clinical trials for the treatment of cirrhosis or fibrosis of the liver utilizing stem cells (63)**.

| Condition | Patient Count | Cell Type | Administration Method | Findings |
|---|---|---|---|---|
| Decompensated Liver Cirrhosis | 219 | Mesenchymal stem cells from the umbilical cord | Intravenous (every 4 weeks for 3 cycles) | Reduced ascites volume; increased serum albumin; improved MELD score |
| Liver Cirrhosis | 6 | Autologous stem cells generated | Intrahepatic injection | Enhanced liver function assessed by METAVIR and Child-Pugh scores |

| | | | | |
|---|---|---|---|---|
| | | from adipose tissue | | |
| Alcoholic Liver Cirrhosis | 12 | Stem cells from allogeneic bone marrow | Hepatic artery | Better Child-Pugh scores; lower levels of TGF-β1, type I collagen, and α-smooth muscle actin |
| Liver Cirrhosis | 9 | Liver-derived mesenchymal stem cells | Not specified | No notable changes in blood parameters |
| Decompensated Liver Cirrhosis | 40 | Dental stem cells | Peripheral vein infusion at weeks 0, 4, 8, 12 | Liver function data not available; noted survival rates in MELD and Child-Pugh scores |
| Decompensated Liver Cirrhosis | 27 | Bone marrow mononuclear cells | Portal vein injection | Improvement in MELD scores observed in the mononuclear group |
| Decompensated Liver Cirrhosis | 14 | Endothelial progenitor cells | Hepatic artery | Notable improvement in MELD score |

**Immunotherapy:**

Years of research have led to the current clinical success of immunotherapy, primarily with immune checkpoint inhibitors. For the treatment of several diseases, including triple negative breast cancer, renal cell carcinoma, melanoma, urothelial carcinoma, head and neck squamous cell carcinomas, Merkel-cell carcinoma, and non-small cell lung cancer, immune checkpoint antibodies to PD-1, CTLA-4, and PD-L1 have demonstrated promise(64). By directly inhibiting negative regulatory signals on T cells or on cells that interact with T cells, such as tumor cells, stromal cells, and antigen-presenting cells, checkpoint inhibition (CPI) boosts preexisting anti-tumor immunity.Pembrolizumab and nivolumab, two PD-1 antagonistic monoclonal antibodies, recently obtained regulatory clearance for clinical use as HCC monotherapy. A few novel medications have more recently demonstrated promising clinical outcomes in first- or second line setting therapy. Also, immunotherapies, particularly those that target the PD-1/PD-L1 pathway and combine it with other treatments, can enhance future HCC therapy approaches. More potent HCC treatments are still desperately needed, despite these developments(65).

**9. Conclusion**

Recent liver cirrhosis management progress can be seen in the transition from invasive biopsy to non-invasive methods such as MRI and elastography, thus making earlier diagnosis and better response to treatment more feasible (68, 69, 70). Liver biopsies that are still necessary in the clinical setup can now be replaced with more patient-friendly imaging diagnostics thanks to modern digital technology. The change in treatment strategy from only symptom management to blocking TGF-beta is very good with modern antifibrotic drugs giving the possibility of reversal of cirrhosis (68, 69). Progress in liver transplantation treatment, which basically involves an extended donor list and the use of modern surgery, has greatly enhanced patient outcomes (68, 72). The post-transplant care offered by new immunosuppressive agents is designed for both survival and high quality of life and promises less rejection and fewer side effects (66, 73). However, personalized therapy is a must for different patients' responses (66, 73). The existing studies and clinical trials will give us hope that the management of cirrhosis will be better and better in the future. The use of AI in the diagnosis of diseases by imaging could lead to the creation of biased data due to the incongruity between the data used in training that will become the source of the AI model and the real data (71).

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