

## A Brief Review on Liver Cirrhosis: Epidemiology, Etiology, Pathophysiology, Symptoms, Diagnosis and Its Management

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# A Brief Review on Liver Cirrhosis: Epidemiology, Etiology, Pathophysiology, Symptoms, Diagnosis and Its Management

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**Abstract:** Cirrhosis is characterized by the formation of regenerative nodules in liver parenchyma surrounded by fibrous septa due to chronic liver injury. Cirrhosis occurs due to necrosis of liver cells followed by fibrosis and nodule formation. The liver structure becomes abnormal and interferes with liver blood flow and function and leads to portal hypertension and impaired hepatocytes function. Chronic liver diseases represent a significant health problem across the globe with liver cirrhosis. The exact prevalence of cirrhosis worldwide is still unknown as the clinical spectrum ranges from indolent, asymptomatic to complete hepatic decompensation. Diagnosis of cirrhosis includes serological test, histological test, transient elastography and radio techniques like ultrasonography, computerised tomography scan and magnetic resonance imaging. Ursodeoxycholic acid is used for treatment of primary biliary cirrhosis. For treatment of autoimmune hepatitis prednisone and azathioprine are used. For hepatitis B and C treatment interferon and antiviral agents are used. For treatment of hemochromatosis phlebotomy is used. For treatment of wilson disease, trientine and zinc are used. Liver transplantation is main curative option for treatment of liver cirrhosis, but it possesses significant risk to the patient.

### INTRODUCTION

Liver fibrosis or scarring of liver is a complex, dynamic change in normal wound healing response to different fibrogenic stimuli leading to activation and trans differentiation of hepatic stellate cells to myofibroblasts which leads to excessive synthesis and deposition of extracellular matrix components like collagen (type I and type III) accompanied by distortion of normal hepatic vasculature, hepatocyte dysfunction, irreversible liver damage, complications and result in death. <sup>[1]</sup> Cirrhosis occurs due to the necrosis of liver cells followed by fibrosis and nodule formation. Impairment in liver function and structure leads to impaired liver blood flow and function. This derangement produces the clinical features of portal hypertension. Cirrhosis represents the common pathway for chronic liver diseases. In 1826, the term cirrhosis was introduced by Laennec. It is derived from the Greek term scirrhus which refers to the orange or tawny surface of the liver. Cirrhosis is defined as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. The progression of liver injury to cirrhosis may occur over weeks to years. Patients with hepatitis C may have chronic hepatitis for as long as 40 years before progressing to cirrhosis. Many forms of liver injury are marked by fibrosis, which is defined as an excess deposition of the components of the extracellular matrix (collagens, glycoproteins and proteoglycans) within the liver. This response to liver injury is potentially reversible while in most patients, cirrhosis is not a reversible process. In addition to fibrosis, the complications of cirrhosis include portal hypertension, ascites, hepatorenal syndrome and hepatic encephalopathy. A poor correlation exists between histologic findings of cirrhosis and the clinical picture. Some

patients with cirrhosis are completely asymptomatic and have a reasonably normal life expectancy while some individuals

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have severe symptoms of end-stage liver disease and limited chance for survival. Common signs and symptoms may arise from decreased hepatic synthetic function (coagulopathy), decreased detoxification capabilities of the liver (hepatic encephalopathy) or portal hypertension (variceal bleeding). <sup>[2]</sup>

### EPIDEMIOLOGY

In the United States, chronic liver disease and cirrhosis result in about 35,000 deaths each year. In the United States, cirrhosis is the 9<sup>th</sup> leading cause of death and account for 1.2% of all US deaths. Fulminant hepatic failure (FHF) accounts for 2000 additional deaths every year. Causes of FHF includes viral hepatitis (Hepatitis A and B), drugs (Acetaminophen), toxins like *Amanita phalloides*, autoimmune hepatitis and Wilson disease. Patients with the FHF have a 50-80% mortality rate unless liver transplantation. <sup>[2]</sup> Different causes of cirrhosis are shown in Table 1.

### PATHOPHYSIOLOGY

The liver plays an important role in synthesis of proteins like albumin, clotting factors, complement factors and detoxification and storage of vitamin A. It participates in the metabolism of lipids and carbohydrates. Cirrhosis is often

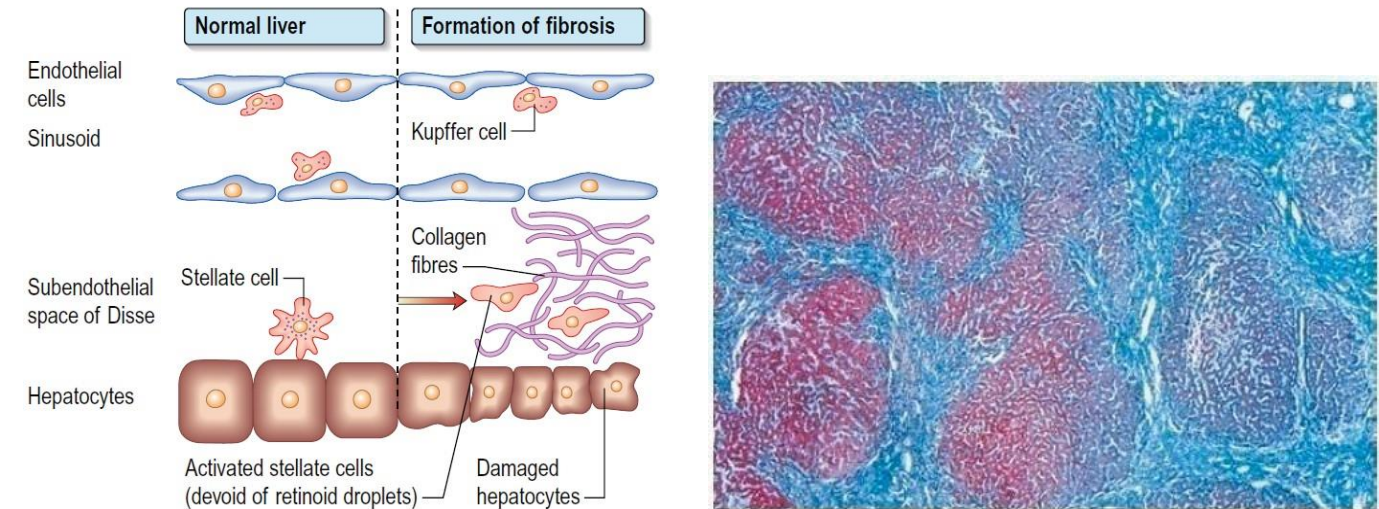
followed by hepatitis and steatosis (fatty liver) independent of the cause. If the cause is resolved at this stage, the changes are completely reversible. In cirrhosis, scar tissue development replaces normal parenchyma and blocks the portal flow of blood to organ and affects the normal function. Research shows the important role of the stellate cell in the development of cirrhosis which generally stores vitamin A. Hepatic parenchyma damage due to the inflammation, activate stellate cell and it increases fibrosis and obstructs the blood flow in the circulation. The formation of fibrous tissue bands separate hepatocyte nodules which replace the entire liver architecture. Chronic injury to the liver results in inflammation, necrosis and subsequently fibrosis as shown in Figure 1.

Fibrosis is initiated by activation of the stellate cells and Kupffer cells, damaged hepatocytes and activated platelets are also involved. Stellate cells are activated by various

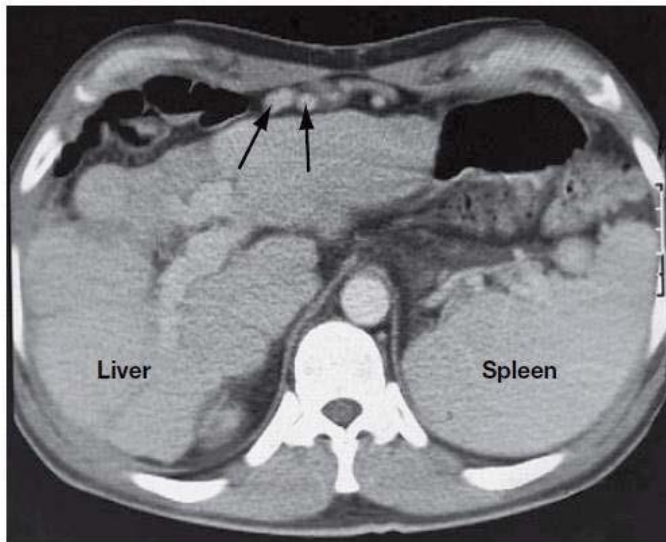
Activation of the stellate cell is followed by proliferation of fibroblasts and the deposition of collagen **Figure 1:** Pathogenesis of fibrosis [3]

Table 1: Etiology

Autoimmune	Autoimmune Hepatitis
Viral/infectious	a. Hepatitis B b. Hepatitis C c. Schistosomiasis
Metabolic	a. Alcohol b. Toxins, medications c. Hereditary hemochromatosis d. Wilson’s disease e. Non alcoholic steatohepatitis f. Insulin resistance
Cholestatic	a. Primary biliary cirrhosis b. Primary sclerosing cholangitis c. Biliary atresia d. Secondary biliary cirrhosis
Vascular	a. Right heart failure b. Budd–Chiari syndrome c. Alpha-1-antitrypsin deficiency d. Sarcoidosis e. Cystic fibrosis



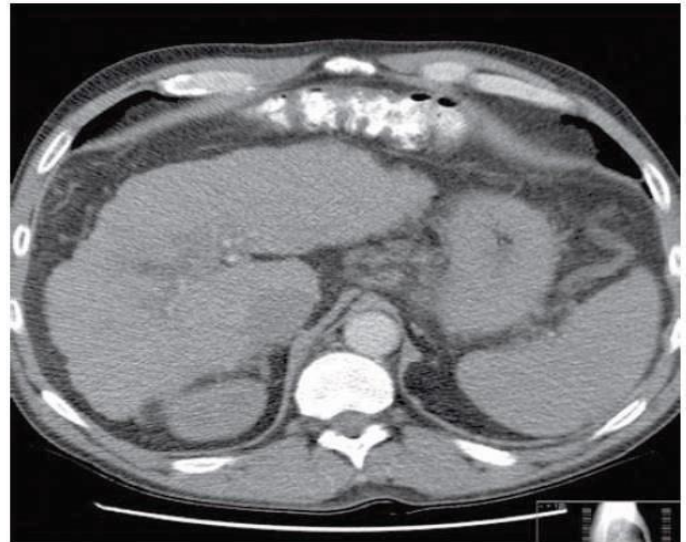
**Figure 2:** Pathology of cirrhosis



**Figure 3:** Irregular lobulated liver

cytokines and their receptors, reactive oxygen intermediates, autocrine signals and paracrine signals. In the early stage of activation, the swollen stellate cells lose retinoids with up regulation of receptors for fibrogenic and proliferative cytokines like transforming growth factor  $\beta 1$  (TGF- $\beta 1$ ) (potent fibrogenic mediator) and platelet derived growth factor (PDGF). Inflammatory cells cause fibrosis due to cytokine secretion. Collagens (type I and III) and fibronectin replace the normal matrix in the space of Disse. Sub endothelial fibrosis leads to loss of the endothelial function and impairs liver function. Collagenases (matrix metalloproteinases) are able to degrade collagen but are inhibited by tissue inhibitors of metalloproteinases (TIMPs) which level is increased in liver fibrosis. In initial stage, liver fibrosis is reversible when the inflammation is reduced by either suppressing or eliminating viruses. The pathologic features of cirrhosis include regenerating nodules separated by fibrous septa and loss of the normal lobular architecture within the nodules which leads to decreased blood flow throughout the liver. Spleen congestion leads to hypersplenism and increased sequestration of platelets as shown in Figure 2. [46] Two types of cirrhosis are described based on the underlying cause (a) Micro nodular cirrhosis in which regenerating nodules size is about less than 3 mm and the involvement of entire liver and often caused by alcohol induced damage or biliary tract disease. (b) Macro nodular cirrhosis in which the variable size nodules are formed and normal acini is seen within the larger nodules and it is often associated with chronic viral hepatitis. [3]

Macroscopically, in the initial stage the liver is enlarged and as disease progresses it becomes smaller. Liver surface becomes irregular with firm consistency and the color is yellow if it is associated with steatosis. There are three macroscopic types depending on the size of the nodules: micro nodular, macro nodular and mixed cirrhosis. In micro



**Figure 4:** Cirrhosis with a patent portal vein and no space occupying lesion

nodular form (Laennec's cirrhosis or portal cirrhosis) regenerating nodules size is less than 3 mm. In

macro nodular cirrhosis (post-necrotic cirrhosis), the nodules size is larger than 3 mm. The mixed cirrhosis consists of nodules with different sizes. Cirrhosis is defined by its pathological features: (a) the presence of regenerating nodules of hepatocytes and (b) the presence of fibrosis or the deposition of connective tissue between these nodules. The pattern of fibrosis depends upon the underlying causes. The fibrosis leads to normal tissue destruction in the liver including sinusoids, the space of Disse and vascular structures which lead to alteration in resistance to blood flow in the liver and portal hypertension. [7] Different entities injured the liver in different ways causing specific abnormalities. (In chronic hepatitis B- infiltration of the liver parenchyma with lymphocytes is seen). [7] In cardiac cirrhosis erythrocytes are present and fibrosis in the tissue surrounding the hepatic veins is seen. [8] In primary biliary cirrhosis fibrosis is seen around the bile duct. The granulomas are also present and in alcoholic cirrhosis neutrophils infiltrate the liver. [7, 9]

#### **SYMPTOMS AND COMPLICATIONS OF CIRRHOSIS**

In early stage of cirrhosis there are usually no symptoms. Progressive condition it causes symptoms like Loss of appetite, Tiredness, Nausea, Weight loss, abdominal pain, Spider-like blood vessels, severe itching and various complications are as follows:

1. Impaired metabolic and endocrine functions: Jaundice
2. Splenomegaly due to portal hypertension.
3. Haematological derangements such as thrombocytopenia.
4. Gastrointestinal varices.

**Table 2: Scoring Systems in Cirrhosis [3]**

<b>(I) Modified Child's-Pugh Classification</b>			
<b>Score</b>	<b>1</b>	<b>2</b>	<b>3</b>
Ascites	None	Mild	Moderate/severe
Encephalopathy	None	Mild	Marked
Bilirubin (μmol/L)	< 34	34–50	> 50
Albumin (g/L)	> 35	28–35	< 28
Prothrombin time (seconds over normal)	< 4	4–6	> 6
<b>Add Above Scores for Your Patient for Survival Figures Below</b>			
<b>Grade (scores)</b>	<b>1 year</b>	<b>% Survival 5 years</b>	<b>10 years</b>
Child's A (< 7)	82	45	25
Child's B (7–9)	62	20	7
Child's C (10+)	42	20	0

**(II) Model of End Stage Liver Disease (MELD)**

$$3.8 * \text{LN bilirubin in (mg/dL)} + 9.6 * \text{LN creatinine in (mg/dL)} + 11.2 * \text{LN (INR)} + 6.4$$

LN- Natural logarithm, INR- International normalized ratio, MELD scores (with no complications): 1 year survival 97% (score<10), 70% (score 30-40)

5. Ascites a severe complication due to portal hypertension.
6. Spontaneous bacterial peritonitis.
7. Hepatocellular carcinoma.
8. Hepatic encephalopathy.
9. Hyponatremia.
10. Hepatorenal syndrome.
11. Spider angiomas due to decreased oestrogen degradation in liver. [10]

**DIAGNOSIS [3, 10-12]**

**Serological Test**

Aspartate aminotransferase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP), bilirubin, prothrombin time, Gamma-glutamyl transpeptidase, albumin, immunoglobulins mainly IgG, creatinine level, sodium level, Low sodium indicates severe liver disease due to excessive diuretic therapy or defective free water clearance. Albumin level decreases below 28 g/l, serum creatinine elevated concentration increased above 130 μmol/l and the prothrombin time is prolonged.

**Histological Test**

Liver biopsy is considered as gold standard for diagnosis and sequential histological grading of fibrosis and to confirm the type and severity of liver disease. Stains are required for copper and iron measurement to confirm diagnosis of Wilson's disease or iron overload and immunocytochemical stains detect viruses, bile ducts and angiogenic structures.

**Radio Techniques 1. Ultrasound Examination**

To detect changes in size, shape of the liver and to detect hepatocellular carcinoma. Fatty change and fibrosis produces high level of echogenicity. In cirrhosis, there may be distortion of the arterial vascular architecture and marginal nodularity of the liver surface. The patency of the portal and hepatic veins are evaluated. Elastography is used for diagnosis and follow up monitoring to avoid liver biopsy.

**2. Computerized Tomography Scan (CT Scan)** Arterial phase contrast enhanced scans are important in the detection of hepatocellular carcinoma. Figure 3 shows hepatosplenomegaly and collateral vessels enlargement

below the anterior abdominal wall (with arrows) due to portal hypertension and Figure 4 shows dilated collaterals in liver disease.

**3. Endoscopy**

For detection and treatment of portal hypertensive gastropathy and varices.

**4. Magnetic Resonance Imaging (MRI) Scan For**

diagnosis of benign tumours (haemangiomas). Magnetic resonance angiography demonstrates the vascular anatomy and Magnetic resonance cholangiography shows the biliary tree.

**Transient Elastography**

Scoring systems in cirrhosis is shown in Table 2.



for NSAID induced renal insufficiency because of prostaglandin inhibition and impairment in renal blood flow. Opiate analgesics must be used with caution in

### **MANAGEMENT OF CIRRHOSIS Nutrition and Exercise**

Many patients complain of anorexia, which may be due to direct compression of ascites on the gastrointestinal tract. Patients should receive adequate calories and protein in diets. In 2010, American Association for the Study of Liver Diseases and the American College of Gastroenterology suggested guidelines for alcoholic liver disease and recommend aggressive treatment of protein calorie malnutrition in alcoholic cirrhosis patients. Multiple feedings per day, Regular exercise including walking and swimming to prevent inactivity and muscle wasting. Debilitated patients get benefit from formal exercise program supervised by a physician. <sup>[13]</sup> Specific therapies are needed in liver diseases to prevent or treatment of the development of cirrhosis. Prednisone and azathioprine used for autoimmune hepatitis, phlebotomy used for hemochromatosis, interferon and other antiviral agents used for hepatitis B and C, ursodeoxycholic acid used for primary biliary cirrhosis and trientine and zinc used for Wilson disease. These therapies become less effective if chronic liver disease evolves into cirrhosis. Once cirrhosis develops, treatment is aimed at the management of complications like variceal bleeding, ascites and hepatic encephalopathy. Zinc deficiency commonly is observed in patients with cirrhosis. Treatment with zinc sulfate at 220 mg orally twice daily may improve dysgeusia, muscle cramps and as a adjunctive therapy for hepatic encephalopathy. Pruritus is seen in cholestatic liver diseases (primary biliary cirrhosis) and noncholestatic chronic liver diseases (hepatitis C). Cholestyramine is used for the treatment of pruritus in liver disease but care should be taken to avoid co administration of Cholestyramine with any other medication to avoid impairment in gastro-intestinal absorption. Other drugs for treatment of pruritus include antihistamines (diphenhydramine, hydroxyzine), ursodeoxycholic acid, ammonium lactate skin cream, doxepin and rifampin and Naltrexone (an opioid antagonist). Patients with severe pruritus may require ultraviolet light therapy or plasmapheresis. Some patients with chronic cholestasis or primary biliary cirrhosis and patients receiving corticosteroids for autoimmune hepatitis require calcium and vitamin D supplementation or use of aminobisphosphonate (alendronate sodium).

### **Vaccination**

Patients with chronic liver disease should receive vaccination to protect against hepatitis A and as a protective measure, vaccination against influenza and pneumococci.

### **Analgesics**

The use of analgesics in patients with cirrhosis can be problematic. Most hepatologists permits the use of acetaminophen doses of up to 2000 mg/day in patients with cirrhosis. NSAID use in patients with cirrhosis may cause gastrointestinal bleeding. Patients with cirrhosis are at risk

patients with hepatic encephalopathy otherwise it may worsen underlying mental function.

### Drug Hepatotoxicity in the Patient with Cirrhosis

Medications associated with drug-induced liver disease include NSAIDs, Isoniazid, Valproic acid, Erythromycin, Amoxicillin/clavulanate, Ketoconazole, Chlorpromazine and Ezetimibe. Statins are frequently associated with mild elevations of alanine aminotransferase level and should be used safely in patients with chronic liver disease.

### Other Drugs

An amino glycoside antibiotic causes nephrotoxicity in patients with cirrhosis and should be avoided. Low dose estrogens and progesterone appear to be safe in the setting of liver disease. [2]

### Liver Transplantation

Liver transplantation has emerged as an important strategy in the management of patients with cirrhosis. Patients should be referred for consideration for liver transplantation after the first signs of hepatic decompensation. Advances in surgical technique, organ preservation and immunosuppression have improved the postoperative survival. In the early 1980s, the percentage of patients surviving 1 year and 5 years after liver transplant were 70% and 15% respectively. Now, patients with 1-year survival rate are about 85-90% and a 5-year survival rate of higher than 70%. Quality of life after liver transplant is good or excellent in most cases. [2]

### CONCLUSION

Cirrhosis represents the common histologic pathway for a variety of chronic liver diseases. The damage to hepatocytes causes impairment in liver functions. Cirrhosis is mainly diagnosed by liver biopsy and other serological laboratory test and radio techniques. Prednisone and azathioprine used for autoimmune hepatitis, interferon and other antiviral agents used for hepatitis B and C, phlebotomy used for hemochromatosis, ursodeoxycholic

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acid used for primary biliary cirrhosis and trientine and zinc used for Wilson disease and liver transplantation.

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