

LIVER CIRRHOSIS: CURRENT INSIGHTS AND EMERGING THERAPIES

Priya Sharma^{1*}, Sourab Dhiman², Dr. Bhartendu Sharma³, Dr. Ravinesh Mishra⁴

^{1*} Assistant Professor, School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, Solan - 173205, Himachal Pradesh, India.

² Student, School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, Solan - 173205, Himachal Pradesh, India.

³ Associate Professor, School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, Solan - 173205, Himachal Pradesh, India.

⁴ Professor, School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, Solan - 173205, Himachal Pradesh, India.

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***Corresponding Author**

Priya Sharma

Assistant Professor, School
of Pharmacy and Emerging
Sciences, Baddi University
of Emerging Sciences &
Technology, Baddi, Solan -
173205, Himachal Pradesh,
India.

ABSTRACT

Liver cirrhosis is a progressive liver disease characterized by the replacement of normal liver tissue with fibrous scar tissue, resulting in the impairment of liver function. The most common causes of cirrhosis include chronic alcohol consumption, viral hepatitis (especially hepatitis B and C), non-alcoholic fatty liver disease (NAFLD), and autoimmune liver disorders. The disease progresses in stages, from compensated cirrhosis, where the liver can still perform its functions, to decompensated cirrhosis, where liver failure occurs, leading to complications such as portal hypertension, variceal bleeding, ascites, and hepatic encephalopathy. Early diagnosis through imaging and liver biopsy, along with monitoring of liver function tests, is crucial for managing cirrhosis. Management focuses on treating the underlying cause, preventing complications, and improving quality of life. In advanced cases, liver transplantation may be required. Despite medical advancements, cirrhosis remains a significant public health concern with high morbidity and mortality rates. This report delves into the pathophysiology, risk factors, diagnostic methods, and treatment

strategies for liver cirrhosis, emphasizing the importance of early intervention and comprehensive care.

KEYWORDS: Endoplasmic Reticulum, Protein Synthesis, Lipid Metabolism, Calcium Signaling, Cell Stress Response.

1. INTRODUCTION

Cirrhosis is typically classified as compensated or decompensated, based on the absence or presence (previous history) of variceal bleeding, ascites, jaundice or encephalopathy.^[1] The significant longer survival, usually symptomless, and better quality of life experienced by patients with compensated cirrhosis compared to those with decompensated cirrhosis, has brought about the concept that compensated and decompensated cirrhosis are distinct clinical states of the disease.^[2]

Further disease states have been identified according to the presence of esophageal varices and to the presence of only one or more disease complication.^[3] Largest internal organ in the body is liver which is essential for the body function properly. Removes or neutralizes poisons from the blood, produces immune agents to control infection removes germs and bacterial from the blood.^[4] The body of evidence support a multistate approach to the clinical course of cirrhosis, which implies a specific statical methodology, since the Kaplan Meier survival curves. May not capture clinical state transition following the occurrence of a competing events before events of interest.^[5]

2. History of Cirrhosis

Its complication resulting improve management, quality of life and life expectancy of cirrhotic patients at present liver transplantation remain the only curative options for a selected group of patients but pharmacological therapies that can halt progression to decompensated Cirrhosis or even reverse cirrhosis are currently being developed.^[6]

- Cirrhosis is typically classified as compensated or decompensated, based on the absence or presences of bleeding, ascites jaundice or encephalopathy.
- Liver Cirrhosis result from different mechanisms of liver injury that lead to necroinflammation and fibrosis.
- Fibrosis progress at variable rates depending on the causes of liner
- Disease environment and host factor Cirrhosis is an advanced
- Stage of liver fibrosis that is accompanied by distortion of the hepatic

- Vasculature it leads to shunting of the portal and arterial blood supply.^[7-8]

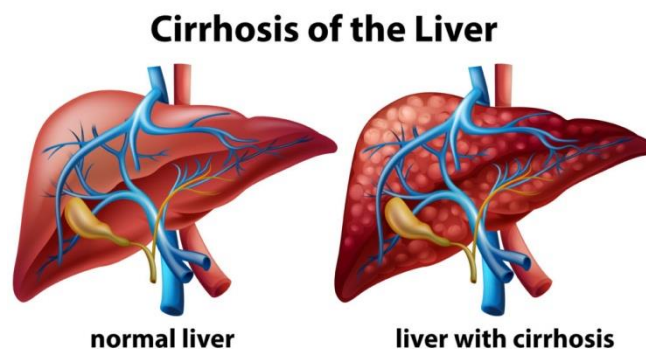


Fig. 1: Cirrhosis of liver.

3. Definition

Cirrhosis is a complication liver disease characterized by abnormal structure and function of the liver. This disease that leads to cirrhosis do so because they injure and kill liver cell after inflammation and repair that is associated with the dying liver cell causes scar tissue to form the liver cell that do not die multiple is an attempt to replace the cell that have died the results in clusters of newly formed liver cell(regenerative) within the scar tissue there are many causes of Cirrhosis including chemical and viruses' toxic metals.^[9] It's a complication of liver disease that involves loss of liver cells and irreversible scarring of the liver

4. Complication of Cirrhosis

- Swelling of the abdomen (ascites) or in the hip, thigh, leg-ankle and foot.
- Bleeding from varices.
- Hepatorenal syndrome.
- Hepatopulmonary syndrome.
- Diagnosis of Cirrhosis can be suggested by history physical examination and blood test and can be confirmed by liver biopsy.

5. Etiology of Cirrhosis

- In cirrhosis the relationship between blood and liver cell is destroyed even though the liver cells that survive or are newly formed may be able to produce and remove substance from the blood they do not have the normal relationship with the blood and this interferes with the liver cell ability to add or remove substance to the blood. In addition, the scarring within the cirrhotic liver obstructs the flow of blood through the liver and blood backs up in the portal vein. The pressure in the portal vein increases a condition called portal

hypertension because the obstruct to flow and high pressure in the portal vein. Blood in the portal vein seeks other vein then to heart. Vein with lower pressure that by pass the liver and loss of the normal contact between blood passing through the liver and liver cell and blood by passing the liver that leads to many of signs of Cirrhosis.^[10]

- Chronic hepatitis B and D: the hepatitis B virus is probably the most common causes of Cirrhosis worldwide but it is less common in the United States. Hepatitis like hepatitis e causes liver inflammation and injury that over several decades can lead to Cirrhosis.
- Auto immune hepatitis- this disease to be caused by the immune system attacking the liver and causing liver infection and inflammation damage and eventually scarring and Cirrhosis.
- Inherited disease alpha 1 antitrypsin deficiency, Wilson disease and glycogen storage disease are among the inherited disease that interfere with the way the liver produce processes enzyme metal other substance.^[11]
- Non-alcoholic steatohepatitis (NASH) for buildup in the liver and eventually causes scar tissue this type of hepatitis to be associated with diabetes, obesity coronary artery disease and treatment with corticosteroid medications.
- Block bile-duct when the duct that carry bile on the liver are blocked in baby blocked bile ducts are most commonly caused by biliary atresia a disease in which the duct is absent or injured.
- Some conditions and disease such as cancer of the bile ducts or cancer of the pancreas can block the bile duct increase the risk cirrhosis.^[12]
- Drug toxins and infection severe reaction to prescription drugs prolonged exposure to environment toxin the parasitic infection schistosomiasis and repeated bouts of heart failure with liver congestion can all lead to Cirrhosis.
- Alcoholic liver disease to many people Cirrhosis of the liver is synonymous with chronic alcoholism but in fact alcoholic cirrhosis developed after more than a decade of heavy drinking the amount of alcohol that can injury the liver varies greatly from person to person in women as few two or three drink per day have been with Cirrhosis.^[13]

6. Sign and Symptoms of Cirrhosis

People with cirrhosis may have few or no Sign and Symptoms of liver disease, some of the Symptom may be non-specific the symptoms of Cirrhosis depend on the stage of disease in the beginning stage may not have any Symptom.^[14]

6.1 Common Sign and Symptoms Cirrhosis include

- Yellowish of the skin jaundice due to the accumulation of bilirubin in the blood
- Fatigue
- Weakness
- Loss of appetite
- Itching
- Easy bruising from decreased production of blood clotting factor by the diseased liver
- Nose bleeding
- Vomiting Blood
- Urine becomes darker
- Fatigue losses of appetite blood capillaries become visible on skin on the abdomen
- Weight loss

6.2 Early Sign and Symptoms of Cirrhosis include

- Loss of appetite
- Feeling weak or tired
- Nausea
- Fever
- Unexpected weight loss
- Redness in the hands
- In women premature menopause
- Fluid accumulation your abdomen
- Infection such as syphilis or brucellosis
- Medication including methotrexate or isoniazid
- Spider like Blood vessel on skin
- Swelling feet or ankles

7. Classification of Cirrhosis

Cirrhosis of the liver may be classified using two classification methods based on etiology and morphology.^[15] Currently, classifying cirrhosis based on morphology is not recommended, as it requires an invasive procedure to examine the gross appearance of the liver, and provides little diagnostic value. Classifying cirrhosis according to etiology is a

more acceptable form of classification, as it may be attained through non-invasive laboratory testing, and has a higher diagnostic value.

7.1 Classification based on etiology

Alcoholic cirrhosis: most of common causes of cirrhosis caused by continue and prolonged alcohol abuse approximately 60-70 percent of all cases of Cirrhosis are due to alcohol abuse. Post necrotic cirrhosis occur after a massive event causes liver cell death viral hepatitis is the most common causes agent that are toxic to the liver may also causes. Biliary Cirrhosis may be due to a blockage in the bile duct and inflammation excess bile in the liver may caused tissue destruction resulting in jaundice.

Cardiac cirrhosis caused by congestive heart failure leading to poor circulation of oxygenated blood to the liver. Poor circulation may result in liver cell death and replacement of dead cell by fibrous tissue.^[16]

7.2 Classification based on morphology

Cirrhosis has historically been classified based on the nodular morphology that is seen on gross appearance of the liver accurate of the liver morphology can only be obtained through surgery, biopsy, or autopsy.^[17] This memorandum provides guidelines on the definition, nomenclature, and classification of cirrhosis, chronic hepatitis, and hepatic fibrosis. These are considered according to morphological characteristics and aetiology. It is hoped that this system will serve as a standard for diagnostic, research, and epidemiological purposes. The relationship of cirrhosis to liver cell carcinoma is briefly discussed and the possible morphological markers of an increased risk of malignancy are defined.

7.2.1 Based on severity

Child pugh scoring system is used for predicting the risk of complication severity of Cirrhosis. It should be noted that different text book and publication use different measure some older.^[18]

7.2.2 Stages

Cirrhosis in itself is already a late stage of liver damage in the early stage of liver disease will be inflammation of the liver if the inflammation is not treated it can lead to scarring. The fibrosis of the liver is not treated it can result in cirrhosis at this stage the scar tissue cannot heal but the progression of the scarring may be prevented or slowed.^[19]

1. Relative mild
2. Moderate
3. Severe

- Doctor also classify cirrhosis as either compensated or decompensated.
- Compensated cirrhosis means that the liver function is normal despite the damage a liver with decompensated Cirrhosis cannot perform its function correctly and usually causes severe symptoms.^[20]

Stage 1: Cirrhosis involves some scarring of the liver but few symptoms this stage is considered compensated cirrhosis there are no complications.

Stage 2: cirrhosis worsening portal hypertension and the development of varices.

Stage 3: involves the development of swelling in the Abdomen and advanced liver scarring. The stage serious complication and possible liver failure.

Stage 4: cirrhosis can be life threatening and people have developed end stage liver disease.

- Preventing further damage to the liver consume a balanced diet and one multivitamin daily, patients with (PBC) with impaired absorption of fat-soluble vitamins may need additional vitamins.
- Avoid drugs (including alcohol) that cause liver damage. All patients with Cirrhosis should avoid alcohol most patients with alcohol, including those who experience an improvement in liver function. With abstinence from alcohol.
- Even hepatitis B and C can substantially reduce liver damage slow the progression toward cirrhosis with abstinence from alcohol.^[21]
- Avoid nonsteroidal anti-inflammatory drugs NSAIDs e.g., ibuprofen
- Damage to the liver is permanent further injury to the liver should be avoided to halt the progression of the disease.
- General management to prevent chronic liver disease includes avoidance of alcohol, vaccination for good nutrition with a balanced diet, weight reduction and early treatment of precipitating factors like dehydration, hypotension and infection.^[22]

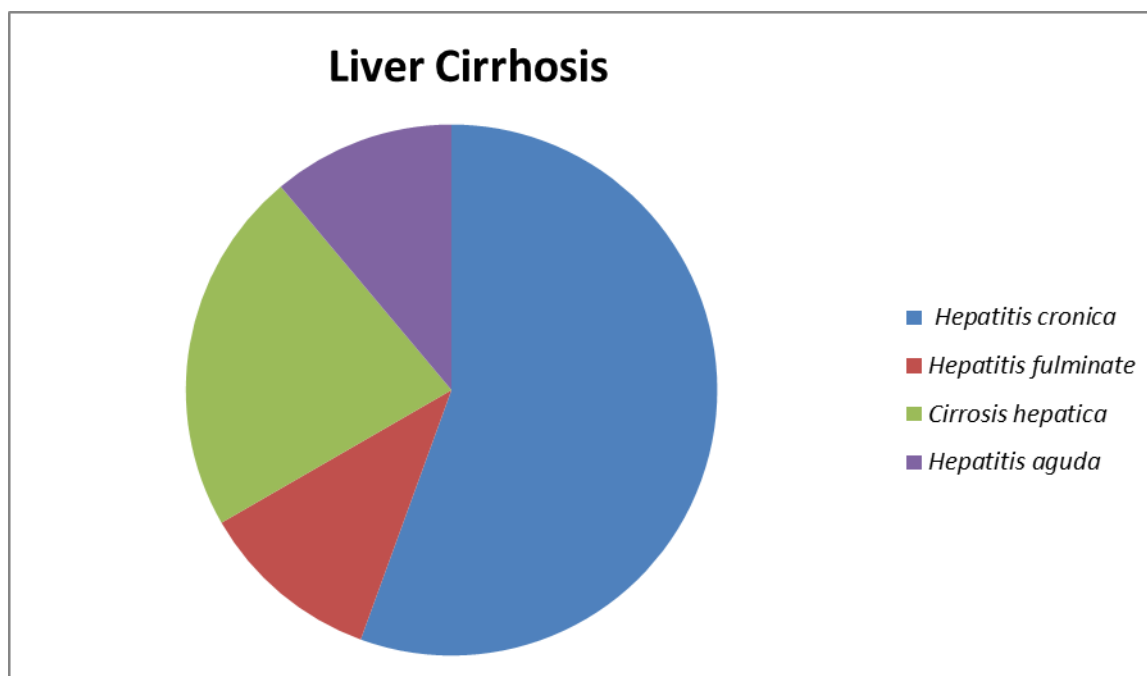


Fig.2 - Clinical presentation of autoimmune hepatitis in children.

8. Pathophysiology of Cirrhosis

The liver plays an important role in synthesis of protein like albumin clotting factor, complement factor and detoxification and storage of vitamin A. It participates in the metabolism of lipid and carbohydrates. Cirrhosis is often followed by hepatitis and steatosis (Fatty liver) independent of the cause. If the causes are resolved at this stage the changes are completely reversible. Cirrhosis scar tissue development replaces normal parenchyma and blocks the portal flow of blood to organ and affects the normal function. A hepatitis parenchyma damage due to inflammation activates stellate cells and increases fibrosis and obstructs the blood flow in the circulation. The formation of fibrous tissue bands separates hepatocyte modules which replace the entire liver architecture. Multiple cells play a role in liver cirrhosis including hepatocytes and sinusoidal lining cells such as hepatic stellate cells (HSCs), SECs, and KCS. HSCs form a part of the wall of the sinusoid and their function is to store Vitamin A. When these cells are exposed to inflammatory cytokines, they get activated, transform into myofibroblasts, and start depositing collagen, resulting in fibrosis. SECs form the endothelial lining and are characterized by the fenestrations they make in the wall that allow the exchange of fluid and nutrients between the sinusoid and hepatocytes. Defenestration of the sinusoidal wall can happen secondary to chronic alcohol use and promote perisinusoidal fibrosis. KCs are satellite macrophages that line the wall of the sinusoidal wall.^[23]

Table no. 1: Stages of liver cirrhosis.

| Stage | Varices | Bleeding | Ascites | 1-Year Mortality (%) |
|-------|---------|----------|---------|----------------------|
| 1 | - | - | - | 1 |
| 2 | + | - | - | 3 |
| 3 | + | + | - | 15 |
| 4 | ± | - | + | 26 |
| 5 | + | + | + | 57 |

9. Diagnosis of Cirrhosis

- Because there are rarely symptoms early in the condition cirrhosis is often diagnosed when the patient is being test for some other conditions or disease.
- Cirrhosis is histologically characterized by fibrous septa between the portal field it comes in micro and macro nodular form^[24], the condition is diagnosed by its characteristics finding on clinical examination laboratory test, and ancillary studies.

➤ The typical finding in cirrhosis includes

- Cutaneous sign of liver disease
- A firm liver on palpation
- Certain risk constellation such as
- Metabolic syndrome
- Heavy alcohol consumption
- Exposure to hepatotoxic substance
- Use of hepatotoxic medication
- Anybody who has the symptom
- Fever with shivering
- Shortness of breath
- Vomiting of blood
- Dark or tarry stool
- Episode of drowsiness.^[25]

➤ The following test may also be followed

1. Blood test: these measures how well the liver is functioning level of ALT and AST are high the pared may have hepatitis.
2. Imaging test ultrasound, CT or MRI scan can be used to see whether the liver is enlarged and detect any scarring.

3. Biopsy a small sample of liver cells is extracted and examined under a microscope the biopsy can confirm cirrhosis and its cause bilirubin level suggest liver is not working properly to remove bilirubin from the blood raised level of liver enzyme (inflammation).^[26]
 - Higher level of iron (may indicate hemochromatosis)
 - Raised level of alpha fetoprotein (indicate presence of liver cancer).
 - Some patients with cirrhosis have enlarged liver or spleen. A doctor can often feel
 - The lower edge of an enlarged liver below the right ribcage and feel the tip of the enlarged spleen below the left ribcage. (palpate)
 - Inherited (genetic) disorder that results in the accumulation of toxic substances in the liver which leads to tissue damage and cirrhosis example include the abnormal accumulation of iron (hemochromatosis or copper (Wilson disease).
 - Jaundice (yellowing of the skin and the whites of the eyes due to elevated bilirubin in the blood) is common among patients with cirrhosis but jaundice can occur in patients with liver disease without cirrhosis and other conditions such as hemolysis.
 - Liver cancer (may be detected by CT and MRI scans or ultrasound of the Abdomen liver cancer most commonly developed in individual with underlying cirrhosis).^[27]

10. Treatment of Cirrhosis

Liver damage from Cirrhosis cannot be reversed but treatment can stop or delay further progression and reduce complication, treatment depend on the cause of Cirrhosis and any complication a person is experience e g Cirrhosis caused by alcohol abuse is treat by from alcohol.^[28]

➤ Treatment of liver Cirrhosis include

1. Prevention further damage to the liver consume a balance diet and one multivitamin daily.
2. PBC with impaired absorption of fats soluble vitamin may need addition vitamins.
3. Avoid drug including alcohol that cause liver damage all patients with cirrhosis should avoid alcohol.
4. Most patients with alcohol including experience an improvement in liver function with abstinence from alcohol.
5. Damage to the liver and permanent further injury to the liver should be avoided to halt the progression to the disease.

6. In liver there are currently no vaccine available for immunizing against hepatitis C avoid non-steroidal anti-inflammatory drugs NSAID's eg. Ibuprofen.^[29]

11. CONCLUSION OF CIRRHOSIS

Liver cirrhosis remains a major global health challenge, with significant morbidity and mortality associated with its progression. Early detection and timely intervention are crucial for managing the disease and preventing further liver damage. While the underlying causes of cirrhosis, such as chronic alcohol use, viral hepatitis, and non-alcoholic fatty liver disease, can often be managed through lifestyle changes and medical treatment, cirrhosis remains irreversible once significant liver damage has occurred. Effective management strategies aim to control the progression of the disease, mitigate complications, and enhance the patient's quality of life. In advanced stages, liver transplantation offers a potential life-saving treatment. Continued research and public health efforts are essential to improve prevention, diagnosis, and treatment outcomes for individuals affected by cirrhosis, ultimately reducing the burden of the disease worldwide.

Liver cirrhosis is a serious, progressive liver disease characterized by the irreversible scarring of liver tissue, often resulting from chronic liver damage due to conditions like alcohol abuse, viral hepatitis, or non-alcoholic fatty liver disease. As the liver becomes increasingly scarred, its ability to function properly deteriorates, leading to complications such as liver failure, portal hypertension, and liver cancer. Early detection and management are key to slowing progression and improving quality of life, as treatments typically focus on addressing the underlying cause, managing symptoms, and preventing further damage. Ultimately, liver transplantation may be necessary for individuals with end-stage cirrhosis. Preventing cirrhosis involves lifestyle changes, regular screenings, and timely treatment of underlying conditions.

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