OPEN ACCESS

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

Review Article **Zoology**

Epidemiology of Liver Cirrhosis, Associated Complications and its Management: A Review

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DOI: https://doi.org/10.36348/sjmps.2024.v10i08.013 | **Received:** 29.06.2024 | **Accepted:** 05.08.2024 | **Published:** 16.08.2024

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Abstract

Cirrhosis is characterised by the formation of regenerative nodules in liver parenchyma surrounded by fibrous septa due to chronic liver injury. It occurs due to necrosis of liver cells followed by fibrosis and nodule formation. Cirrhosis is the final stage of chronic liver disease and has many causes including viral hepatitis, excessive alcohol intake and non alcoholic steatohepatitis. Liver cirrhosis effects the quality of life and patient survival. Cirrhotic patients are in need of early diagnosis and careful follow up to prevent further complications.This review article covers the clinical aspects of cirrhosis and its management strategies.

Keywords: Liver Cirrhosis, Epidemiology, Complications Management, Hepatitis.

INTRODUCTION

Cirrhosis is a condition in which scar tissue gradually replaces healthy liver cells. It usually happens over a long period, often due to infection, other diseases, or alcohol addiction. Cirrhosis is characterized by fibrosis and nodule formation of the liver, secondary to a chronic injury, which leads to alteration of the normal lobular organization of the liver. Liver cirrhosis is a late stage of chronic liver disease, and results in various complications due to decreased hepatic function and portal hypertension; it is also associated with a high likelihood of developing liver cancer. Since the liver is the principal organ responsible for metabolizing nutrients, liver cirrhosis results in defective nutrient metabolism, leading to complications or poor prognosis [1, 2]. In other words Cirrhosis is defined as the fibrotic replacement of liver tissue that can result from any chronic liver disease.

Most prevalent cases of cirrhosis are caused by alcohol use disorder (approximately 45% of all cirrhosis cases), hepatitis C (41%), and non alcoholic fatty liver disease (26%), with many patients having overlapping causes [3]. However, hepatitis C is now curable with direct-acting antivirals and most newly diagnosed cirrhosis is due to non alcoholic fatty liver disease (NAFLD) (accounting for 61.8% of incident cases) and alcohol use disorder (accounting for 20.0%) [4].

The progressive course of cirrhosis can generally include asymptomatic stages, such as compensated cirrhosis, and decompensated stages, which are frequently associated with the development of a range of complications, such as ascites, gastro-esophageal variceal (GEV) bleeding, and hepatic encephalopathy (HE); furthermore, cirrhosis may advance to liver failure and lead to death [5]. These complications impose a heavy burden on global public health in terms of significant quality of life impairment and associated high mortality in patients [6]. Despite the global prevalence and disease burden of cirrhosis, there is less public awareness and concern regarding cirrhosis than for other common chronic diseases, such as congestive heart failure, chronic obstructive pulmonary disease, and chronic kidney disease.Currently, there remains an insufficient understanding of the clinical relevance of cirrhosis, which can therefore lead to unnecessary disease progression and outcome [7].

Symptoms of Cirrhosis:

Many times, there aren't noticeable symptoms of cirrhosis until the condition has progressed. Symptoms begin to occur because scarring on the liver

has reached the point where the organ is limited in its ability to:

- Purify the blood
- Break down toxins
- Produce clotting proteins
- Help with the absorption of fats and fat-soluble vitamins.

Some of the Noticeable Symptoms of Cirrhosis Are:

- Decreased appetite
- Fatigue
- Unintentional weight loss
- Mild pain on the upper right side of your abdomen
- Nausea
- Vomiting
- Enlarged or swollen veins (varices or varicose veins)

More Serious Symptoms Include:

- Yellow discoloration of skin and eyes (jaundice)
- Confusion and difficulty thinking clearly
- Bruising or bleeding easily
- Very itchy skin
- Urine that looks darker than usual
- Abdominal swelling (ascites)
- Swelling of your legs (edema)
- The stages of cirrhosis
- Symptoms of cirrhosis fall into two technical stages: compensated cirrhosis and decompensated cirrhosis.
- If caught early enough and treated, it's possible to reverse from the decompensated to compensated stage.

Compensated Cirrhosis

This is the asymptomatic (showing no symptoms) stage. There may still be scarring on the liver, but it has not progressed enough to cause many, or any, symptoms.

Decompensated Cirrhosis

This is the stage where most of the symptoms like jaundice or ascites occur. This is a very serious stage. In some situations, if able to manage the reason cirrhosis started in the first place (e.g., heavy drinking), you may be able to reverse the diagnosis back to compensated.

Epidemiology of Cirrhosis

Cirrhosis has a large burden of disease. It is the eighth leading cause of death and is responsible for 1.2% of all deaths in the USA. According to the Global Burden of Disease study, the world wide prevalence of cirrhosis is increasing. In the USA, the most common causes of cirrhosis are Chronic Hepatitis C Virus (HCV) and non-alcoholic liver disease [8]. In Europe, liver cirrhosis accounts for 1.8% of all deaths, amounting to 170,000 deaths per year. Worryingly, the reported incidence of cirrhosis remains stable or is increasing in several countries, including both the UK and Ireland in Europe, the main causes are alcoholic liver disease, NASH, and HCV. The four most frequent causes of cirrhosis world wide are chronic hepatitis B virus (HBV) and HCV, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and haemochromatosis. A variety of other diseases can result in cirrhosis, although these are less frequent [9].

Alcohol

Excessive alcohol intake remains the number one cause of cirrhosis in Western countries. A daily intake of ≥60 g/day for men, and ≥40 g/day for women is considered harmful. Chronic intake of alcohol can also accelerate the natural progression of chronic HBV or HCV, and haemochromatosis.Alcohol abstinence is the cornerstone of treatment and can reverse the disease course [10].

Viral Hepatitis

Chronic HBV and HCV are leading causes of cirrhosis, especially in endemic regions like South East Asia and Sub Saharan Africa. According to the disease stage, finite treatment with pegylated interferon or long-term therapy with nucleotide analogues is appropriate in HBV patients. The introduction of interferon-free treatment for HCV has been important, as it has resulted in improved treatment response without significant side effects [11]. However, access to these new direct-acting agents remains a challenge due to high costs.Hepatitis A and E do not develop into chronic hepatitis in immuno compentent patients and are not considered risk factors for cirrhosis.

Non-Alcoholic Fatty Liver Disease (NAFLD)

It is related to the presence of metabolic syndrome in association with obesity, diabetes, and/or arterial hypertension. A subset of these patients will develop signs of NASH, which can lead to the development of fibrosis and subsequently cirrhosis [12]. It is an increasing health problem, especially in the Western world. Treatment is based on dietary measures and exercise.

Haemochromatosis

Hereditary haemochromatosis is an autosomal recessive disorder characterised by excessive intestinal absorption of dietary iron, which results in a pathological increase in total body iron stores. End-organ liver damage can occur, in turn leading to cirrhosis. Phlebotomy has been indicated to remove excessive iron stores [13].

Autoimmune Hepatitis

Autoimmune hepatitis is a rare disease affecting 16–18 cases per 100,000 inhabitants in Europe. More than 30% of adult patients and ~50% of children have cirrhosis at diagnosis, due to an insidious disease course.

Treatment is based on immunosuppressive agents including corticosteroids and azathioprine [14].

Primary Biliary Cholangitis and Primary Sclerosing Cholangitis

Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are autoimmune diseases that affect the small and the large bile ducts, respectively. PBC can lead to progressive fibrosis resulting in cirrhosis. In PSC patients, prolonged extrahepatic cholestasis can induce the development of portal fibrosis leading to cirrhosis [15]. Ursodeoxycholic acid can slow down disease progression in PBC and can be used in PSC. In PBC, newer agents, like obeticholic acid, are promising treatment options.

Rare Causes of Cirrhosis

Other causes of cirrhosis include a reaction to drugs, Budd-Chiari syndrome, Wilson's disease, alpha-1 antitrypsin deficiency, granulomatous liver diseases, right-sided heart failure, and veno-occlusive disease amongst others. A specific aetiology can be determined in 85–90% of patients [16].

Diagnosis

Laboratory Findings

Laboratory abnormalities may be the first indication of liver cirrhosis. Though bilirubin levels may be normal in compensated cirrhosis, the levels rise as cirrhosis progresses. Levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are moderately elevated in cirrhosis; however, normal aminotransferase levels do not exclude cirrhosis. Alkaline phosphatase is usually mildly elevated in cirrhosis. Levels higher than 2 or 3-times the upper limit of normal suggest an underlying cholestatic liver disease, such as PSC or PBC [17]. Gamma-glutamyl transpeptidase levels correlate well with alkaline phosphatase, but are more elevated in alcohol induced chronic liver disease. Once the synthetic function of the liver is affected, albumin levels decrease and prothrombin time levels increase as key proteins involved in the coagulation cascade are produced in hepatocytes. Low platelets can appear in the case of hypersplenism.

Imaging

Ultrasonography is the first step in liver imaging. It is non-invasive, widely available, affordable, and well accepted by patients. Liver volume can be normal, enlarged, or diminished, especially in advanced cirrhosis. Often a nodular deformation of the liver can be observed. Other typical signs include atrophy of the right lobe of the liver, and hypertrophy of the caudate or left lobes. When portal hypertension develops, Doppler imaging can reveal an enlarged portal vein, enlarged collateral veins, and decreased portal flow. Ultrasonography is useful for the detection of hepatic nodules and is the backbone of screening programmes for the early detection of HCC. Detection of hepatic nodules demands further characterisation using computed tomography or magnetic resonance imaging [18].

Liver Biopsy

The gold standard for the diagnosis of cirrhosis is a histological examination. However, this should not be performed in all cirrhotic patients. A biopsy should be considered in patients in whom the diagnosis is in question, and when knowledge of a specific diagnosis is likely to alter the management of the disease. A liver biopsy can be performed percutaneously, transjugularly, or laparoscopically. There is an inherent risk of bleeding, and severe bleeding occurs in between 1 in 2,500 and 1 in 10,000 biopsies performed using an intercostal percutaneous approach.

Cirrhosis Management

The primary goals of liver disease management are to prevent cirrhosis complications, liver decompensation, and death. These goals are accomplished with rigorous prevention counseling, monitoring, and management by primary care physicians, in consultation with subspecialists as needed.

Prevention Counselling

For all patients with liver disease, counseling points should be discussed, including avoidance of alcohol; maintenance of a healthy weight; nutrition; medication and supplement review; prevention of infections (including receiving vaccinations); screening and treatment of causative factors; and avoidance of unnecessary surgical procedures.

Monitoring of Patient with Cirrhosis

For patients with cirrhosis, a basic metabolic panel, liver function tests, complete blood count, and PT/INR should be completed every six months to recalculate Child-Pugh and Model for End-Stage Liver Disease scores. Patients with a Model for End-Stage Liver Disease score of 15 or higher should be referred for liver transplantation evaluation, patients with ascites, hepatic encephalopathy, or variceal hemorrhage should also be referred [20].

Screening and Management for Specific Complications

Patients with cirrhosis are at risk of multiple complications, including hepatic decompensation, hepatocellular carcinoma, and other more common conditions (e.g., malnutrition, leg cramps, umbilical hernias).

Common Complications in Decompensated Cirrhosis

Ascites, which develops in 5% to 10% of patients with cirrhosis per year, leads to decreased quality of life, frequent hospitalizations, and directly increases risk of further complications such as spontaneous bacterial peritonitis, umbilical hernias, and respiratory compromise. It also portends a poor

prognosis, with a 30% five-year survival. Hepatic encephalopathy, which occurs in 5% to 25% of patients within five years of a cirrhosis diagnosis, is likewise associated with increased medical cost and mortality, with a reported 15% inpatient mortality rate [21].

Screening for Varices

Portal hypertension predisposes patients with cirrhosis to develop esophageal varices. Patients with varices have a one in three chance of developing a variceal bleed in the two years after diagnosis, with a 20% to 40% mortality rate per episode. Endoscopy is the preferred screening method for esophageal varices. Many experts and guidelines recommend screening all patients with cirrhosis, however, newer recommendations suggest targeted screening of patients with clinically significant portal hypertension.A liver stiffness greater than 20 kPa, alone or combined with a low platelet count (less than 150,000 per mm3) and increased spleen size, and/or the presence of portosystemic collaterals on imaging may be sufficient to diagnose clinically significant portal hypertension and warrant endoscopic screening for varices. Repeat endoscopy should be performed every one to two years if small varices are found and every two to three years if no varices are found [22].

Consultation

Varices, hepatic encephalopathy, and ascites herald hepatic decompensation; these conditions warrant referral for subspecialist evaluation. The management of acute or refractory complications of cirrhosis (e.g., spontaneous bacterial peritonitis, acute gastrointestinal bleeding, hepatorenal syndrome, unresponsive portal hypertension, hepatic encephalopathy, ascites) is best addressed in the inpatient or referral setting.

Status of Liver Cirrhosis in India

A recent Study conducted by AIIMS which analysed published reports on non alcoholic fatty liver disease (NAFLD) in India states that over one third (38/) of Indians have fatty liver or NAL disease .The phenomena is not restricted to adults, but affects nearly 35/ of the children as well, say the Study published in the journal of Clinical and experimental Hepatology in June 2022.

NAFL disease is often unrecognised since it does not causes symptoms in early stage, but may progress in some patients with severe liver disease. In India Cirrhosis of liver is a major health problem .According to the latest WHO data published in 2017 deaths due to liver disease in India reached upto 259,749 or 2.95/ of total deaths, accounting for 1/5(18.3/) of all cirrhosis death globally.

CONCLUSION

Cirrhosis is the final stage of chronic liver disease. The aim of a clinician dealing with cirrhosis should be to prevent the development of major complications. A new trend in this field is the adoption of non-invasive techniques, e.g. Transient elastgraphy (TE) for diagnosis of cirrhosis and follow-up of cirrhotic patients, as they are an emerging tool for risk stratification. In cirrhotic patients the performance of an ultrasonograph every 6 months remains of utmost importance for early detection of Hepatocellular Carcinoma (HCC). Decompensated patients have a dismal prognosis and should be referred to a specialised hepatological centre, as liver transplantation should be considered in these patients.

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