

# Unraveling Hepatic Cirrhosis through its Pathophysiology, Diagnosis, and Predictors of Mortality: A Literature Review

Gabriel Damarwibawa Setianto<sup>a\*</sup>, Umami Maimunah<sup>b</sup>

<sup>a</sup>Medical Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

<sup>b</sup>Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

<sup>c</sup>Department of Radiology, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

\*Corresponding author: ummima@gmail.com

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## Abstract

This literature review provides a comprehensive examination of hepatic cirrhosis, focusing on its pathophysiology, diagnosis, and predictors of mortality. Hepatic cirrhosis, characterized by fibrosis and nodular formations resulting from continuous scarring, irreversibly alters liver structure and function. The disease progression involves the activation of the extracellular matrix, particularly collagen accumulation, leading to hepatocellular dysfunction and portal hypertension. Epidemiologically, liver cirrhosis poses a significant global health burden, with a substantial increase in prevalence reported in recent years, particularly in the Asia Pacific region. The etiology of cirrhosis involves various factors, including viral infections (hepatitis B and C), alcohol abuse, autoimmune diseases, metabolic disorders, and more. Understanding the pathophysiology is crucial, with hepatic stellate cells, liver sinusoidal endothelial cells, Kupffer cells, and hepatocytes playing key roles in fibrogenesis. Clinical manifestations range from asymptomatic cases in compensated cirrhosis to severe complications in decompensated cirrhosis, such as ascites, jaundice, encephalopathy, variceal bleeding, and hepatocellular carcinoma. Accurate diagnosis is essential for effective management. Liver biopsy, serological tests, and various imaging modalities, including ultrasound, contrast-enhanced ultrasonography, magnetic resonance elastography, and CT scans, aid in distinguishing between compensated and decompensated cirrhosis. Complications, including portal hypertension, hepatic encephalopathy, esophageal varices, hepatocellular carcinoma, ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome, further contribute to the complexity of cirrhosis. The paper also explores predictor factors of mortality in cirrhosis patients, including age, comorbidities, Model for End-Stage Liver Disease with Sodium (MELD-Na) score, and Child-Turcotte-Pugh (CTP) score. Understanding these factors enhances prognostic accuracy, facilitating improved patient care and timely interventions. Overall, this review aims to provide a comprehensive understanding of hepatic cirrhosis, aiding healthcare professionals in its diagnosis, management, and risk stratification.

Keywords: Hepatic cirrhosis, Liver disease, Predictor of Mortality, Treatment.

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## 1. Introduction

Hepatic cirrhosis, a chronic and progressive liver disease, stands as a formidable global health challenge with far-reaching implications for affected individuals and healthcare systems. This literature review seeks to offer an extensive exploration of hepatic cirrhosis, delving into its pathophysiology, diagnostic modalities, and predictors of mortality. The intricate interplay of factors contributing to the development and progression of cirrhosis necessitates a thorough understanding of its underlying mechanisms, diagnostic techniques, and prognostic indicators. In its essence, hepatic cirrhosis is defined by the formation of fibrosis and nodules

within the liver tissue, a consequence of continuous scarring that fundamentally alters the normal architecture and function of this vital organ. Fibrosis, characterized by the excessive accumulation of fibrous connective tissue, particularly collagen, is a hallmark of cirrhosis (Wynn and Ramalingam, 2013). The activation of the extracellular matrix emerges as a pivotal mediator in the transformation of liver structures, resulting in hepatocellular dysfunction and the onset of portal hypertension (Wynn and Ramalingam, 2013). Notably, portal hypertension further complicates the condition, posing risks of severe complications such as ascites, variceal bleeding, and hepatic encephalopathy (Iwakiri and Trebicka, 2021).

Epidemiologically, hepatic cirrhosis has emerged as a significant burden on health services globally. A notable increase in its prevalence has been observed in recent years, with a surge of 10.14% reported in 2017 alone, estimating a staggering 1.4 billion cases worldwide. The Asia Pacific region, in particular, has witnessed a substantial impact, contributing to 48.2% of total deaths caused by liver cirrhosis in 2015 (Jing-Hang Xu et al., 2020). The diverse etiology of cirrhosis, encompassing factors such as viral infections (hepatitis B and C), alcohol abuse, autoimmune diseases, and metabolic disorders, underscores the complexity of this disease (Sarin et al., 2015; Bashir Sharma and John, 2019).

Understanding the pathophysiological mechanisms involved in hepatic cirrhosis is pivotal for effective diagnosis and management. Parenchymal cells (hepatocytes) and non-parenchymal cells (liver sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells) play crucial roles in the pathogenesis (Zhou et al., 2014). Activation of hepatic stellate cells is particularly significant, characterized by cell proliferation, migration, and collagen production, initiating and progressing liver fibrosis (Zhou et al., 2014). Liver sinusoidal endothelial cells and Kupffer cells also contribute to the fibrotic process, while hepatocytes, as the target of hepatotoxic agents, release reactive oxygen species and fibrogenic mediators upon injury (Zhou et al., 2014). Clinical manifestations of hepatic cirrhosis vary depending on disease severity. In compensated cirrhosis, patients are often asymptomatic, while decompensated cirrhosis manifests with severe complications such as ascites, jaundice, encephalopathy, variceal bleeding, and hepatocellular carcinoma (Soresi et al., 2014). Accurate diagnosis is essential for effective management, with liver biopsy, serological tests, and various imaging modalities playing crucial roles (Soresi et al., 2014).

This review also explores predictor factors of mortality in cirrhosis patients, including age, comorbidities, Model for End-Stage Liver Disease with sodium (MELD-Na) score, and Child-Turcotte-Pugh (CTP) score (Lominchar et al., 2019; Wu et al., 2018). Understanding these factors enhances prognostic accuracy, facilitating improved patient care and timely interventions. Overall, this review aims to provide a comprehensive understanding of hepatic cirrhosis, aiding healthcare professionals in its diagnosis, management, and risk stratification.

## **1. Review Content**

### **2.1 Hepatic Cirrhosis**

#### **2.1.1 Definition**

Liver cirrhosis is defined by the formation of fibrosis and nodule that are caused by continuous scarring that leads to an alteration of the liver cell structure. Fibrosis itself can be interpreted as an excessive accumulation of fibrous connective tissue. Fibrous connective tissue itself is an important component of the extracellular matrix such as pectin and collagen. As in all diseases causing fibrosis, activation of the extracellular matrix is an important mediator of fibrous connective tissue transformation. Excessive collagen accumulation will change the normal structure of the liver which can lead to hepatocellular dysfunction and portal hypertension (Wynn and Ramalingam, 2013). If the nodule and fibrous tissue that was formed earlier

experiences necrosis, it can be called cirrhosis. If cirrhosis occurs, liver function disruption may occur which can result in blood circulation disturbances. Thus, cirrhosis can be interpreted as a diffuse hepatic process characterized by fibrosis and conversion of liver structures to abnormal nodule structures. The condition of fibrosis is reversible; however, if a patient reaches the cirrhosis stage, it is irreversible (A Suva, 2014). Liver cirrhosis can be divided into two, namely compensated and decompensated. Compensated cirrhosis is a condition when cirrhosis has not caused any clinical manifestations and on the other hand decompensated is a condition where cirrhosis has caused a clinical manifestation

### 2.1.2 Epidemiology

Chronic liver disease is believed to be a burden for health service providers throughout the world. Jing-Hang Xu et al. (2020) stated that in 2017, there was an increase of 10.14% of liver cirrhosis prevalence, with an estimation of 1.4 billion cases of the disease. In the Asia Pacific region alone in 2015, deaths caused by liver cirrhosis reached 630,843, or around 48.2% of total patients. Liver cirrhosis is a clinical manifestation caused by various liver diseases such as hepatitis B, hepatitis C, alcohol abuse, auto-immunity, and non-alcoholic fatty liver disease. Sarin et al. (2015) stated that from the data obtained from WHO's 2015 Global Health Estimates, an infection caused by hepatitis B was recorded as much as 37% contributing to death in patients with liver cirrhosis and 35.2% for hepatitis C. However, due to the lack of disease surveillance and lack of reports from the public, the latest data is difficult to obtain. However, a study conducted in 2015 in 33 provinces in Indonesia found that there was a decrease in the prevalence of HBsAg (Hepatitis B Surface Antigen) from 9.4% in 2007 to 7.1% in 2013. On the other hand, data obtained from RISKESDAS in 2013 showed that the prevalence of hepatitis C in children aged 1-14 years is 0.6%. Even so, Red Cross Indonesia estimates that in 2014, there were 284,000 people with viremia and in 2023, the number is expected to increase to 1,303,000 people

### 2.1.3 Etiology

Cirrhosis can develop as a result of exogenous or toxic mutations, infections, toxins or allergies, immunopathology or autoimmune, vascular pathology, or metabolic diseases. Hepatitis C virus (HCV), alcoholic liver disease, and non-alcoholic steatohepatitis (NASH) are the most common causes of cirrhosis in industrialized countries. In contrast, hepatitis B virus (HBV), and HCV, are the most common causes in underdeveloped countries. In addition, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, Budd-Chiari syndrome, drug-induced liver cirrhosis, and chronic right heart failure are other causes of cirrhosis. Cirrhosis with an unknown etiology is determined as cryptogenic cirrhosis (Bashar Sharma and John, 2019). 2.1.4 Pathophysiology In liver cirrhosis the parenchyma cells (hepatocytes) and non-parenchymal cells (liver sinusoidal endothelial cells or LSECs), Kupffer cells (KCs), and hepatic stellate cells (HSCs) play a role in the pathogenesis. Extended liver injury or exposure to cytokines can activate HSCs, where activation of HSCs is characterized by cell proliferation and migration, contraction after myofibroblast formation, and also generation of large amounts of collagen. According to Zhou et al. (2014), activation of HSC is important in the progression and initiation of liver fibrosis. On the other hand, LSEC is characterized by the fenestration of the outer layer of the endothelium which functions as filtration and fluid change. If there is excessive alcohol consumption, an impact on defenestration and a decrease in the number of fenestrations may occur. Defenestration and capillarization of the hepatic endothelium are believed to be a precursor to perisinusoidal fibrosis, which occurs due to altered retinol metabolism. Kupffer cells (KCs) are located in the lining walls of sinusoids. KC activation produces soluble harmful substances that act as mediators and antigen-presenting cells during viral infection which can destroy hepatocytes. KC itself also plays a role in

HSC activation. On the other hand parenchyma cells, hepatocytes, also play a role in liver cirrhosis. Hepatocytes are largely the target of hepatotoxic agents that induce apoptosis or compensate for hepatocytes. If apoptosis or destruction of hepatocytes occurs, hepatocytes release reactive oxygen species (ROS) and fibrogenic mediators that can activate HSC.

### **2.1.5 Clinical Manifestation**

Liver cirrhosis cause symptoms depending on the severity of the liver cirrhosis suffered by each patient. In patients with compensated cirrhosis, most of them are detected due to accidental elements when carrying out laboratory tests, physical examinations, and imaging examinations. On the other hand, uncompensated liver cirrhosis has clinical manifestations such as hepatic dysfunction and portal hypertension. When a patient with cirrhosis is diagnosed with ascites, jaundice, hepatic encephalopathy, variceal bleeding, or hepatocellular cancer, it marks a change from the compensated to the decompensated stage of the disease.

### **2.1.6 Diagnosis**

Liver cirrhosis can be clinically divided into compensated cirrhosis decompensated. Decompensated liver cirrhosis is easier to diagnose using various tests such as ascites, spider naevi, encephalopathy, esophageal varices, gastrointestinal bleeding, thrombocytopenia, and hypoalbuminemia. On the other hand, compensated liver cirrhosis is more difficult to diagnose, especially because it is difficult to distinguish from acute hepatitis. Soresi et al (2014) mentioned the following diagnostic labs that can be performed for liver cirrhosis patients.

#### **2.1.6.1 Liver Biopsy**

Liver biopsies are usually performed on patients with hepatitis C, one of the common precursors of liver cirrhosis. Liver biopsy is an invasive procedure so it has several limitations. The quality of the liver biopsy is determined by the length, width, fragmentation, and number of complete portal tracts. If the biopsies are scanty, the diagnosis of fibrosis and cirrhosis may be missed. Although liver biopsy is an active procedure, it is relatively safe, liver biopsy can cause some complications (20%) and moderate (0.5%) or severe (0.03%) mortality. Nevertheless, liver biopsy remains the gold standard in the diagnosis of patients with cirrhosis.

#### **2.1.6.2 Serological Test**

Serological tests offer a less expensive and non-invasive test compared to liver biopsies. Serology tests themselves are divided into direct serology and indirect serology. Direct serology is one of the molecules from the extracellular matrix or a molecule produced by the activation of hepatic stellate cells. One example with high efficacy is hyaluronan. Hyaluronan is an anionic, non-sulfate glycosaminoglycan distributed widely throughout connective, epithelial, and nervous tissue. Hyaluronan has a specification for fibrosis of 80% -100%. On the other hand, indirect serology is a molecule produced by the hepatic parenchyma when there is damage to hepatocytes or cholangiocytes. In addition to the damage to these two cells, indirect serology also measures molecules in case of disturbances in hepatic synthesis such as bilirubin and also INR (International Normalized Ratio).

### 2.1.6.3 Imaging Test

There are several imaging modalities that are available for diagnosing liver cirrhosis, which includes:

1. Ultrasound is often used in the diagnosis of chronic liver disease. Its use which is not invasive, relatively cheap, and also familiar to the patient are some of the reasons why ultrasound is often used. Ultrasound can show morphological changes in the liver itself as in complications of cirrhosis such as portal hypertension. In patients with cirrhosis, it is generally illustrated that there is atrophy in the right lobe of the liver which is accompanied by hypertrophy of the left lobe of the liver and the caudate lobe (Soresi, 2014).
2. Contrast-enhanced Ultrasonography Contrast-enhanced ultrasonography (CEUS) is an ultrasonography tool used to measure intrahepatic transit time and hyperdynamic flow from the liver. In patients with cirrhosis, shunting occurs in the arteries and veins and also arterIALIZATION of the capillaries so that there is a by-pass from the sinusoids and goes straight to the hepatic veins and this is what is called hyperdynamic flow and also the transit time from intrahepatic (Soresi, 2014).
3. Magnetic Resonance Elastography Magnetic resonance elastography (MRE) has a way of working that is not much different from ultrasound elastography. MRE uses low-frequency vibrations to induce shear waves from the liver. The advantage of using MRE is that it can be used in obese patients as well as in patients with ascites. MRE is also not limited by the presence of narrow intercostal spaces. Moreover, compared to elastography in general, MRE has a higher sensitivity in finding fibrosis (Soresi, 2014).
4. MRI has several advantages over other imaging techniques, including high-resolution images with excellent contrast to other soft tissue lesions and a number of different techniques facilitating the diagnostic evaluation of organ morphology, physiology, and function. On examination of cirrhosis with MRI (Magnetic Resonance Imaging), MultiScan (Perspectum Ltd.) is the modality that has had the most studies. In this modality iron (T1) is being evaluated as a substitute for fibrosis and inflammation and T2 as a substitute for iron accumulation. Comparing MRI results to liver histopathology, MR measurements correlated strongly with histology with or the diagnosis of fibrosis, steatosis, and hemosiderosis, respectively (Alzoubi et al, 2022).
5. CT Scan CT Scan or Computed Tomography Scan is more effective for detecting morphological changes in the liver. In patients with cirrhosis can be found nodules and obvious heterogeneity of the liver parenchyma. In patients with cirrhosis because of shrinkage of the right lobe and medial segment of the left lobe and concomitant enlargement of the caudate lobe and lateral segment of the left lobe, the porta hepatis and interlobar fissures are often enlarged. CT scans can make changes in size and volume distribution very clear (Yeom, 2015).

### 2.1.7 Complications

#### 2.1.7.1 Portal Hypertension

Portal hypertension is defined as increased pressure in the portal vein, where the portal vein itself connects the liver with the spleen and the gastrointestinal tract. The increased pressure occurs because of the buildup of the hepatic sinusoidal circulation. Dysfunction of the hepatic sinusoidal endothelium activates hepatic macrophage stellate cells, which when activated can increase pressure in the portal vein. Portal hypertension can also lead to other complications in patients with liver cirrhosis such as ascites and hepatic

encephalopathy. Patients with portal hypertension usually show signs such as repeated hospitalizations and are described as unstable decompensated hepatic cirrhosis (Iwakiri and Trebicka, 2021).

#### **2.1.7.2 Hepatic Encephalopathy**

Hepatic encephalopathy is a reversible syndrome of reduced brain ability that usually occurs in patients with advanced liver disease. The pathogenesis of liver disease that causes hepatic encephalopathy itself still requires more in-depth research, but so far ammonia is one of the substances that is believed to have an effect on hepatic encephalopathy. In a healthy liver, ammonia is cleared from the portal vein and converted to glutamine, thereby preventing it from entering the circulatory system. However, in advanced liver disease, there is a change in liver function which causes an increase in ammonia in the blood. In patients with cirrhosis, there is swelling of astrocytes due to hyper ammonia, this is believed to be important in the occurrence of hepatic encephalopathy in cirrhotic patients (Ferenci, 2017).

#### **2.1.7.3 Esophageal Varices and Hematemesis Melena**

Esophageal varices usually occur in cirrhotic patients with portal hypertension. Esophageal varices are defined as dilatation of the distal portion of the esophageal submucosa connecting the portal vein and systemic circulation. Because the portal vein has no valves, resistance will cause backflow or retrograde and increase in pressure. Over time this causes occlusion of the submucosal venous plexus which then enlarges and is tortuous distally. If it continues, this enlargement can rupture and produce bleeding (Meseeha and Maximos Attia, 2019). Hematemesis itself can be interpreted as vomiting blood and melena can be interpreted as changing the color of the stool to black because there is blood mixed with stomach acid.

#### **2.1.7.4 Hepatocellular Carcinoma (HCC)**

Cirrhosis has a high probability of developing into hepatocellular carcinoma. Chronic inflammation may be a key mechanism for the development of HCC in cirrhosis. In addition, increased DNA synthesis in hepatocytes of cirrhotic patients is suggested as a possible mechanism for the development of HCC (Tarao et al. 2019).

#### **2.1.7.5 Ascites and Spontaneous Bacterial Peritonitis**

In cirrhotic patients with portal hypertension, vasodilation occurs as a result of hypoperfusion. Then there is an activation of the system the renin-angiotensin-aldosterone, then converts angiotensinogen into Angiotensin I which in turn turns into Angiotensin II. Angiotensin II has a role to obtain fluids and fluid retention. This can be said to be a leak because of an increase in retained blood volume. This leakage occurs from the surface of the liver into the mesenteric vessels. Then there is an increase in hydrostatic pressure and vascular permeability and a decrease in osmotic fluid retention in the form of absolute or relative hypoalbuminemia (Moore, 2013). Overall, ascites can be defined as the accumulation of lymphatic fluid in the peritoneal cavity. Ascites may be exacerbated by the presence of spontaneous bacterial peritonitis. This occurs due to bacterial translocation along the intestinal wall. *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus* spp., and *Enterobacteriaceae* family. Bacterial translocation occurs because in cirrhotic patients there is, especially in decompensated cirrhosis, a defect in the phagocytic activity of neutrophils and macrophages. If the immune system is disabled, there will be an increase in the growth of microbiota in the intestine and also an increase in the permeability of the intestine itself (Al-Osaimi et al, 2014).



#### **2.1.7.6 Hepatorenal Syndrome**

Hepatorenal syndrome is a disorder of the kidneys and is a development of renal failure that occurs in patients with advanced liver disease such as cirrhosis. In patients with liver cirrhosis who develop portal hypertension, there are increased levels of splanchnic vasodilators such as nitric oxide. Due to the high levels of vasodilators, there is vasodilatation of the splanchnic nerves followed by reduced arterial filling. Furthermore, renal vasoconstriction occurs and decreased levels of renal vasodilators such as prostaglandins lead to renal fluid retention and perfusion which then lead to hepatorenal syndrome. Cirrhotic patients with hepatorenal syndrome have reduced cardiac output (Ng et al, 2007).

### **2.2 Predictor Factors of Mortality in Cirrhosis Patient**

#### **2.2.1 Age**

Along with increasing age, the liver also undergoes physiological changes, there is a 1/3 decrease from normal size and also a 1/3 decrease in hepatic blood flow. From a metabolic perspective, glucogenesis decreases with age, but lipid accumulation increases the risk of steatosis. Cells in the liver such as sinusoid, Kupffer, and hepatocytes have decreased. In patients with advanced age, there is an increase in apoptosis. Older patients are more likely to have undetected liver cirrhosis and a higher incidence of complications. However, liver status does not affect the death rate of older patients (Lominchar et al, 2019). The relationship between age and mortality in patients with liver cirrhosis cannot be determined whether they influence one another. Therefore, further studies must be conducted to determine the correlation.

#### **2.2.2 Comorbidity**

Comorbidities in patients with liver cirrhosis can increase mortality in patients. Comorbidities themselves must be distinguished from complications such as ascites, variceal bleeding, and hepatic encephalopathy. Complications can be interpreted as a consequence of portal hypertension and decreased liver function due to cirrhosis, while comorbidities are neither the cause nor the result of liver cirrhosis. Referring to a study conducted by Jepsen (2014) comorbidities in liver cirrhosis patients can be calculated using a scoring system such as Cirrhosis Comorbidity Index (CirCom), Charlson Comorbidity Index and Charlson Comorbidity Index-Orthopic Liver Transplant (CCI-OLT). The purpose of this score is to facilitate communication regarding the comorbidity burden of the patient concerned. A study of the effects of individual comorbidities on the clinical course of cirrhosis can provide insight into the pathophysiology of cirrhosis. And from this scoring system a few component will be taken as variabel to become a predictor of mortality in cirrhosis patient that previous study had already mentioned the corelation regarding increasing the mortality of cirrhosis patient.

#### **2.2.3 MELD-Na**

In determining the predictor factors of liver cirrhosis, there is a scoring system that has been used, for example, Child-Turcotte-Pugh (CTP), Model for End-Stage Liver Disease score (MELD), and MELD-Na. In this study, the scoring system that will be applied to predict death in patients with liver cirrhosis is MELD-Na. Referring to a study conducted by Wu et al (2018) from 16 studies conducted on 2,337 patients with decompensated liver cirrhosis, it was found that CTP was considered more subjective than MELD-Na. In this study, it was also said that in a 12-month period MELD-Na had a more accurate

prognostic than MELD and CTP and was a better model for predicting death in patients with decompensated cirrhosis of the two. Subjectivity child-pugh can be found in the ascites and encephalopathy variables because these two variables can differ depending on each clinician and depend on the use of diuretics and lactulose (Peng et al, 2016). However, CTP still cannot replace MELD-Na in absolute terms because of its easier use and also the effectiveness of the prognosis within 6 months. The difference between MELD and MELD-Na is in the use of serum sodium. A retrospective study conducted by Goudsmit et al (2020) stated that there is a need for additional hyponatremia as an independent prognostic factor, where in patients with cirrhosis portal hypertension is closely related to the concentration of serum sodium. This study concluded that MELD-Na had a better predictive ability than MELD in the context of a 90-day liver transplant waiting list.

#### **2.2.4 Child Turcotte Pugh (CTP)**

To predict mortality in cirrhotic patients, the Child-Pugh scoring system—also called the Child-Pugh-Turcotte score—was developed. It was first conceived by Child and Turcotte in 1964 to help in the selection of patients who would benefit from elective surgery for portal decompression. Patients were divided into three categories: A. which denoted good hepatic function, B. which denoted moderately impaired hepatic function, and C. which denoted advanced hepatic dysfunction. Five clinical and laboratory parameters, including serum bilirubin, serum albumin, ascites, neurological dysfunction, and clinical nutrition status, were utilized in their original scoring system to classify patients.

## **2. Conclusion**

In conclusion, this comprehensive review illuminates the intricate landscape of hepatic cirrhosis, encompassing its pathophysiology, diagnostic methods, and predictors of mortality. By unraveling the complexities of this chronic liver disease, healthcare professionals can better comprehend its multifaceted nature, leading to improved diagnostic accuracy and timely interventions. The exploration of epidemiology, etiology, and clinical manifestations underscores the global health burden posed by cirrhosis. The emphasis on predictor factors, including age, comorbidities, and scoring systems like MELD-Na and CTP, highlights crucial aspects for prognostic assessment. Ultimately, this review serves as a valuable resource, contributing to a deeper understanding of hepatic cirrhosis and facilitating enhanced patient care.

## **Acknowledgements**

The authors would like to thank all the supervisors, enabling the successful implementation of this study.



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