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Pathogenesis of Biliary Cirrhosis and Modern Clinical Diagnostic Methods

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Abstract: General Background: Cirrhosis is the final stage of liver fibrosis, characterized by significant structural disruption due to the formation of regenerative nodules and excessive fibrous tissue. It remains a major global health concern due to its chronic progression and potential complications.

Specific Background: In developed countries, cirrhosis is primarily caused by chronic alcohol consumption, viral hepatitis B and C, or metabolic-associated fatty liver disease (MAFLD). In Asia and Africa, chronic hepatitis B remains the leading cause. Complications such as portal hypertension and hepatic encephalopathy significantly impact patient prognosis.

Knowledge Gap: Cirrhosis has traditionally been diagnosed through clinical evaluation and imaging techniques. However, there is still a pressing need for more precise, non-invasive diagnostic markers and targeted treatment strategies to slow disease progression.

Aims: This study explores the mechanisms, clinical presentation, and modern diagnostic approaches of biliary cirrhosis to improve early detection and management.

Results: The findings highlight the complex interactions between growth factors, cytokines, and intrahepatic blood flow patterns in the formation of regenerative nodules. Angiogenesis plays a crucial role in the development of portal

hypertension, worsening disease severity. Accurate diagnosis continues to rely on laboratory tests, advanced imaging techniques such as transient elastography and MRI elastography, and selective liver biopsy.

Novelty: This review provides an updated analysis of the causes and diagnostic advancements in biliary cirrhosis, with a particular focus on emerging non-invasive imaging techniques.

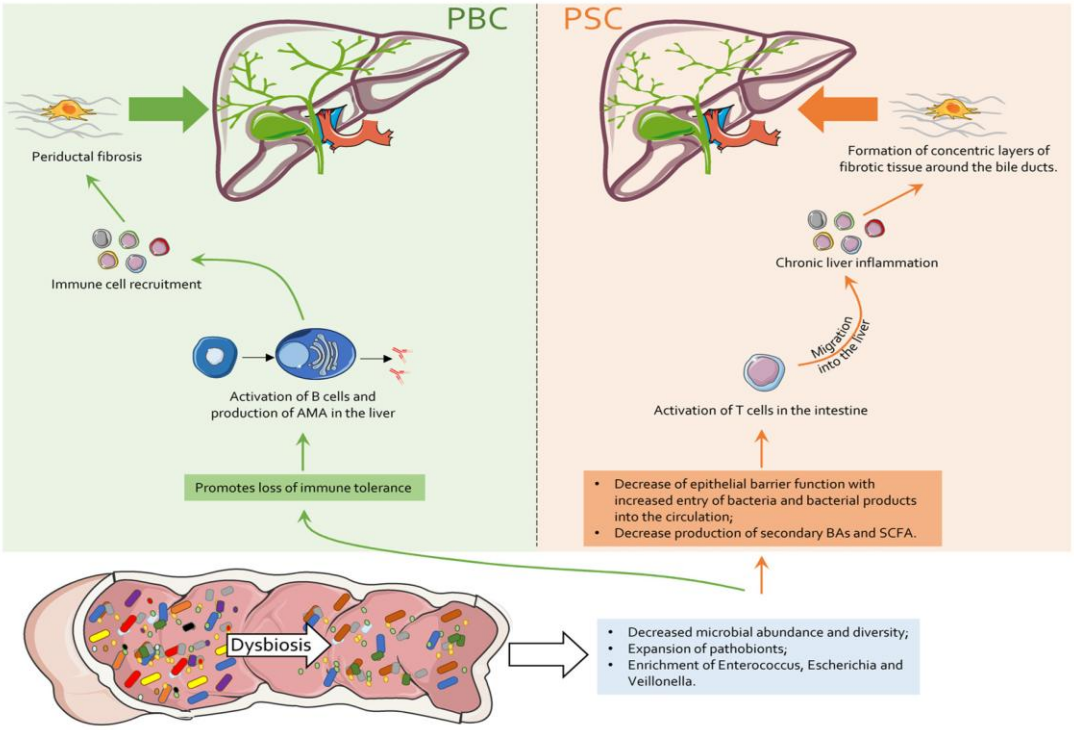
Implications: The study underscores the importance of early diagnosis, routine screening for hepatocellular carcinoma, and comprehensive treatment strategies to reduce complications and improve patient outcomes.

Keywords: Etiology, Pathophysiology, Clinical manifestations, Diagnostics, Treatment, Prognosis

Introduction: The causes of liver cirrhosis are similar to those of liver fibrosis (see table: Diseases and drugs/substances that can cause liver fibrosis). In resource-rich countries, most cases are caused by chronic alcohol consumption, chronic viral hepatitis (hepatitis B and C), or metabolically related fatty liver disease ([MAFLD], formerly non-alcoholic fatty liver disease/NAFLD). In parts of Asia and Africa, cirrhosis is caused by endemic chronic hepatitis B. (For more information on hepatitis B and C, see the Hepatitis Virus Characteristics table.) Cirrhosis of unknown etiology (cryptogenic cirrhosis) is rare, as many specific causes have been identified (e.g., chronic hepatitis C, MAFLD). Injury to the bile ducts, as well as mechanical obstruction of the bile ducts, as in primary biliary cholangitis and primary sclerosing cholangitis, can also lead to cirrhosis. [1]

Research methods and materials: In response to damage and loss of liver mass, regulatory mechanisms induce hepatocellular hyperplasia (leading to the formation of regenerative nodules). Among the regulatory factors, cytokines and liver growth factors (e.g., epithelial growth factor, hepatocyte growth factor, transforming growth factor-alpha, tumor necrosis factor) should be noted. Insulin, glucagon, and the pattern of intrahepatic blood flow help determine how and where the nodules develop.[2]

Angiogenesis causes new blood vessels to form in the fibrous capsule surrounding the nodules. These new vessels connect the hepatic artery and portal vein with the hepatic venules, restoring the intrahepatic circulation. These interconnected vessels provide a relatively low-volume, high-pressure venous drainage that cannot accommodate such a large volume of blood. As a result, pressure in the portal vein increases. Such disruptions in blood flow contribute to portal hypertension, which is exacerbated when the regenerative nodules compress the hepatic venules.



The progression of fibrosis to cirrhosis and the morphology of cirrhosis vary among patients. It is likely that the duration of exposure to the noxious stimulus and the individual response are the reasons for such changes.[3]

Portal hypertension is the most common serious complication of cirrhosis and can, in turn, lead to the following complications:

Gastrointestinal bleeding from esophageal, gastric, or rectal varices, as well as portal hypertensive gastropathy

a) Thrombocytopenia

b) Ascites

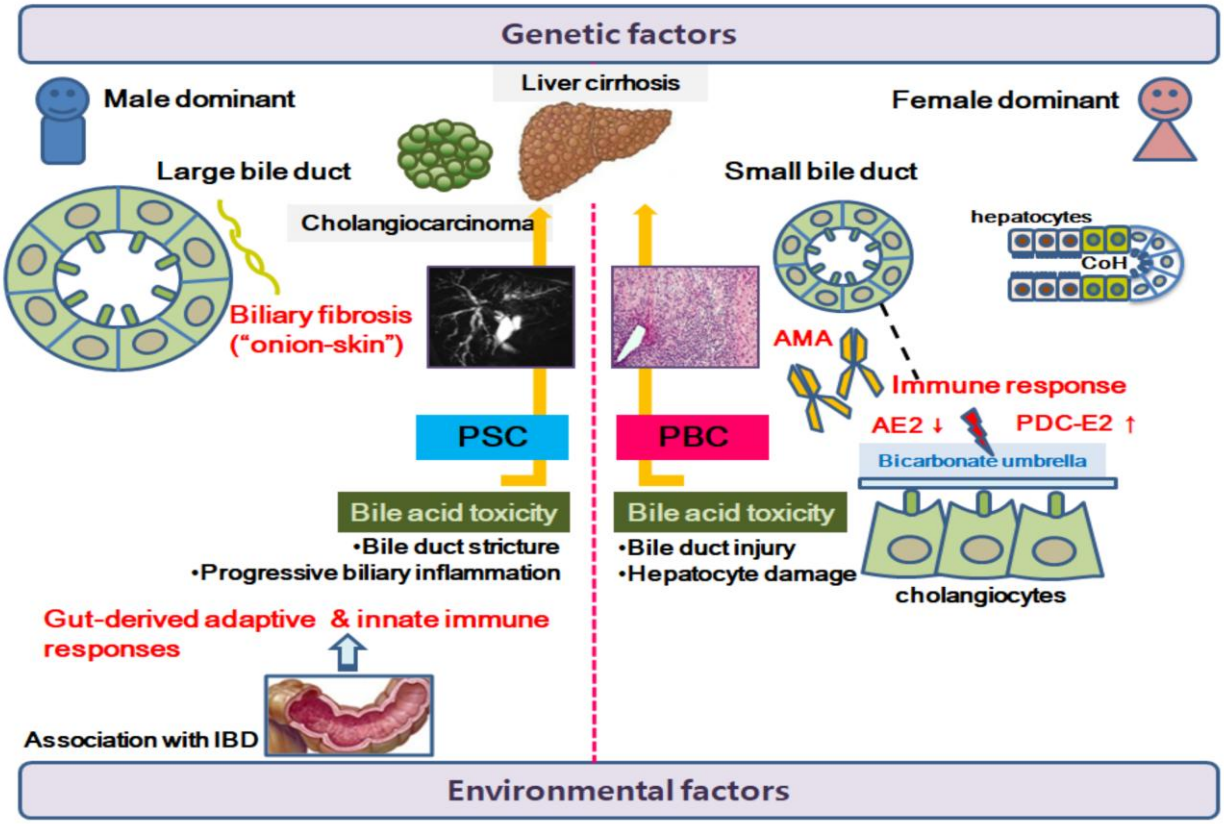
c) Acute kidney injury (hepatorenal syndrome)

d) Pulmonary hypertension (portopulmonary hypertension)

e) Hepatopulmonary syndrome (intrapulmonary shunt)

Ascitic fluid can become infected (spontaneous bacterial peritonitis). Portopulmonary hypertension may be accompanied by symptoms of heart failure. Complications of portal hypertension usually result in significant morbidity and mortality.

Cirrhosis can cause other cardiovascular complications. Vasodilation, right-to-left intrapulmonary shunting, and ventilation/perfusion mismatch can lead to hypoxia (hepatopulmonary syndrome).



Progressive deterioration of hepatic architecture leads to renal failure, which leads to coagulopathy, acute kidney injury (hepatorenal syndrome), and hepatic encephalopathy. Hepatic encephalopathy is characterized by asterixis, confusion, or hepatic coma and results from the liver's inability to metabolize toxins from the gastrointestinal (GI) tract. Elevated serum ammonia levels can be helpful in diagnosing hepatic encephalopathy, but these levels correlate poorly with the severity of hepatic encephalopathy.[4]

Hepatocytes secrete less bile, which contributes to the development of cholestasis and jaundice. Less bile in the intestine leads to malabsorption of dietary fats (triglycerides) and a deficiency of fat-soluble vitamins. Impaired absorption of vitamin D can contribute to the development of osteoporosis. Malnutrition and sarcopenia are common. They can occur as a result of reduced food intake or anorexia caused by malabsorption in patients with alcoholic liver disease or pancreatic insufficiency.

Blood disorders are common. Anemia is usually caused by hypersplenism, chronic gastrointestinal bleeding, folic acid deficiency (especially in alcoholism), and hemolysis.

Cirrhosis leads to decreased production of prothrombotic and antithrombotic factors. Hypersplenism and altered thrombopoietin expression lead to thrombocytopenic purpura. Thrombocytopenia and decreased clotting factors can lead to unexpected clotting, increasing the risk of bleeding and thromboembolism (even when the international normalized ratio [INR] is high). Leukopenia is also common; it is mediated by hypersplenism, altered erythropoietin, and granulocyte colony-stimulating factors.

In patients with liver cirrhosis, even with an elevated INR, thromboembolic complications should be considered.

Cirrhosis of any etiology is often complicated by hepatocellular carcinoma (which justifies clinical observation). The incidence of hepatocellular carcinoma in cirrhosis of the liver of specific etiology is presented below (1):

a) Chronic hepatitis B: 3-8% per year

b) Chronic hepatitis C: 3-5% per year

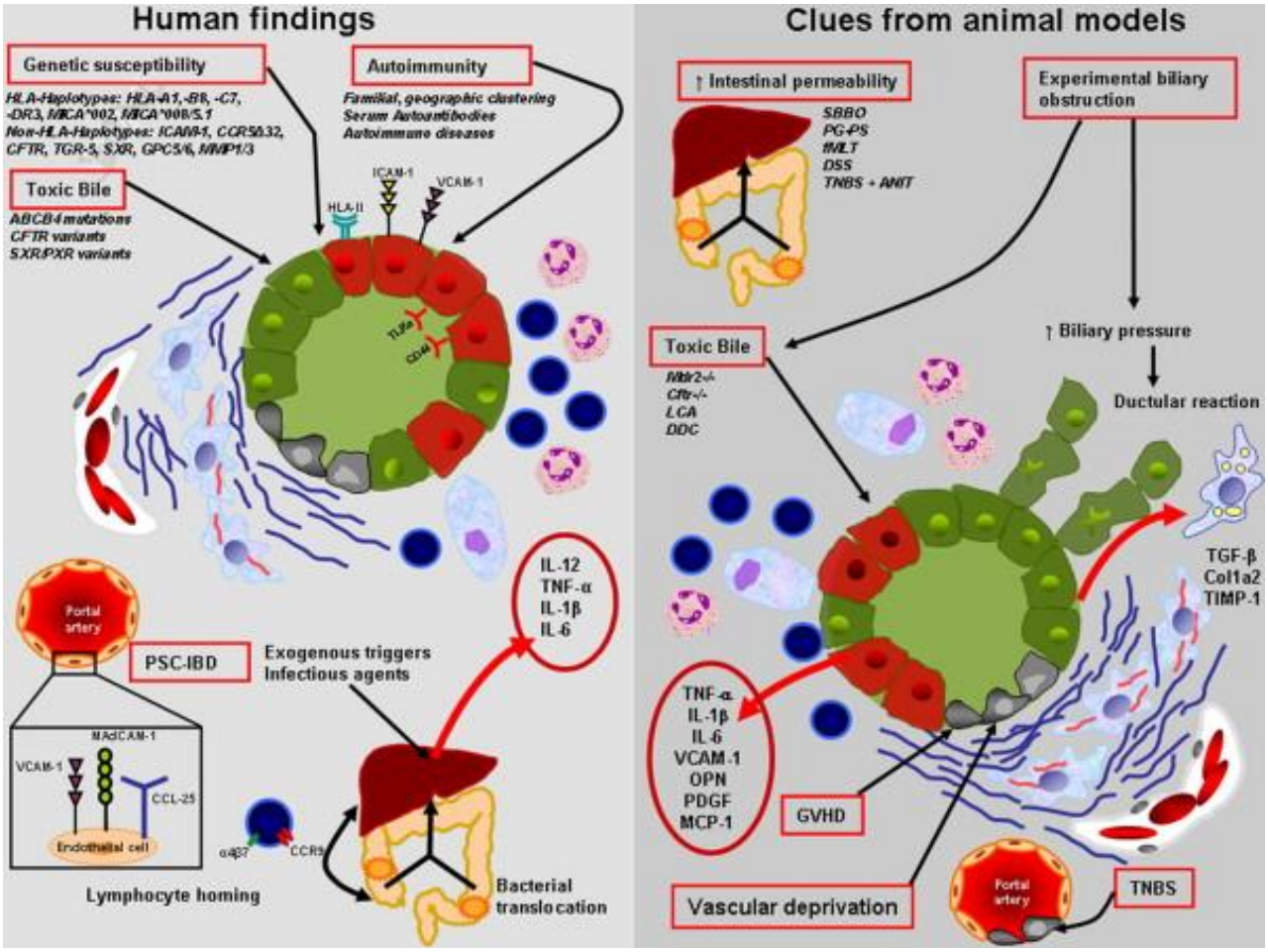
c) Primary biliary cholangitis: 3-5% per year

d) Metabolic fatty liver disease: 0.3 to 2.6% per year

e) Cirrhosis of other etiologies, such as hemochromatosis, alcoholic liver disease, alpha-1-antitrypsin deficiency, Wilson's disease: more than 1.5% per year.

Conclusions: Cirrhosis is characterized by the presence of regenerative nodules and bridging fibrosis. Incompletely formed hepatic nodules, nodules without signs of fibrosis (nodular regenerative hyperplasia), and congenital hepatic fibrosis (i.e., widespread fibrosis without regenerative nodules) cannot be classified as true cirrhosis.

Cirrhosis can be micronodular or macronodular. Micronodular cirrhosis is characterized by the formation of small nodules (< 3 mm in diameter) and thick regular septa of connective tissue. Typically, the nodules lack a lobular structure, and the terminal (central) hepatic venules and portal triads are obliterated. Over time, macronodular cirrhosis often develops. The nodules vary in size (3-5 mm in diameter) and have a relatively normal lobular organization of the portal triads and terminal hepatic venules. Broad fibrous septa of varying thickness surround the large nodules. Disruption of the normal architecture of the liver may indicate a concentration of portal triads within fibrous scars. Mixed cirrhosis (incomplete septal cirrhosis) combines micronodular and macronodular elements. Differentiating these morphological types of cirrhosis is of limited clinical significance.[5]



Cirrhosis may be asymptomatic for many years until decompensation occurs. Often the first symptoms are nonspecific; they include general fatigue (due to cytokine release), anorexia, weakness, and weight loss (see table: Common signs and symptoms of cirrhosis of the liver). The

liver is usually tender to palpation, has a firm consistency with blunt edges, sometimes the liver is reduced in size and difficult to palpate. Nodules are usually not palpable.

Clinical signs suggestive of chronic liver disease or chronic alcohol abuse that are not specific to cirrhosis include muscle wasting, palmar erythema, parotid gland enlargement, white nails, hourglass nails, Dupuytren's contracture, spider veins, gynecomastia, axillary hair loss, testicular atrophy, and peripheral neuropathy.

After the development of any complications of liver cirrhosis, the likelihood of further manifestations of decompensation (characterized by gastrointestinal bleeding, ascites, or hepatic encephalopathy) is greater.

a) The most common signs and symptoms of liver cirrhosis

b) Diagnosis of cirrhosis

c) Liver function tests, coagulation tests, complete blood count (CBC), and viral serology tests

d) Standard methods of liver imaging: ultrasound, CT, MRI

Non-invasive assessment of fibrosis using imaging techniques: transient elastography, acoustic radiation force pulse imaging (ARFI), two-dimensional shear wave elastography (2D-SWE), magnetic resonance elastography proton density fat fraction (MRI-PDFF)

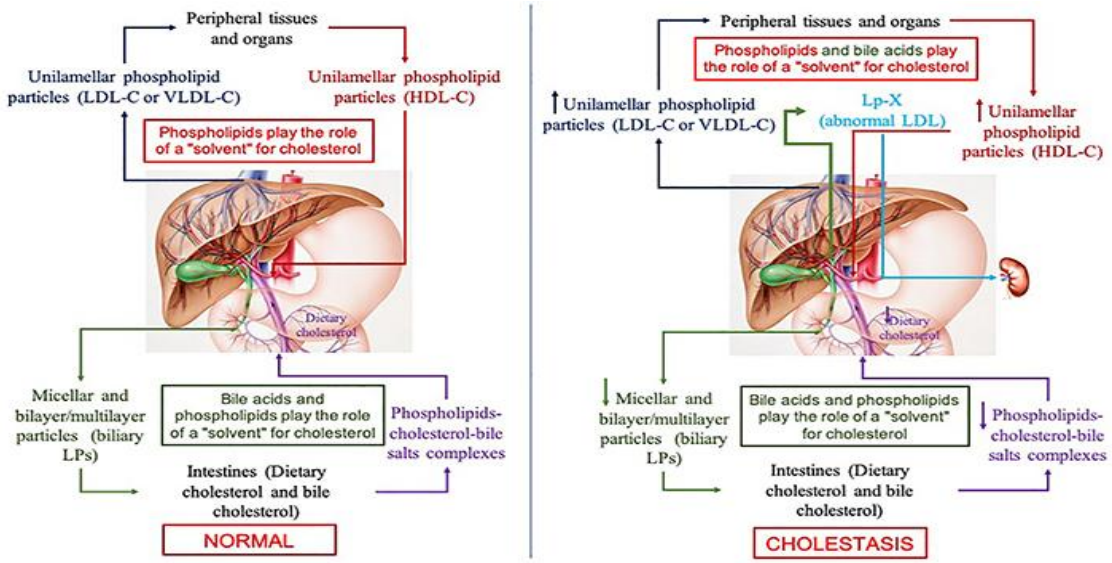
Identify the cause based on clinical assessment, perform routine screening for common causes, and perform random screening for less common causes

Sometimes a liver biopsy (for example, when clinical and noninvasive studies are inconclusive or when biopsy results may change the treatment approach)

Discussion: Cirrhosis is suspected in patients with signs of its complications (see table. Common signs and symptoms of complications of cirrhosis of the liver), especially portal hypertension or ascites. Early cirrhosis should be considered in patients with nonspecific symptoms or characteristic laboratory abnormalities detected incidentally on laboratory tests, especially in patients with diseases or taking medications that can cause fibrosis.

Diagnostic workup begins with liver function tests, coagulation tests, a complete blood count, and serological tests for chronic viral hepatitis (see tables: Serological Diagnosis of Hepatitis B and Serological Diagnosis of Hepatitis C). Laboratory data alone can raise the suspicion of cirrhosis but cannot confirm or rule out the diagnosis.

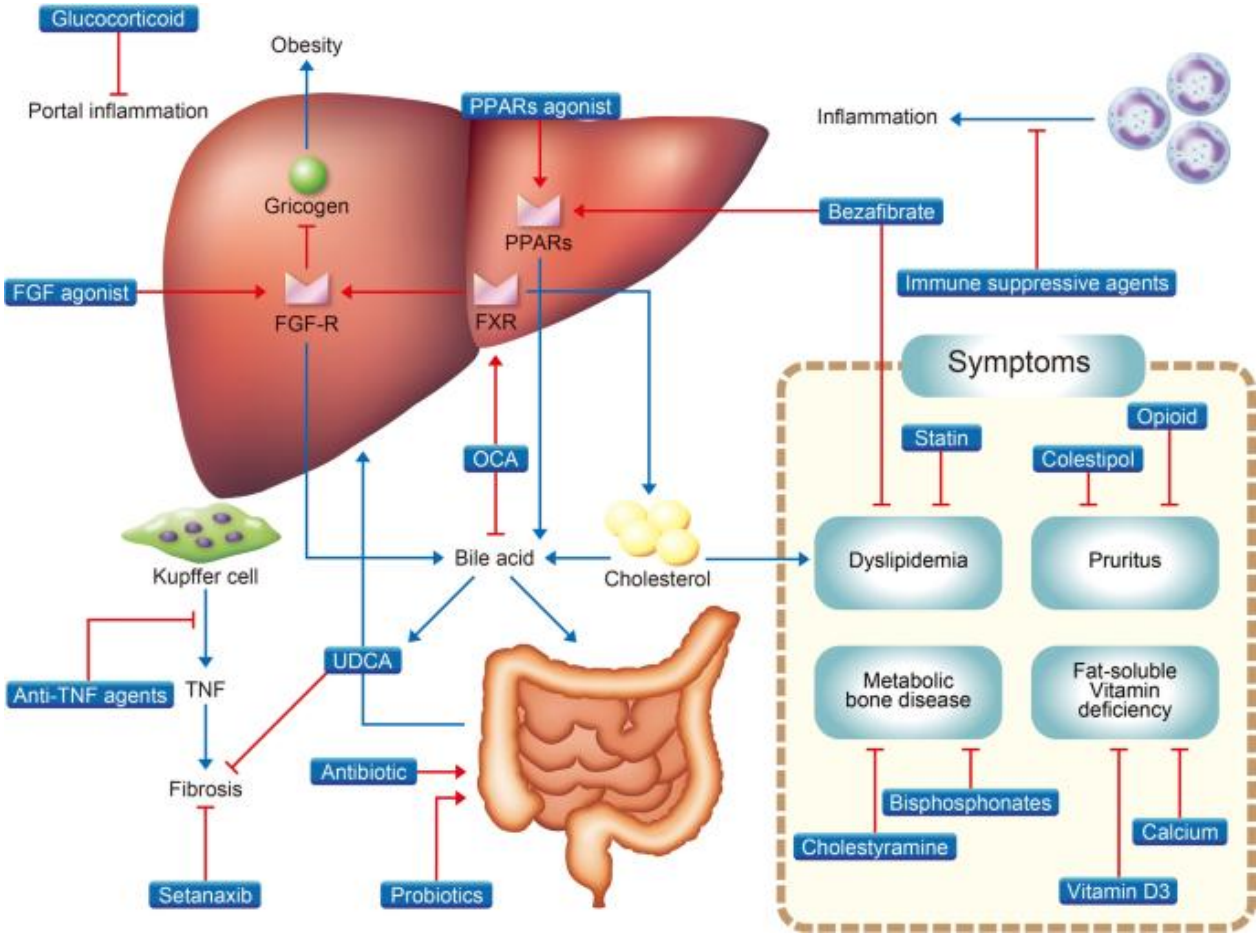
Test results may be normal or may show nonspecific abnormalities. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are often moderately elevated but may be normal. Alkaline phosphatase and gamma-glutamyl transpeptidase (GGT) are usually within normal limits; if they are elevated, this indicates cholestasis. Bilirubin is usually normal but increases with the development of cirrhosis, especially in primary biliary cholangitis. Decreased serum albumin and increased prothrombin time (PT) directly reflect impaired hepatic synthetic function - this is usually observed in the late stages of the disease. Albumin levels may also be reduced due to malnutrition.



Anemia is common and usually normocytic, with a high index of red blood cell heterogeneity. Anemia is often multifactorial; contributing factors include chronic gastrointestinal bleeding (usually causing microcytic anemia), folate deficiency (causing macrocytic anemia, especially with chronic alcohol abuse), hemolysis, and hypersplenism. Clinical blood tests may also reveal leukopenia, thrombocytopenia, or pancytopenia.

Imaging tests alone are not very sensitive or specific for diagnosing cirrhosis, but they can often detect its complications. Noninvasive imaging studies (eg, transient elastography, pulsed acoustic emission imaging, two-dimensional shear wave elastography, and magnetic resonance elastography) are useful in detecting early cirrhosis when conventional imaging findings are equivocal and portal hypertension is not evident.

In advanced cirrhosis, ultrasound shows a small, nodular liver. Ultrasound also shows signs of portal hypertension and ascites.



Contrast-enhanced and non-contrast CT and MRI can detect nodular texture, varicose veins, portal/splenic vein thrombosis, and liver lesions in cases of suspected hepatocellular carcinoma. Radionuclide liver scanning using technetium-99m-labeled colloidal sulfur can demonstrate irregular hepatic uptake of the radioactive drug with increased splenic and bone marrow uptake, but its use is limited in modern practice.

A history of alcoholism is a possible cause in patients with documented alcoholism and laboratory values of AST higher than ALT (especially AST/ALT ratio > 2), elevated gamma-glutamyl transpeptidase (GGT), and macrocytic anemia due to B12 and folic acid deficiency. The presence of acute alcoholic hepatitis is manifested by fever, painful hepatomegaly, and jaundice.

Detection of serum hepatitis C antibodies (anti-HCV) and HCV RNA indicates hepatitis C. Detection of hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBcAb) confirms chronic hepatitis B. Chronic hepatitis B with very low HBV viral load may occur in HBV/HDV co-infection. Most doctors routinely screen for the following conditions:

Autoimmune hepatitis: confirmed by high titers of antinuclear antibodies (low titers are nonspecific and do not always require further evaluation) and hypergammaglobulinemia (IgG), as well as the presence of other autoantibodies (e.g., smooth muscle antibodies or liver-1 renal microsomes).

Hemochromatosis: suggested by increased serum iron and transferrin saturation and confirmed by genetic screening for the homeostatic iron regulator (HFE).

Alpha-1 antitrypsin deficiency: suspected by low serum alpha-1 antitrypsin levels and confirmed by genotyping/phenotyping:

The presence of antimitochondrial antibodies (95%) and elevated IgM levels suggest primary biliary cholangitis (PBC), which should be confirmed by biopsy.

Strictures and dilatation of the intrahepatic and extrahepatic bile ducts detected by magnetic

resonance cholangiopancreatography (MRCP) suggest the presence of primary sclerosing cholangitis;

Decreased serum ceruloplasmin and characteristic copper results may indicate Wilson's disease;

A history of obesity and diabetes suggests metabolically associated fatty liver disease (MAFLD), and the diagnosis is made by exclusion unless confirmed by liver biopsy.

Liver biopsy is an invasive procedure and is subject to sampling errors, but it remains the gold standard for diagnosing cirrhosis. Liver biopsy is necessary in the following cases:

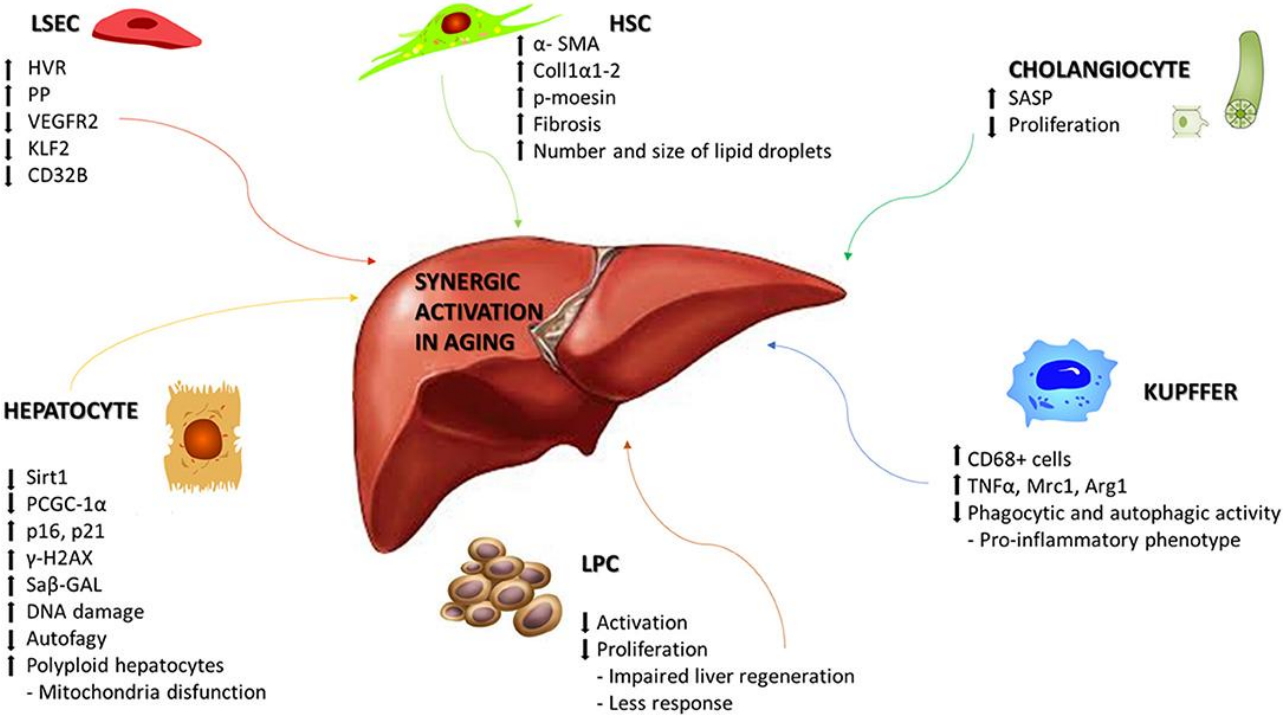
If clinical criteria and noninvasive tests do not allow the diagnosis of liver cirrhosis or its etiology to be made (e.g., when there is clinical suspicion of well-compensated cirrhosis and imaging results are inconclusive)

To confirm certain causes of cirrhosis (such as amyloidosis, PBC, or small duct PSC)

Assessing the severity and/or activity of certain causes of cirrhosis (e.g., autoimmune hepatitis) to determine the intensity of treatment.

Noninvasive imaging to assess fibrosis to confirm liver cirrhosis in some conditions where formal confirmation is not possible (e.g., pregnancy, congestive hepatopathy, and rare liver diseases)

In cases of severe coagulopathy, portal hypertension, ascites, and cirrhosis with liver failure, biopsy is not required unless the results affect the management of the patient. In patients with ascites, coagulopathy, and thrombocytopenia, the safest method is transjugular biopsy. This method allows measurement of pressure and therefore the trans-sinusoidal pressure gradient.



Conclusion: All patients with cirrhosis, regardless of the cause, should be routinely screened for hepatocellular carcinoma. Abdominal ultrasound with or without serum alpha-fetoprotein (AFP) measurement is recommended every 6 months. If abnormalities suggestive of HCC are detected, contrast-enhanced MRI or triple-phase abdominal CT (precontrast, arterial, and venous phases) should be performed. Certain contrast-enhanced imaging features (5 Liver Imaging Reporting and Data System [LI-RADS] criteria, including early arterial phase enhancement, portal phase washout, and contrast-enhanced “pseudocapsule”) may be useful in confirming the presence of HCC, sparing the patient the need for biopsy. Ultrasound appears promising as an alternative to CT or MRI, but is still under investigation.

According to the Baveno VII consensus recommendations, patients with compensated cirrhosis should be screened for clinically significant portal hypertension (defined as a hepatic venous pressure gradient ≥ 10 mmHg) (1). The recommended diagnostic criteria for the diagnosis of clinically significant portal hypertension using noninvasive methods include (2):

a) Liver density (LD) ≥ 25 kPa by transient elastography (TE)

b) PP for TE 20-25 kPa and platelet count < 150 c/ml

c) For TE, PP is 15-20 kPa and platelet count is < 110 c/ml

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