BMJ Best Practice

# Cirrhosis

Straight to the point of care

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# Summary

Cirrhosis is the pathological end-stage of any chronic liver disease and most commonly results from chronic hepatitis B and C, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease.

The main complications of cirrhosis are related to the development of liver insufficiency and portal hypertension and include ascites, variceal haemorrhage, jaundice, portosystemic encephalopathy, acute kidney injury and hepatopulmonary syndromes, and the development of hepatocellular carcinoma.

Once a patient with cirrhosis develops signs of decompensation, survival is significantly impaired.

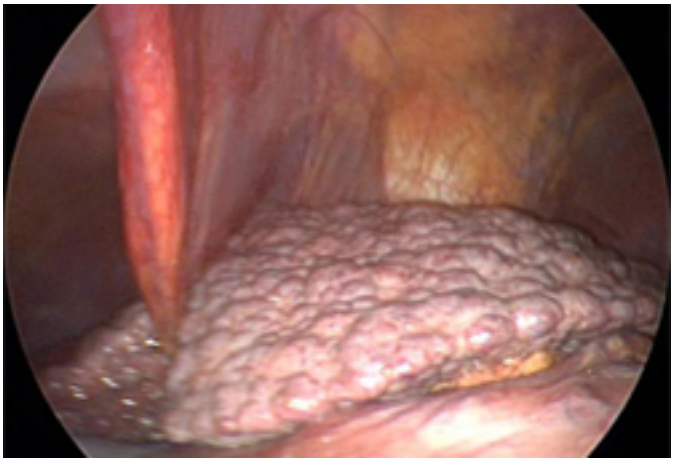
Management of cirrhosis includes treating underlying liver disease, avoiding superimposed injury, and managing complications. Timely referral for liver transplantation may be the only curative treatment option for patients with decompensated cirrhosis.

Chronic liver disease and cirrhosis are significant causes of premature mortality.

# Definition

Cirrhosis is a diffuse pathological process, characterised by fibrosis and conversion of normal liver architecture to structurally abnormal nodules known as regenerative nodules.[1]

It can arise from a variety of causes and is the final stage of any chronic liver disease. It can lead to portal hypertension, liver failure, and hepatocellular carcinoma. In general, it is considered to be irreversible in its advanced stages, although there can be significant recovery if the underlying cause is treated.



*Laparoscopic view of a cirrhotic liver*

*Courtesy of Dr Eugene Schiff and Dr Lennox Jeffers; used with permission*

THEORY

# Epidemiology

Cirrhosis is an important cause of morbidity and mortality. Cirrhosis and other chronic liver diseases are ranked as the 14th most common cause of death globally.[4] In 2019, about 2.4% of global deaths were due to cirrhosis.[5] An estimated 1.5 billion people globally have chronic liver diseases, with an age-standardised incidence of chronic liver diseases and cirrhosis of 25.35 per 100,000 people in 2019.[4] [6] In 2017, the global prevalence of compensated cirrhosis was estimated to be 112 million cases and global prevalence of decompensated disease was estimated to be 10.6 million cases.[7]

In the US, cirrhosis affects around 2.2 million adults and is associated with mortality rates of 21.9 per 100,000 people.[3] Hospital admissions related to liver cirrhosis have increased in the US, from 3056 per 100,000 hospital admissions in 2012 to 3757 per 100,000 hospital admissions in 2016.[8]

In the UK, cirrhosis is a significant cause of premature mortality and years of working life lost.[9]

The majority of cases of chronic liver disease are accounted for by viral hepatitis, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD).[7] Incidence of cirrhosis due to viral hepatitis has reduced following implementation of successful vaccination programmes.[6] [10] The prevalence of MASLD has increased in parallel with the obesity epidemic.[10] If this trend continues, it is expected that MASLD will become the most common cause of advanced liver disease and liver failure in the 21st century.[11] [12]

In Europe, cirrhosis related to either viral infection (21% [13% hepatitis C virus infection; 7% hepatitis B virus infection]) or alcohol misuse (19%) are the main indications for liver transplant. Dual aetiology liver cirrhosis caused by viral hepatitis and alcohol-related liver disease represents 3% of cases.[13]

# Aetiology

Any chronic liver disease may cause cirrhosis. The most common causes of cirrhosis are alcohol-related liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and chronic viral hepatitis.[6] [14]

Other less common but important causes of cirrhosis include cholestatic, autoimmune, and metabolic liver diseases.

When the aetiology of cirrhosis cannot be determined, it is considered 'cryptogenic'. The number of cases of cryptogenic cirrhosis is significantly declining, in part because it is becoming more evident that many cases are undiagnosed MASLD.

The various causes of cirrhosis are listed below.

- Chronic viral hepatitis: hepatitis C and hepatitis B (with or without coexisting hepatitis D)
- Alcohol-related liver disease
- Metabolic disorders: MASLD, haemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, glycogen storage diseases, abetalipoproteinaemia
- Immune-mediated liver disease: primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, autoimmune cholangiopathy, immunoglobulin G4-related disease
- Biliary obstruction: mechanical obstruction, biliary atresia, cystic fibrosis
- Hepatic venous outflow obstruction: Budd-Chiari syndrome, sinusoidal obstruction syndrome, right-sided heart failure
- Drugs and toxins: amiodarone, methotrexate

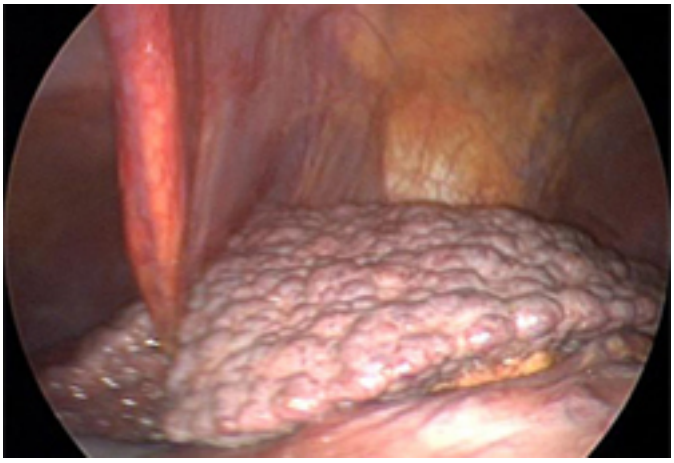
- Intestinal bypass: anastomosis of the jejunum to the ileum to shorten the length of the digestive tract in class III obesity (body mass index ≥40 kg/m²), or to bypass a diseased area or blockage
- Indian childhood cirrhosis (environmental copper poisoning, now rare)
- Cryptogenic cirrhosis.

# Pathophysiology

Liver fibrosis has been described as a reversible, wound-healing response to either acute or chronic cellular injury which reflects a balance between liver repair and scar formation.[15] It occurs in most patients with any type of chronic liver injury and may ultimately evolve into cirrhosis with nodule formation.

The central event in hepatic fibrosis is the activation of hepatic stellate cells, which are the major source of extracellular matrix. This leads to an accumulation of collagen types I and III in the hepatic parenchyma and space of Disse.[3] [15] [16]

The result of collagen deposition in the space of Disse is termed 'capillarisation' of the sinusoids, a process in which the hepatic sinusoids lose their characteristic fenestration, thereby altering the exchange between hepatocytes and plasma. With activation, hepatic stellate cells become contractile, which may be a major determinant of increased portal resistance during liver fibrosis and cirrhosis.[17]



*Laparoscopic view of a cirrhotic liver*

*Courtesy of Dr Eugene Schiff and Dr Lennox Jeffers; used with permission*

This process is usually progressive and perturbs blood flow through the liver, thereby leading to increased pressure within the portal venous system, as well as shunting blood away from the liver.

In addition to architectural changes causing a fixed component of portal hypertension, dynamic changes to vascular tone resulting from an acute insult such as infection can influence portal pressure and result in acute decompensation.

These changes lead to portal hypertension, which underlies the development of ascites and gastro-oesophageal varices, and promotes the diversion of nutrient-carrying blood away from the liver, contributing to hepatic encephalopathy.[15] [16]

An increase in vasoconstrictor signalling (such as endothelin-1) and decrease in the production of vasodilators (e.g., nitric oxide) may be seen in chronic liver injury, leading to restricted blood flow.[3] Vascular resistance is also increased by inflammation due to alcohol or steatosis. Further, chronic liver injury may also cause loss of hepatocytes and reduce the capacity of the liver to perform metabolic activities such as protein

synthesis, detoxification, nutrient storage, and bilirubin clearance.[3] Patients may progress over time from a compensated state without clinical manifestations to a decompensated state with variceal haemorrhage, ascites, or hepatic encephalopathy.[3] Portal hypertension (pressure gradient of ≥10 mmHg) may promote the development of varices. Gut-derived toxins such as ammonia and bacterial products that induce systemic inflammation result in hepatic encephalopathy.[3] [18]

Cirrhosis can lead to malnutrition and importantly sarcopenia. This leads to frailty, which is increasingly recognised as a poor prognostic marker.[19] [20] Sarcopenia results from anorexia; hypermetabolism; hyperammonaemia; malabsorption due to intraluminal bile acid deficiency and/or chronic pancreatitis; altered macronutrient metabolism; and micronutrient deficiencies.[21] Sarcopenia may affect about one third of patients with cirrhosis and is associated with approximately twofold increased mortality.[22] [23] Risk factors for sarcopenia in patients with cirrhosis include older age, male sex, lower body mass index, and presence of alcohol-related liver disease.[24]

Inadequate synthesis due to hepatic impairment combined with a catabolic state results in hypoalbuminaemia, which can worsen complications of liver cirrhosis such as ascites.

An immune system dysfunction can be seen in cirrhosis, disposing patients to bacterial, fungal, and viral infections.[25] Such patients are prone to develop multi-organ failure, which is associated with high mortality.[25] Bacterial infections are most common, with spontaneous bacterial peritonitis being the most frequently encountered bacterial infection.

Cirrhosis is a dynamic disease state with potential for reversibility if ongoing liver injury is halted. For example, a patient with decompensated cirrhosis related to alcohol may clinically recompensate with abstinence.[26] Similarly, serial biopsy studies have shown improvement of liver fibrosis following treatment of chronic viral hepatitis.[27]

There is likely a point after which liver cirrhosis is considered irreversible and the only treatment at that stage is liver transplantation. This may relate to the deposition of hepatic elastin, which is more resistant to remodelling.[28]

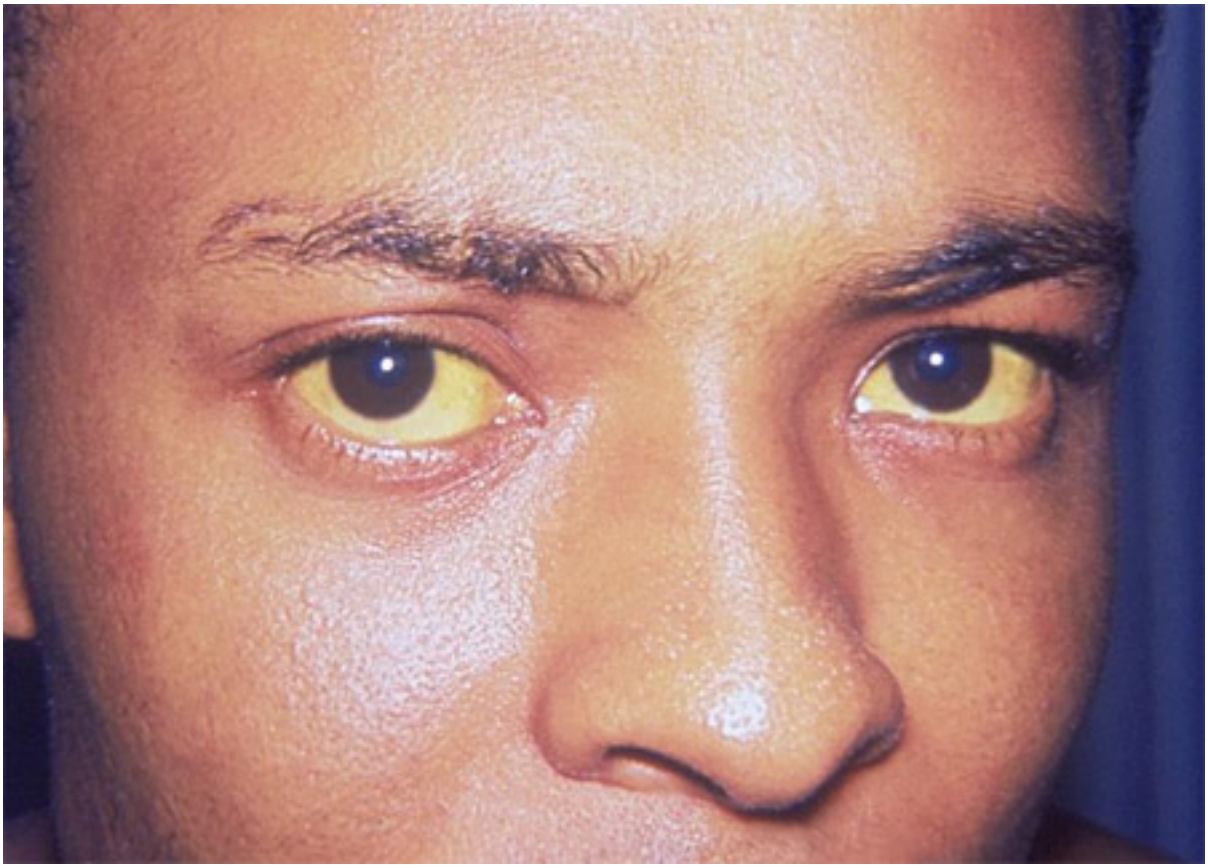
# Classification

## Compensated cirrhosis

In compensated cirrhosis, biochemical, radiological, or histological findings consistent with the pathological process of cirrhosis are present. Liver synthetic function is preserved and there is no evidence of complications related to portal hypertension, such as ascites, gastro-oesophageal varices and variceal bleeding, hepatic encephalopathy, and/or jaundice.

## Decompensated cirrhosis

Cirrhosis is regarded as decompensated when there is evidence of the development of complications of liver dysfunction with reduced hepatic synthetic function and portal hypertension including ascites, variceal bleeding, hepatic encephalopathy, and/or jaundice. Decompensated cirrhosis is an umbrella term for a spectrum of disease. It usually occurs when the portal pressure gradient is ≥10 mmHg (known as ‘clinically significant portal hypertension’).[2]



*Icterus or jaundice*

*CDC. Dr Thomas F. Sellers/Emory University; used with permission*

# Case history

## Case history #1

A 56-year-old man with a remote history of intravenous drug use presents to an initial visit complaining of increased abdominal girth but denies jaundice. He drinks about 2 to 4 glasses of wine with dinner and recalls having had abnormal liver enzymes in the past. Physical examination reveals spider naevi, a palpable firm liver, mild splenomegaly, and shifting dullness consistent with the presence of ascites. Liver function is found to be deranged with elevated aminotransferases (aspartate aminotransferase [AST]: 90 U/L, alanine aminotransferase [ALT]: 87 U/L), and the patient is positive for anti-hepatitis C antibody.

## Case history #2

A 60-year-old woman with a past medical history of obesity, diabetes, and dyslipidaemia is noted to have abnormal liver enzymes with elevated aminotransferases (ALT: 68 U/L, AST: 82 U/L), and normal alkaline phosphatase and bilirubin. She denies significant alcohol consumption, and tests for viral hepatitis and autoimmune markers are negative. An abdominal ultrasound reveals evidence of fatty infiltration of the liver and slight enlargement of the spleen.

## Other presentations

In the early stages of cirrhosis, patients may be completely asymptomatic or complain of unexplained fatigue, weakness, and/or weight loss. Patients may experience muscle cramps (about 64% prevalence), pruritus (39% prevalence), poor-quality sleep (63% prevalence), and sexual dysfunction (53% prevalence).[3]

Liver enzymes may be within the normal range or show only mild abnormality.

# Approach

Patients with cirrhosis often show no signs or symptoms for many years.[34] Around 40% of patients are diagnosed when they present with complications such as hepatic encephalopathy or ascites.[3] Screening for cirrhosis is recommended for patients with established chronic liver disease with abnormal liver enzymes, hepatic steatosis on imaging, or viral hepatitis, but not for the general population.[3]

Cirrhosis can be identified by presence of clinical findings plus laboratory tests that reflect the underlying pathophysiology.[35] Simple laboratory tests and clinical findings that increase the likelihood of cirrhosis have been discussed in one meta-analysis.[35] These include: presence of ascites, platelet count of $<160 \times 10^9$/L (<160,000/microlitre), spider naevi, or a combination of simple laboratory tests with the Bonacini cirrhosis discriminant score of >7.[35]

The evaluation of a patient with suspected chronic liver disease and cirrhosis should begin with a detailed history identifying the presence of risk factors for the different causes of cirrhosis. Patients should then undergo a thorough physical examination in order to elicit any signs of chronic liver disease or complications of cirrhosis.

A full panel of blood tests should be undertaken to establish the aetiology of chronic liver disease and to ascertain the degree of disease severity. Liver imaging and screening endoscopy may be required. Liver biopsy, which was performed as a standard test, is now being increasingly replaced with non-invasive tests.[3]

Cirrhosis should be differentiated from non-cirrhotic conditions that can also lead to portal hypertension. These include disorders such as constrictive pericarditis; vascular disorders such as Budd-Chiari syndrome, portal vein and splenic vein thrombosis, and inferior vena cava obstruction; infectious agents such as schistosomiasis; and sarcoidosis, nodular regenerative hyperplasia, and idiopathic portal hypertension, also known as hepatoportal sclerosis. It is important to exclude exposure to substances that may cause portal hypertension such as vitamin A intoxication, arsenic, and vinyl chloride toxicity.

Certain non-hepatic conditions may lead to the development of cirrhosis, where congestive heart failure or cardiopulmonary disease lead to passive hepatic congestion, which may lead to cirrhosis with time.

## History

Presenting features[35]

- Patients with cirrhosis may be asymptomatic or have non-specific constitutional symptoms, such as fatigue, weakness, and weight loss, as well as recurrent infections and decreased libido.
- Symptoms of decompensation include:
    - Abdominal distension due to ascites
    - Vomiting of blood (haematemesis) and black stool (melaena) secondary to variceal haemorrhage
    - Altered mental status in hepatic encephalopathy
    - Peripheral oedema
    - Jaundice.
- Less common symptoms associated with pulmonary complications of portal hypertension include dyspnoea on exertion. In patients with hepatopulmonary syndrome, platypnoea (shortness of breath with sitting up) and orthodeoxia (deoxygenation with sitting up) are classically described;



patients may also develop clubbing and cyanosis. In portopulmonary hypertension, patients may develop syncope and chest pain/pressure.

Past medical history

- Check whether the patient has already been diagnosed with a chronic liver disease.
- Elicit any history of metabolic syndromes (diabetes, dyslipidaemia, obesity, hypertension) or autoimmune disorders.
- Knowledge of the patient's past medical history may be helpful in identifying exposure to hepatotoxic drugs.
- Patients should be asked about previous history of blood transfusion.

Drug history

- A complete drug history should be taken. Long-term use of certain drugs such as methotrexate and amiodarone has been implicated in the development of liver cirrhosis.[36] However, one evidence-based review found that advanced liver fibrosis and cirrhosis previously attributed to methotrexate were caused by metabolic liver disease or other chronic liver diseases and not by methotrexate itself.[37]
- It is important to elicit the use of over-the-counter drugs, vitamins, and herbal and dietary supplementation, which may account for liver injury and may not be volunteered by the patient.[38]

Family history

- A family history of haemochromatosis, Wilson's disease, or alpha-1 antitrypsin deficiency provides an important diagnostic clue.
- Chronic hepatitis B may be transmitted from mother to child, and asking about a family history of viral hepatitis is important.[30]
- Patients should be asked whether there is a family history of liver cirrhosis or hepatocellular carcinoma as genetic susceptibility to liver injury is likely to play a role in risk.[39]
- A history of metabolic risk factors in the family, particularly diabetes, should raise suspicion for metabolic dysfunction-associated steatotic liver disease.

Social history and risk factors

- Patients should be asked sensitively about risk-taking behaviours, such as intravenous drug use, unprotected intercourse, and tattoos.[33]
- A detailed alcohol history should be taken in order to assess the patient's level and pattern of alcohol consumption, and the number of units consumed per week should be documented.[29]
- A thorough travel history should also be taken, including country of birth and ethnic origin of parents, as well as a history of dental or surgical procedures performed abroad.[32]
- A history of patterns of weight gain/loss should be taken.

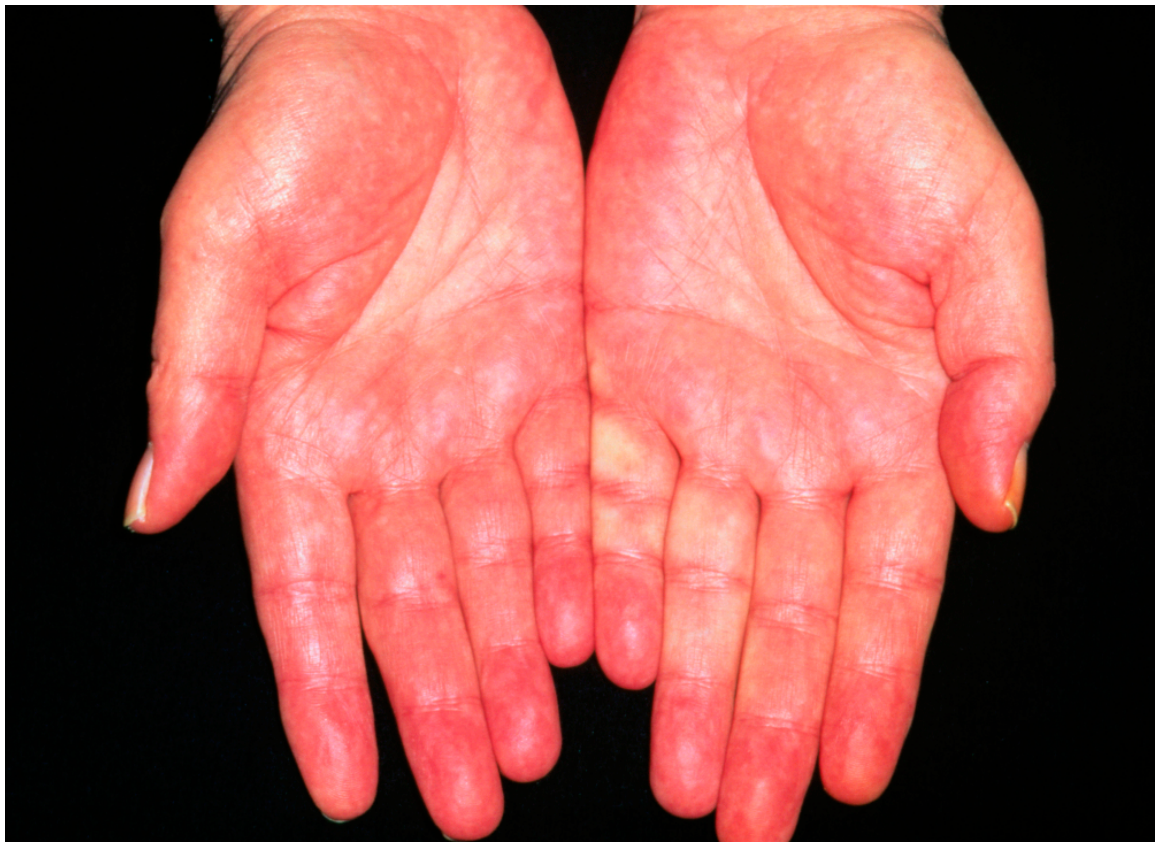
## Physical examination

Chronic liver disease and cirrhosis have a variety of physical characteristics, some of which are specific to the underlying causative disease.

Hand and nail features

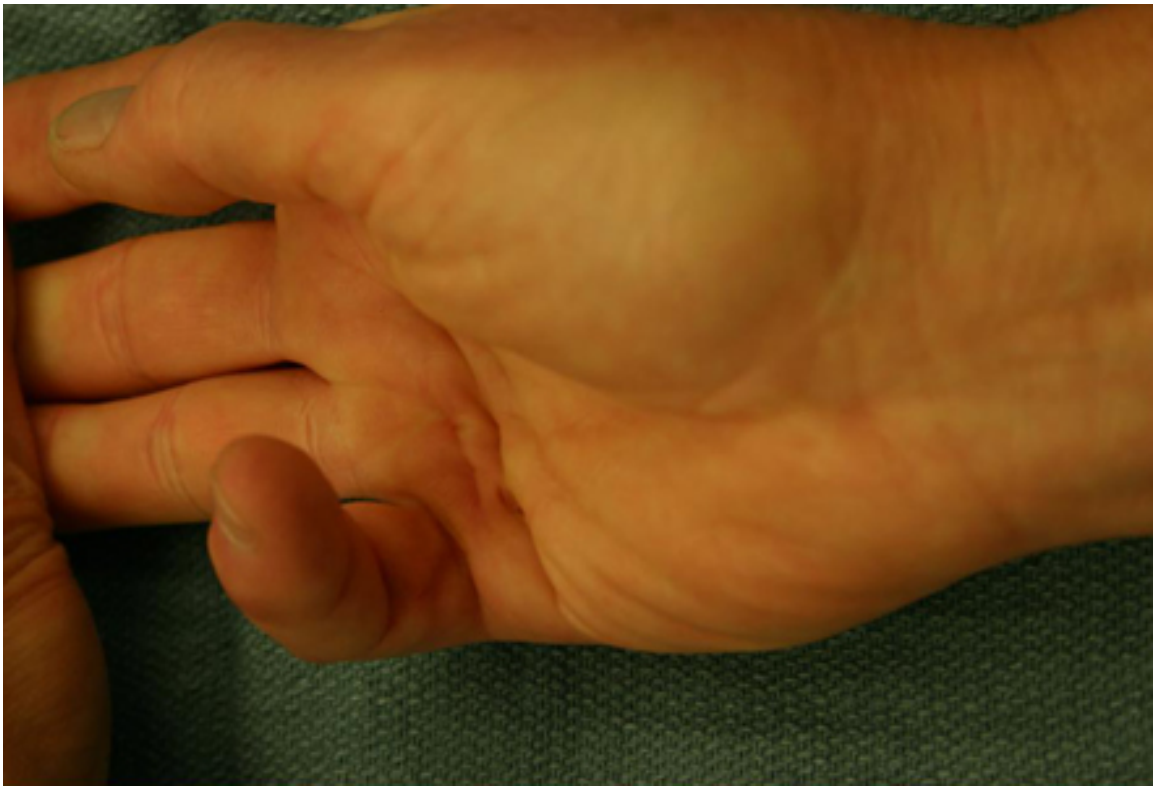
- Leukonychia (white nails) secondary to hypoalbuminaemia
- Polished nails secondary to excessive scratching in pruritus
- Palmar erythema
- Spider naevi

- Bruising
- Finger clubbing and cholesterol deposits in palmar creases in primary biliary cholangitis
- Dupuytren contracture in alcohol-related liver disease
- Cyanosis and finger clubbing in patients with hepatopulmonary syndrome.[35] [40]



*Liver palms erythema of adult alcoholic*

*Dr P. Marazzi / Science Photo Library; used with permission*

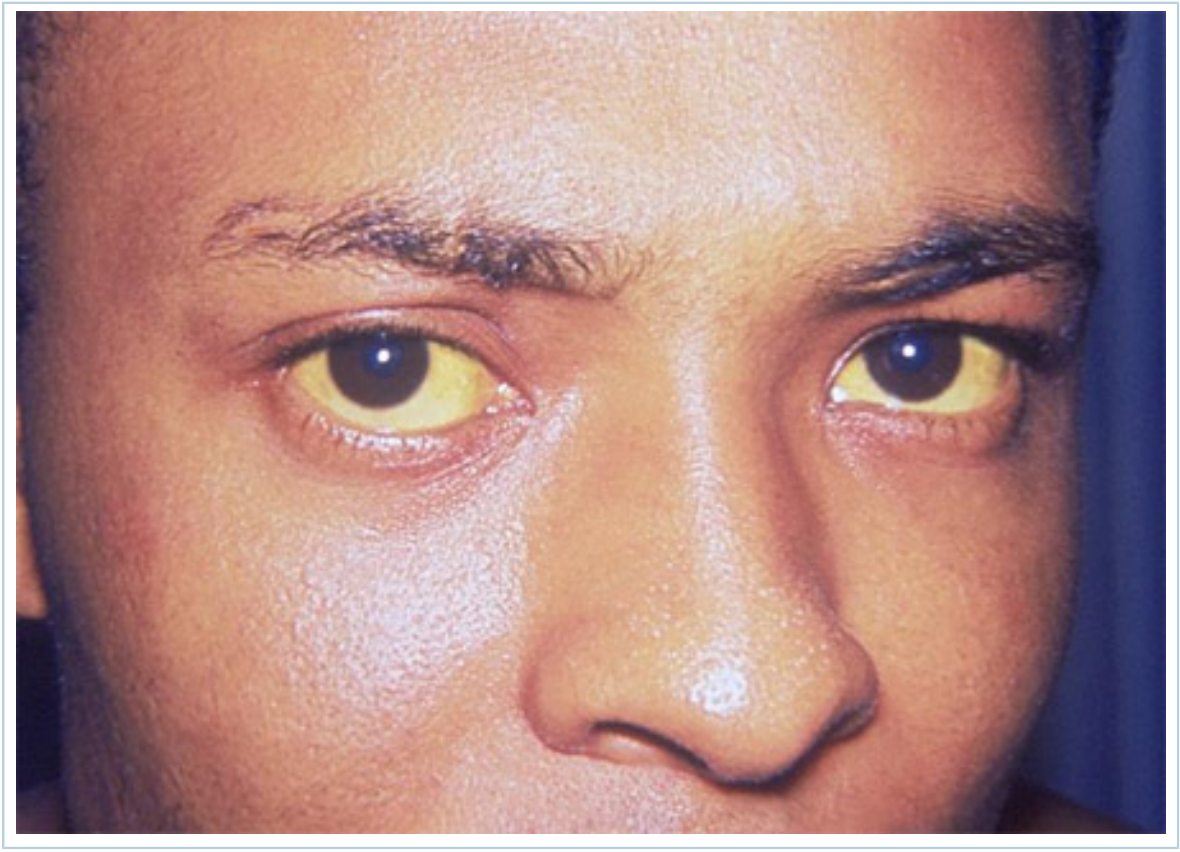


*Preoperative view of a small finger flexion contracture*

*From the collection of Dr C.M. Rodner; used with permission*

Facial features

- Telangiectasia
- Spider naevi
- Bruising
- Rhinophyma (lobulated and hypertrophied appearance of the nose secondary to sebaceous gland hyperplasia)
- Parotid gland swelling
- Glossitis
- Skin has the appearance of a US dollar note ('paper-money' skin, randomly distributed thready blood vessels)
- Seborrhoeic dermatitis
- Jaundiced sclerae
- Xanthelasma in primary biliary cholangitis.



*Icterus or jaundice*

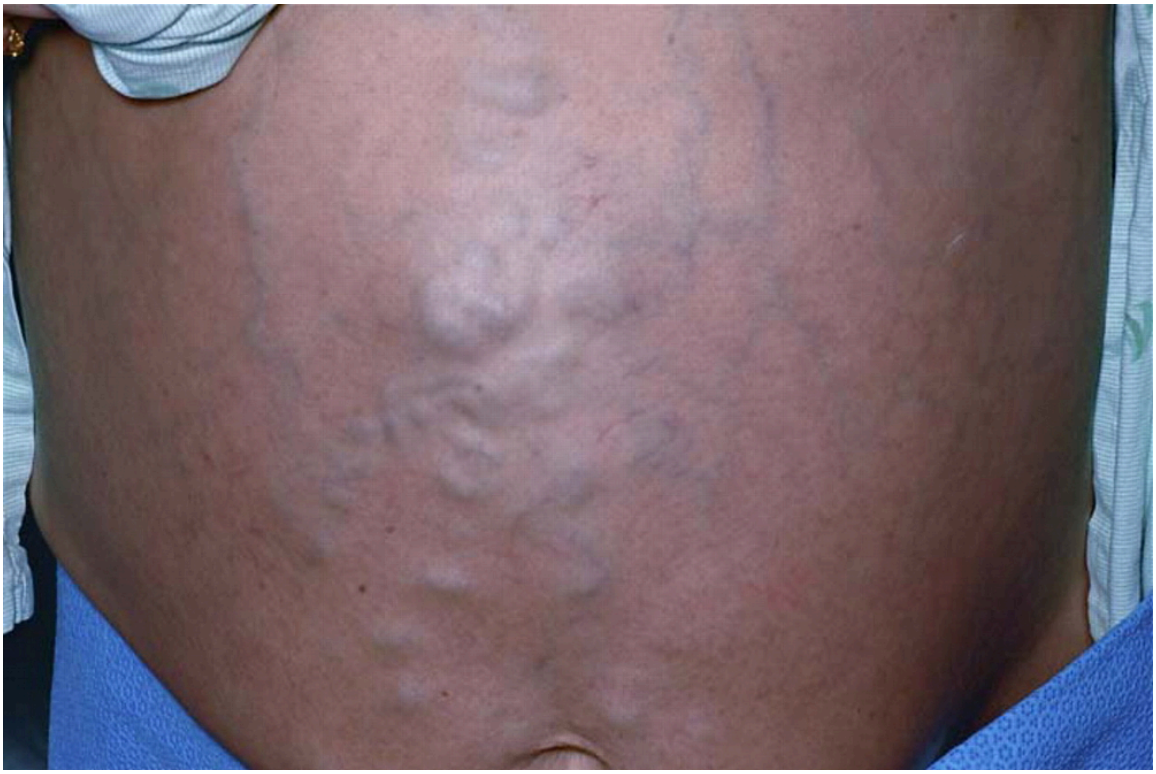
*CDC. Dr Thomas F. Sellers/Emory University; used with permission*

Chest wall features

- Gynaecomastia (tender and firm enlarged breast bud) and loss of secondary sexual hair in men
- Breast atrophy in women.

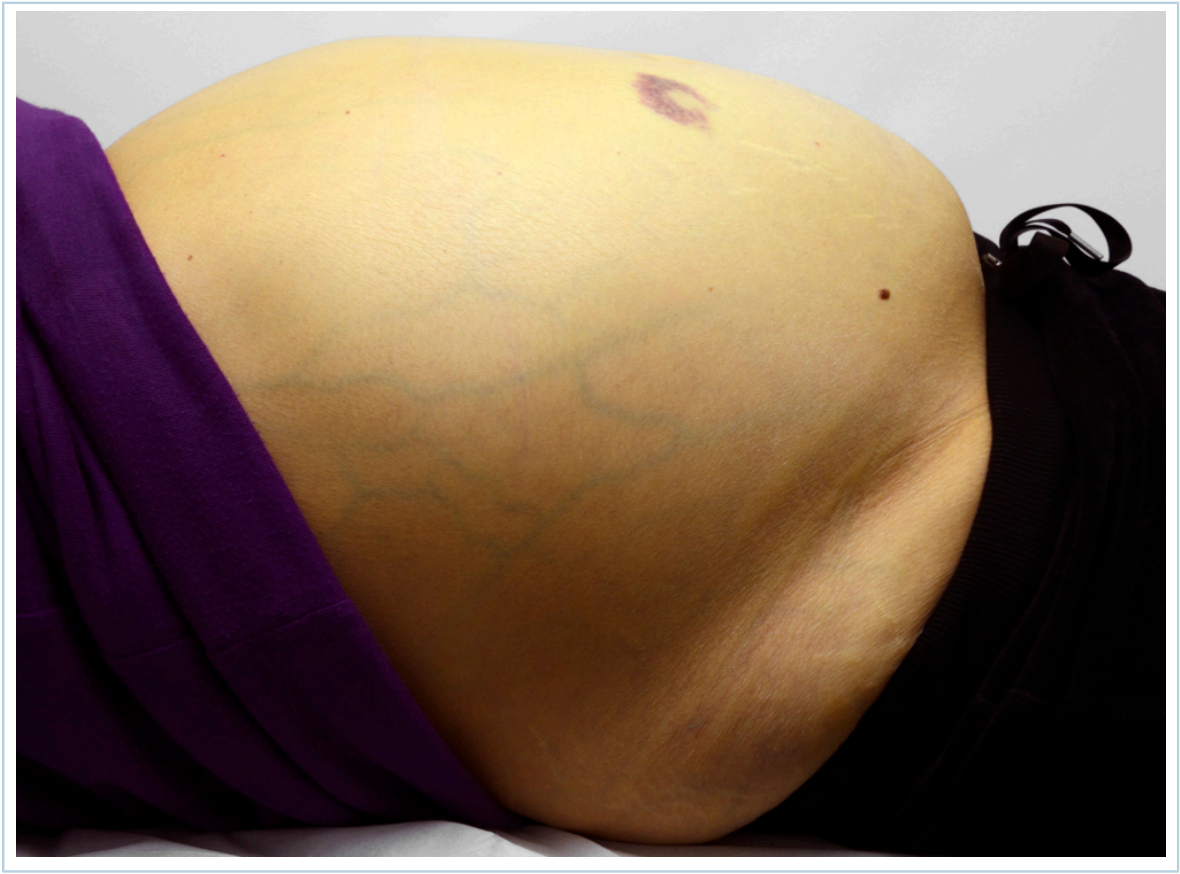
Abdominal features

- Collateral circulation of the abdominal wall around the umbilicus (caput medusa)
- Bruising
- Hepatomegaly
- Splenomegaly
- Abdominal distension (particularly in the flanks) with shifting dullness and fluid thrill secondary to ascites
- Hepatic bruit may be present with a vascular hepatoma
- Loss of secondary sexual hair and testicular atrophy in men.



*Caput medusa: dilated superficial (superior and inferior) epigastric veins radiating from a central large venous varix*

*Singh NK, Cheema U, Khalil A. Caput medusae. Case Reports. 2010;2010:bcr0320102795; used with permission*



*Ascites. View of the abdomen of a female patient with alcohol-related liver disease and cirrhosis, showing swelling due to ascites (accumulation of fluid in the peritoneal cavity), jaundice (yellowing of the skin), and bruising*

*Science Photo Library; used with permission*

Other physical findings include hepatic fetor, muscle wasting, and peripheral oedema, and findings of elevated right heart pressure such as elevated jugular venous pulse, increased split of the second heart sound, and pulsatile liver in patients with portopulmonary hypertension.

## Blood tests

All patients should receive a liver screen on presentation in order to identify the underlying cause and severity of the cirrhosis.

Liver function tests

These tests show characteristic results depending on the nature of the hepatic insult.

- Aminotransferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) levels increase with hepatocellular damage and are usually elevated to some degree.
    - Normal AST and ALT levels do not preclude the diagnosis of cirrhosis.[41]
    - Aminotransferase levels bear little to no relationship to frequency of complications or death.[42]
    - ALT levels are greater than those of AST in most chronic liver diseases (except for alcohol-related liver disease), but this finding may be reversed with progression of liver disease.
    - An AST/ALT ratio of ≥1 is thought to be a predictor of cirrhosis.[43]



- Alkaline phosphatase and gamma-glutamyl transferase (GGT) levels increase in cholestasis (resulting from primary biliary cholangitis and primary sclerosing cholangitis), with minimal derangement of AST and ALT.
- Total bilirubin may be normal in patients with compensated cirrhosis, but as the cirrhosis progresses, serum levels generally rise.
- It is important to recognise that these tests can be elevated in conditions other than liver disease. For example, aminotransferases can be elevated in systemic diseases without primary liver involvement, such as thyroid disease, muscle disorders (including cardiac ischaemia), and coeliac disease. Alkaline phosphatase can be elevated with bone disease and total bilirubin will be elevated in the setting of haemolysis.

Gamma-glutamyl transferase (GGT)

- Increase in this liver microsomal enzyme represents enzyme activation, which can be induced by alcohol and certain drugs, and is also observed in metabolic dysfunction-associated steatotic liver disease (MASLD).
- GGT is increased in cholestasis along with alkaline phosphatase (ALP).
- GGT is not significantly present in bone, such that concomitant elevated GGT and ALP indicate the liver as the source of the ALP.

Albumin

- A decrease in serum albumin is a marker of hepatic synthetic dysfunction.

Electrolytes

- Hyponatraemia is a common finding in patients with cirrhosis with associated ascites, and worsens as the liver disease progresses.
- Hyperkalaemia is frequently observed in patients with cirrhosis (12% to 14% of those hospitalised with cirrhosis).[44] It may indicate a poor prognosis, and can present a challenge to treat.[44] [45]

Full blood count and clotting

- Prolongation of the prothrombin time is a marker of hepatic synthetic dysfunction. (Although prothrombin time can be prolonged in patients with vitamin K deficiency, it is readily reversed by vitamin K replacement, which does not occur in the setting of hepatic dysfunction.)
- Coagulopathy in liver disease is complex. A prolonged prothrombin time does not necessarily mean that the patient is at increased risk of bleeding, and correction of coagulopathy with blood products outside the context of acute bleeding is not usually warranted.[46] Expert consensus recommends that International Normalised Ratio testing is not required for diagnostic or therapeutic paracentesis or diagnostic endoscopy, and that plasma transfusion should be avoided for all paracenteses and gastroscopy.[47]
- The presence of thrombocytopenia (platelet count <150,000/microlitre) is the most sensitive and specific laboratory finding for the diagnosis of cirrhosis in the setting of chronic liver disease and results from portal hypertension with hypersplenism and platelet sequestration.[48]

Viral serology

- Presence of immunoglobulin G (IgG) antibodies to hepatitis C virus, confirmed with hepatitis C virus RNA, is indicative of chronic hepatitis C infection.[49] Hepatitis C genotype is ordered once infection is confirmed in order to guide treatment decisions.
- A detectable hepatitis B surface antigen (HBsAg) or viraemia on a highly sensitive hepatitis B DNA assay indicates chronic hepatitis B infection.[49] Hepatitis B e-antigen/e-antibody, genotype, and viral load should be measured to assess disease phase and guide further treatment.[49]

Iron studies

- The initial screening tests for haemochromatosis are total iron and TIBC, in order to calculate the transferrin saturation (iron/TIBC), and serum ferritin. If the transferrin saturation and ferritin are elevated, HFE genotyping is performed.[50]

Auto-antibody screen

- Auto-antibodies: antinuclear (ANA), antismooth muscle (SMA), and liver kidney microsomal antibody (anti-LKM) for autoimmune hepatitis; antimitochondrial (AMA) for primary biliary cholangitis, more specifically the M2 antibody.

Serum immunoglobulins

- Assessment of serum immunoglobulins (IgA, IgG, and IgM) should be undertaken. Levels are frequently elevated in patients with cirrhosis.[51]

Ceruloplasmin

- Serum ceruloplasmin is decreased in Wilson's disease.

Alpha-1 antitrypsin

- Approximately 15% of adults with alpha-1 antitrypsin deficiency develop cirrhosis.[52]
- Plasma alpha-1 antitrypsin levels are used as a screening test.
- Alpha-1 antitrypsin is an acute phase protein and may be elevated in inflammation.
- Further testing can be done to confirm the diagnosis with protein electrophoresis and phenotyping.

Alpha-fetoprotein

- The finding of elevated alpha-fetoprotein in a patient with cirrhosis should raise concern for the development of hepatocellular carcinoma.[53] However, this tumour marker may also be elevated on the basis of chronic liver disease and inflammation in the absence of hepatocellular carcinoma; therefore, cross-sectional imaging is indicated to exclude the presence of hepatic lesions.

## Endoscopy

An upper gastrointestinal endoscopy should be performed in selected patients with cirrhosis to screen for oesophago-gastric varices. The selection of these patients is based on non-invasive assessment of their liver comprising platelet count and liver stiffness measurement (LSM).[54] In particular, patients with compensated cirrhosis, who have a liver stiffness <20 kPa (as measured by transient elastography) and platelet count >150 × $10^9$ cells/L, have a very low risk of having varices requiring treatment and can avoid screening endoscopy.[54] In practice, however, many centres offer baseline endoscopy to all patients with liver cirrhosis. Meta-analysis has shown that ultra-thin gastroscopy may be a better tolerated method for screening for varices where indicated.[55]

Patients with cirrhosis have historically been offered baseline upper gastrointestinal endoscopy for screening of gastro-oesophageal varices at the time of diagnosis, and at 1- to 3-year intervals thereafter.[56] However, guideline recommendations vary regarding screening intervals.

Primary prophylaxis (to prevent variceal bleeding) with either non-selective beta-blockers (propranolol, nadolol, or carvedilol) or endoscopic variceal ligation (EVL), which requires several sessions to obliterate varices, should be implemented if high-risk gastro-oesophageal varices are present.[57] One meta-analysis reported that, for primary prevention of variceal bleeding, variceal-band ligation plus beta-blocker resulted in a lower bleed rate compared with beta-blocker alone, but was also associated with a higher adverse event rate.[58] One competing-risk meta-analysis reported no added benefit of EVL plus non-

selective beta-blocker combination over non-selective beta-blocker alone in patients with compensated cirrhosis and high-risk varices.[59] A significant improvement in survival was observed with non-selective beta-blocker alone, thus making it a preferred option for preventative therapy.[59] Combination therapy is not recommended for primary prophylaxis.

## Imaging

Signs of cirrhosis or portal hypertension may be detected using ultrasound, computed tomography (CT) scan, and magnetic resonance imaging (MRI).[60] [61] The choice of imaging modality is dependent on the pathology requiring investigation and physician preference.

Ultrasound with Doppler assessment of flow within the hepatic vasculature is the preferred test for the initial evaluation of patients with suspected cirrhosis. It avoids radiation and contrast risks associated with other imaging modalities.

If there are features suspicious for hepatocellular carcinoma on ultrasound, or if the patient has unexplained abdominal pain, further evaluation with CT or MRI is recommended.[62]

Liver surface nodularity or a small liver with or without hypertrophy of the left/caudate lobe is detectable on ultrasound, CT, and MRI. Signs of advanced cirrhosis may be detected using ultrasound, CT scan, or MRI.

There is no radiological test sensitive enough to be used as the sole diagnostic tool for cirrhosis. However, the radiological findings described above, in combination with a strong clinical suspicion, suffice for the diagnosis of cirrhosis without the need for a confirmatory liver biopsy.

Imaging studies in patients with cirrhosis are an important tool for early detection of hepatocellular carcinoma and are routinely used for surveillance of this condition.

## Liver biopsy

Liver biopsy remains the most specific and sensitive test for the diagnosis of cirrhosis. However, it is not necessary in patients with advanced liver disease and typical clinical, laboratory, and/or radiological findings of cirrhosis, unless there is a need to determine the degree of inflammation.

In addition to confirming the diagnosis, liver biopsy may help to determine the aetiology of the underlying liver disease, although this is not always possible as characteristic features of the primary insult (e.g., MASLD or autoimmune hepatitis) may no longer be detectable by the time the procedure is carried out.

Liver biopsy is also helpful in diagnosing coexistent liver diseases (e.g., steatotic liver disease and viral hepatitis, haemochromatosis and viral hepatitis) and autoimmune overlap syndromes, as well as infiltrative and infectious disorders.

Liver biopsy may help guide management of specific causes of chronic liver disease and cirrhosis. In patients with cirrhosis and hepatic lesions, liver biopsy may be necessary in some cases in order to differentiate benign lesions from primary liver cancer and metastatic liver disease.

Liver biopsy is associated with risk of bleeding, perforation, and pneumothorax, among other complications.[63]

## Severity scoring

The two most commonly used scoring systems to determine disease severity are the Child-Pugh-Turcotte (CPT) and, more recently, the Model of End-Stage Liver Disease (MELD). Other scoring systems continue to be evaluated.[64] [65] [66] [67]

Child-Pugh-Turcotte (CPT)

Based on the presence of ascites and hepatic encephalopathy, serum bilirubin, albumin, and clotting (prothrombin time and international normalised ratio [INR]) and is divided into Child A, B, and C with increasing disease severity.

| Parameter | Points assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Hepatic encephalopathy | None | Grade 1-2 | Grade 3-4 |
| Bilirubin micromol/L (mg/dL) | <34.2 (<2) | 34.2-51.3 (2-3) | >51.3 (>3) |
| Albumin g/L (g/dL) | >35 (>3.5) | 28-35 (2.8-3.5) | <28 (<2.8) |
| Prothrombin time<br>Seconds over control<br>INR | <br><4<br><1.7 | <br>4-6<br>1.7-2.3 | <br>>6<br>>2.3 |
| CPT classification:<br>Child A: score 5-6 (well compensated);<br>Child B: score 7-9 (significant functional compromise);<br>Child C: score 10-15 (decompensated) | | | |

*Child-Pugh-Turcotte scoring system*

*From the collection of Dr Keith Lindor; used with permission*

Model of End-Stage Liver Disease (MELD)

Electronically calculated from the serum bilirubin, sodium, creatinine, and clotting (INR and prothrombin time) by a specific computer programme.[67] [68] This is the classification system used for the allocation of livers for transplantation in the US.

## Non-invasive tests

Serological and indirect markers of fibrosis have a good negative predictive value for cirrhosis, and are often used in community settings to risk-stratify patients with risk factors for liver disease. The American Association for the Study of Liver Diseases (AASLD) suggests a combination of imaging-based and blood-based techniques to detect significant fibrosis and advanced fibrosis, particularly in those undergoing initial fibrosis staining.[69]

Imaging-based techniques to detect fibrosis

Imaging-based tests may be preferentially incorporated into the initial fibrosis staging process owing to their higher accuracy over blood-based techniques. These tests are recommended for the identification of significant fibrosis, advanced fibrosis, and cirrhosis in adults with chronic hepatitis B and hepatitis C infections and in those with MASLD.[69] Imaging-based non-invasive testing may also be used in



adults with alcohol-related liver disease or chronic cholestatic liver disease to detect advanced fibrosis or cirrhosis.

Either transient elastography or magnetic resonance elastography is recommended by the AASLD to stage fibrosis in adults with chronic liver disease.[69] The AASLD advises against using imaging-based tests as a standalone test to assess regression or progression of liver fibrosis.[69]

Transient elastography is an ultrasound-based technique for detecting hepatic fibrosis and cirrhosis without the need for liver biopsy.

As with non-invasive blood tests for fibrosis evaluation, transient elastography has best diagnostic performance in excluding liver cirrhosis. The accuracy falls in intermediate stages of fibrosis. The Society of Radiologists in Ultrasound recommends a low cut-off value to exclude significant fibrosis, and a high cut-off value to indicate compensated advanced chronic liver disease.[70] Meta-analyses and prospective studies of transient elastography report excellent diagnostic accuracy for the diagnosis of cirrhosis (independent of the underlying disease) and the identification of fibrosis in patients with recurrent hepatitis C infection after liver transplantation.[71] [72] [73] [74] [75] [76] [77] [78] [79]

As with transient elastography, acoustic radiation force impulse (ARFI) imaging employs ultrasound to perform elastography.

Magnetic resonance elastography is effective in measuring fibrosis, but its application is limited by cost, and it may not be possible if older metal prostheses are present in the patient. Staging of fibrosis may be possible using gadoxetic acid-enhanced MRI.[80]

FibroScan® is a non-invasive modality that helps quantify and stage hepatic steatosis and fibrosis (especially advanced fibrosis and cirrhosis) by measuring the degree of liver stiffness using vibration-controlled transient elastography.[81] [82] It can distinguish normal liver or minimal fibrosis from cirrhotic livers.[82] FibroScan® can also be considered for the assessment of fibrosis or cirrhosis outside secondary and specialist care as it has a potential to detect liver disease earlier. It should be used in accordance with the national guidelines. The test should be recommended if it benefits people who lack adequate healthcare access (such as disabled people, people living in rural areas, or people from lower socio-economic backgrounds) and should be performed by trained operators.[82]

Blood-based techniques to detect fibrosis

Several fibrosis markers have been assessed. Some of these use combinations of routinely collected blood tests (e.g., NAFLD fibrosis score, fibrosis-4 [FIB-4], Enhanced Liver Fibrosis [ELF] test, AST to platelet ratio index [APRI], AST/ALT ratio). Others use specific molecular markers of fibrogenesis (e.g., enhanced liver fibrosis). The utility of these markers is predominantly for excluding severe fibrosis, with normal values being reassuring. They do not perform well at differentiating intermediate stages of fibrosis. The AASLD recommends initial testing with APRI or FIB-4 markers to detect significant fibrosis, advanced fibrosis, or cirrhosis in adults with chronic hepatitis B and hepatitis C infections undergoing fibrosis staging prior to antiviral therapy.[83] The European Association for the Study of the Liver recommends that among non-invasive methods, the use of transient elastography has been mostly studied and seems to offer a higher diagnostic accuracy for the detection of cirrhosis in patients with chronic hepatitis B.[84]

## Portal pressure assessment

Clinically significant portal hypertension is defined by a portal pressure gradient of ≥10 mmHg, which is also a predictor of clinical decompensation.[2] The gold standard method to assess portal pressure

in patients with cirrhosis is hepatic venous pressure gradient.[2] Calculating hepatic venous pressure gradient is an invasive procedure and, as a result, it is not routinely used in all patients with liver cirrhosis and portal hypertension. In some patients with obesity or metabolic dysfunction-associated steatohepatitis (previously known as non-alcoholic steatohepatitis), hepatic venous pressure gradient may underestimate portal pressure.

Non-invasive assessment of clinically significant portal hypertension may be performed using a combination of LSM and platelet count.[2] [85] An LSM of ≥20 kPa suggests clinically significant portal hypertension.[86] Clinically significant portal hypertension is present in all patients with varices.

# History and exam

## Key diagnostic factors

### presence of risk factors (common)

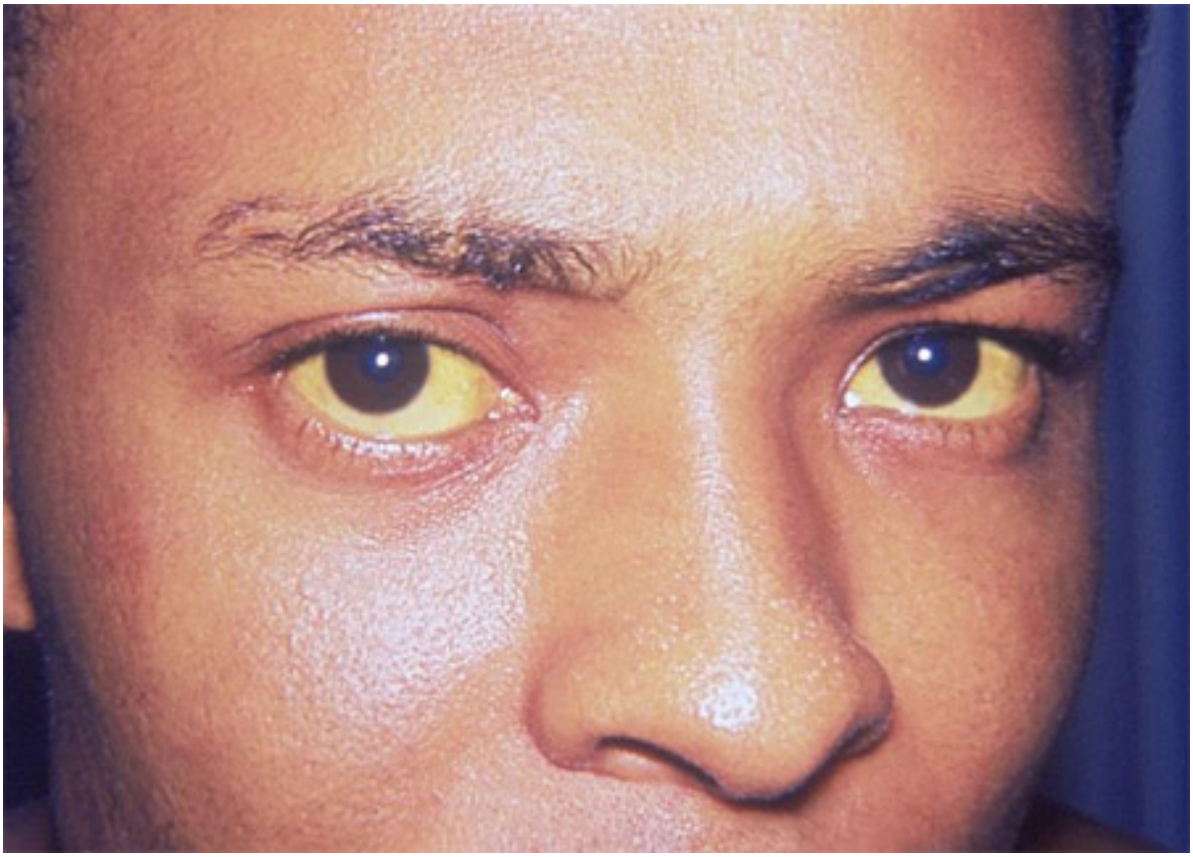
- Risk factors include alcohol misuse, intravenous drug use, unprotected intercourse, obesity, and blood transfusion.

### abdominal distension (common)

- Symptom of decompensated cirrhosis secondary to ascites in portal hypertension.

### jaundice and pruritus (common)

- Suggestive of decompensated cirrhosis secondary to reduced hepatic excretion of conjugated bilirubin into the biliary tree. Pruritus is secondary to impaired bile secretion.



*Icterus or jaundice*

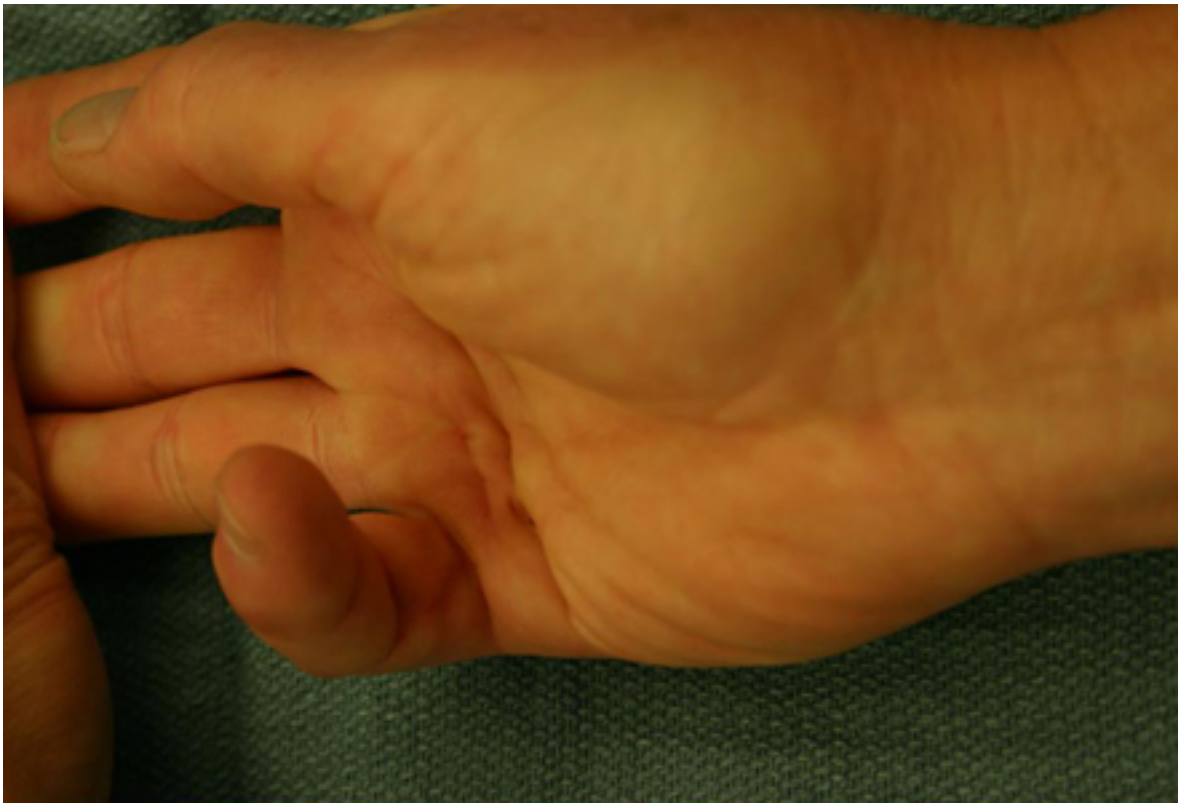
*CDC. Dr Thomas F. Sellers/Emory University; used with permission*

### blood in vomit (haematemesis) and black stool (melaena) (common)

- Symptoms of decompensated cirrhosis secondary to gastrointestinal haemorrhage from gastro-oesophageal varices in portal hypertension.

### hand and nail features (e.g., leukonychia, palmar erythema, spider naevi) (common)

- Characteristic physical findings in the hands and nails in chronic liver disease include: leukonychia (white nails) secondary to hypoalbuminaemia, polished nails secondary to excessive scratching in pruritus, palmar erythema (redness of thenar and hypothenar eminences), spider naevi (blanch on pressure and spider-like branches fill from a central arteriole), bruising, finger clubbing, and cholesterol deposits in palmar creases in primary biliary cholangitis, and Dupuytren contracture in alcohol-related liver disease.[40]



*Preoperative view of a small finger flexion contracture*

*From the collection of Dr C.M. Rodner; used with permission*

### facial features (e.g., telangiectasia, spider naevi, jaundiced sclera) (common)

- Characteristic physical findings in the face in chronic liver disease include: telangiectasia (red focal lesions resulting from irreversible dilatation of small blood vessels in the skin), spider naevi (blanch on pressure and spider-like branches fill from a central arteriole), bruising, rhinophyma, parotid gland swelling, paper-money appearance of the skin (randomly distributed thready blood vessels), and red tongue in alcohol-related liver disease; seborrhoeic dermatitis, jaundiced sclera, and xanthelasma (yellow plaques on eyelids secondary to lipid deposition) in primary biliary cholangitis.

### abdominal features (e.g., collateral circulation, hepatosplenomegaly, distension) (common)

- Characteristic physical findings in the abdomen in chronic liver disease include: collateral circulation of the abdominal wall around the umbilicus (caput medusa), bruising, hepatomegaly, splenomegaly, abdominal distension (particularly in the flanks) with shifting dullness and fluid thrill secondary to ascites, hepatic bruit (may be present with a vascular hepatoma), and loss of secondary sexual hair and testicular atrophy in men.

### altered mental status (uncommon)

- Symptom of decompensated cirrhosis secondary to portosystemic encephalitis.

## Other diagnostic factors

### constitutional symptoms (common)

- Patients with cirrhosis may be asymptomatic or have non-specific constitutional symptoms such as fatigue, weakness, and weight loss.

### lower extremity swelling (common)

- Symptom of decompensated cirrhosis secondary to peripheral oedema due to hypoalbuminaemia.

### hepatic fetor (common)

- Sweet, putrid smell of the breath in decompensated cirrhosis secondary to portosystemic shunting.

### muscle wasting (common)

- Common physical finding in chronic liver disease secondary to malnutrition and a hypercatabolic state.

### peripheral oedema (common)

- Sign of decompensated cirrhosis secondary to salt retention and reduced hepatic synthetic function leading to hypoalbuminaemia.

### recurrent infections (uncommon)

- Can be present in patients with decompensated cirrhosis secondary to impaired cellular immunity.

### decreased libido (uncommon)

- Symptom of decompensated cirrhosis secondary to hormonal changes and testicular atrophy, most commonly seen in patients with alcohol-related liver disease and haemochromatosis.

### chest wall features (e.g., gynaecomastia) (uncommon)

- Characteristic physical findings in the chest in chronic liver disease include gynaecomastia (tender and firm enlarged breast bud) and loss of secondary sexual hair in men, and breast atrophy in women.

### dyspnoea (uncommon)

- Dyspnoea on exertion is an uncommon symptom associated with pulmonary complications of portal hypertension. In patients with hepatopulmonary syndrome, platypnoea and orthodeoxia are classically described; patients may also develop clubbing and cyanosis. Dyspnoea may occur with hepatic hydrothorax.

### chest pain (uncommon)

- May occur in portopulmonary hypertension.

### syncope (uncommon)

- May occur in portopulmonary hypertension.

# Risk factors

## Strong

### alcohol misuse

- Alcohol-related liver disease, secondary to excessive alcohol consumption, is one of the most common causes of cirrhosis in the developed world.[6] [14] [29]

### intravenous drug use

- People who inject drugs are at risk of contracting hepatitis B and C, both of which are known to cause cirrhosis.[30] [31]

### unprotected intercourse

- Intercourse without the use of barrier contraception puts people at risk of contracting hepatitis B and C, both of which are known to cause cirrhosis.[30] [31]

### obesity

- Metabolic dysfunction-associated steatotic liver disease, secondary to obesity and diabetes, is one of the most common causes of cirrhosis.[6] [12]

### country of birth

- Hepatitis B and C are endemic in certain global regions.[32]

## Weak

### blood transfusion

- Hepatitis B or C, both of which are known causes of cirrhosis, may be contracted from contaminated blood products, although this risk is extremely small due to the routine screening of blood donors and products for viral hepatitides.[30] [31] Blood transfusion before 1992, or clotting factor transfusion before 1987, are risk factors in the US.

### tattooing

- Tattooing is a risk factor when universal precautions are not adequately observed.[33] Patients should be counselled about this.

# Investigations

## 1st test to order

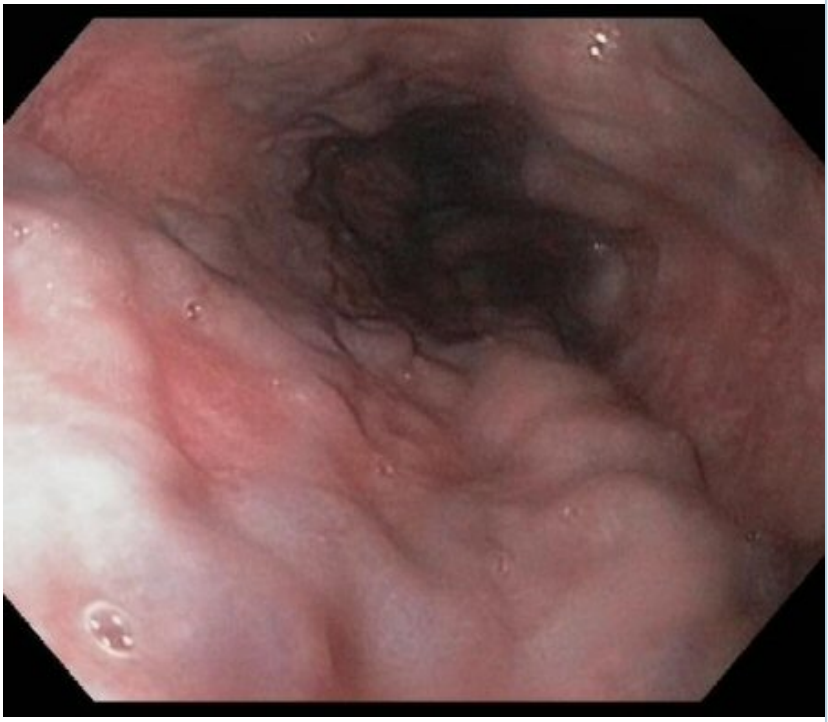
| Test | Result |
|---|---|
| **liver function tests**<br>• Aminotransferase (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) levels increase with hepatocellular damage. Normal AST and ALT levels do not preclude the diagnosis of cirrhosis.[41] Aminotransferase levels bear little to no relationship to frequency of complications or death.[42]<br>• ALT levels are greater than those of AST in most chronic liver diseases (except for alcohol-related liver disease), but this finding may be reversed with progression of liver disease. An AST/ALT ratio of ≥1 is thought to be a predictor of cirrhosis.[43]<br>• Alkaline phosphatase and gamma-glutamyl transferase (GGT) levels increase in cholestasis (resulting from primary biliary cholangitis and primary sclerosing cholangitis), with minimal derangement of AST and ALT.<br>• Total bilirubin may be normal in patients with compensated cirrhosis, but as the cirrhosis progresses, serum levels generally rise. | **usually deranged** |
| **gamma-glutamyl transferase (GGT)**<br>• Increase in this liver microsomal enzyme represents enzyme activation, which can be induced by alcohol and certain drugs and is also observed in metabolic dysfunction-associated steatotic liver disease (MASLD).<br>• Increased in cholestasis along with alkaline phosphatase (ALP).<br>• GGT is not significantly present in bone, such that concomitant elevated GGT and ALP indicate the liver as the source of the ALP. | **elevated** |
| **serum albumin**<br>• A decrease in serum albumin is a marker of hepatic synthetic dysfunction. | **reduced** |
| **serum sodium**<br>• Hyponatraemia is a common finding in patients with cirrhosis with associated ascites, and worsens as the liver disease progresses. | **reduced** |
| **serum potassium**<br>• Hyperkalaemia is frequently observed in patients with cirrhosis (12% to 14% of those hospitalised with cirrhosis).[44] It may indicate a poor prognosis, and can present a challenge to treat.[44] [45] | **may be elevated** |
| **prothrombin time**<br>• Prolongation of the prothrombin time is a marker of hepatic synthetic dysfunction. | **prolonged** |
| **platelet count**<br>• The presence of thrombocytopenia (platelet count <150,000/microlitre) is the most sensitive and specific laboratory finding for the diagnosis of cirrhosis in the setting of chronic liver disease and results from portal hypertension with hypersplenism and platelet sequestration.[48] | **reduced** |

| Test | Result |
| --- | --- |
| **antibodies to hepatitis C virus**<br>• Presence of immunoglobulin G (IgG) antibodies to hepatitis C virus (confirmed with hepatitis C virus-RNA) is indicative of chronic hepatitis C infection.[49] | **present if patient has chronic hepatitis C infection** |
| **hepatitis B surface antigen ± hepatitis B DNA assay**<br>• A detectable HBsAg or viraemia on a highly sensitive hepatitis B DNA assay indicates chronic hepatitis B infection.[49]<br>• Hepatitis B e-antigen/e-antibody, genotype, and viral load should be measured to assess disease phase and guide further treatment. | **HBsAg present or hepatitis B viraemia detected if patient has hepatitis B infection** |

## Other tests to consider

| Test | Result |
|---|---|
| **total iron, total iron binding capacity (TIBC), transferrin saturation, and serum ferritin**<br>• The initial screening tests for haemochromatosis are total iron and total iron binding capacity, in order to calculate the transferrin saturation (iron/TIBC), and serum ferritin.<br>• If the transferrin saturation is elevated (>45%), further testing with ferritin and possible genetic testing (C282Y and H63D mutation analysis) should be undertaken.<br>• If the transferrin saturation and ferritin are elevated, HFE genotyping is performed.[50] | **elevated transferrin saturation and elevated ferritin in haemochromatosis** |
| **antinuclear antibody**<br>• Tests for autoimmune hepatitis | **present in autoimmune hepatitis** |
| **antismooth muscle antibody** | **present in autoimmune hepatitis** |
| **liver kidney microsomal antibody**<br>• Liver kidney microsomal antigen antibodies (anti-LSM) are autoantibodies that target the CYP2D6 enzyme which is primarily found in the liver cells. Development of anti-LSM antibodies is associated with autoimmune hepatitis. | **present in autoimmune hepatitis** |
| **antimitochondrial antibody**<br>• Specifically the M2 antibody. | **present in primary biliary cholangitis** |
| **serum immunoglobulins**<br>• IgA, IgG, and IgM levels should be evaluated. | **frequently elevated in patients with cirrhosis** |
| **serum ceruloplasmin** | **low in Wilson's disease** |
| **plasma alpha-1 antitrypsin**<br>• Approximately 15% of adults with alpha-1 antitrypsin deficiency develop cirrhosis.[52]<br>• Plasma alpha-1 antitrypsin levels are used as a screening test.<br>• Alpha-1 antitrypsin is an acute phase protein and may be elevated in inflammation.<br>• Further testing can be done to confirm the diagnosis with protein electrophoresis and phenotyping. | **reduced in alpha-1 antitrypsin deficiency** |
| **alpha-fetoprotein**<br>• The finding of elevated alpha-fetoprotein in a patient with cirrhosis should raise concern for the development of hepatocellular carcinoma.[53] However, this tumour marker may also be elevated on the basis of chronic liver disease and inflammation in the absence of hepatocellular carcinoma; therefore, cross-sectional imaging is indicated to exclude the presence of hepatic lesions. | **normal or raised** |

| Test | Result |
| --- | --- |
| **abdominal ultrasound**<br>• Signs of advanced cirrhosis may be detected using abdominal ultrasound.<br>• Signs of portal hypertension: ascites, splenomegaly, increased diameter of the portal vein (≥13 mm), or collateral vessels.<br>• In combination with a strong clinical suspicion, the above findings suffice for the diagnosis of cirrhosis without the need for a confirmatory liver biopsy.<br>• A normal abdominal ultrasound does not exclude significant liver disease. | **liver surface nodularity, small liver, possible hypertrophy of left/ caudate lobe, ascites, splenomegaly, increased diameter of the portal vein (≥13 mm), or collateral vessels** |
| **abdominal CT**<br>• Signs of advanced cirrhosis may be detected using abdominal cross-sectional imaging.<br>• Signs of portal hypertension: ascites, splenomegaly, collateral circulation.<br>• In combination with a strong clinical suspicion, the above findings suffice for the diagnosis of cirrhosis without the need of a confirmatory liver biopsy. | **liver surface nodularity, small liver, possible hypertrophy of left/ caudate lobe, evidence of ascites, or collateral circulation** |
| **abdominal MRI**<br>• Signs of advanced cirrhosis may be detected using MRI of the liver.<br>• Signs of portal hypertension: ascites, splenomegaly, collateral circulation.<br>• In combination with a strong clinical suspicion, the above findings suffice for the diagnosis of cirrhosis without the need of a confirmatory liver biopsy. | **liver surface nodularity, small liver, possible hypertrophy of left/ caudate lobe, evidence of ascites, or collateral circulation** |
| **upper gastrointestinal endoscopy**<br>• Identifies the presence of gastro-oesophageal varices or portal hypertensive gastropathy secondary to portal hypertension in patients with chronic liver disease, thus aiding the diagnosis of cirrhosis.<br>• The Baveno VII criteria have been validated in several patient cohorts (with compensated advanced chronic liver disease) and suggest that screening endoscopy could be reserved for specific patients, based on liver stiffness measurement (LSM) and platelet count assessment.[54] In particular, patients with compensated cirrhosis, who have a liver stiffness <20 kPa (as measured by transient elastography) and platelet count >150 × $10^9$ cells/L, have a very low risk of having varices requiring treatment and can avoid screening endoscopy.[54] In practice, however, many centres still offer baseline endoscopy to all patients with liver cirrhosis.<br>• In compensated patients with no or small varices at screening endoscopy, expanded Baveno VI criteria recommend screening for gastro-oesophageal varices at 1- to 3-year intervals thereafter.[87]<br>• Baveno VII consensus guidelines conclude that patients who avoid screening endoscopy can be followed up by yearly repetition of transient elastography and platelet count. If LSM increases (≥20 | **gastro-oesophageal varices, portal hypertensive gastropathy** |

| Test | Result |
| --- | --- |
| kPa) or platelet count declines (≤150 × $10^9$/L), these patients should undergo screening endoscopy.[54]<br>•  <br>*Oesophageal varices in a patient with portal hypertension*<br>*From the collection of Douglas G. Adler, MD* | |
| **liver biopsy**<br>• Liver biopsy remains the most specific and sensitive test for the diagnosis of cirrhosis. However, it is not necessary in patients with advanced liver disease and typical clinical, laboratory, and/or radiological findings of cirrhosis unless there is a need to determine the degree of inflammation.<br>• In addition to confirming the diagnosis, liver biopsy may help to determine the aetiology of the underlying liver disease, although this is not always possible as characteristic features of the primary insult (e.g., metabolic dysfunction-associated steatotic liver disease or autoimmune hepatitis) may no longer be detectable by the time the procedure is carried out.<br>• Liver biopsy is associated with risk of bleeding, perforation, and pneumothorax, among other complications.[63] | **architectural distortion of the liver parenchyma with formation of regenerative nodules** |
| **imaging-based non-invasive tests**<br>• The American Association for the Study of Liver Diseases (AASLD) suggests a combination of imaging-based and blood-based techniques to detect significant fibrosis and advanced fibrosis, particularly in those undergoing initial fibrosis staining.[69] Imaging-based tests may be preferentially incorporated into the initial fibrosis staging process owing to their higher accuracy over blood-based techniques. These tests are recommended for the identification of significant fibrosis, advanced fibrosis, and cirrhosis in adults with chronic hepatitis B and hepatitis C infections and in those with metabolic dysfunction-associated steatotic liver disease (MASLD).[69] Imaging-based non-invasive testing may also be used in adults with alcohol-related liver disease or chronic | **staging of fibrosis** |

| Test | Result |
| --- | --- |
| cholestatic liver disease to detect advanced fibrosis or cirrhosis. Either transient elastography or magnetic resonance elastography is recommended by the AASLD to stage fibrosis in adults with chronic liver disease.[69] The AASLD advises against using imaging-based tests as a standalone test to assess regression or progression of liver fibrosis.[69] Ultrasound-based transient elastography is a useful tool for detecting hepatic fibrosis and cirrhosis without the need for liver biopsy. The Society of Radiologists in Ultrasound recommends a low cut-off value to exclude significant fibrosis, and a high cut-off value to indicate compensated advanced chronic liver disease.[70] Meta-analyses and prospective studies of transient elastography report excellent diagnostic accuracy for the diagnosis of cirrhosis (independent of the underlying disease) and the identification of fibrosis in patients with recurrent hepatitis C infection after liver transplantation.[71] [72] [73] [74] [75] [76] [77] [78] [79]<br>• As with transient elastography, acoustic radiation force impulse (ARFI) imaging employs ultrasound to perform elastography. Magnetic resonance elastography is effective in measuring fibrosis, but its application is limited by cost, and it may not be possible if older metal prostheses are present in the patient. Staging of fibrosis may be possible using gadoxetic acid-enhanced MRI.[80] FibroScan® is a non-invasive modality that helps quantify and stage hepatic steatosis and fibrosis (especially advanced fibrosis and cirrhosis) by measuring the degree of liver stiffness using vibration-controlled transient elastography.[81] [82] It can distinguish normal liver or minimal fibrosis from cirrhotic livers.[82] FibroScan® can be used as an option for the assessment of fibrosis or cirrhosis outside secondary and specialist care as it has a potential to detect liver disease earlier. It can be used in accordance with the national guidelines. The test should be recommended if it benefits people who lack adequate healthcare access (such as disabled people, people living in rural areas, or people from lower socio-economic backgrounds) and should be performed by trained operators.[82] | |
| **blood-based non-invasive tests**<br>• The American Association for the Study of Liver Diseases (AASLD) suggests a combination of imaging-based and blood-based techniques to detect significant fibrosis and advanced fibrosis, particularly in those undergoing initial fibrosis staining.[69] Several fibrosis markers have been assessed. Some of these use combinations of routinely collected blood tests (e.g., non-alcoholic fatty liver disease [NAFLD] fibrosis score, fibrosis-4 [FIB-4], AST to platelet ratio index [APRI], AST/ALT ratio). Others use specific molecular markers of fibrogenesis (e.g., enhanced liver fibrosis [ELF]). The utility of these markers is predominantly for excluding severe fibrosis, with normal values being reassuring. They do not perform well at differentiating intermediate stages of fibrosis. The AASLD recommends initial testing with APRI or FIB-4 markers to detect significant fibrosis, advanced fibrosis, or cirrhosis in adults with chronic hepatitis B and hepatitis C infections undergoing fibrosis staging prior to antiviral therapy.[83] The European Association for the Study of the Liver recommends that among non-invasive methods, the use of transient elastography has been mostly studied and seems to offer a higher diagnostic accuracy for the detection of cirrhosis in patients with chronic hepatitis B.[84] | **staging of fibrosis** |



| Test | Result |
| --- | --- |
| **portal pressure assessment**<br>• The gold standard method to assess portal pressure in patients with cirrhosis is hepatic venous pressure gradient.[2] Calculating hepatic venous pressure gradient is an invasive procedure and, as a result, it is not routinely used in all patients with liver cirrhosis and portal hypertension.<br>• Non-invasive assessment of clinically significant portal hypertension may be performed using a combination of liver stiffness measurement (LSM) and platelet count.[2] [85] An LSM of ≥20 kPa suggests clinically significant portal hypertension.[86] Clinically significant portal hypertension is present in all patients with varices. | **LSM of ≥20 kPa suggests clinically significant portal hypertension** |

# Differentials

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| **Budd-Chiari syndrome** | • Abdominal pain, diarrhoea, and progressively worsening ascites. | • Doppler ultrasound and abdominal CT: absence of hepatic vein filling.<br>• Abdominal CT: rapid contrast clearing of caudate lobe. |
| **Portal vein thrombosis** | • Signs and symptoms of the underlying cause such as acute pancreatitis (severe upper abdominal pain radiating through to the back, vomiting, absent bowel sounds, pyrexia, hypovolaemic shock, skin discoloration periumbilically [Cullen's sign] and in the flanks [Grey Turner's sign]), ascending cholangitis (pyrexia, malaise, rigors, right upper quadrant pain, jaundice, dark urine, and pale stools), or abdominal sepsis (pyrexia, abdominal pain, signs of peritonism). | • Magnetic resonance (indirect) or direct angiography: normal hepatic venous pressure gradient (measure of portal pressure).<br>• Doppler ultrasound and abdominal CT: portal vein filling defect, absence of flow in the portal vein. |
| **Splenic vein thrombosis** | • Signs and symptoms of pancreatitis: severe upper abdominal pain radiating through to the back, vomiting, absent bowel sounds, pyrexia, hypovolaemic shock, and skin discoloration periumbilically (Cullen's sign) and in the flanks (Grey Turner's sign) in acute pancreatitis; non-specific abdominal pain exacerbated by eating, diarrhoea, steatorrhoea, weight loss, and mild pyrexia in chronic pancreatitis. | • Abdominal ultrasound and CT: evidence of splenic vein thrombosis.<br>• Magnetic resonance (indirect) or direct angiography: normal hepatic venous pressure gradient (measure of portal pressure). |
| **Nodular regenerative hyperplasia** | • No differentiating signs and symptoms. | • Liver biopsy: small regenerative nodules with minimal or no fibrosis on reticulin staining. |
| **Idiopathic portal hypertension (hepatoportal sclerosis)** | • No differentiating signs and symptoms. | • Liver biopsy: no evidence of cirrhosis. |

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| **Constrictive pericarditis** | • Raised jugular venous pressure, tachycardia, and atrial fibrillation.<br>• Heart sounds: quiet, third heart sound (ventricular knock) present. | • ECG: tachycardia, atrial fibrillation, low-voltage QRS complexes, T-wave abnormalities.<br>• Doppler ultrasound: ventricular filling abnormalities. |
| **Inferior vena cava (IVC) obstruction** | • Signs and symptoms of renal cell carcinoma: classic triad of haematuria, flank pain, and flank/abdominal mass with weight loss and hypertension. | • Abdominal ultrasound and CT: evidence of IVC obstruction. |
| **Schistosomiasis** | • History of travel to endemic areas.<br>• Constitutional symptoms of febrile illness: malaise, rigors, sweating, weight loss, anorexia, vomiting, diarrhoea, headache, muscular aches and weakness, and abdominal pain.<br>• Signs of febrile illness: urticarial rash, pyrexia, and lymphadenopathy. | • Magnetic resonance (indirect) or direct angiography: normal hepatic venous pressure gradient (measure of portal pressure). |
| **Sarcoidosis** | • Lung involvement: dry cough and dyspnoea.<br>• Skin involvement: altered pigmentation (hypo- or hyperpigmented); maculopapular skin lesions on face, back, and extremities; and erythema nodosum on legs.<br>• Eye involvement: anterior or posterior uveitis, dry eyes (sicca), and glaucoma. | • Chest x-ray findings are dependent on the stage of disease progression: hilar lymphadenopathy, diffuse reticulonodular shadowing (parenchymal disease), and upper lobe fibrosis.<br>• Liver biopsy: non-necrotising/caseating granulomas. |
| **Vitamin A intoxication, arsenic, and vinyl chloride toxicity** | • No differentiating signs and symptoms. | • History generally reveals exposure. |



# Criteria

## Child-Pugh-Turcotte (CPT)[64] [65]

One of the most commonly used scoring systems to determine disease severity in cirrhosis.[64] [65] The CPT score is based on the presence of ascites and hepatic encephalopathy, serum bilirubin, albumin, and clotting (prothrombin time and international normalised ratio [INR]) and is divided into Child A, B, and C with increasing disease severity.

| Parameter | Points assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Hepatic encephalopathy | None | Grade 1-2 | Grade 3-4 |
| Bilirubin micromol/L (mg/dL) | <34.2 (<2) | 34.2-51.3 (2-3) | >51.3 (>3) |
| Albumin g/L (g/dL) | >35 (>3.5) | 28-35 (2.8-3.5) | <28 (<2.8) |
| Prothrombin time<br>Seconds over control<br>INR | <br><4<br><1.7 | <br>4-6<br>1.7-2.3 | <br>>6<br>>2.3 |
| CPT classification:<br>Child A: score 5-6 (well compensated);<br>Child B: score 7-9 (significant functional compromise);<br>Child C: score 10-15 (decompensated) | | | |

*Child-Pugh-Turcotte scoring system*
*From the collection of Dr Keith Lindor; used with permission*

## Model of End-Stage Liver Disease (MELD)[68]

A more recent scoring system for the determination of severity in cirrhosis, the MELD score is electronically calculated from the serum bilirubin, sodium, creatinine, and clotting (INR and prothrombin time) by a specific computer programme.[67] [68] This is the classification system used for the allocation of livers for transplantation in the US.

## Hepatorenal syndrome-acute kidney injury (HRS-AKI)

Acute kidney injury (AKI) is an absolute increase in serum creatinine of ≥26.4 micromoles/L (≥0.3 mg/dL) in less than 48 hours, or a percentage increase in serum creatinine of at least 1.5-fold from baseline in less than 7 days, or a reduction in urine output of 0.5 mL/kg/h for more than 6 hours.[88] [89] [90] AKI has three stages, as defined by the International Club of Ascites (ICA-AKI criteria):[91]

- Stage 1: an increase in serum creatinine ≥26.4 micromoles/L (≥0.3 mg/dL) or an increase in serum creatinine ≥1.5-fold to twofold from baseline at diagnosis of AKI
- Stage 2: an increase in serum creatinine greater than twofold to threefold from baseline
- Stage 3: an increase of serum creatinine greater than threefold from baseline or serum creatinine ≥352 micromoles/L (≥4.0 mg/dL) with an acute increase ≥26.4 micromoles/L (≥0.3 mg/dL) or initiation of renal replacement therapy.

European Association for the Study of the Liver (EASL) guidelines recommend using an adapted staging system for AKI that splits AKI stage 1 into stage 1A and 1B according to a serum creatinine value of <133 micromoles/L (<1.5 mg/dL) or ≥133 micromoles/L (≥1.5 mg/dL), respectively.[88]

International Club of Ascites (ICA) diagnostic criteria for HRS-AKI:[89]

- Cirrhosis with ascites
- Diagnosis of AKI according to ICA-AKI criteria
    - Increase in serum creatinine ≥26.4 micromoles/L (≥0.3 mg/dL) within 48 hours, or

- A percentage increase serum creatinine ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days.

- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin
- Absence of shock
- No current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, or iodinated contrast media)
- No macroscopic signs of structural kidney injury. Structural kidney injury is indicated by proteinuria (>500 mg/day), micro-haematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography.

## Screening

Screening for cirrhosis is recommended for patients with established chronic liver disease with abnormal liver enzymes, hepatic steatosis on imaging, or viral hepatitis, but not for the general population.[3]

# Approach

The mainstay of therapy for liver cirrhosis remains the treatment of the underlying chronic liver disease, when possible, and prevention of superimposed hepatic insult, which could result in acute-on-chronic liver failure (ACLF). Early detection, control, and treatment of complications is essential; patients who develop complications should be referred for liver transplant evaluation.

Patients should be advised of the necessity for adequate nutrition, regular exercise, and the avoidance of hepatotoxins.[92]

## Treatment of underlying chronic liver disease and prevention of superimposed hepatic insult

As cirrhosis is the pathological end-stage of any chronic liver disease, it is essential to treat the underlying causative condition in order to slow or halt the progression of cirrhosis. Oral direct-acting antivirals are considered a first-line treatment for chronic hepatitis C virus infection. One systematic review and meta-analysis found that early treatment with direct-acting antivirals reduced the recurrence of hepatocellular carcinoma, liver decompensation, and all-cause mortality, and prevented hepatocellular carcinoma in patients with compensated cirrhosis and without cirrhosis but did not prevent liver transplantation.[93] Regimens depend on the genotype and presence or absence of cirrhosis.[94] Local guidance should be consulted. See Hepatitis C .

Antivirals may be indicated for patients with chronic hepatitis B.[84] [95] See Hepatitis B .

Superimposed hepatic insult may be prevented through the avoidance of alcohol and other hepatotoxic drugs (e.g., non-steroidal anti-inflammatory drugs [NSAIDs] and high doses of paracetamol [>2-3 g/day]), immunisation against hepatitis A and B for susceptible patients, management of metabolic risk factors, maintenance of adequate nutrition, and regular exercise.

## Monitoring for complications

Cirrhosis is associated with serious complications including portal hypertension causing ascites (further complicated by spontaneous bacterial peritonitis and hepatic hydrothorax), gastro-oesophageal varices and portosystemic encephalopathy, acute kidney injury and hepatopulmonary syndromes, portopulmonary hypertension, ACLF, and hepatocellular carcinoma.

Prompt detection and treatment of these complications is essential in order to minimise related morbidity and mortality. Imaging tests include:

- Abdominal ultrasound for the detection of ascites and surveillance for hepatocellular carcinoma
- Upper gastrointestinal endoscopy for the detection of gastro-oesophageal varices
- Abdominal ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) for the detection of hepatocellular carcinoma.

Other specialised tests may be required depending on individual symptoms.

## Ascites

The most common complication of cirrhosis.

Every patient with new-onset ascites should undergo a diagnostic paracentesis: cell count with differential, albumin, and total protein should be measured in the ascitic fluid. Ascitic fluid should also be sent for culture and cytology.

The serum-ascites albumin gradient (SAAG) should be calculated: a SAAG of ≥11 g/L with low ascitic fluid total protein is consistent with portal hypertension secondary to cirrhosis.

Ascites develops in part due to activation of the renin-angiotensin-aldosterone system, resulting in sodium retention. Evidence suggests that severe dietary sodium restriction may be more harmful than beneficial, and many clinicians advise a no-added-salt diet rather than a low-salt diet.[101] This means excluding additional table salt being added to foods and avoidance of foods with high salt content, such as crisps and some processed meals. This results in a moderate sodium restriction with daily intake of not more than 5 to 6.5 g.

First-line choice of diuretic should be spironolactone due to its effects on aldosterone and maintaining normal serum potassium.[101] Furosemide may be added in patients who do not respond. Renal function and electrolytes should be monitored carefully when initiating diuretics and after dose escalation.

NSAIDs, ACE inhibitors, and other nephrotoxins should be avoided in patients with ascites.[90]

Large volume refractory ascites

Some patients may develop large volume ascites refractory to medical treatment because of lack of efficacy, or unacceptable adverse effects or complications. These patients may require recurrent large-volume paracentesis (LVP) with albumin replacement for symptom control.[102]

Patients not suitable for liver transplantation should be considered for transjugular intrahepatic portosystemic shunt (TIPS) placement.[103] Meta-analyses indicate that TIPS is more effective than paracentesis for control of refractory ascites, but is associated with a higher incidence of hepatic encephalopathy.[103] [104] [105] [106] [107] [108] [109] Overall mortality does not appear to differ between the two interventions, but TIPS may confer a modest benefit with respect to transplant-free survival.[103] [104] [105] [106] [107] [108] [109] TIPS placement can improve the nutritional status of patients with cirrhosis, indicated by an increase in ascites-free weight, body mass index, and muscle mass.[110] One individual patient data meta-analysis found that TIPS treatment decreased the overall risk of a further decompensation and improved survival compared with standard of care.[111] One Cochrane systematic review and network meta-analysis reported that the overall certainty (quality) of evidence was very low, primarily because of unclear or high risk of bias in trials assessing interventions for the treatment of refractory ascites in patients with cirrhosis.[103] Disease severity at the time of TIPS placement is an important predictive factor for outcomes.[112]

The prognosis of patients with refractory ascites is poor. If TIPS/transplantation are not viable options, then long-term drain placement for intermittent small-volume paracentesis may be considered as a palliative measure.[113] Prospective randomised controlled trials are warranted.

The use of vaptans (vasopressin V2-receptor antagonists) may have a slight beneficial effect on ascites and hyponatraemia, but they do not reduce mortality, liver complications, or renal failure.[114] [115]

## Gastro-oesophageal varices

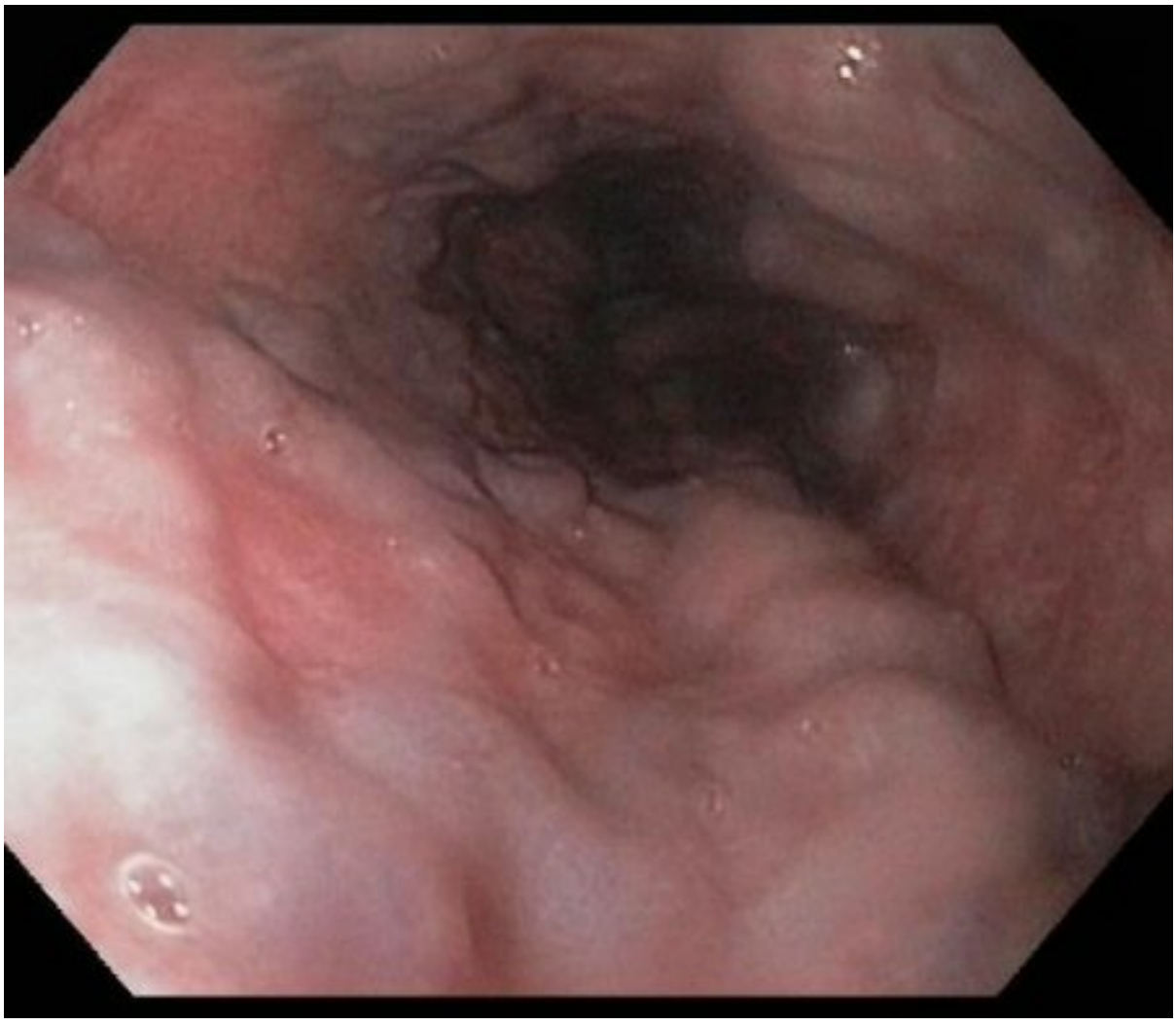
Varices are present in 50% of patients with cirrhosis. Variceal bleeding is a life-threatening complication of cirrhosis with an associated mortality of 20% at 6 weeks.[116] Patients with cirrhosis have historically

been offered upper gastrointestinal endoscopy for screening of gastro-oesophageal varices at the time of diagnosis, and at 1- to 3-year intervals thereafter.[56] However, guideline recommendations vary regarding screening intervals.

The Baveno VII criteria suggest that screening endoscopy could be reserved for a subgroup of patients, based on liver stiffness measurement (LSM) and platelet count assessment.[54] In particular, patients with compensated cirrhosis, who have a liver stiffness <20 kPa (as measured by transient elastography) and platelet count >150 × $10^9$ cells/L, have a very low risk of having varices requiring treatment and can avoid screening endoscopy.[54] In practice, however, many centres still offer baseline endoscopy to all patients with liver cirrhosis.

In compensated patients with no or small varices at screening endoscopy, expanded Baveno VI criteria recommend screening for gastro-oesophageal varices at 1- to 3-year intervals thereafter.[87]

Baveno VII consensus guidelines conclude that patients who avoid screening endoscopy can be followed up by yearly repetition of transient elastography and platelet count. If LSM increases (≥20 kPa) or platelet count declines (≤150 × $10^9$/L), these patients should undergo screening endoscopy.[54]



*Oesophageal varices in a patient with portal hypertension*

*From the collection of Douglas G. Adler, MD*



Primary prophylaxis of bleeding

Prophylaxis with either non-selective beta-blockers (propranolol, nadolol, or carvedilol) or endoscopic variceal ligation (EVL), which requires several sessions to obliterate varices, should be implemented if high-risk oesophageal varices are present, due to the increased risk of variceal bleeding.[57] High-risk varices include small varices with red signs, medium or large varices irrespective of Child-Pugh classification, or small varices in Child-Pugh C patients.[88]

Non-selective beta-blockers

Advantages of non-selective beta-blockers include low cost and ease of administration. Once a patient is on a non-selective beta-blocker, there is no need for repeat oesophagogastroduodenoscopy (OGD), and haemodynamic responders to non-selective beta-blockers have a lower incidence of decompensation and death. Disadvantages are that approximately 15% of patients may have absolute or relative contraindications to therapy, and another 15% require dose reduction or discontinuation attributed to common adverse effects (e.g., fatigue, weakness, and shortness of breath) that resolve upon discontinuation, but that may discourage patients and their physicians from using these drugs.

Monitoring haemodynamic response while treating a patient with beta-blockers is associated with a lower risk of variceal bleeding, but large cohort randomised controlled trials are required to confirm these findings.[117] There is ongoing debate regarding the safety of non-selective beta-blockers in patients with cirrhosis and refractory ascites. The expanded Baveno VI criteria proposed that in patients with refractory ascites and (i) systolic blood pressure <90 mmHg, or (ii) serum creatinine >133 micromoles/L (>1.5 mg/dL), or (iii) hyponatraemia <130 millimoles/L, the beta-blocker should be reduced in dose or even temporarily discontinued.[87] However, there is evidence to suggest that the risk of harm may not be significant.[118] [119] [120] [121]

Endoscopic variceal ligation (EVL)

EVL is a local therapy that involves placing elastic bands around oesophageal varices until they are obliterated. EVL can theoretically be performed in the same session as screening endoscopy with hardly any contraindications. Disadvantages of EVL include the risks associated with sedation, plus the risk of causing dysphagia, oesophageal ulceration, strictures, and bleeding. Adverse effects associated with EVL may be severe, with reports of deaths resulting from EVL-induced bleeding ulcers. EVL is unable to prevent complications other than variceal haemorrhage. Surveillance endoscopies are necessary after variceal eradication, at least annually, to detect variceal recurrence.[122] Child-Pugh class C, ascites, or low prothrombin index are all indicators for high risk of early bleeding following EVL.[123]

The choice of whether to use non-selective beta-blockers or EVL should be based on local resources and expertise, patient preference and characteristics, contraindications, and adverse events.[87] One meta-analysis that included 1023 patients compared prophylactic EVL with beta-blockers and found that there was no difference between the treatments with regard to gastrointestinal haemorrhage, all-cause mortality, or haemorrhage-related mortality. While there was a decrease in variceal haemorrhage with EVL compared with beta-blockers (relative risk [RR] 0.72, 95% CI 0.4 to 0.96), variceal haemorrhage was not significantly different between the two groups when only high-quality trials were considered (RR 0.84, 95% CI 0.60 to 1.17).[124] Subjective factors influence the physician's choice in selecting non-selective beta-blockers versus EVL, as illustrated in an interview-based study in which gastroenterologists who spent at least half their time performing endoscopy were more likely to choose EVL, whereas physicians who had a less procedural-based practice were more likely to choose non-selective beta-blockers.[125]

Transjugular intrahepatic portosystemic shunts (TIPS)

TIPS may be used as a secondary treatment option for oesophageal varices in cirrhosis but is not recommended for primary prophylaxis of variceal haemorrhage.[2] [126] Evidence obtained from trials of prophylactic surgical shunt therapy show a significantly higher rate of encephalopathy and a tendency for a higher mortality in patients randomised to shunt surgery.[127] [128]

Due to very low-certainty evidence, conclusions cannot be drawn about the benefits and harms of portosystemic shunts compared with endoscopic interventions for people with cirrhosis and previous hypertensive portal bleeding (i.e., secondary prophylaxis).

Gastric varices

Gastric varices are present in about 20% of patients with cirrhosis and can present either as isolated gastric varices or as gastro-oesophageal varices.[129] In the latter, the oesophageal varices extend below the cardia into the lesser curvature of the stomach (type 1 gastro-oesophageal varices [GOV 1]) or into the fundus (type 2 gastro-oesophageal varices [GOV 2]).[129] They have different physiology and clinical characteristics compared with oesophageal varices. Gastric varices bleed less frequently but more significantly than oesophageal varices. Bleeding is less directly related to the degree of portal hypertension and more related to the size of the varix and wall tension.[129] There is little literature regarding the management of gastric varices compared with oesophageal varices. Hence, most recommendations are based on expert opinion.[129] Currently, non-selective beta-blockers are suggested for primary prevention of variceal bleeding from GOV 2 or isolated gastric varices. Treatment for GOV 1 should follow the above guidance for oesophageal varices.

Acute variceal haemorrhage

An episode of acute variceal haemorrhage should be managed as a medical emergency with intravascular volume support, blood transfusion (with the aim of keeping the haemoglobin around 70-80 g/L [7-8 g/dL]), and a combination of endoscopic and pharmacological therapy.[130] [131]

Terlipressin (a vasopressin analogue), or somatostatin (or its analogue octreotide) should be initiated as soon as a variceal bleed is suspected and continued for 2-5 days if it is confirmed.[132]

Upper gastrointestinal endoscopy should be performed within 24 hours to confirm the diagnosis and allow treatment with EVL or sclerotherapy.[133]

Short-term (up to 7 days) antibiotic prophylaxis should be instituted in all patients following a gastrointestinal haemorrhage (regardless of the presence of ascites) as this has been shown to decrease the rate of bacterial infections and increase survival.[134] Ceftriaxone is the first choice in patients with decompensated cirrhosis, in those already on fluoroquinolone prophylaxis, and in hospital settings with high prevalence of fluoroquinolone-resistant bacterial infections. Oral fluoroquinolones should be used in the remaining patients.[135] [136]

Life-threatening bleeding may be controlled with a Sengstaken-Blakemore tube or a Danis stent until haemostasis can be achieved endoscopically, or with TIPS, with or without embolisation.[137]

## Malnutrition and sarcopenia

It is recommended that patients hospitalised with cirrhosis receive formal dietician assessment, and steps should be taken to minimise the fasting period prior to procedures (e.g., by giving them a pre-

bedtime snack or early-morning snack if the procedure will be in the late afternoon).[138] Parenteral supplementation may be required for those who cannot meet their nutritional intake needs orally. Recommended protein intake for adults with cirrhosis is 1.2 to 1.5 g/kg (ideal body weight) per day, and 1.2 to 2 g/kg (ideal body weight) per day if critically ill.

## Hepatocellular carcinoma

See Hepatocellular carcinoma (Management approach) .

## Spontaneous bacterial peritonitis

A peritoneal fluid absolute neutrophil count >250 cells/mm³ is the accepted criterion for the diagnosis for spontaneous bacterial peritonitis.[88]

Treatment is with intravenous antibiotics, such as cefotaxime or a fluoroquinolone, and intravenous human albumin solution. Albumin has been shown to reduce mortality in patients with cirrhosis with spontaneous bacterial peritonitis.[139] [140]

All patients who have survived an episode of spontaneous bacterial peritonitis require lifelong secondary antibiotic prophylaxis.

Patients with ascites and an ascitic fluid total protein level of ≤10 g/L are at high risk of developing spontaneous bacterial peritonitis, and should be considered for primary antibiotic prophylaxis.[88] [141] [142] There appears to be an increased risk of spontaneous bacterial peritonitis with the use of proton-pump inhibitors.[143] High-quality evidence for this intervention is lacking and further trials are needed to establish whether antibiotic prophylaxis for people with cirrhosis is beneficial.[144]

See Spontaneous bacterial peritonitis (Management approach) .

## Hepatic hydrothorax

Occurs in approximately 5% to 10% of patients with cirrhosis, usually in patients with ascites.[145] Hepatic hydrothorax may cause dyspnoea. Management is similar to that of ascites. In some patients, long-term indwelling pleural catheters are required for symptomatic management.[146] [147] Patients with hepatic hydrothorax should be evaluated for liver transplantation.[148]

## Portosystemic hepatic encephalopathy

Approximately 11% of patients with cirrhosis have hepatic encephalopathy at the time of cirrhosis diagnosis.[149] Around 30% to 40% of patients with cirrhosis have an episode of hepatic encephalopathy during their illness, and there is a 30% to 40% chance of recurrence in the following year.[150]

Hepatic encephalopathy is characterised by changes in consciousness, behaviour, and personality with disorientation, drowsiness, forgetfulness, confusion, agitation, and eventual coma. Slurred speech, asterixis (liver flap), increased muscle tone, and extensor plantar reflexes may be present.

Precipitating factors include gastrointestinal haemorrhage, constipation, diarrhoea and vomiting, hypoglycaemia, and electrolyte imbalance; drugs (diuretics, sedatives) and medical procedures (paracentesis, TIPS); infection, anaemia, hypoxia, and hypotension. Gut-derived toxins such as ammonia and bacterial products that induce systemic inflammation cause hepatic encephalopathy.[3] [18] There appears to be an increased risk of hepatic encephalopathy with the use of proton-pump inhibitors.[151] [152]

Treatment involves identification and correction of reversible precipitating factors and lactulose, used alone or in combination with antibiotics such as rifaximin.[153] [154] [155] [156] [157] [158] [Evidence B] Management of hepatic encephalopathy is not affected by ammonia levels.[3] [18] Dietary protein restriction is not recommended.[159]

See Hepatic encephalopathy (Management approach) .

## Hepatorenal syndrome-acute kidney injury (HRS-AKI)

In patients with cirrhosis, the causes of acute kidney injury can be hypovolaemia, acute tubular necrosis, or hepatorenal syndrome with either acute kidney injury or acute kidney disease. Investigations to determine the cause include a careful history, physical examination, blood biochemistry, microscopic examination and chemical analysis of urine, select urine biomarkers and renal ultrasound.[90]

HRS-AKI (formerly known as type-1 hepatorenal syndrome) can be diagnosed if patients meet the following criteria, as defined by the International Club of Ascites (ICA):[89]

- Cirrhosis with ascites
- Diagnosis of AKI according to ICA-AKI criteria (i.e., increase in serum creatinine ≥26.4 micromoles/L [≥0.3 mg/dL] within 48 hours; or a percentage increase in serum creatinine ≥50% from baseline which is known, or presumed, to have occurred within the previous 7 days); the American Gastroenterological Association (AGA) also include a reduction of urine output to below 0.5 mL/kg/h for >6 hours[90]
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, or iodinated contrast media)
- No macroscopic signs of structural kidney injury. Structural kidney injury is indicated by proteinuria (>500 mg/day), microhaematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography.

European Association for the Study of the Liver (EASL) guidelines recommend using an adapted staging system for AKI that splits AKI stage 1 into stage 1A and 1B according to a serum creatinine value of <133 micromoles/L (<1.5 mg/dL) or ≥133 micromoles/L (≥1.5 mg/dL), respectively.[88]

Measures can be taken to prevent HRS-AKI from developing in patients with cirrhosis, and include:[90]

- Advising patients to avoid alcohol
- Monitoring serum creatinine levels and electrolytes when diuretics are given and avoiding excessive diuretics
- Avoiding large-volume paracentesis without albumin replacement
- Giving prophylactic antibiotics when infection is strongly suspected (investigations should include diagnostic paracentesis to evaluate for spontaneous bacterial peritonitis)
- Avoiding use of non-selective beta-blockers and nephrotoxic drugs (e.g., ACE inhibitors, angiotensin-II receptor antagonists, and NSAIDs).

Once diagnosed, treatment of the precipitating cause should be initiated and any non-selective beta-blockers, diuretics, and NSAIDs held or stopped. Fluid losses should be replaced and fluid status monitored.[90] Vasoconstrictors and albumin are recommended in all patients and should be expeditiously used. Terlipressin plus albumin should be considered as the first-line therapeutic option.[132] Noradrenaline (norepinephrine) can be an alternative to terlipressin. However, there are

several limitations associated with its use. Midodrine plus octreotide can be an option when terlipressin or noradrenaline are unavailable, but its efficacy is much lower than that of terlipressin.[88] [160] In one phase 3 trial to confirm the efficacy and safety of terlipressin plus albumin in adults with HRS-AKI, terlipressin was more effective than placebo in improving renal function, but was associated with serious adverse events, including respiratory failure, and cases of sepsis or septic shock.[161]

For further information, see Hepatorenal syndrome (Management approach) .

## Hyponatraemia

Patients with cirrhosis commonly develop hyponatraemia, especially with progression of liver disease. Hyponatraemia is usually well tolerated.

Initial management consists of discontinuation of diuretic therapy once serum sodium <130 mEq/L. Fluid restriction is usually necessary for serum sodium levels <115-120 mEq/L.

In patients with severe hyponatraemia treatment with vaptans may increase serum sodium, but their use does not reduce mortality, liver complications or renal failure.[88] [114]

## Hyperkalaemia

Hyperkalaemia is frequently observed in patients with cirrhosis (12% to 14% of those hospitalised with cirrhosis).[44] It may indicate a poor prognosis and can present a challenge to treat.[44] [45] The standard treatment of an insulin-glucose protocol to reduce serum potassium may be ineffective in the setting of cirrhosis, and therefore adjunct treatments may be preferred.[162]

## Hepatopulmonary syndrome

Results from portal hypertension and occurs in at least 5% of patients awaiting liver transplantation.[163] Symptoms include dyspnoea and platypnoea. The diagnosis includes the finding of hypoxaemia with increased alveolar-arterial gradient, orthodeoxia, and the determination of intrapulmonary vascular dilation on contrast-enhanced echocardiography.

The presence of hepatopulmonary syndrome should prompt immediate evaluation for liver transplantation. The condition usually resolves following liver transplantation.[164]

## Portopulmonary hypertension

This complication is diagnosed when findings of unexplained pulmonary hypertension are present in association with portal hypertension. Unlike hepatopulmonary syndrome, this condition may not completely resolve following liver transplantation.

Patients with severe pulmonary hypertension that does not improve with the use of vasodilators such as epoprostenol, bosentan, iloprost, or sildenafil are not candidates for liver transplantation in view of the high risk of death associated with the procedure.

In one randomised controlled trial, macitentan, an endothelin-receptor antagonist, significantly reduced pulmonary vascular resistance in patients with portopulmonary hypertension compared with placebo.[165]

## Acute-on-chronic liver failure

ACLF is a severe form of acutely decompensated cirrhosis with organ failure and a high risk of short-term mortality.[166] It is a heterogeneous syndrome; affected patients have features of hepatic failure

(coagulopathy, elevated bilirubin) and may also have extrahepatic organ failure (kidney, lung, brain, or circulation). ACLF may be precipitated by alcohol use, viral hepatitis, drug-induced liver injury, surgery, ischaemia, or infection. It is a potentially reversible condition that may occur in people with chronic liver disease.

Treatment includes resuscitation, treatment of the precipitating factor, support of failing organs, and assessment for and early treatment of infection. Patients should be cared for in the intensive care unit. Some patients may benefit from early liver transplantation.[167]

Treatment of shock in ACLF can be challenging. Society of Critical Care Medicine guidelines recommend using albumin as a resuscitation fluid over other fluids, particularly when serum albumin is below 3 mg/dL.[168] Guidelines recommend aiming for a mean arterial pressure of 65 mmHg alongside invasive haemodynamic monitoring.[168] [169] In patients with ACLF and hypotension, human albumin or crystalloids should be used for initial fluid therapy.[166] If vasopressors are required, noradrenaline is more effective than dopamine in reversing hypotension. EASL recommends against the use of dopamine in patients with ACLF.[166] Low-dose vasopressin can be added to noradrenaline in patients with ACLF who remain hypotensive despite fluid resuscitation. The American Association for the Study of Liver Diseases (AASLD) and EASL recommend noradrenaline as the first-line agent and vasopressin as the second-line agent for managing patients with hypotension.[166] [169] The possible mortality benefit with the addition of vasopressin must be weighed against increased risk of digital ischaemia. As well as addressing the treatment of shock, guidelines also provide recommendations for managing endocrine, haematological, pulmonary, and renal features of ACLF in the intensive care unit setting.[168] [169]

## Liver transplantation

Patients who develop complications of cirrhosis such as hepatocellular carcinoma or signs of decompensation (ascites, jaundice, variceal haemorrhage, portal systemic encephalopathy, hepatopulmonary syndrome, or hepatorenal syndrome) should be referred for liver transplant evaluation without delay. Transplant assessment may be a prolonged process and early referral is preferable. Some patients with ACLF may benefit from early liver transplantation.[167]

Orthotopic liver transplantation remains the only curative treatment option for patients with decompensated cirrhosis.

Systems of liver allocation vary. In the US, liver allocation is based on the Model for End-Stage Liver Disease (MELD) score, which estimates the risk of 3-month mortality.[68] A survival benefit from undergoing liver transplantation is seen when the MELD score is ≥15. In children aged <12 years, a complementary version of MELD score called Paediatric End-Stage Liver Disease (PELD) score is used.[170]

There is, however, a shortage of organ donors. In 2021, 9236 liver transplants were performed in the US, with the current waiting list standing at 11,185 candidates.[171] As a result, a significant number of patients die while waiting for an organ donor.

Presence of sarcopenia or frailty can affect liver transplantation outcomes. In one study, sarcopenia was found to be associated with adverse outcomes after liver transplantation in patients with decompensated cirrhosis.[172] One systematic review of 34 studies concluded that patients with mild to moderate frailty or sarcopenia should be prioritised for liver transplantation due to increased mortality on the waiting list, but if the frailty or sarcopenia is severe, patients may be removed from the list as the prognosis is poor.[173]

### Palliative care

As cirrhosis is a life-limiting condition, palliative care should be offered alongside other curative therapies, and may be relevant for patients with compensated cirrhosis and decompensated cirrhosis.[174] The American Gastroenterological Association and the AASLD have both published guidelines on palliative care in patients with cirrhosis. These promote advanced care planning, assessment and management of symptoms (including pain, breathlessness, muscle cramps, sexual dysfunction, insomnia, daytime sleepiness, fatigue, pruritus, anxiety, and depression), screening for carer needs, and early liaison with local palliative care teams.[174] [175] Particular note is given to chronic pain management in the setting of diminished liver function and novel treatments for refractory ascites.[175]

## Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

| Ongoing | | ( summary ) |
|---|---|---|
| **all patients** | | |
| | **1st** | **treatment of underlying chronic liver disease and prevention of superimposed hepatic insult** |
| | **plus** | **monitoring for complications** |
| | **plus** | **supportive and palliative care** |
| | **adjunct** | **sodium restriction and diuretic therapy for ascites** |
| | **2nd** | **liver transplantation** |
| | **2nd** | **transjugular intrahepatic portosystemic shunt (TIPS)** |

# Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

## Ongoing

### all patients

**1st** **treatment of underlying chronic liver disease and prevention of superimposed hepatic insult**

» As cirrhosis is the pathological end-stage of any chronic liver disease, it is essential to treat the underlying causative condition.

» Oral direct-acting antivirals are considered a first-line treatment for chronic hepatitis C virus infection. One systematic review and meta-analysis found that early treatment with direct-acting antivirals reduced the recurrence of hepatocellular carcinoma, liver decompensation, and all-cause mortality, and prevented hepatocellular carcinoma in patients with compensated cirrhosis and without cirrhosis but did not prevent liver transplantation.[93] Regimens depend on the genotype and presence or absence of cirrhosis.[94] Local guidance should be consulted. See Hepatitis C . Antivirals may be indicated for patients with chronic hepatitis B.[84] [95] See Hepatitis B .

» Superimposed hepatic insult may be prevented through the avoidance of alcohol and other hepatotoxic drugs (e.g., non-steroidal anti-inflammatory drugs [NSAIDs] and high doses of paracetamol [>2-3 g/day]), immunisation against hepatitis A and B for susceptible patients, management of metabolic risk factors, maintenance of adequate nutrition, and regular exercise.

**plus** **monitoring for complications**

Treatment recommended for ALL patients in selected patient group

» Cirrhosis is associated with serious complications including portal hypertension causing ascites (further complicated by spontaneous bacterial peritonitis and hepatic hydrothorax), gastro-oesophageal varices and portosystemic encephalopathy, acute kidney injury and hepatopulmonary syndromes, portopulmonary hypertension, hepatocellular carcinoma, and acute-on-chronic liver failure.

» Prompt detection and treatment of these complications is essential in order to minimise

## Ongoing

related morbidity and mortality. Imaging tests include: abdominal ultrasound for the detection of ascites; upper gastrointestinal endoscopy in selected patients for the detection of gastro-oesophageal varices; and abdominal ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) for the detection of hepatocellular carcinoma.

» Other specialised tests may be required depending on individual symptoms.

» See Oesophageal varices , Spontaneous bacterial peritonitis , Hepatic encephalopathy , Hepatorenal syndrome , and Hepatocellular carcinoma .

**plus** **supportive and palliative care**

Treatment recommended for ALL patients in selected patient group

» It is recommended that patients hospitalised with cirrhosis receive formal dietician assessment, and steps should be taken to minimise the fasting period prior to procedures (e.g., by giving them a pre-bedtime snack or early-morning snack if the procedure will be in the late afternoon).[138] Parenteral supplementation may be required for those who cannot meet their nutritional intake needs orally. Recommended protein intake for adults with cirrhosis is 1.2 to 1.5 g/kg (ideal body weight) per day, and 1.2 to 2 g/kg (ideal body weight) per day if critically ill.

» As cirrhosis is a life-limiting condition, palliative care should be offered alongside other curative therapies, and may be relevant for patients with compensated cirrhosis and decompensated cirrhosis.[174] The American Gastroenterological Association and the American Association for the Study of Liver Disease have both published guidelines on palliative care in patients with cirrhosis. These promote advanced care planning, assessment and management of symptoms (including pain, breathlessness, muscle cramps, sexual dysfunction, insomnia, daytime sleepiness, fatigue, pruritus, anxiety, and depression), screening for carer needs, and early liaison with local palliative care teams.[174] [175] Particular note is given to chronic pain management in the setting of diminished liver function and novel treatments for refractory ascites.[175]

**adjunct** **sodium restriction and diuretic therapy for ascites**

## Ongoing

Treatment recommended for SOME patients in selected patient group

### Primary options

» spironolactone: 100 mg orally once daily initially, titrate as needed every 3-5 days, maximum 400 mg/day

**OR**

» spironolactone: 100 mg orally once daily initially, titrate as needed every 3-5 days, maximum 400 mg/day
**-and-**
» furosemide: 40 mg orally once daily initially, titrate as needed every 3-5 days, maximum 160 mg/day

» Ascites is the most common complication of cirrhosis.

» Every patient with new-onset ascites should undergo a diagnostic paracentesis: cell count with differential, albumin, and total protein should be measured in the ascitic fluid. Ascitic fluid should also be sent for culture and cytology.

» The serum-ascites albumin gradient (SAAG) should be calculated: a SAAG of ≥11 g/L with low ascitic fluid total protein is consistent with portal hypertension secondary to cirrhosis.

» Treatment involves a no-added-salt diet (daily intake of not more than 5 to 6.5 g) and the use of diuretics.[101] First-line diuretic should be spironolactone due to its effects on aldosterone and maintaining normal serum potassium. Furosemide may be added to patients who do not respond to spironolactone.[101] Once-daily dosing is typically preferred. The doses of both oral diuretics can be increased simultaneously every 3-5 days (maintaining the 100 mg to 40 mg ratio) if weight loss and natriuresis are inadequate.[176] Serum sodium, potassium, and creatinine should be monitored.

» Non-steroidal anti-inflammatory drugs (NSAIDs), ACE inhibitors, and other nephrotoxins should be avoided in patients with ascites.[90]

**2nd** **liver transplantation**

» Patients who develop complications of cirrhosis such as hepatocellular carcinoma or signs of decompensation (ascites, jaundice, variceal haemorrhage, hepatopulmonary syndrome, hepatic hydrothorax, portal systemic

## Ongoing

encephalopathy, or hepatorenal syndrome) should be referred for liver transplant evaluation without delay. Transplant assessment may be a prolonged process and early referrals are preferable. Some patients with acute-on-chronic liver failure may benefit from early liver transplantation.[167]

» Orthotopic liver transplantation remains the only curative treatment option for patients with decompensated cirrhosis.

» A survival benefit from undergoing liver transplantation is seen when the Model of End-Stage Liver Disease (MELD) score is ≥15.

**2nd** **transjugular intrahepatic portosystemic shunt (TIPS)**

» Patients not suitable for liver transplantation should be considered for TIPS placement.[103]

» Meta-analyses indicate that TIPS is more effective than paracentesis for control of refractory ascites, but is associated with a higher incidence of hepatic encephalopathy.[103] [104] [105] [106] [107] [108] [109] Overall mortality does not appear to differ between the two interventions, but TIPS may confer a modest benefit with respect to transplant-free survival.[103] [104] [105] [106] [107] [108] [109] One Cochrane systematic review and network meta-analysis reported that the overall certainty (quality) of evidence was very low, primarily because of unclear or high risk of bias in trials assessing interventions for the treatment of refractory ascites in patients with cirrhosis.[103]

» Disease severity at the time of TIPS placement is an important predictive factor for outcomes.[112]

# Emerging

## Antifibrotic agents

There are many antifibrotic agents being considered for therapeutic use in chronic liver disease, (e.g., silymarin, transforming growth factor [TGF]-beta antagonists, endothelin-receptor antagonists, ACE inhibitors, and relaxin). As it stands, there are no clinically approved therapies for liver fibrosis. Several are in phase 2 and 3 clinical trials, including drugs targeting the farnesoid X receptor, peroxisome proliferator-activated receptors (PPARs), and chemokine receptors.[177] Macitentan, an endothelin-receptor antagonist, may benefit patients with portopulmonary hypertension, but is not approved for this indication.[165]

## Pentoxifylline

Pentoxifylline is a phosphodiesterase inhibitor with anti-inflammatory properties that lowers blood viscosity and improves erythrocyte flexibility. Pro-inflammatory cytokines, including tumour necrosis factor (TNF)-alpha and interleukin-6, are elevated in patients with cirrhosis in response to endotoxaemia. These cytokines lead to a pro-inflammatory, hyperdynamic state. Pentoxifylline has been shown not only to decrease levels of TNF-alpha but also to increase systemic vascular resistance, directly opposing splanchnic vasodilation without precipitating an increase in the pressure in the portal venous system. In one randomised placebo-controlled trial of patients with advanced cirrhosis, pentoxifylline reduced the risk of complications, including bacterial infections, renal insufficiency, hepatic encephalopathy, and gastrointestinal haemorrhage, compared with placebo.[178] It did not improve short-term mortality.[178] Pentoxifylline added to the standard care of volume expansion with albumin and vasoconstriction appeared to be safe in one small randomised controlled trial of patients with type-1 hepatorenal syndrome, but further large-scale prospective studies are needed to validate the efficacy of this treatment.[179]

## Cyanoacrylate injection

Although a single study suggested that cyanoacrylate injection is more effective than propranolol in preventing first bleeding in patients with large type 2 gastro-oesophageal varices or isolated gastric varices, there were no differences in survival, and further research is necessary.[54]

## Microbiome-targeted therapy

Dysregulation of the gut-liver axis contributes to the development of liver disease.[180] Studies have found that the gut microbiome may be affected in cirrhosis.[181] [182] Modulating the gut microbiome using targeted therapies may slow liver deterioration, reduce hepatic venous pressure gradient, and reduce the inflammation of the liver.[180] [183][184] Probiotics, prebiotics, synbiotics, or fecal microbiota transplantation may be used for the modulation.[180] [181][182]

## Mesenchymal stem cells (MSCs)

MSCs have been found to be promising for the treatment of patients with chronic liver disease.[185] [186] One meta-analysis reported improved liver function and survival rates among patients with end-stage liver disease upon treatment with MSCs.[185] Another systematic review and meta-analysis reported that MSCs had a protective effect on complications of cirrhosis and the incidence of hepatocellular carcinoma, in addition to improving liver function.[187] Further trials are needed to establish the benefits of MSCs in patients with cirrhosis.

# Primary prevention

Methods of primary prevention include:

- Prevention strategies aimed at reducing excessive alcohol consumption, intravenous drug use, and unprotected intercourse
- Vaccination programmes for hepatitis B

- Public health strategies to control the rising incidence of obesity and diabetes
- Screening patients with risk factors for liver disease with non-invasive markers of liver fibrosis to identify liver disease before cirrhosis develops
- Treatment of any underlying chronic liver disease to prevent the progression to cirrhosis
- Appropriate screening of family members of patients with cirrhosis secondary to haemochromatosis or Wilson's disease
    - See Haemochromatosis (screening) and Wilson's disease (screening)
- Screening of blood donors and products for viral hepatitides.

# Secondary prevention

The following secondary preventive strategies are aimed at minimising the level of superimposed hepatic insult in an established cirrhotic liver:

- Treatment of any underlying chronic liver disease
- Avoidance of alcohol and other hepatotoxins such as non-steroidal anti-inflammatory drugs and high doses of paracetamol (>2-3 g/day)
- Immunisation against hepatitis A and B for susceptible patients.
    - In particular, the US Advisory Committee on Immunization Practices recommends that all patients with cirrhosis should be vaccinated against hepatitis A and B.[209]

There is some evidence to suggest that long-term treatment with beta-blockers (propranolol or carvedilol) increases decompensation-free survival, compared with placebo, in patients with compensated cirrhosis and clinically significant portal hypertension.[210] [211] Non-selective beta-blockers such as carvedilol may be considered to prevent decompensation in patients with compensated advanced chronic liver disease with clinically significant portal hypertension, except in those with contraindications such as asthma, advanced heart block, and bradyarrhythmias.[2] [212] The American Association for the Study of Liver Diseases recommends against the use of non-selective beta-blockers to prevent decompensation in patients with cirrhosis without clinically significant portal hypertension.[2]

# Patient discussions

Patients with cirrhosis should be advised of the following in order to minimise any further insult to the liver:

- Avoidance of alcohol and other hepatotoxins such as non-steroidal anti-inflammatory drugs and high doses of paracetamol (>2-3 g/day).
- Careful nutritional intake with adequate lean protein and a carbohydrate-based snack before bed. Decompensated patients should be advised to adhere to a no-added-salt diet.[203] Late evening snacks may help improve malnutrition and maintain glucose homeostasis.[204]
- Patients with compensated cirrhosis and obesity should be advised to lose weight.
- Attendance for immunisation against influenza and pneumococcus.
- Regular exercise. Exercise appears to be safe for patients with cirrhosis and can increase endurance.[205] [206] [207] [208]

# Monitoring

## Monitoring

Patients with cirrhosis should be monitored every 6-12 months with laboratory tests (renal function/electrolytes, liver function tests, albumin, full blood count, prothrombin time, alpha-fetoprotein) and imaging studies (6 monthly abdominal ultrasound) to check for:

- Signs and symptoms of advanced liver disease
- Disease progression
- Development of complications of portal hypertension such as ascites, hepatic encephalopathy, jaundice, and variceal bleeding.

Screening for hepatocellular carcinoma (HCC) in patients with cirrhosis is reported to be of high value, enabling early detection and treatment, and improving chances of survival.[200] All patients with cirrhosis, especially those with viral hepatitis (type B and C), alcohol-related liver disease, and haemochromatosis, are at high risk of developing hepatocellular carcinoma and should undergo surveillance with ultrasound, with or without alpha-fetoprotein, every 6 months.[170] In clinical practice, computed tomography (CT) is used as a second-line diagnostic imaging modality. However, it may lack accuracy in ruling out HCC; one meta-analysis found that if CT is used in the detection of HCC of any size and stage, 22.5% of people with HCC would be missed, and 8.7% of people without HCC would be unnecessarily treated. However, all included studies were judged to be at high risk of bias, limiting the authors' ability to confidently draw conclusions based on these results.[201] In another network meta-analysis, the multi-target HCC blood test was found to have higher sensitivity than ultrasound examination for early-stage detection; the sensitivity was comparable with ultrasound plus alpha-fetoprotein test combination.[202]

FOLLOW UP

# Complications

| Complications | Timeframe | Likelihood |
|---|---|---|
| **ascites** | **variable** | **high** |

The most common complication of cirrhosis. Treatment involves a no-added-salt diet and diuretics. Evidence suggests that severe dietary sodium restriction may be more harmful than beneficial, and many clinicians advise a no-added-salt diet rather than a low-salt diet.[101] This means excluding additional table salt being added to foods and avoidance of foods with high salt content, such as crisps and some processed meals. This results in a moderate sodium restriction with daily intake of not more than 5 to 6.5 g. First-line choice of diuretic should be spironolactone due to its effects on aldosterone. Furosemide may be added in patients who do not respond. Renal function and electrolytes should be monitored carefully when initiating diuretics and after dose escalation. Non-steroidal anti-inflammatory drugs, ACE inhibitors, and other nephrotoxins should be avoided in patients with ascites.

Every patient with new-onset ascites should undergo a diagnostic paracentesis: cell count with differential, albumin, and total protein should be measured in the ascitic fluid. Ascitic fluid should also be sent for culture and cytology.

Patients with refractory ascites (maximum diuretic doses not sufficient to control ascites or unacceptable adverse effects/complications with diuretic therapy) can be managed with large-volume paracentesis (LVP) and albumin replacement for symptom control. Patients not suitable for liver transplantation should be considered for transjugular intrahepatic portosystemic shunt (TIPS) placement.[103] Meta-analyses indicate that TIPS is more effective than paracentesis for control of refractory ascites, but is associated with a higher incidence of hepatic encephalopathy.[103] [104] [105] [106] [107] [108] [109] Overall mortality does not appear to differ between the two interventions, but TIPS may confer a modest benefit with respect to transplant-free survival.[103] [104] [105] [106] [107] [108] [109] One Cochrane systematic review and network meta-analysis reported that the overall certainty (quality) of evidence was very low, primarily because of unclear or high risk of bias in trials assessing interventions for the treatment of refractory ascites in patients with cirrhosis.[103] Disease severity at the time of TIPS placement is an important predictive factor for outcomes.[112]

Long-term abdominal drains may be used in the palliative care setting.[113] Prospective randomised controlled trials are warranted.

The use of vaptans (vasopressin V2-receptor antagonists) may have a slight beneficial effect on ascites and hyponatraemia, but they do not reduce mortality, liver complications, or renal failure.[114] [115]

| | | |
|---|---|---|
| **gastro-oesophageal varices** | **variable** | **high** |

Varices are present in 50% of patients with cirrhosis, and variceal bleeding is the most common lethal complication of cirrhosis with an associated mortality of 20% at 6 weeks.[116] Patients with cirrhosis have historically been offered upper gastrointestinal endoscopy for screening of gastro-oesophageal varices at the time of diagnosis, and at 1- to 3-year intervals thereafter.[56] However, guideline recommendations vary regarding screening intervals. The Baveno VII criteria suggest that screening endoscopy could be reserved for a subgroup of patients, based on liver stiffness measurement and platelet count assessment.[54] In particular, patients with compensated cirrhosis, who have a liver stiffness <20 kPa (as measured by transient elastography) and platelet count >150 × $10^9$ cells/L, have a very low risk of having varices requiring treatment and can avoid screening endoscopy.[54] In practice, however, many centres offer baseline endoscopy to all patients with liver cirrhosis.

Prophylaxis of bleeding

Prophylaxis with either non-selective beta-blockers (propranolol, nadolol, or carvedilol) or endoscopic variceal ligation (EVL), which requires several sessions to obliterate varices, should be implemented if high-risk oesophageal varices are present, due to the increased risk of variceal bleeding.[57] High-

| Complications | Timeframe | Likelihood |
|---|---|---|

risk varices include small varices with red signs, medium or large varices irrespective of Child-Pugh classification, or small varices in Child-Pugh C patients.[88] Isolated gastric varices or oesophageal varices extending below the cardia into the gastric fundus should also be considered for non-selective beta-blockers for primary prophylaxis.[54]

Advantages of non-selective beta-blockers include low cost and ease of administration. In addition, once a patient is on non-selective beta-blockers, there is no need for repeat oesophagogastrosduodenoscopy (OGD), and haemodynamic responders to non-selective beta-blockers have a lower incidence of decompensation and death. Disadvantages are that approximately 15% of patients may have absolute or relative contraindications to therapy, and another 15% require dose reduction or discontinuation attributed to common adverse effects (e.g., fatigue, weakness, and shortness of breath) that resolve upon discontinuation, but that may discourage patients and their physicians from using these drugs.

Monitoring haemodynamic response while treating a patient with beta-blockers is associated with a lower risk of variceal bleeding, but large cohort randomised controlled trials are required to confirm these findings.[117]

There is ongoing debate regarding the safety of non-selective beta-blockers in patients with cirrhosis and refractory ascites. The expanded Baveno VI criteria proposed that in patients with refractory ascites and (i) systolic blood pressure <90 mmHg, or (ii) serum creatinine >133 micromoles/L (>1.5 mg/dL), or (iii) hyponatraemia <130 millimoles/L, the beta-blocker should be reduced in dose or even temporarily discontinued.[87] However, there is evidence to suggest that the risk of harm may not be significant.[118] [119] [120] [121]

EVL is an alternative to non-selective beta-blockers. It is a local therapy that involves placing elastic bands around oesophageal varices until they are obliterated. EVL can theoretically be performed in the same session as screening endoscopy with hardly any contraindications. Disadvantages of EVL include the risks associated with sedation, plus the risk of causing dysphagia, oesophageal ulceration, strictures, and bleeding. Adverse effects associated with EVL may be severe, with reports of deaths resulting from EVL-induced bleeding ulcers. EVL is unable to prevent complications other than variceal haemorrhage. Surveillance endoscopies are necessary after variceal eradication, at least annually, to detect variceal recurrence.[122] Child-Pugh class C, ascites, or low prothrombin index are all indicators for high risk of early bleeding following EVL.[123]

The choice of whether to use non-selective beta-blockers or EVL should be based on local resources and expertise, patient preference and characteristics, contraindications, and adverse events.[87] One meta-analysis that included 1023 patients compared prophylactic EVL with beta-blockers and found that there was no difference between the treatments with regard to gastrointestinal haemorrhage, all-cause mortality, or haemorrhage-related mortality. While there was a decrease in variceal haemorrhage with EVL compared with beta-blockers (relative risk [RR] 0.72, 95% CI 0.4 to 0.96), variceal haemorrhage was not significantly different between the two groups when only high-quality trials were considered (RR 0.84, 95% CI 0.60 to 1.17).[124] Subjective factors influence the physician's choice in selecting non-selective beta-blockers versus EVL, as illustrated in an interview-based study in which gastroenterologists who spent at least half their time performing endoscopy were more likely to choose EVL, whereas physicians who had a less procedural-based practice were more likely to choose non-selective beta-blockers.[125]

Transjugular intrahepatic portosystemic shunts (TIPS)

TIPS may be used as a secondary treatment option for oesophageal varices in cirrhosis but is not recommended for primary prophylaxis of variceal haemorrhage.[2] [126] Evidence obtained from trials of prophylactic surgical shunt therapy show a significantly higher rate of encephalopathy and a tendency for a higher mortality in patients randomised to shunt surgery.[127]

Management of acute variceal haemorrhage

| Complications | Timeframe | Likelihood |
|---|---|---|

An episode of acute variceal haemorrhage should be managed as a medical emergency with intravascular volume support, blood transfusion (with the aim of keeping the haemoglobin around 70-80 g/L [7-8 g/dL]), and a combination of endoscopic and pharmacological therapy.[131] Terlipressin (a vasopressin analogue), or somatostatin (or its analogue octreotide) should be initiated as soon as a variceal bleed is suspected and continued for 2-5 days if it is confirmed.[132] Upper gastrointestinal endoscopy should be performed within 24 hours to confirm the diagnosis and allow treatment with EVL or sclerotherapy.[133]

Short-term (up to 7 days) antibiotic prophylaxis should be instituted in all patients following a gastrointestinal haemorrhage (regardless of the presence of ascites) as this has been shown to decrease the rate of bacterial infections and increase survival.[134] Ceftriaxone is the first choice in patients with decompensated cirrhosis, in those already on fluoroquinolone prophylaxis, and in hospital settings with high prevalence of fluoroquinolone-resistant bacterial infections. Oral fluoroquinolones should be used in the remaining patients.[135] [136]

Life-threatening bleeding may be controlled with a Sengstaken-Blakemore tube or a Danis stent until haemostasis can be achieved endoscopically, or with TIPS, with or without embolisation.[137]

| malnutrition and sarcopenia | variable | high |
|---|---|---|

It is recommended that patients hospitalised with cirrhosis receive formal dietician assessment, and steps should be taken to minimise the fasting period prior to procedures (e.g., by giving them a pre-bedtime snack or early-morning snack if the procedure will be in the late afternoon).[138] Parenteral supplementation may be required for those who cannot meet their nutritional intake needs orally. Recommended protein intake for adults with cirrhosis is 1.2 to 1.5 g/kg (ideal body weight) per day, and 1.2 to 2 g/kg (ideal body weight) per day if critically ill.

| hepatocellular carcinoma | variable | high |
|---|---|---|

Patients with cirrhosis, especially those with viral hepatitis (type B and C), alcohol-related liver disease, and haemochromatosis, are at high risk of developing hepatocellular carcinoma and should therefore undergo surveillance with ultrasound, with or without alpha-fetoprotein, every 6 months.[170] Alpha-fetoprotein cannot be recommended as a single test because it is neither sensitive nor specific for hepatocellular carcinoma.

There are several different treatment options for hepatocellular carcinoma depending on its stage and the degree of liver dysfunction. These include liver transplantation, surgical resection, radiofrequency ablation, microwave ablation, and transarterial chemoembolisation. Advanced hepatocellular carcinoma may be treated using sorafenib as palliative chemotherapy.

The Barcelona Clinic Liver Center (BCLC) classification for staging and treatment of hepatocellular carcinoma is endorsed by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver.[62] [170] The BCLC staging system correlates each of its stages with treatment modalities and estimates the life expectancy based on prior studies.[170]

| bleeding and thrombosis | variable | high |
|---|---|---|

The haemostatic balance in liver disease is fragile, and the risk of bleeding/thrombosis is poorly predicted by routinely used diagnostic tests, such as international normalised ratio (INR).

Patients with advanced liver disease often have thrombocytopenia due to hypersplenism. There is a concurrent reduction in synthesis of clotting factors, leading to elevations in INR. Portal hypertension or hyperfibrinolysis may give rise to bleeding. Lusutrombopag and avatrombopag are approved for thrombocytopenia in adults with chronic liver disease undergoing invasive procedures.[195]

Anticoagulation is frequently withheld from hospitalised patients with cirrhosis because of concerns over laboratory parameters. Thromboelastography may ultimately have a role in the evaluation of clotting in

| Complications | Timeframe | Likelihood |
|---|---|---|
| patients with cirrhosis, but validated target levels are lacking.[196] [197] [198] It has been increasingly recognised that patients with cirrhosis are at significant risk of venous thromboembolism (VTE), with typical incidence rates of 0.5% to 1.9%, but in some studies considerably higher.[46] [199] In hospitalised patients with cirrhosis who otherwise meet standard guidelines for the use of VTE prophylaxis, standard anticoagulation prophylaxis should be used.[46]<br><br>The American Gastroenterological Association has published guidelines with recommendations for achieving haemostasis, as well as the prevention and treatment of thrombosis, in patients with cirrhosis.[46] | | |
| **spontaneous bacterial peritonitis** | **variable** | **medium** |
| A peritoneal fluid absolute neutrophil count >250 cells/mm³ is the accepted criterion for the diagnosis for spontaneous bacterial peritonitis.[88]<br><br>Treatment is with intravenous antibiotics, such as cefotaxime or a fluoroquinolone, and intravenous human albumin solution. Albumin has been shown to reduce mortality in patients with cirrhosis with spontaneous bacterial peritonitis.[139] [140]<br><br>All patients who have survived an episode of spontaneous bacterial peritonitis require lifelong secondary antibiotic prophylaxis.[192]<br><br>Patients with ascites and an ascitic fluid total protein level of ≤10 g/L are at high risk of developing spontaneous bacterial peritonitis and should be considered for primary antibiotic prophylaxis.[88] [141] [142] There appears to be an increased risk of spontaneous bacterial peritonitis with the use of proton-pump inhibitors.[143] High-quality evidence for this intervention is lacking and further trials are needed to establish whether antibiotic prophylaxis for people with cirrhosis is beneficial.[144] | | |
| **hepatic hydrothorax** | **variable** | **medium** |
| Occurs in approximately 5% to 10% of patients with cirrhosis, usually in patients with ascites.[145]<br><br>Hepatic hydrothorax may cause dyspnoea.<br><br>Management is similar to that of ascites. In some patients, long-term indwelling catheters are required for symptomatic management.[146] [147] Patients with hepatic hydrothorax should be evaluated for liver transplantation.[148] | | |
| **portosystemic encephalopathy** | **variable** | **medium** |
| Approximately 11% of patients with cirrhosis have hepatic encephalopathy at the time of cirrhosis diagnosis.[149] Around 30% to 40% of patients with cirrhosis have an episode of hepatic encephalopathy during their illness, and there is a 30% to 40% chance of recurrence in the following year.[150]<br><br>Hepatic encephalopathy is characterised by changes in consciousness, behaviour, and personality, with disorientation, drowsiness, forgetfulness, confusion, agitation, and eventual coma. Slurred speech, asterixis (liver flap), increased muscle tone, and extensor plantar reflexes may be present.<br><br>Precipitating factors include gastrointestinal haemorrhage, constipation, diarrhoea and vomiting, hypoglycaemia, and electrolyte imbalance; drugs (diuretics, sedatives) and medical procedures (paracentesis, transjugular intrahepatic portosystemic shunt [TIPS]); infection, anaemia, hypoxia, and hypotension.<br><br>Serum ammonia levels are usually elevated, but there is poor correlation between ammonia level and the degree of encephalopathy. | | |

| Complications | Timeframe | Likelihood |
|---|---|---|
| There appears to be an increased risk of hepatic encephalopathy with the use of proton-pump inhibitors.[151] [152]<br><br>Treatment involves identification and correction of reversible precipitating factors and lactulose, used alone or in combination with antibiotics such as rifaximin.[153] [154] [155] [156] [157] [158] [193]<br><br>Dietary protein restriction is not recommended.[159] | | |
| **hepatorenal syndrome-acute kidney injury (HRS-AKI)** | **variable** | **medium** |
| HRS-AKI (formerly known as type-1 hepatorenal syndrome) can be diagnosed if patients meet the following criteria, as defined by the International Club of Ascites: cirrhosis with ascites; diagnosis of AKI according to ICA-AKI criteria (i.e., increase in serum creatinine ≥26.4 micromoles/L [≥0.3 mg/dL] within 48 hours, or a percentage increase in serum creatinine ≥50% from baseline which is known, or presumed, to have occurred within the previous 7 days; [the American Gastroenterological Association (AGA) also include a reduction of urine output to below 0.5 mL/kg/h for >6 hours]); no response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin; absence of shock; no current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, or iodinated contrast media); no macroscopic signs of structural kidney injury (structural kidney injury is indicated by proteinuria [>500 mg/day], microhaematuria [>50 red blood cells per high-power field], and/or abnormal renal ultrasonography).[89] [90]<br><br>European Association for the Study of the Liver (EASL) guidelines recommend using an adapted staging system for AKI that splits AKI stage 1 into stage 1A and 1B according to a serum creatinine value of <133 micromoles/L (<1.5 mg/dL) or ≥133 micromoles/L (≥1.5 mg/dL), respectively.[88]<br><br>Measures can be taken to prevent HRS-AKI from developing in patients with cirrhosis, and include: advising patients to avoid alcohol; monitoring serum creatinine levels and electrolytes when diuretics are given and avoiding excessive diuretics; avoiding large-volume paracentesis without albumin replacement; giving prophylactic antibiotics when infection is strongly suspected (investigations should include diagnostic paracentesis to evaluate for spontaneous bacterial peritonitis); and avoiding use of non-selective beta-blockers and nephrotoxic drugs (e.g., ACE inhibitors, angiotensin II receptors blockers, and non-steroidal anti-inflammatory drugs [NSAIDs]).[90]<br><br>Once diagnosed, treatment of the precipitating cause should be initiated and any non-selective beta-blockers, diuretics and NSAIDS held or stopped. Fluid losses should be replaced and fluid status monitored.[90]<br><br>Vasoconstrictors and albumin are recommended in all patients and should be expeditiously used. Terlipressin plus albumin should be considered as the first-line therapeutic option.[132] Noradrenaline (norepinephrine) can be an alternative to terlipressin. However, there are several limitations associated with its use. Midodrine plus octreotide can be an option when terlipressin or noradrenaline are unavailable, but its efficacy is much lower than that of terlipressin.[88] [194] In one phase 3 trial to confirm the efficacy and safety of terlipressin plus albumin in adults with HRS-AKI, terlipressin was more effective than placebo in improving renal function, but was associated with serious adverse events, including respiratory failure, and cases of sepsis or septic shock.[161] | | |
| **hepatopulmonary syndrome** | **variable** | **low** |
| Results from portal hypertension and occurs in at least 5% of patients awaiting liver transplantation.[163] Symptoms include dyspnoea and platypnoea. The diagnosis includes the finding of hypoxaemia with increased alveolar-arterial gradient, orthodeoxia, and the determination of intrapulmonary vascular dilatation on contrast-enhanced echocardiography.<br><br>The presence of hepatopulmonary syndrome should prompt immediate evaluation for liver transplantation.<br><br>The condition usually resolves following liver transplantation.[164] | | |

| Complications | Timeframe | Likelihood |
|---|---|---|
| **portopulmonary hypertension** | **variable** | **low** |

This complication is diagnosed when findings of unexplained pulmonary hypertension are present in association with portal hypertension.

Unlike hepatopulmonary syndrome, this condition may not completely resolve following liver transplantation. Patients with severe pulmonary hypertension that does not improve with the use of vasodilators such as epoprostenol, bosentan, iloprost, or sildenafil are not candidates for liver transplantation in view of the high risk of death associated with the procedure.

In one randomised controlled trial, macitentan, an endothelin-receptor antagonist, significantly reduced pulmonary vascular resistance in patients with portopulmonary hypertension compared with placebo.[165]

| | | |
|---|---|---|
| **acute-on-chronic liver failure** | **variable** | **low** |

Acute-on-chronic liver failure (ACLF) is a severe form of acutely decompensated cirrhosis with organ failure and a high risk of short-term mortality.[166] It is a heterogeneous syndrome; affected patients have features of hepatic failure (coagulopathy, elevated bilirubin) and may also have extrahepatic organ failure (kidney, lung, brain, or circulation). ACLF may be precipitated by alcohol use, viral hepatitis, drug-induced liver injury, surgery, ischaemia, or infection. It is a potentially reversible condition that may occur in people with chronic liver disease.

Treatment includes resuscitation, treatment of the precipitating factor, support of failing organs, and assessment for and early treatment of infection. Patients should be cared for in the intensive care unit. Some patients may benefit from early liver transplantation.[167]

Treatment of shock in ACLF can be challenging. Society of Critical Care Medicine guidelines recommend using albumin as a resuscitation fluid over other fluids, particularly when serum albumin is below 3 mg/dL.[168] Guidelines recommend aiming for a mean arterial pressure of 65 mmHg alongside invasive haemodynamic monitoring.[168] [169] In patients with ACLF and hypotension, human albumin or crystalloids should be used for initial fluid therapy.[166] If vasopressors are required, noradrenaline (norepinephrine) is more effective than dopamine in reversing hypotension. The European Association for the Study of the Liver (EASL) recommends against the use of dopamine in patients with ACLF.[166] Low-dose vasopressin can be added to noradrenaline in patients with ACLF who remain hypotensive despite fluid resuscitation. The American Association for the Study of Liver Diseases (AASLD) recommends noradrenaline as the first-line agent and vasopressin as the second-line agent for managing patients with hypotension.[169] The possible mortality benefit with the addition of vasopressin must be weighed against increased risk of digital ischaemia. As well as addressing the treatment of shock, the guidelines also provide recommendations for managing endocrine, haematological, pulmonary, and renal features of ACLF in the intensive care unit setting.[168] [169]

| | | |
|---|---|---|
| **hypogonadism and feminisation** | **variable** | **low** |

Cirrhosis is associated with an oestrogenic/androgenic imbalance with reduced circulating levels of testosterone and a relative increase in oestrogen. This leads to hypogonadism and feminisation in men. Hypogonadism is characterised by testicular atrophy, impotence, and loss of libido, while gynaecomastia and a female pattern of hair distribution are features of feminisation. Testicular atrophy and reduced libido are most commonly seen in patients with underlying alcohol-related liver disease and haemochromatosis.

In women, this endocrine imbalance may cause amenorrhoea, infertility, acne vulgaris, and the development of benign breast cysts.

FOLLOW UP

| Complications | Timeframe | Likelihood |
|---|---|---|
| **hepatic osteodystrophy** | **variable** | **low** |
| This is the term given to the combination of osteoporosis and osteomalacia associated with chronic liver disease. Hepatic osteodystrophy most commonly occurs with underlying cholestatic disease (primary biliary cholangitis and primary sclerosing cholangitis), but can occur with any chronic liver disease. Osteoporosis results from reduced bone mineralisation and formation secondary to decreased activity of osteoblasts. This leads to pathological fractures, particularly of the vertebrae; back pain; and kyphosis. Osteomalacia is less common and results from reduced bone mineralisation. Its main symptom is bone pain. Vitamin D deficiency is a contributory factor in the development of hepatic osteodystrophy. | | |

# Prognosis

## Overall prognosis

The overall median survival of patients with cirrhosis is approximately 10 years, but prognosis depends on the stage of the disease.

The 10-year survival rate in patients with compensated cirrhosis is approximately 90%, and the likelihood of transitioning to decompensated cirrhosis within 10 years is 50%.[188] The median survival time in patients with decompensated cirrhosis is approximately 2 years.[188] [189] The median survival time following onset of hepatic encephalopathy is 0.92 years and following onset of ascites is 1.1 years.[3] Patients with chronic liver disease have a higher mortality rate from COVID-19 infection, and mortality is associated with liver disease severity.[190] [191]

In clinical practice, the Child-Pugh-Turcotte score and the Model for End-Stage Liver Disease score are the most commonly used scoring systems for the prediction of mortality related to liver disease.

Four clinical stages of cirrhosis have been identified and each is associated with a different prognosis.[188]

Stage 1

- Patients without gastro-oesophageal varices or ascites have a mortality of approximately 1% per year.

Stage 2

- Patients with gastro-oesophageal varices (but no bleeding) and no ascites have a mortality of approximately 4% per year.

Stage 3

- Patients with ascites with or without gastro-oesophageal varices (but no bleeding) have a mortality of approximately 20% per year.

Stage 4

- Patients with gastrointestinal bleeding due to portal hypertension with or without ascites have a 1-year mortality of 57%.

# Diagnostic guidelines

## United Kingdom

### Cirrhosis in over 16s: assessment and management (https://www.nice.org.uk/guidance/ng50)

**Published by:** National Institute for Health and Care Excellence **Last published:** 2023

### Guidelines on the use of liver biopsy in clinical practice (https://www.bsg.org.uk/clinical-resource/guidelines-on-the-use-of-liver-biopsy)

**Published by:** British Society of Gastroenterology **Last published:** 2020

### Liver disease (https://www.nice.org.uk/guidance/qs152)

**Published by:** National Institute for Health and Care Excellence **Last published:** 2017

### Management of abnormal liver blood tests (https://www.bsg.org.uk/clinical-resource/guidelines-on-abnormal-liver-blood-tests)

**Published by:** British Society of Gastroenterology **Last published:** 2017

## Europe

### EASL clinical practice guidelines on acute-on-chronic liver failure (https://easl.eu/publications/clinical-practice-guidelines)

**Published by:** European Association for the Study of the Liver **Last published:** 2023

### Non-invasive tests for evaluation of liver disease severity and prognosis (https://easl.eu/publications/clinical-practice-guidelines)

**Published by:** European Association for the Study of the Liver **Last published:** 2021

### Management of alcohol-related liver disease (https://easl.eu/publications/clinical-practice-guidelines)

**Published by:** European Association for the Study of the Liver **Last published:** 2018

## North America

### AASLD practice guideline on blood-based noninvasive liver disease assessment of hepatic fibrosis and steatosis (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2024

### AASLD practice guideline on imaging-based noninvasive liver disease assessment of hepatic fibrosis and steatosis (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2024

### AASLD practice guideline on noninvasive liver disease assessment of portal hypertension (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2024

### AASLD practice guidance on acute-on-chronic liver failure and the management of critically ill patients with cirrhosis (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2024

### ACR appropriateness criteria: abnormal liver function tests (https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria)

**Published by:** American College of Radiology **Last published:** 2023

### Acute-on-chronic liver failure clinical guidelines (https://gi.org/guidelines)

**Published by:** American College of Gastroenterology **Last published:** 2022

### Diagnosis and treatment of alcohol-associated liver diseases (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2019

### The role of elastography in the evaluation of liver fibrosis (https://gastro.org/clinical-guidance)

**Published by:** American Gastroenterological Association **Last published:** 2017

### Evaluation of abnormal liver chemistries (https://gi.org/guidelines)

**Published by:** American College of Gastroenterology **Last published:** 2017

## Asia

### Evidence-based clinical practice guidelines for liver cirrhosis 2020 (https://link.springer.com/article/10.1007/s00535-021-01788-x)

**Published by:** Japanese Society of Gastroenterology **Last published:** 2021

# Treatment guidelines

## United Kingdom

### Cirrhosis in over 16s: assessment and management (https://www.nice.org.uk/guidance/ng50)

**Published by:** National Institute for Health and Care Excellence **Last published:** 2023

### Outpatient management of cirrhosis – part 1: compensated cirrhosis (https://www.bsg.org.uk/clinical-resource?category=Guidance)

**Published by:** British Society of Gastroenterology **Last published:** 2023

### Outpatient management of cirrhosis – part 2: decompensated cirrhosis (https://www.bsg.org.uk/clinical-resource?category=Guidance)

**Published by:** British Society of Gastroenterology **Last published:** 2023

### Outpatient management of cirrhosis – part 3: special circumstances (https://www.bsg.org.uk/clinical-resource?category=Guidance)

**Published by:** British Society of Gastroenterology **Last published:** 2023

### UK guidelines on the management of variceal haemorrhage in cirrhotic patients (https://www.bsg.org.uk/clinical-resource?category=Guidelines)

**Published by:** British Society of Gastroenterology **Last published:** 2022

### National clinical guidelines for the treatment of HCV in adults (https://publichealthscotland.scot/publications/national-clinical-guidelines-for-the-treatment-of-hcv-in-adults)

**Published by:** NHS National Services Scotland **Last published:** 2018

### Liver disease (https://www.nice.org.uk/guidance/qs152)

**Published by:** National Institute for Health and Care Excellence **Last published:** 2017

## Europe

### EASL clinical practice guidelines on acute-on-chronic liver failure (https://easl.eu/publications/clinical-practice-guidelines)

**Published by:** European Association for the Study of the Liver **Last published:** 2023

### Baveno VII: renewing consensus in portal hypertension (https://www.bavenocoop.net/baveno/last-baveno-consensus)

**Published by:** Baveno Cooperation (endorsed by the European Association for the Study of the Liver) **Last published:** 2022

### Clinical practice guidelines on the management of hepatic encephalopathy (https://easl.eu/publications/clinical-practice-guidelines)

**Published by:** European Association for the Study of the Liver **Last published:** 2022

### Clinical practice guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis (https://www.journal-of-hepatology.eu/article/S0168-8278(21)02033-X/fulltext)

**Published by:** European Association for the Study of the Liver **Last published:** 2022

### Management of alcohol-related liver disease (https://easl.eu/publications/clinical-practice-guidelines)

**Published by:** European Association for the Study of the Liver **Last published:** 2018

### Management of patients with decompensated cirrhosis (https://easl.eu/publications/clinical-practice-guidelines)

**Published by:** European Association for the Study of the Liver **Last published:** 2018

### Clinical practice guidelines on nutrition in chronic liver disease (https://easl.eu/publications/clinical-practice-guidelines)

**Published by:** European Association for the Study of the Liver **Last published:** 2018

### Clinical practice guidelines on the management of hepatitis B virus infection (https://easl.eu/publications/clinical-practice-guidelines)

**Published by:** European Association for the Study of the Liver **Last published:** 2017

## International

### Hepatic encephalopathy in chronic liver disease (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases; European Association for the Study of the Liver **Last published:** 2014

## North America

### AASLD practice guidance on risk stratification and management of portal hypertension and varices in cirrhosis (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2024

### AASLD practice guidance on acute-on-chronic liver failure and the management of critically ill patients with cirrhosis (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver **Last published:** 2024

### AGA clinical practice update on the evaluation and management of acute kidney injury in patients with cirrhosis: expert review (https://gastro.org/clinical-guidance)

**Published by:** American Gastroenterological Association **Last published:** 2022

### Acute-on-chronic liver failure clinical guidelines (https://gi.org/guidelines)

**Published by:** American College of Gastroenterology **Last published:** 2022

### Palliative care and symptom-based management in decompensated cirrhosis (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2022

### Drug, herbal, and dietary supplement-induced liver injury (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2022

### Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2021

### Clinical practice guideline on the management of coagulation disorders in patients with cirrhosis (https://gastro.org/clinical-guidance)

**Published by:** American Gastroenterological Association **Last published:** 2021

### Malnutrition, frailty, and sarcopenia in patients with cirrhosis (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2021

### Clinical practice update on palliative care management in cirrhosis: expert review (https://gastro.org/clinical-guidance)

**Published by:** American Gastroenterological Association **Last published:** 2020

## North America

### Guidelines for the management of adult acute and acute-on-chronic liver failure in the ICU: cardiovascular, endocrine, hematologic, pulmonary, and renal considerations (https://www.sccm.org/Clinical-Resources/Guidelines/Guidelines)

**Published by:** Society of Critical Care Medicine **Last published:** 2020

### Diagnosis and treatment of alcohol-associated liver diseases (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases **Last published:** 2019

### Evaluation for liver transplantation in adults (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases; American Society of Transplantation **Last published:** 2014

### Evaluation of the pediatric patient for liver transplantation (https://www.aasld.org/practice-guidelines)

**Published by:** American Association for the Study of Liver Diseases; American Society of Transplantation; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition **Last published:** 2014

## Asia

### Guidelines on management of ascites in liver disease (https://link.springer.com/article/10.1007/s12072-023-10536-7)

**Published by:** Asia-Pacific Association for Study of Liver **Last published:** 2023

### Evidence-based clinical practice guidelines for liver cirrhosis 2020 (https://link.springer.com/article/10.1007/s00535-021-01788-x)

**Published by:** Japanese Society of Gastroenterology **Last published:** 2021

# Evidence tables

## Can non-absorbable disaccharides help to prevent or treat hepatic encephalopathy in people with cirrhosis?

This table is a summary of the analysis reported in a Cochrane Clinical Answer that focuses on the above important clinical question.

Cochrane Clinical Answers

View the full source Cochrane Clinical Answer (https://www.cochranelibrary.com/cca/doi/10.1002/cca.1475/full)

Evidence B *

Confidence in the evidence is moderate or low to moderate where GRADE has been performed and the intervention may be more effective/beneficial than the comparison for key outcomes.

**Population:** Adults with cirrhosis (mean age 41 to 61 years)
**Intervention:** Non-absorbable disaccharides (lactulose or lactitol) [a]
**Comparison:** Placebo or no intervention

| | † | ‡ |
|---|---|---|
| Mortality (follow-up up to 7 months) | Favours intervention | Moderate |
| Hepatic encephalopathy (follow-up up to 7 months) | Favours intervention | Moderate |
| Serious adverse events (follow-up up to 7 months) | Occurs more commonly with placebo or no intervention compared with disaccharides (favours intervention) | Moderate |
| Quality of life (follow-up up to 3 months): sickness impact profile - change from baseline | Favours intervention [b] | Very Low |
| Quality of life (follow-up up to 3 months): sickness impact profile - end of treatment | No statistically significant difference | Very Low |
| Non-serious adverse events: overall [c] | Occurs more commonly with disaccharides compared with placebo or no intervention (favours comparison) | Very Low |

**Note**

[a] Treatment duration was dependent on type of encephalopathy (mean duration: 5 days for acute; 74 days for chronic, 70 days for minimal and 207 days for the prevention of hepatic encephalopathy).

[b] This outcome was only reported in studies of lactulose versus placebo.

[c] A statistically significant difference between treatment groups favouring placebo or no treatment was found for two subgroups (diarrhoea and bloating) while disaccharides was favoured for a third subgroup (constipation). GRADE assessment was not performed for any of these subgroups. Trials assessing other outcomes (nausea, hyponatraemia, anal fissure, and hyperglycaemia) were underpowered.

## * Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

### Confidence in evidence

**A -** High or moderate to high

**B -** Moderate or low to moderate

**C -** Very low or low

## †

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

## ‡ Grade certainty ratings

| | |
|---|---|
| High | The authors are very confident that the true effect is similar to the estimated effect. |
| Moderate | The authors are moderately confident that the true effect is likely to be close to the estimated effect. |
| Low | The authors have limited confidence in the effect estimate and the true effect may be substantially different. |
| Very Low | The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different. |

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

## Key articles


- Kaplan DE, Ripoll C, Thiele M, et al. AASLD practice guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology. 2024 May 1;79(5):1180-211. Full text (https://journals.lww.com/hep/fulltext/2024/05000/aasld_practice_guidance_on_risk_stratification_and.22.aspx) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37870298?tool=bestpractice.bmj.com)
- de Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII: renewing consensus in portal hypertension. J Hepatol. 2022 Apr;76(4):959-74. Full text (https://www.journal-of-hepatology.eu/article/S0168-8278(21)02299-6/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35120736?tool=bestpractice.bmj.com)
- National Institute for Health and Care Excellence. Cirrhosis in over 16s: assessment and management. Sep 2023 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng50)
- European Association for the Study of the Liver. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis: 2021 update. J Hepatol. 2021 Sep;75(3):659-89. Full text (https://www.journal-of-hepatology.eu/article/S0168-8278(21)00398-6/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34166721?tool=bestpractice.bmj.com)
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- Rogal SS, Hansen L, Patel A, et al. AASLD practice guidance: palliative care and symptom-based management in decompensated cirrhosis. Hepatology. 2022 Sep;76(3):819-53. Full text (https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep.32378) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35103995?tool=bestpractice.bmj.com)


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3. Tapper EB, Parikh ND. Diagnosis and management of cirrhosis and its complications: a review. JAMA. 2023 May 9;329(18):1589-602. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10843851) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37159031?tool=bestpractice.bmj.com)

4. Wu XN, Xue F, Zhang N, et al. Global burden of liver cirrhosis and other chronic liver diseases caused by specific etiologies from 1990 to 2019. BMC Public Health. 2024 Feb 3;24(1):363. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10837876) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/38310221?tool=bestpractice.bmj.com)

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# Images

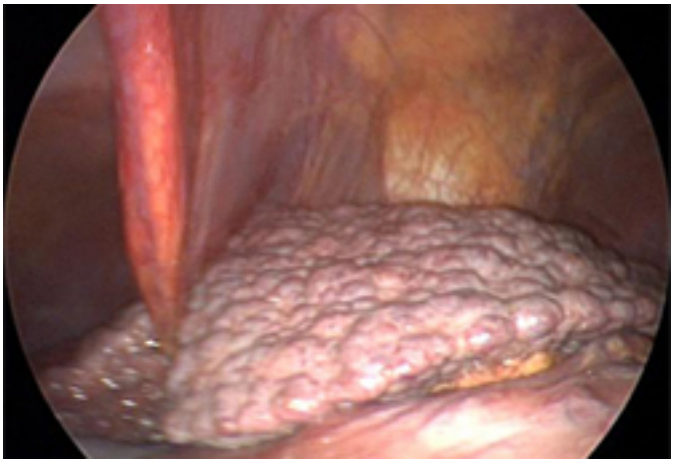

*Figure 1: Laparoscopic view of a cirrhotic liver*

*Courtesy of Dr Eugene Schiff and Dr Lennox Jeffers; used with permission*

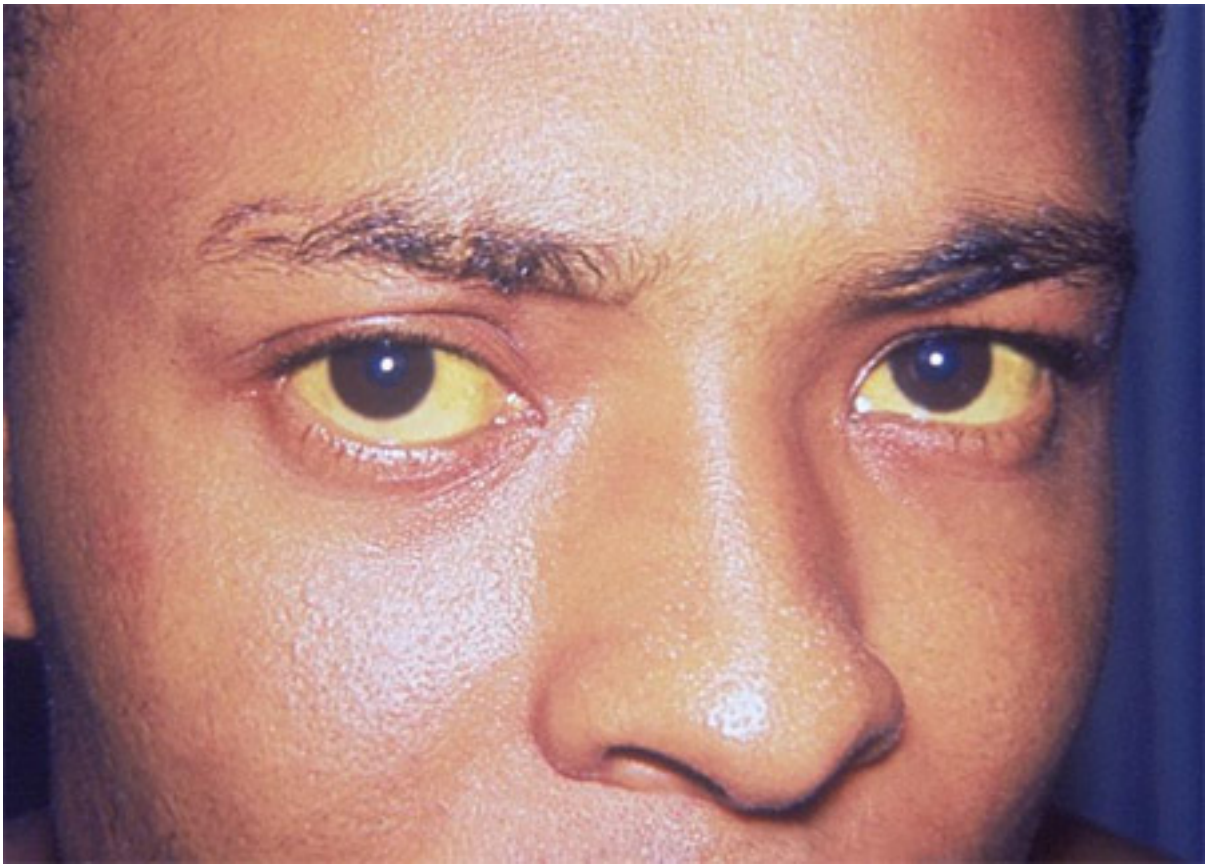

*Figure 2: Icterus or jaundice*

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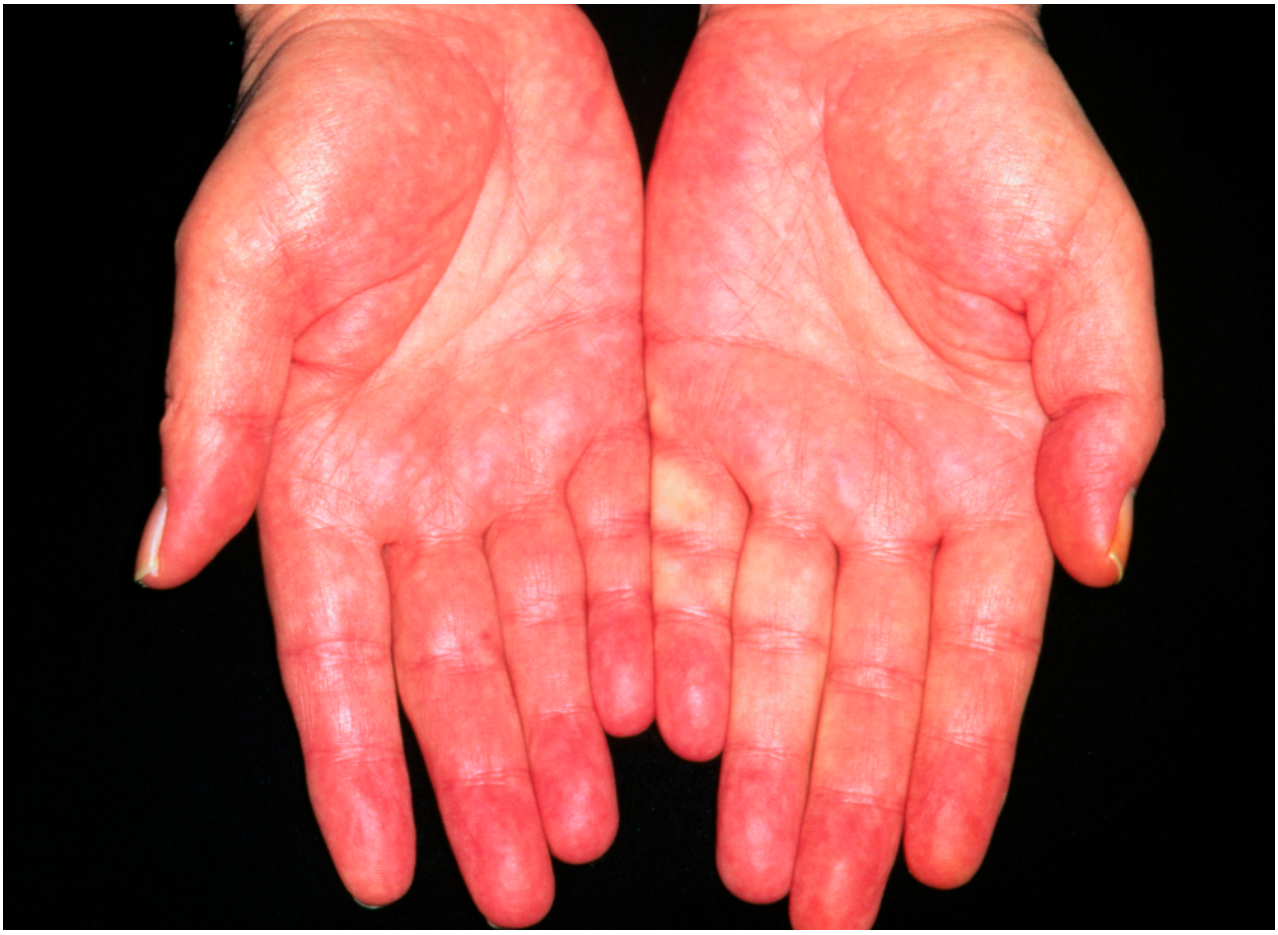

*Figure 3: Liver palms erythema of adult alcoholic*

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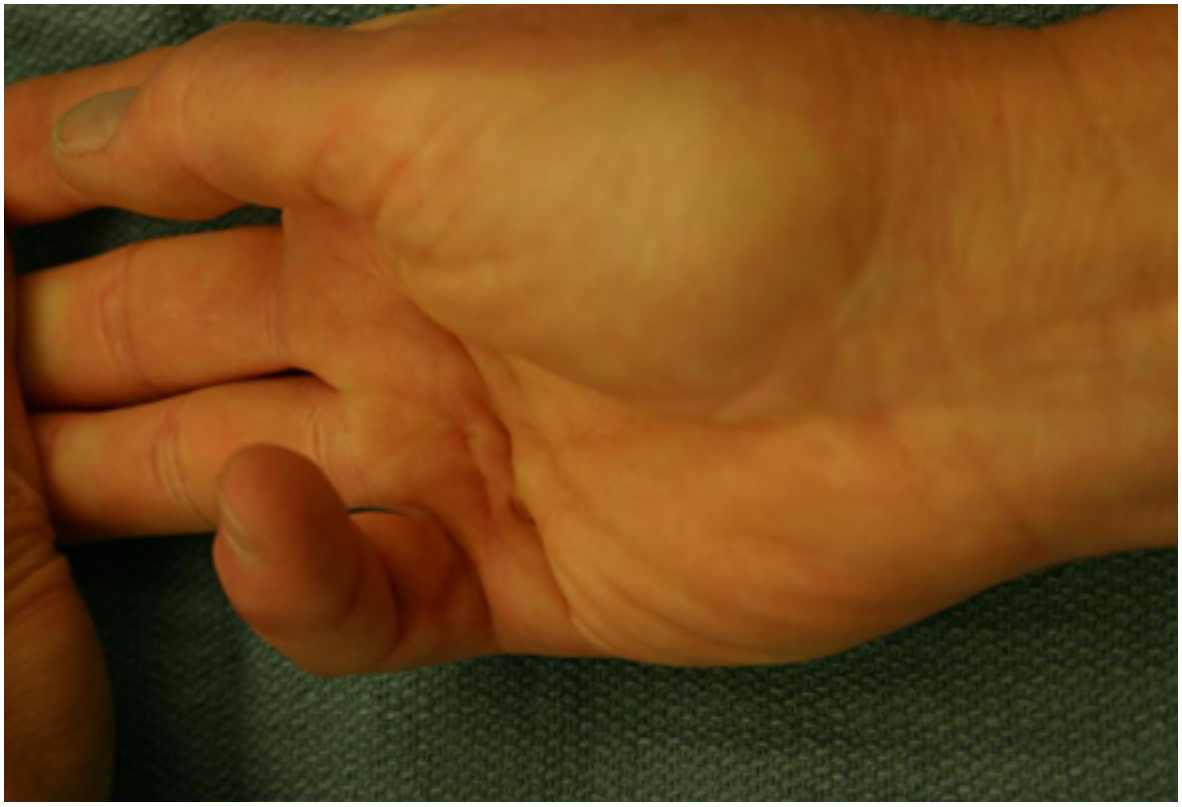

*Figure 4: Preoperative view of a small finger flexion contracture*

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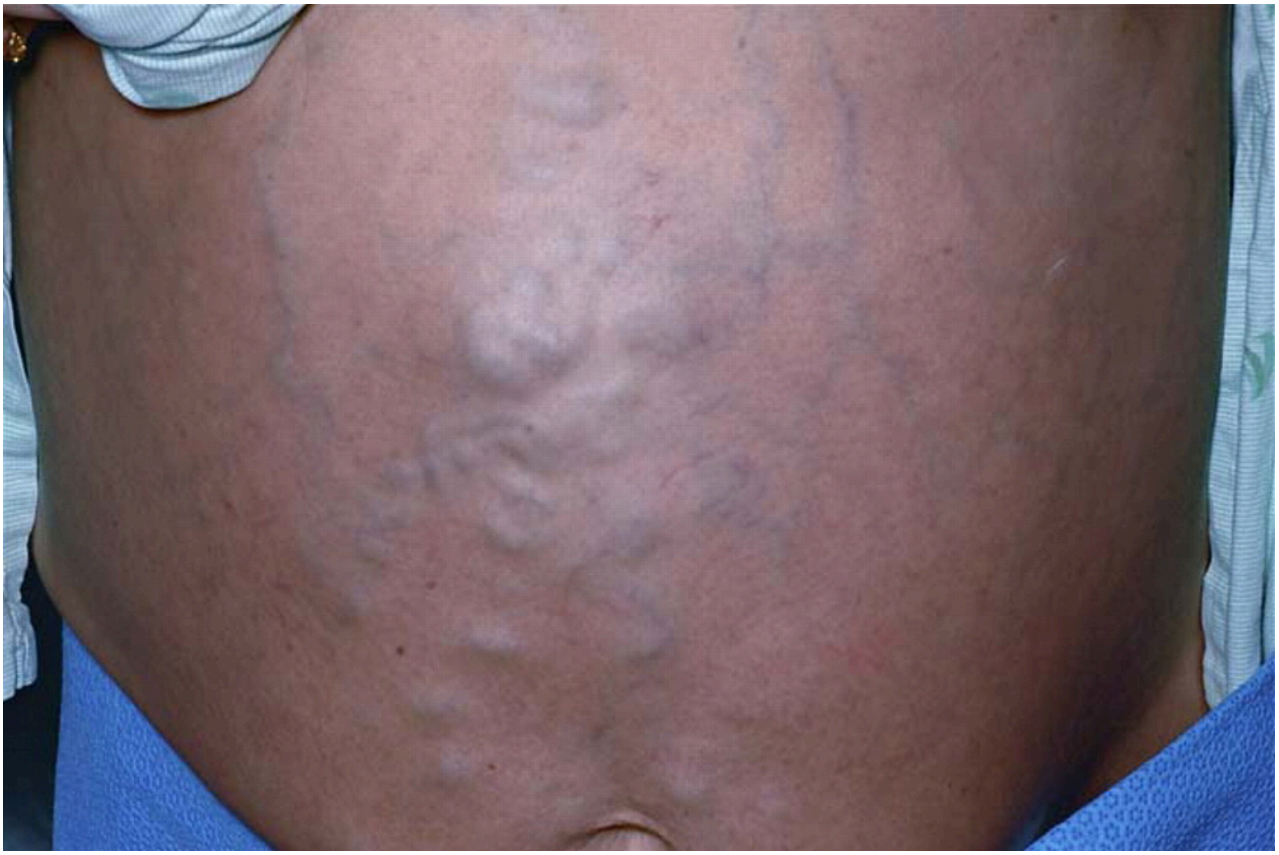

*Figure 5: Caput medusa: dilated superficial (superior and inferior) epigastric veins radiating from a central large venous varix*

*Singh NK, Cheema U, Khalil A. Caput medusae. Case Reports. 2010;2010:bcr0320102795; used with permission*

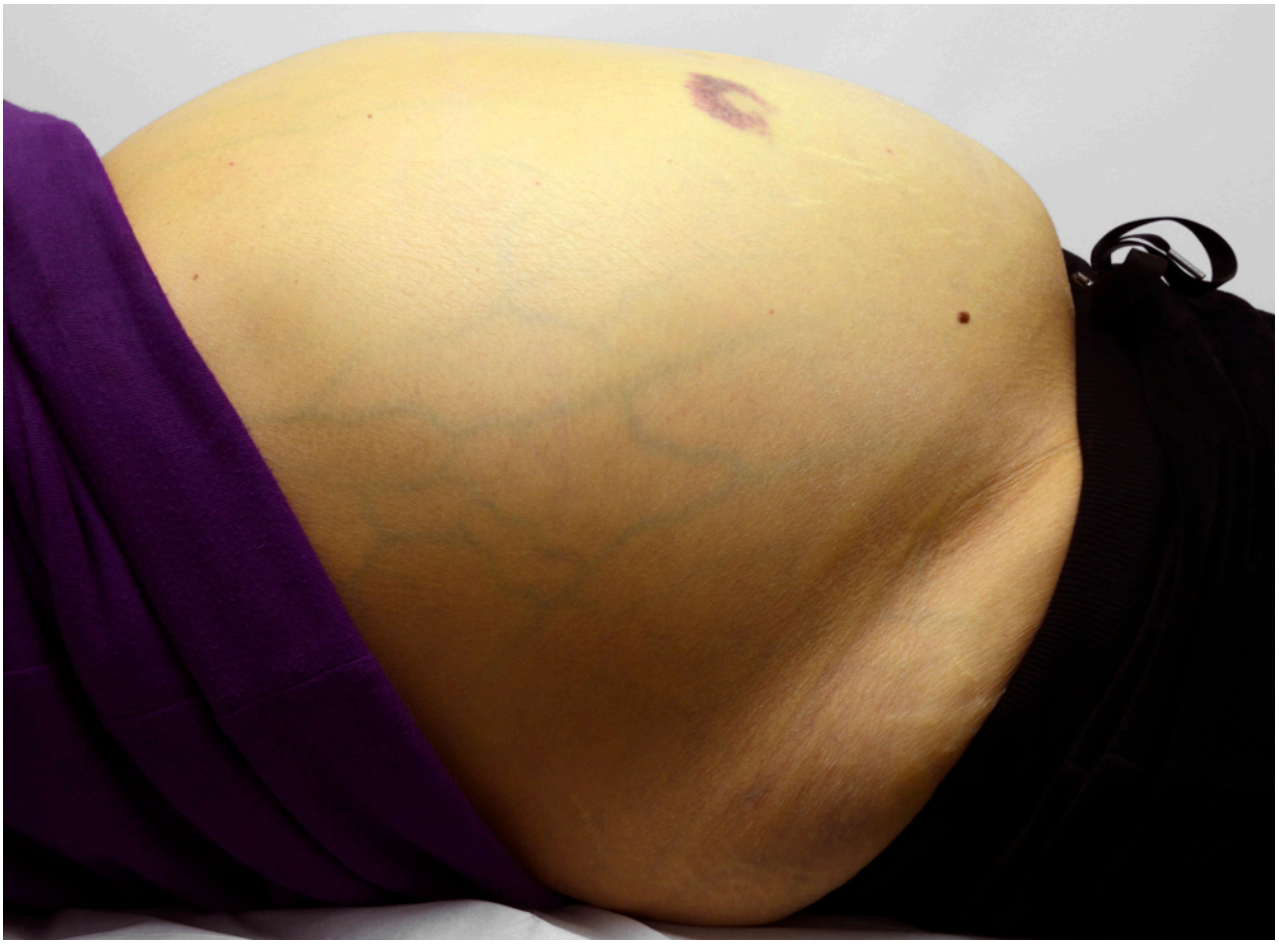

*Figure 6: Ascites. View of the abdomen of a female patient with alcohol-related liver disease and cirrhosis, showing swelling due to ascites (accumulation of fluid in the peritoneal cavity), jaundice (yellowing of the skin), and bruising*

*Science Photo Library; used with permission*

| Parameter | Points assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Hepatic encephalopathy | None | Grade 1-2 | Grade 3-4 |
| Bilirubin micromol/L (mg/dL) | <34.2 (<2) | 34.2-51.3 (2-3) | >51.3 (>3) |
| Albumin g/L (g/dL) | >35 (>3.5) | 28-35 (2.8-3.5) | <28 (<2.8) |
| Prothrombin time<br>Seconds over control<br>INR | <br><4<br><1.7 | <br>4-6<br>1.7-2.3 | <br>>6<br>>2.3 |
| CPT classification:<br>Child A: score 5-6 (well compensated);<br>Child B: score 7-9 (significant functional compromise);<br>Child C: score 10-15 (decompensated) | | | |

*Figure 7: Child-Pugh-Turcotte scoring system*

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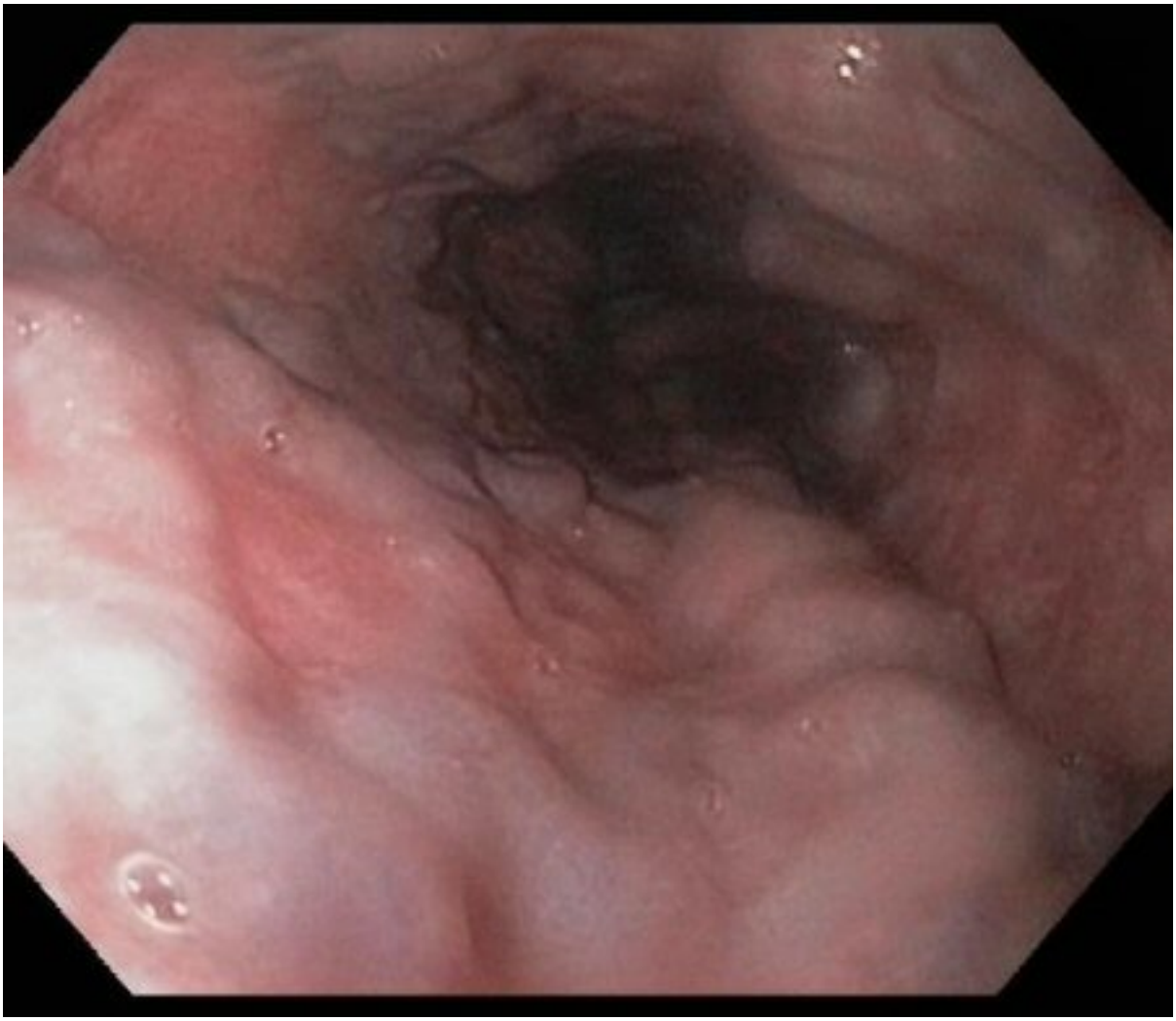

*Figure 8: Oesophageal varices in a patient with portal hypertension*

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BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

**Figure 1 – BMJ Best Practice Numeral Style**



 

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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