Liver cirrhosis

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Cirrhosis is widely prevalent worldwide and can be a consequence of different causes, such as obesity, non-alcoholic fatty liver disease, high alcohol consumption, hepatitis B or C infection, autoimmune diseases, cholestatic diseases, and iron or copper overload. Cirrhosis develops after a long period of inflammation that results in replacement of the healthy liver parenchyma with fibrotic tissue and regenerative nodules, leading to portal hypertension. The disease evolves from an asymptomatic phase (compensated cirrhosis) to a symptomatic phase (decompensated cirrhosis), the complications of which often result in hospitalisation, impaired quality of life, and high mortality. Progressive portal hypertension, systemic inflammation, and liver failure drive disease outcomes. The management of liver cirrhosis is centred on the treatment of the causes and complications, and liver transplantation can be required in some cases. In this Seminar, we discuss the disease burden, pathophysiology, and recommendations for the diagnosis and management of cirrhosis and its complications. Future challenges include better screening for early fibrosis or cirrhosis, early identification and reversal of causative factors, and prevention of complications.

Introduction

Liver cirrhosis is widely prevalent in both low-income and middle-income countries and in high-income countries, and is associated with high morbidity and mortality.[1] Cirrhosis is a consequence of chronic liver inflammation that is followed by diffuse hepatic fibrosis, wherein the normal hepatic architecture is replaced by regenerative hepatic nodules, which eventually leads to liver failure.[2] Chronic liver inflammation does not progress to cirrhosis in all patients, but when progression does occur, the rate at which it happens varies from weeks (in patients with complete biliary obstruction) to decades (in patients with longer-term causes, such as viral hepatitis C). The asymptomatic (initial) phase of cirrhosis can be followed by a relatively short symptomatic phase of months to years. The symptomatic phase, usually designated as decompensated cirrhosis, is associated with various complications that result in frequent hospital admission, impaired quality of life of patients and caregivers, and patient death in the absence of liver transplantation.[3–6]

Patients with cirrhosis without any symptoms are termed to have compensated cirrhosis. Complications such as ascites, variceal bleeding, hepatic encephalopathy, or non-obstructive jaundice, which can develop with cirrhosis of any origin, herald the onset of decompensated cirrhosis. In the presence of cirrhosis, superimposed hepatic injury (due to viral, drug-induced, or alcohol-associated hepatitis) or other complications, particularly bacterial infections, can lead to hepatic and extrahepatic organ failure—a condition known as acute-on-chronic liver failure—that is associated with high short-term mortality.[7] Most deaths in patients with decompensated cirrhosis result from hepatic and extrahepatic organ failure. Deaths during the compensated stage are largely due to cardiovascular disease, malignancy, and renal disease.

Cirrhosis appears to receive less public attention than other chronic diseases, such as congestive heart failure, chronic obstructive pulmonary disease, and chronic kidney disease, which is partly attributable to the stigmatisation of cirrhosis and the perception that the disease is largely related to alcohol consumption.[8,9] Public awareness of the relevance of cirrhosis is still low and the disease is not commonly diagnosed during the development phase, which leads to missed opportunities to mitigate causative factors and prevent subsequent progression.

Important research efforts over the past 20 years have improved our understanding of the pathogenesis, diagnosis, and treatment of the disease. In this Seminar, we summarise the current understanding of cirrhosis, and present a brief discussion on hepatocellular carcinoma.

Global burden of cirrhosis

About 2 million deaths worldwide annually are attributable to liver disease: 1 million due to cirrhosis and 1 million due to viral hepatitis and hepatocellular carcinoma. More than 60% of all liver disease-related deaths are in men.[1] Cirrhosis is the 11th most common cause of death, the third leading cause of death in people aged 45–64 years, and together with liver cancer, accounts for 3·5% of all deaths worldwide.[10] Age-standardised deaths due to cirrhosis are highest in Egypt (where the prevalence of hepatitis C and hepatitis B is very high) and lowest in Singapore.[1] Cirrhosis is the seventh highest

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Search strategy and selection criteria

We searched the Cochrane Library (from Jan 1, 2010, to March 1, 2021), MEDLINE (from Jan 1, 2000, to March 1, 2021), and Embase (from Jan 1, 2008, to March 1, 2021) for publications in English exclusively. We used the search terms "liver cirrhosis" or "cirrhosis of the liver" in combination with "ascites", "prognosis", "gastrointestinal bleeding", "bacterial infections", "acute kidney injury", "hepatic encephalopathy", "acute-on-chronic liver failure", "chronic liver diseases", "liver disease burden", "liver fibrosis", "hepatic fibrosis", "compensated cirrhosis", and "decompensated cirrhosis". We selected publications mainly from the past 5 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

cause of disability-associated life-years in people aged 50–74 years, the 12th top cause in the 25–49 age range, and the 15th top cause in all ages.[11]

The most common causes of cirrhosis worldwide are alcohol-related liver disease (also known as alcohol-associated liver disease),[12] non-alcoholic fatty liver disease (also known as metabolic-associated fatty liver disease, although this new terminology is not yet established),[13] and chronic viral hepatitis B and C. Among the 2 billion people worldwide who consume any amount of alcohol, more than 75 million are at risk of

alcohol-related liver disease due to high alcohol consumption (ie, any pattern of alcohol use that is damaging to health). Approximately 2 billion adults worldwide who are obese or overweight and 400 million adults worldwide who have diabetes are also at risk of non-alcoholic fatty liver disease. The burden of alcohol-related liver disease and non-alcoholic fatty liver disease is predicted to continue to increase in the next few decades.

Cause-specific mortality data are scarce in many regions where liver disease is highly prevalent, particularly in Africa. Globally, in 2017, 31·5% of deaths in male patients with cirrhosis were related to hepatitis B; 25·5% were related to hepatitis C; 27·3% were related to alcohol-related liver disease; 7·7% were associated with non-alcoholic steatohepatitis, and 8·0% resulted from other causes.[1] Deaths caused by cirrhosis associated with hepatitis B (24·0%) and alcohol-related liver disease (20·6%) were lower in women; the proportion related to hepatitis C was similar (26·7%); and the proportions associated with non-alcoholic fatty liver disease (11·3%) and other causes (17·3%) were higher.[1]

Causes and risk factors

The causes of cirrhosis are outlined in panel 1.[14] The occurrence of more than one causative factor in a single patient can lead to more rapid progression to cirrhosis. Aetiology might also influence the comorbidities associated with cirrhosis: for example, metabolic syndrome is more frequent in patients with non-alcoholic fatty liver disease.

Table 1 summarises the main risk factors of, and diagnostic methods for, the most common causes of cirrhosis. The risk of non-alcoholic fatty liver disease and alcohol-related liver disease is linked to some genetic risk variants. Although several single-nucleotide polymorphisms have been identified,[15] the Ile148Met variant of *PNPLA3* (rs738409) has the largest effect, increasing the risk of non-alcoholic fatty liver disease, alcohol-related cirrhosis, and hepatocellular carcinoma by two to three times.[16,17] A variant in the *HSD17B13* gene seems to be protective against these complications.[18] Such variants might partly explain the vast differences in individual susceptibility to alcohol-related and obesity-related liver diseases.[19,20] The risk of alcohol-related cirrhosis is closely associated with drinking patterns,[21,22] and increases substantially with more than three drinks (with one drink equating to 10 g of pure alcohol) per day. However, up to 15% of people with such drinking habits have a normal liver histology.[19] In addition, components of metabolic syndrome and alcohol use disorder often coexist and constitute a cumulative risk.[23,24] Similarly, alcohol overuse often overlaps with chronic hepatitis C infection as a risk factor, and coinfection with hepatitis B and hepatitis C is estimated to be between 1% and 15%, depending on geographical region.[25] Among susceptible individuals, the risk of progression to cirrhosis and of development of complications is dependent on several factors, such as

Panel 1: Aetiology of cirrhosis[14]

Viral
- Hepatitis B*
- Hepatitis C*
- Hepatitis D (usually superimposed on a hepatitis B infection)

Alcohol-related
- Alcohol-related liver disease*

Metabolic and genetic
- Non-alcoholic fatty liver disease*
- Haemochromatosis
- Wilson's disease
- α1-antitrypsin deficiency
- Cystic fibrosis
- Lysosomal acid lipase deficiency
- Progressive familial intrahepatic cholestasis
- Tyrosinaemia type 1
- Type IV glycogen storage disease

Autoimmune
- Autoimmune hepatitis
- Primary biliary cholangitis
- Primary sclerosing cholangitis

Biliary
- Biliary atresia
- Biliary strictures

Vascular
- Budd-Chiari syndrome
- Veno-occlusive disease
- Fontan-associated liver disease
- Cardiac cirrhosis

Drug-related (long-term use)†
- Methotrexate
- Amiodarone
- Methyldopa
- Vitamin A

Cryptogenic cirrhosis (cause uncertain)

*Common causes of cirrhosis. †Long-term not defined because the duration of use that associates with cirrhosis varies with factors such as obesity and concomitant alcohol consumption.

	Causative factors	Main drivers or contributing factors	Risk of cirrhosis*	Primary tests	Confirmatory tests†	Main differential diagnosis
Metabolism	Alcohol consumption	Lifestyle	5–10%	Alcohol use disorder identification test; blood tests for γ-glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, and mean corpuscular volume; liver elastography‡	Urinalysis for ethyl glucuronide, liver biopsy, and liver elastography‡	Any other cause mentioned in this table
Metabolism	Obesity, type 2 diabetes, metabolic syndrome	Genetic polymorphisms (ie, mutations in the *PNPLA3* gene) and alcohol consumption	1–2%	Body-mass index, HbA$_{1c}$, aspartate aminotransferase, alanine aminotransferase, fibrosis-4 index, and liver elastography‡	Liver biopsy to detect non-alcoholic steatohepatitis, and liver elastography‡	Any other cause mentioned in this table
Infection	Hepatitis B (90% of infants and 5–10% of adults infected with the hepatitis B virus develop chronic hepatitis)	Living in high-endemicity areas (>2% prevalence), including prisons; high-risk sexual behaviours; intravenous drug use; immunosuppressive therapy; haemodialysis	Up to 40% if untreated	HBsAg testing	Presence of hepatitis B virus DNA	Any other cause mentioned in this table
Infection	Hepatitis C (75–80% of all infected patients with the hepatitis C virus develop chronic hepatitis)	Living in high-risk environments (eg, prisons); high-risk sexual behaviours; intravenous drug use; immunosuppressive therapy; haemodialysis; working with blood products or needles	10–20% if untreated	Anti-hepatitis C virus antibodies testing	Presence of hepatitis C virus RNA	Any other cause mentioned in this table
Genetic predisposition	Haemochromatosis, mutations in the *HFE* gene	..	2–4%	Serotransferrin (also known as transferrin) saturation >45% (screening test); high serum ferritin	*HFE* test for Cys282Tyr homozygosity or other *HFE* genotypes	High alcohol consumption, metabolic syndrome, hepatitis B, hepatitis C, inflammatory states, iron supplementation, and frequent blood transfusions
Genetic predisposition	α-1 antitrypsin deficiency, mutations in the *SERPINA1* gene	..	15% with a ZZ genotype for α-1 antitrypsin	Low serum levels of α-1 antitrypsin	*SERPINA1* test for ZZ, SZ, or MZ genotypes	High alcohol consumption, amyloidosis, glycogen storage disease
Genetic predisposition	Wilson's disease, mutations in the *ATP7B* gene	..	Insufficient data available	Low serum ceruloplasmin	Urinary copper in 24 h, liver biopsy, genetic analysis	Any other cause mentioned in this table
Host and environmental triggers	Autoimmune hepatitis	Female sex (male to female prevalence ratio: approximately 1:3)	Insufficient data available	Alanine aminotransferase, IgG, ANA, smooth muscle antibody, liver-kidney microsomal antibody, liver cytosolic antigen type 1	Liver biopsy	Non-alcoholic steatohepatitis, hepatitis B, hepatitis C, primary sclerosing cholangitis, primary biliary cholangitis, Wilson's disease
Host and environmental triggers	Primary biliary cholangitis	Female sex (male to female prevalence ratio: approximately 1:4)	Approximately 33% if untreated	Elevation of serum alkaline phosphatase, γ-glutamyltransferase, conjugated bilirubin, or all	Serum antimitochondrial antibodies, primary biliary cholangitis-specific ANA, normal MRCP, and liver biopsy§	Primary sclerosing cholangitis, secondary sclerosing cholangitis, IgG4-associated cholangitis
Host and environmental triggers	Primary sclerosing cholangitis	Male sex (male to female prevalence ratio: approximately 2:1); two-thirds of patients with primary sclerosing cholangitis have concomitant inflammatory bowel disease	Most patients will require liver transplantation for complications	Elevation of serum alkaline phosphatase and γ-glutamyltransferase	MRCP, liver biopsy§, ERCP§	Secondary sclerosing cholangitis

ERCP=endoscopic retrograde cholangiopancreatography. HbA$_{1c}$=glycated haemoglobin. MRCP=magnetic resonance cholangiopancreatography. *Risk of cirrhosis is defined as the percentage of people in the population with the corresponding risk factor who will receive a diagnosis of cirrhosis at any time in their life. †To assess the severity of fibrosis, presence of cirrhosis, or portal hypertension, all patients must be assessed with abdominal ultrasound and elastography. ‡Although useful, liver elastography is not available as primary test in most countries. §Not essential for diagnosis, but can be useful for differential diagnosis.

Table 1: **Aetiology and diagnosis of the most common causes of cirrhosis by risk factor**

lifestyle modification (abstinence from alcohol and weight loss), vaccination against hepatitis B, control of inflammation (eg, as caused by autoimmune hepatitis and hepatitis B), or eradication of disease (in the case of hepatitis C).

Diagnosis of cirrhosis

The diagnostic evaluation of patients suspected to have cirrhosis depends on the phase of the disease. In patients with suspected compensated cirrhosis, the aim is to
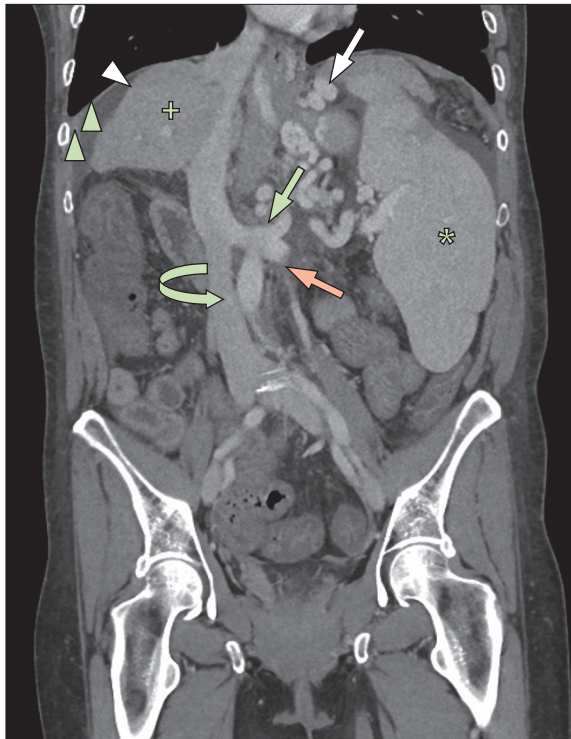
***Figure 1:* Coronal CT image of the abdomen in a patient with cirrhosis**
The liver is shrunken (green cross), shows nodularity (white arrowhead), and is surrounded by ascites (green arrowheads). The spleen is enlarged (star). Gastro-oesophageal varices are seen (white arrow). There is a splenorenal shunt between a tributary of the splenic vein (green arrow) and the left renal vein (red arrow). The left renal vein is seen entering the inferior vena cava (curved green arrow).

quantify the degree of hepatic fibrosis,[19,26,27] assess the presence of portal hypertension[28] (figure 1), and determine the cause or causes of the disease (table 1). These factors are strongly associated with the risk of progression and of subsequent development of complications of cirrhosis, and inform the kind of follow-up required.[29]

An assessment of hepatic fibrosis is required to identify patients at risk of cirrhosis. Liver fibrosis is commonly classified into four stages of increasing severity (figure 2). Stage 3 fibrosis and stage 4 fibrosis (which classify as cirrhosis) associate strongly with future liver-associated morbidity and mortality,[26,27,30,31] and thus represent an important point for timely intervention to prevent further progression.[32,33]

A liver biopsy is the gold standard for the assessment of liver fibrosis. However, the current indication for liver biopsy is mainly to determine the cause of liver disease in selected cases, and not to stage fibrosis. Standard liver biochemistry and ultrasonography have low sensitivity and specificity (less than 60%) in assessing liver fibrosis and are not recommended for this purpose.[34,35] However, several indices combining various markers (ie, panels), such as the Fibrosis-4 Index,[36] the Non-Alcoholic Fatty Liver Disease Fibrosis Score,[37] and FibroTest,[38] are available to assess the degree of fibrosis. These panels

can all be used as first-line screening tests in primary care to assess hepatic fibrosis. Some non-invasive tests are commonly used to assess hepatic fibrosis, with suggested cutoff values being applied to guide clinical decision making (table 2).[38–41] Besides indirect fibrosis indices, other more direct methods, such as the enhanced liver fibrosis test and liver elastography, can be used to assess the degree of hepatic fibrosis.[41] Elastography, which measures the stiffness of the liver, correlates well with the degree of fibrosis in the fasted state, in the absence of inflammation, biliary obstruction, and hepatic congestion.[41,42] Transient elastography has been validated for the assessment of various causes of liver disease[41–43] and is the preferred test for its ease of use and utility as a point-of-care assessment, but is not generally available in primary care. Hepatic fibrosis can also be assessed by point shear wave elastography and two-dimensional shear wave elastography.[44] MRI-based methods might be superior to the aforementioned tests in assessing both hepatic fibrosis and steatosis, but are more expensive and less widely available.[45,46]

Pathophysiology of cirrhosis

The histological structural abnormalities of cirrhosis lead to a distortion of the hepatic angioarchitecture, which increases resistance to portal blood and is the initial factor leading to portal hypertension.[47–50] In addition, an imbalance in the intrahepatic circulation of vasoconstrictive and vasodilating agents results in net vasoconstriction leading to a dynamic component in hepatic resistance that can induce rapid changes in portal pressure.[51] The most thoroughly studied vasoactive agent is nitric oxide. In the cirrhotic liver, the sinusoidal endothelial cells produce less nitric oxide, and this production might decrease further in response to acute events such as infections. The ensuing decrease in nitric oxide results in further increases in hepatic resistance, which contributes to increases in portal pressure.[52]

The initial increase in portal pressure as a result of higher intrahepatic vascular resistance leads to circulatory abnormalities, the most important of which is the development of splanchnic arterial vasodilation.[53] In contrast to what occurs in hepatic circulation, in splanchnic circulation the production of nitric oxide by endothelial cells is increased:[54] initially as a response to vascular shear stress, and later in the disease exacerbated by bacterial translocation (the passage of viable bacteria or bacterial products through the gut mucosa to the systemic circulation) and by the sustained inflammatory response typical of advanced cirrhosis.[52–55] Vasodilation in the splanchnic capillary beds and arterioles results in an increase in portal blood flow that, in combination with an increase in intrahepatic vascular resistance, results in increased portal pressure (known as portal hypertension). Because the splanchnic vascular bed accounts for about 25% of the total systemic vascular resistance, progressive splanchnic vasodilation results in a decrease in the
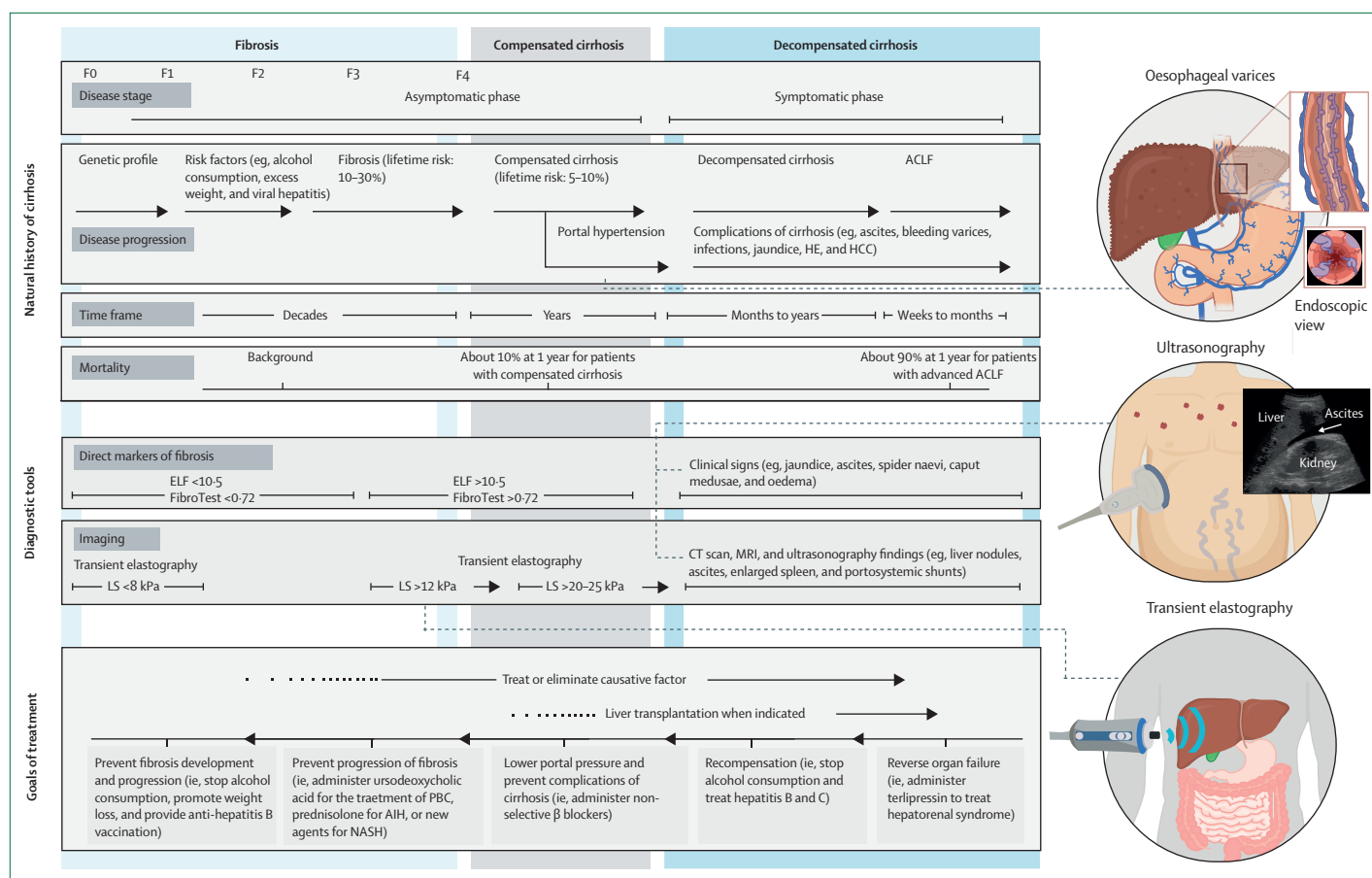
Figure 2: The clinical spectrum of chronic liver disease

Natural history, diagnostic tools, and goals of treatment according to different stages of chronic liver diseases, from early fibrosis to advanced fibrosis, compensated cirrhosis, and decompensated cirrhosis. Lifetime risk refers to the lifetime risk of developing cirrhosis. The differently weighted dots in the Goals of treatment panel represent the starting point differences depending on aetiology, country, and time of diagnosis; no clear consensus exists for early-stage disease approaches. ACLF=acute-on-chronic liver failure. AIH=autoimmune hepatitis. ELF=enhanced liver fibrosis test. F=fibrosis stage. HCC=hepatocellular carcinoma. HE=hepatic encephalopathy. LS=liver stiffness. NASH=non-alcoholic steatohepatitis. PBC=primary biliary cholangitis.

effective arterial blood volume causing systemic hypotension, arterial underfilling, and activation of neurohumoral vasoconstrictive systems (ie, sympathetic nervous system, renin–angiotensin–aldosterone system, and non-osmotic release of vasopressin). These systems aim to counteract vasodilation and lead to sodium and water retention, which results in an increase in plasma volume. Part of the excessive plasma volume is compartmentalised to the peritoneal space as ascites, a result of portal hypertension. With the progression of cirrhosis, vasodilation increases and systemic blood pressure progressively decreases, with maximal activation of vasoconstrictors factors. The result is intense vasoconstriction in the renal circulation, culminating in hepatorenal syndrome, a form of acute kidney injury.[56]

The increased plasma volume causes an increase in cardiac output, which leads to a hyperdynamic circulatory state and, together with splanchnic vaso-dilation, increases portal blood inflow and perpetuates portal hypertension (figure 3). The increased portal pressure causes a reversal in flow and dilation of pre-existing collateral channels at sites where systemic and portal circulation come together (such as at the gastro-oesophageal junction) and activation of angiogenesis, which promotes the formation of new collaterals.[57] The most clinically relevant portosystemic collaterals are gastro-oesophageal varices. When the pressure in these varices exceeds the elastic capacity of the vessel wall, variceal bleeding occurs. Portosystemic shunting, together with the deterioration in liver function, contributes to hepatic encephalopathy by decreasing the clearance of gut-derived ammonia.

The relevance of portal hypertension in driving complications of cirrhosis has been shown by the close association between the degree of portal hypertension and the risk of complications, and by the decrease in risk that results from decreasing portal pressure.[58] Arroyo and colleagues[55] have postulated that the development of systemic inflammation with the progression of cirrhosis might have an important role in acute hepatic decompensation. Inflammation is triggered by bacterial

	Rule out fibrosis if the value is	Rule in fibrosis up to stage 2 if the value is	Rule in fibrosis stage 3 or 4 if the value is
Fibrosis-4 Index*	Lower than 1·3	Between 2·67 and 3·25	Higher than 3·25
NAFLD Fibrosis Score†	Lower than −1·455	Not established	Higher than 0·676
FibroTest‡	Lower than 0·31	Between 0·48 and 0·72	Higher than 0·72
ELF§	Lower than 7·7	Between 9·8 and 10·5	Higher than 10·5
Transient elastography	Lower than 6 kPa	Between 8 kPa and 12 kPa	Higher than 12 kPa

All markers to rule in fibrosis shown here have a sensitivity of more than 90%. All markers to rule out fibrosis shown here have a specificity of more than 90%. Liver fibrosis is graded into four categories (stage 1 to stage 4), where stage 1 corresponds to mild fibrosis, stage 2 corresponds to substantial fibrosis, and stages 3 and 4 refer to the presence of advanced fibrosis or cirrhosis. NAFLD=non-alcoholic fatty liver disease. ELF=enhanced liver fibrosis test. *The fibrosis-4 index is based on age and alanine aminotransferase, aspartate aminotransferase, and platelet serum values and is available as an online calculator.[39] †The NAFLD Fibrosis Score is based on age, body-mass index, aspartate aminotransferase to alanine aminotransferase ratio, platelets, serum albumin, and presence of diabetes and is available as an online calculator.[40] ‡The FibroTest is calculated from α2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin and γ-glutamyl transpeptidase values.[38] §The ELF is based on the measurement of amino terminal peptide of type III procollagen, metalloproteinase inhibitor 1, and hyaluronic acid.[41]

Table 2: Commonly used non-invasive tests to assess the presence of liver fibrosis and cirrhosis and suggested cutoff values to rule liver fibrosis out or in

translocation, known to occur frequently in decompensated cirrhosis. Translocation is facilitated by gut bacterial overgrowth, delayed intestinal transit, and an increase in gut permeability that occurs in the context of marked changes in gut microbiota composition and function.[59,60] In the past 10 years, evidence has been accumulating to describe the alteration in gut microbiota composition that is seen in cirrhosis, mainly characterised by loss of genetic diversity, decrease in autochthonous species, and enrichment with uncommon gut bacteria, such as *Enterococcus* spp. Alterations worsen in parallel with cirrhosis progression.[60] Although the mechanisms by which changes in microbiota composition lead to disease progression are not completely elucidated, one hypothesis is that changes in microbiota composition are associated with an impairment in microbiota function, leading to intestinal inflammation, disruption of intestinal barrier, and increased permeability, aggravating the already existing bacterial translocation. Enrichment by pathogenic species might also contribute to increased endotoxaemia, resulting in enhanced systemic inflammation.[61]

Furthermore, whereas the healthy liver acts as a barrier between the gut and the systemic circulation,[62] cirrhosis disrupts this protection through liver dysfunction and portosystemic shunting. Portal hypertension, impaired hepatic function, and the immune dysfunction observed in decompensated cirrhosis[63] work in concert to predispose patients with cirrhosis to infection.

Clinical features

Physical findings suggestive of cirrhosis are seen almost exclusively in patients with decompensated disease. The hands can show palmar erythema (red coloration of the thenar and hypothenar eminences); Terry's nails (a highly specific, but insensitive marker of cirrhosis, characterised by proximal nail-bed pallor predominantly involving the thumb and index finger); and clubbing of the fingernails in case of concomitant hepatopulmonary syndrome. Dupuytren's contracture, which mainly affects the ring and little fingers and occurs mostly in men older than 60 years and of northern European descent, is a manifestation of excessive alcohol consumption rather than of cirrhosis.[64] Other signs of cirrhosis include parotid enlargement, especially in patients with alcohol-associated cirrhosis; scleral icterus; gynecomastia; loss of secondary sexual characteristics; and spider angiomas visible as a central arteriole with radiating vessels. The exact causes of the peripheral manifestations of cirrhosis are unclear. Some of the vascular manifestations, such as spider nevi, previously attributed to impaired metabolisation of oestrogens, might be related to an increased expression of VEGFA.[65] Abdominal examination can, on occasion, show caput medusae (abdominal veins distended by blood flow radiating from the umbilicus). In addition, a physical examination can show an enlarged left hepatic lobe and splenomegaly. The likelihood of cirrhosis is higher in the presence of ascites (likelihood ratio 7·2 [95% CI 2·9–12·0]) and spider nevi (4·3 [2·4–6·2]), and lower in the absence of hepatomegaly (0·37 [0·24–0·51]).[35] Of note, however, is that the liver shrinks with disease progression. Additional clinical findings related to cardiopulmonary, neurological, and other complications of cirrhosis are summarised in table 3.[66–87] Patients with decompensated cirrhosis usually die of complications of portal hypertension or of hepatocellular carcinoma.

Portal hypertension and its complications
Ascites

Ascites manifests as an increase in abdominal circumference with abdominal discomfort. Ascites is graded as grade 1 (mild) ascites, which is only detected on ultrasonography; grade 2 (moderate) ascites, characterised by moderate abdominal distension, discomfort, and shifting dullness; and grade 3 (severe) ascites, which manifests as tense abdominal distension with a fluid wave.[29] Ascites is further classified as uncomplicated or complicated (ie, recurrent or refractory; table 3), the development of which is associated with poor prognosis (median survival from diagnosis 6 months). Therefore, patients with refractory ascites should be evaluated for liver transplantation. Recurrent ascites consists of the reappearance of grade 2 or grade 3 ascites within 4 weeks of initial mobilisation.
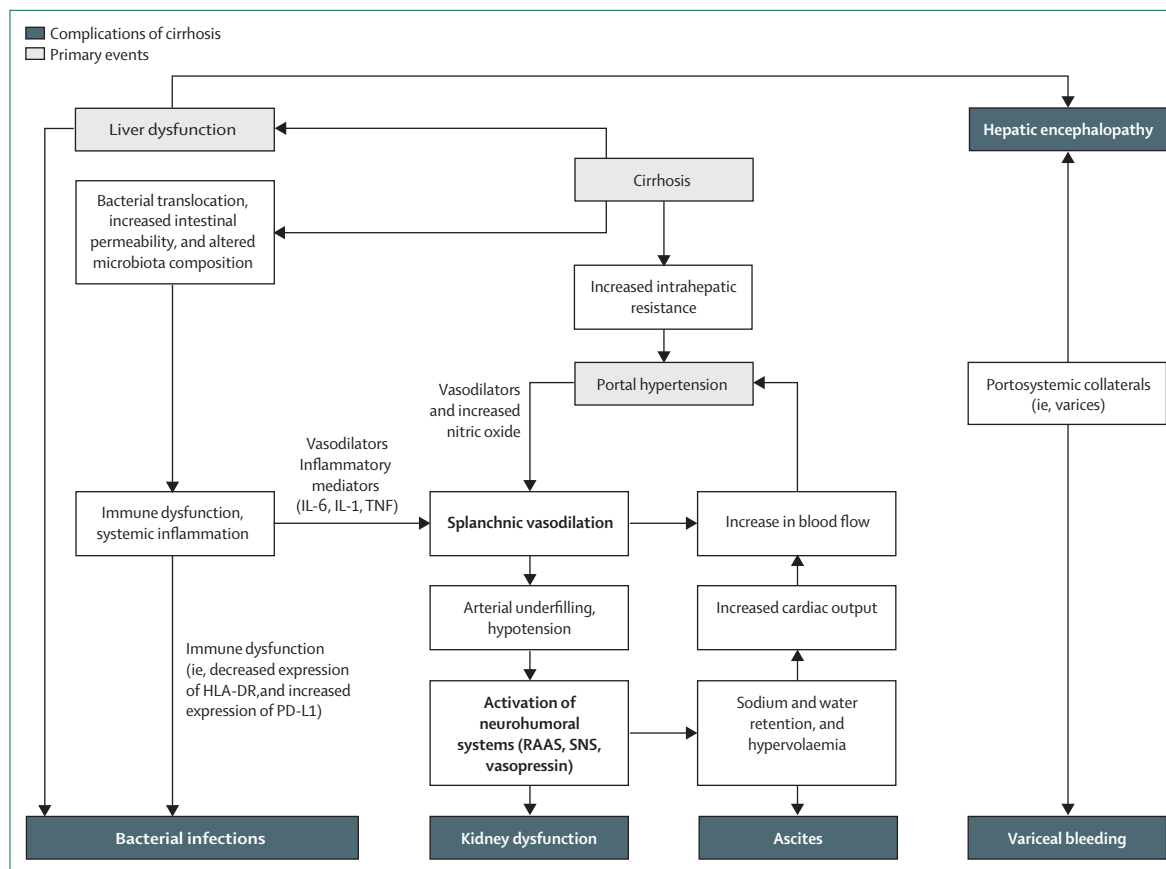
***Figure 3:* Summary of the pathophysiology of cirrhosis complications**
The increase in hepatic resistance (due to structural abnormalities and dynamic changes) leads to an initial increase in portal pressure, resulting in a cascade of disturbances in the splanchnic and systemic circulation characterised by vasodilation, sodium and water retention, and plasma volume expansion, which have a key role in causing ascites and hepatorenal syndrome. These alterations also lead to an increase in portal blood inflow, which contributes to maintaining and aggravating portal hypertension despite the development of collaterals (ie, varices). Collaterals can form into gastrointestinal varices and cause variceal bleeding and portosystemic shunting that, together with liver dysfunction, cause hepatic encephalopathy. Disease progression is associated with the development of systemic inflammation that contributes to the impairment of systemic circulatory function through the release of vasodilators. Systemic inflammation is triggered by bacterial translocation that occurs in the context of increased intestinal permeability and altered microbiota composition. Impaired liver function and immune dysfunction existing in decompensated cirrhosis lead to higher predisposition to bacterial infections. HLA-DR=human leukocyte antigen-DR isotype. RAAS=renin–angiotensin–aldosterone system. SNS=sympathetic nervous system.

Portal hypertension-related bleeding

After ascites, gastrointestinal bleeding is the second most common complication in patients with cirrhosis. Variceal bleeding is the most common cause of bleeding, is overt, and constitutes a medical emergency. Despite improvements in management, variceal bleeding is associated with a risk of mortality of approximately 20% at 6 weeks after onset; mortality is even higher in the presence of infection. Prevention and treatment of bacterial infections are associated with improved survival. The risk of variceal bleeding is mainly related to the size of the varices, but the risk is further increased by the severity of liver dysfunction and the presence of high-risk red signs on endoscopy. Primary prophylaxis (to prevent variceal bleeding) and secondary prophylaxis (to prevent recurrent variceal bleeding) are essential to improve the outcomes of patients with cirrhosis.[88] Bleeding from portal hypertension-related gastropathy, enteropathy, or colopathy might be more insidious than that from varices and usually manifests as anaemia.

Hepatic encephalopathy

Hepatic encephalopathy is defined as the spectrum of potentially reversible neuropsychiatric abnormalities secondary to hepatic dysfunction, portosystemic shunting, or both,[89] and ranges from covert (grades 0 and 1) to overt (grades 2, 3, and 4) hepatic encephalopathy.

Covert hepatic encephalopathy consists of subclinical alterations detectable only by neuropsychological or electrophysiological testing, and is not evident at physical examination.[89,90] Despite the absence of clinically evident symptoms, covert hepatic encephalopathy places patients at risk of motor vehicle accidents[91] and is associated with a reduced quality of life. Diagnosis is done by neuropsychological or electrophysiological testing. The

easy-to-administer psychometric hepatic encephalopathy score is one of the most widely used tests to diagnose covert hepatic encephalopathy.[89,90] In 2017, the animal naming test was introduced to appraise impaired cognitive function (mainly executive functions) in the early stages of hepatic encephalopathy.[92] In this simple semantic fluency test, the patient is asked to identify a series of animals in 60 seconds.[92] Identifying less than ten animals correctly is associated with a high likelihood of covert hepatic encephalopathy.

Overt hepatic encephalopathy comprises grade 2 to grade 4 hepatic encephalopathy and is accompanied by clinically detectable neuropsychiatric abnormalities in a wide severity spectrum. Grade 2 hepatic encephalopathy is characterised by lethargy or apathy, minimal disorientation for time or place, personality changes,

	Definition and diagnostic criteria	Treatment	Treatment objectives	Data sources
Uncomplicated ascites	Ascites that can be controlled with sodium restriction and diuretics and that is not associated with infection or AKI	Low-sodium diet and diuretics (spironolactone, or spironolactone plus furosemide); in patients with tense ascites, large-volume paracentesis with albumin replacement (6–8 g of albumin per L of ascites fluid removed) should be performed; the role of repeated intravenous albumin administration to patients with uncomplicated ascites is uncertain	Symptomatic relief of ascites and extension of survival	Non-blinded RCT including 440 patients with uncomplicated ascites requiring diuretics showing that weekly administration of intravenous albumin improved survival at 18 months (77% vs 66% with standard of care);[66] double-blind RCT including 196 patients with ascites on the waiting list for liver transplantation that compared combination therapy with albumin every 2 weeks and oral midodrine with double placebo showing no survival differences[67]
Recurrent or refractory ascites	Ascites requiring more than three therapeutic paracenteses despite optimal medical therapy or that cannot be mobilised, or the early recurrence of which cannot be prevented because of poor response to sodium restriction and diuretic treatment or because of diuretic-induced complications that preclude the use of an effective diuretic dosage[68]	First-line treatment is large-volume paracentesis with albumin replacement; TIPS should be considered for suitable candidates (younger than 70 years, preserved liver function with bilirubin <3 mg/dL, no previous severe encephalopathy, and no heart dysfunction); patients must be on intensive diuretic therapy (spironolactone 400 mg/day plus furosemide 160 mg/day) for at least 1 week and on a sodium-restricted diet of less than 88 mEq/day; an absence of response is characterised by a mean weight loss of up to 0·8 kg over 4 days and by a urinary sodium output inferior to sodium intake	Control of ascites and extension of survival	Meta-analysis showing that TIPS is more effective than paracentesis in controlling ascites;[69] in the latest RCT using the current standard TIPS technique (polytetrafluoroethylene-covered stents), TIPS improved transplant-free survival compared with paracentesis[70]
Hepatic hydrothorax	Pleural effusion in the absence of cardiac, pulmonary, or pleural disease	Response to diuretic therapy is limited; thoracocentesis is required for symptom relief; TIPS can be beneficial for some patients by providing longer-term relief	Symptomatic relief	Observational data
Acute variceal haemorrhage	Bleeding from dilated portosystemic collateral veins at the gastro-oesophageal junction due to portal hypertension (bleeding from varices at sites other than the oesophagus and stomach is termed ectopic variceal bleeding)	Cautious transfusion in stable patients after volume resuscitation (transfusion threshold of 7 g/dL); haemostatic treatments include vasoactive treatments (octreotide, somatostatin, or terlipressin) and endoscopic treatment (variceal ligation); rescue TIPS in patients with uncontrolled bleeding; prophylactic antibiotics (eg, ceftriaxone) should be given for 7 days or until discharge; in patients at high risk of recurrent haemorrhage (Child-Turcotte-Pugh B score with active bleeding or Child-Turcotte-Pugh C score 10–13 points), pre-emptive TIPS within 72 hours of admission improves survival; patients not at high risk can be treated with combined β-blockers and variceal ligation	Control of bleeding, prevention of recurrent bleeding, extension of survival, and prevention of infections	RCT showing decreased mortality with conservative transfusion;[71] meta-analysis showing improved outcomes with a combination of drugs and endoscopic therapy;[72] meta-analysis showing that antibiotic prophylaxis improves survival by preventing infections;[73] conflicting results from RCTs regarding prevention in patients at high risk of haemorrhage[74-76] (benefits observed in trials including mainly patients with alcohol-associated cirrhosis[75]); for patients not at high risk, improved outcomes with combination therapy versus endoscopic therapy alone have been observed;[77] in patients with refractory ascites, β-blockers should be discontinued if systolic blood pressure cannot be maintained above 90 mm Hg, or if the patient has kidney dysfunction or hyponatraemia[78]
Overt (grades 2–4) hepatic encephalopathy	Clinically detectable neuropsychiatric abnormalities	Identification and treatment of the trigger can control the acute episode in many patients; non-absorbable disaccharides (lactulose or lactitol) are the first-line treatment for the acute episode and for preventing recurrence; patients presenting a recurrence of hepatic encephalopathy on lactulose should be treated with long-term rifaximin	Symptomatic control of hepatic encephalopathy	Meta-analysis[79] and RCT with 299 patients[80] showing that oral rifaximin 550 mg twice a day decreased recurrence from 46% to 22% over a period of 6 months

(Table 3 continues on next page)

	Definition and diagnostic criteria	Treatment	Treatment objectives	Data sources
(Continued from previous page)				
AKI–hepatorenal syndrome	Cirrhosis with ascites; diagnosis of AKI–hepatorenal syndrome according to International Club of Ascites criteria; absence of shock; no response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g per kg of bodyweight); no current or recent use of nephrotoxic substances (eg, non-steroidal anti-inflammatory drugs, aminoglycosides, contrast media); and no macroscopic signs of structural kidney injury (absence of proteinuria [>500 mg/dL], absence of microhaematuria [>50 red blood cells per high power field], and normal findings on renal ultrasonography)	First-line therapy for AKI–hepatorenal syndrome is terlipressin* plus albumin; combinations of midodrine, octreotide, and albumin, or norepinephrine infusion and albumin can also be used	Reversal of hepatorenal syndrome and extension of of survival	Meta-analysis showing efficacy of terlipressin and albumin in reverting hepatorenal syndrome, but no differences in survival;[81] midodrine, octreotide, and albumin, or norepinephrine and albumin are markedly less effective than terlipressin and albumin (on the basis of very scarce evidence)[82]
SBP	The diagnosis of SBP is based on a diagnostic paracentesis (ascitic fluid neutrophil count >250 cells per μL; the evidence to support the use of reagent strips for the diagnosis of SBP is insufficient); a positive ascitic fluid bacterial culture is not required for the diagnosis of SBP because it is positive in <50% of patients (nonetheless, ascitic fluid cultures are recommended to guide antibiotic treatment[29])	Intravenous antibiotics selected on the basis of local experience and risk of multidrug-resistant bacteria; intravenous albumin; patients with an episode of SBP should receive antibiotic prophylaxis indefinitely (norfloxacin is the first choice)	Control of infection, extension of survival, and prevention of recurrent SBP	RCT including 126 patients with SBP showing that the administration of albumin (1·5 g/kg on day 1 and 1 g/kg on day 3) decreases mortality (from 29% to 10%);[83] the efficacy of norfloxacin might be decreasing in recent years[84]
Bacterial infections other than SBP	Urinary tract infection, pneumonia, soft tissue infections, and spontaneous bacteraemia are among the most common infections in cirrhosis; the diagnosis of infections other than SBP should be based on the same criteria used in the general population[85]	Intravenous antibiotics selected on the basis of local experience and risk of multidrug-resistant bacteria	Control of infection and extension of survival	Observational data
Hepatopulmonary syndrome	Arterial hypoxaemia in patients with cirrhosis and portal hypertension secondary to intrapulmonary vascular dilatation or shunting; a contrast echocardiography can be positive in up to 40% of patients awaiting liver transplantation, but the gold standard to show intrapulmonary vascular shunting is a lung perfusion scan	Liver transplantation is the only effective treatment	Resolution of hepatopulmonary syndrome	Observational data
Portopulmonary hypertension	Elevated mean pulmonary artery pressure (>25 mm Hg) at rest in the presence of portal hypertension and pulmonary capillary wedge pressure ≤15 mm Hg; pulmonary hypertension is secondary to increased pulmonary vascular resistance (≥3 Wood units [240 dynes/s per cm⁻⁵])	Macitentan reduces mean pulmonary arterial pressure in patients with portopulmonary hypertension; other potential therapies include phosphodiesterase type 5 inhibitors, iloprost, and ambrisentan, or liver transplantation†	Improvement of mean pulmonary arterial pressure; overall functioning capacity, and transplantation eligibility†	RCT including 85 patients with portopulmonary hypertension showing that macitentan reduces mean pulmonary artery pressure;[86] no RCTs of ambrisentan exclusively in patients with portopulmonary hypertension

AKI=acute kidney injury. RCT=randomised controlled trial. SBP=spontaneous bacterial peritonitis. TIPS=transjugular intrahepatic portosystemic shunts. *Terlipressin is not yet available in the USA and Canada. †Portopulmonary hypertension in itself is not an indication for liver transplantation, but might be a contraindication when mean pulmonary arterial pressure is >35 mm Hg.[87] Pharmacological therapy might improve the transplantability of patients with portopulmonary hypertension. Most patients improve after liver transplantation.

Table 3: Diagnosis, clinical manifestations, and treatment of specific complications of cirrhosis

inappropriate behaviours, construction apraxia, and asterixis. Somnolence to semi-stupor responsive to stimuli, confusion, gross disorientation, and bizarre behaviours are hallmarks of grade 3 hepatic encephalopathy. Grade 4 hepatic encephalopathy corresponds to coma, in which the patient is unresponsive to stimuli. Overt manifestations of hepatic encephalopathy develop in 30–45% of patients with cirrhosis and in 10–50% of patients after placement of a transjugular intrahepatic portosystemic shunt.[90] Hepatic encephalopathy is the complication that most frequently leads to admission and readmission to hospital, and greatly affects quality of life of both patients and caregivers.[5]

Acute kidney injury and hepatorenal syndrome

Acute kidney injury is prevalent in up to 30–50% of hospitalised patients with decompensated cirrhosis[56,93] and is associated with increased mortality. Acute kidney injury in cirrhosis is defined as an increase in serum creatinine equal to or greater than 0·3 mg/dL (≥26·5 μmol/L) within 48 hours, or as percentage increase in serum creatinine equal to or greater than

50% from baseline, known or presumed to have occurred within the previous 7 days. Acute kidney injury is classified into different stages (1A, 1B, 2, or 3) according to the magnitude of the serum creatinine increase; stages 2 and 3 are associated with the worst prognosis.[29]

Bacterial infections, diuretic overdose, gastrointestinal bleeding, or nephrotoxic drugs (eg, non-steroidal anti-inflammatory drugs) are among the most common precipitating factors for acute kidney injury. Patients with cirrhosis can present with acute kidney injury due to a variety of causes: prerenal, hepatorenal syndrome, intrinsic, or postrenal acute kidney injury. Prerenal acute kidney injury is the most frequent cause of acute kidney injury in hospitalised patients with cirrhosis (causing up to 68% of cases). Patients with decompensated cirrhosis can also present with glomerulopathies, but intrinsic acute kidney injury in these patients is mainly due to acute tubular necrosis that can be secondary to shock or nephrotoxicity. Postrenal acute kidney injury in patients with cirrhosis is quite uncommon.

Acute kidney injury–hepatorenal syndrome is a unique form of functional kidney failure that develops in patients with advanced cirrhosis and is frequently associated with other complications of the disease.[56] It has no specific clinical signs or symptoms, but is characterised by a marked reduction in renal blood flow leading to a reduction in glomerular filtration rate, and arterial hypotension is a common finding. After the definition of acute kidney injury in cirrhosis was revised, in 2015, the terms type 1 and type 2 hepatorenal syndrome are no longer used, with type 1 hepatorenal syndrome now called acute kidney injury–hepatorenal syndrome, and type 2 hepatorenal syndrome classed as not meeting the criteria for acute kidney injury (non-acute renal injury–hepatorenal syndrome). Non-acute kidney injury is further subdivided into acute kidney disease–hepatorenal syndrome if the estimated glomerular filtration rate is less than 60 mL/min per 1·73 m² for less than 3 months, or chronic kidney disease–hepatorenal syndrome if the estimated glomerular filtration rate is less than 60 mL/min per 1·73 m² for more than 3 months. Chronic kidney disease–hepatorenal syndrome is increasingly common in patients with non-alcoholic fatty liver disease-related cirrhosis.

Although bacterial infection is the most frequent precipitating factor, acute kidney injury–hepatorenal syndrome can also occur without any identifiable precipitating factor.[56] There are no laboratory tests or markers specific for the diagnosis of acute kidney injury–hepatorenal syndrome, the diagnosis of which is made only after ruling out other causes of acute kidney injury and confirming the absence of markers of intrinsic acute kidney injury, such as haematuria, proteinuria, or kidney abnormalities on ultrasonography (table 3). Classic biomarkers such as urine sodium, fractional excretion of sodium, or urine osmolality have limitations in patients with cirrhosis and ascites because urine sodium in these patients might be particularly low due to renal sodium retention, or high as a consequence of diuretic treatment. New biomarkers of tubular damage, particularly the iron-trafficking protein NGAL, can be useful in the differential diagnosis of acute kidney injury–hepatorenal syndrome.[29,94]

Bacterial infections

Patients with cirrhosis have a risk of sepsis 2·6 times higher than patients without underlying liver disease. The prevalence of bacterial infections in patients admitted to hospital because of cirrhosis ranges from 25% to 46%.[95,96] The development of bacterial infections is usually associated with the occurrence of other cirrhosis-related complications, such as hepatic encephalopathy or gastrointestinal bleeding. Most importantly, bacterial infections are a frequent cause of hospital readmissions and increase the probability of mortality by four times.[63] In addition, the development of bacterial infections frequently leads to dysfunction and failure of other organs in addition to the liver. Bacterial infections are, therefore, one of the main triggers of acute kidney injury and acute-on-chronic liver failure, and are one of the major complications and cause of death in these patients.[7] Patients with acute-on-chronic liver failure associated with bacterial infections show worse clinical course and higher mortality at 90 days than patients with acute-on-chronic liver failure without bacterial infections.[97]

Together with urinary tract infection, spontaneous bacterial peritonitis is the most common type of infection in patients with cirrhosis, followed by pneumonia, skin and soft tissue infections, and spontaneous bacteraemia (table 3).

Spontaneous bacterial peritonitis is defined as a bacterial infection of the ascitic fluid, without any identifiable, intra-abdominal, surgically treatable source of infection.[63] Clinical presentation of spontaneous bacterial peritonitis is very heterogeneous and manifestations include abdominal pain, vomiting, diarrhoea, and non-specific symptoms; it can also be asymptomatic. A diagnostic paracentesis should be done for all patients hospitalised for cirrhosis with ascites or other complications of cirrhosis to rule out the presence of spontaneous bacterial peritonitis. Neutrophil count and ascitic fluid culture in blood culture bottles should also be done (table 3). Although early diagnosis and appropriate management has improved the prognosis of spontaneous bacterial peritonitis over the years, in-hospital mortality remains at approximately 20%.[29]

Of note, patients with cirrhosis who have bacterial infections other than spontaneous bacterial peritonitis can present with only some of the following features: signs of systemic inflammation (ie, fever, high white blood cell count, high C-reactive protein, and tachycardia); worsening liver function; hepatic encephalopathy; acute kidney injury; gastrointestinal bleeding; or shock. Bacterial infections should be ruled out in all patients presenting with complications of cirrhosis or worsening

of liver or kidney function. Health care-associated or nosocomial spontaneous bacterial peritonitis carries a high risk of infection with multidrug-resistant bacteria.

Acute-on-chronic liver failure

Acute-on-chronic liver failure occurs in approximately 30% of patients hospitalised for cirrhosis and is associated with a grave prognosis.[98,99] There is wide variation in the definitions of acute-on-chronic liver failure across different continents, probably because of disagreement regarding whether it is a distinct syndrome or a terminal stage in all patients with cirrhosis. However, there is broad agreement that acute-on-chronic liver failure is a syndrome characterised by acute decompensation of cirrhosis associated with rapid deterioration in the condition of the patient due to the development of multiple organ failure. Given the poor prognosis in these patients, there is an urgent need to harmonise the definition of acute-on-chronic liver failure worldwide to facilitate studies on effective management. In most patients with acute-on-chronic liver failure, a precipitating factor that varies depending on geographical region can be identified. Bacterial infections and alcohol consumption are the most frequent precipitating factors in Europe and the USA; exacerbation of or superimposed viral hepatitis is an additional risk factor in Asia.[100] In some patients, no precipitating factor can be identified.

Frailty and sarcopenia

Malnutrition and, consequently, sarcopenia and physical frailty parallel the severity of cirrhosis. Both adipose tissue and muscle mass can be depleted in these patients. Malnutrition is present in more than 50% of patients with decompensated cirrhosis and is associated with a higher probability of other complications, such as bacterial infections and hepatic encephalopathy, and with increased mortality.[101,102] Considering its high frequency and weight on prognosis, nutritional and sarcopenia screening is recommended for all patients with decompensated cirrhosis and in patients at high risk of malnutrition. A body-mass index of less than 18.5 kg/m² and advanced cirrhosis (class C in the Child-Turcotte-Pugh score) are factors predictive of malnutrition and sarcopenia.[103,104] Handgrip strength is recommended as an easy-to-measure, inexpensive, and effective point-of-care tool to assess malnutrition and frailty in patients with cirrhosis.[105]

Patients with cirrhosis have an increased prevalence of obesity than the general population, but reduced muscle mass and frailty can still occur in these patients in parallel with the progression of the liver disease. Therefore, a combination of obesity, sarcopenia, and frailty, which has been defined as sarcopenic obesity, can coexist in patients with cirrhosis.[105–107]

Portal vein thrombosis

Cirrhosis is associated with an increased risk of portal vein thrombosis, the prevalence of which increases with the severity of cirrhosis (from 10% in patients with compensated cirrhosis to 26% in patients considered candidates for transplantation).[108] Cirrhosis results in a decrease in both procoagulant and anticoagulant factors, together with an increase in coagulation factor VIII and von Willebrand factor.[109] Therefore, patients with advanced cirrhosis are frequently in a prothrombotic state that, together with the decrease in the portal vein flow velocity characteristic of cirrhosis, might facilitate portal vein thrombosis. Although, theoretically, portal vein thrombosis might increase portal pressure and thus the risk of complications, whether portal vein thrombosis contributes to decompensation or is just a manifestation of a more advanced stage of the disease is still unclear.[110] Anticoagulation therapy increases the chances of portal vein recanalisation,[111] but the benefits of anticoagulation are unclear for patients other than those on the waiting list for transplantation, for whom extensive portal vein thrombosis might pose a challenge to a successful transplantation.

Management of liver cirrhosis
General considerations

After cirrhosis is confirmed in a patient, the goal of management is to reverse the cause of the disease whenever possible, delay hepatic decompensation, carry out surveillance for hepatocellular carcinoma and oesophageal varices, manage complications, determine the prognosis, and assess suitability for liver transplantation.

The aim of the initial laboratory evaluation in all patients with cirrhosis includes determining the aetiology (table 1). Ultrasonography, including doppler ultrasound, is the initial imaging modality used for patients with suspected cirrhosis; direct or indirect signs detected by ultrasound can help to confirm the diagnosis. The presence of splenomegaly, portosystemic collaterals, and ascites on ultrasonography are indicative of portal hypertension and of high risk of progression to decompensated cirrhosis.[28] Patients with cirrhosis must undergo endoscopic surveillance for gastro-oesophageal varices to identify candidates to primary prophylaxis against variceal bleeding. However, in patients with A-score cirrhosis on the Child-Turcotte-Pugh score, liver stiffness on transient elastography (<20 kPa), and normal platelet count (or even transient elastography of <25 kPa and platelet count >110 000/mm³), the likelihood of having oesophageal varices requiring treatment is very low and endoscopy can be avoided.[88,112,113] Patients with large varices should be treated with β-blockers (eg, nadolol, propranolol, or carvedilol) or repeated endoscopic variceal band ligation.[88] In a randomised controlled trial including 201 patients with compensated cirrhosis who had clinically significant portal hypertension, non-selective β-blockers decreased the risk of decompensation (from 27% to 17% over a median follow-up of 37 months) mostly by decreasing the risk of ascites.[114] The trial selected patients on the basis of

hepatic venous pressure gradient measurements, which is not feasible in clinical practice. However, developments in non-invasive tests over the past 10 years (figure 2) might allow the non-invasive diagnosis of clinically significant portal hypertension, which could lead to early initiation of β-blockers.

Non-invasive markers of fibrosis and transient elastography should not be used in the evaluation of patients with decompensated cirrhosis and cannot be used to exclude the need for surveillance endoscopy, which is mandatory in the decompensated phase. All patients with ascites require a diagnostic paracentesis to assess for spontaneous bacterial peritonitis and rule out non-cirrhotic causes of ascites.[29]

The daily energy intake in patients who are not obese should be 35 kcal/kg, including a daily protein intake 1·2–1·5 g/kg, along with vitamin and zinc supplementation as required. Advising small and frequent high-calorie meals along with a bedtime snack is the easiest way to achieve this goal.[105] Aerobic and resistance exercises with emphasis on balance and flexibility should be emphasised.[115] Patients with cirrhosis from any cause should abstain from alcohol and be advised on smoking cessation.

Immunisation against hepatitis A virus, hepatitis B virus, pneumococcal pneumonia, and influenza should be administered to all patients with cirrhosis. If analgesic drugs are required, paracetamol in doses of up to 2 g daily can be safely used in patients with cirrhosis, but non-steroidal anti-inflammatory drugs should be avoided (especially in patients with decompensated cirrhosis) because they can precipitate acute kidney injury.[116] ACE inhibitors and angiotensin receptor blockers can cause hypotension and kidney failure in patients with ascites and should also be avoided. Statins are safe for patients with compensated cirrhosis, but should be used with caution and at low doses because of the risk of rhabdomyolysis.[117]

Treatment of the cause should be considered for patients with cirrhosis at any stage because reversing the cause of the disease is associated with a lower risk of hepatic decompensation and increased chances of achieving recompensation.[29] Weight loss, which is the mainstay of treatment of non-alcoholic fatty liver disease, can have a beneficial effect in patients with obesity and cirrhosis of any cause.[118]

Management of decompensated cirrhosis

The treatment of decompensated cirrhosis is directed at each specific complication, which frequently presents in combination with others. Challenging this concept, a recent randomised controlled trial assessed if 20% albumin infusions could improve the prognosis (risk of infection, kidney dysfunction, or death) of 777 patients hospitalised for decompensated cirrhosis with any complication of the disease and serum albumin below 30 g/L.[119] Repeated albumin infusions did not show any benefit over the standard of care. Detailing the specific management of each complication would fall beyond the scope of this Seminar, and a summary is presented in table 3. Thus far, no available therapies other than treating the direct cause have an effect on the overall course of decompensated cirrhosis, and the development of disease-modifying agents is still an area of research. Liver transplantation is the definitive therapy for patients with decompensated cirrhosis and should be considered when the expected survival with transplantation is better than that without. On that basis, patients with decompensated cirrhosis or a Model for End-Stage Liver Disease (MELD) score of 15 points or more should be considered for liver transplantation.[120]

Prognosis and disease scores

Patients with cirrhosis can be broadly classified as having compensated cirrhosis (with a low risk of mortality) or decompensated cirrhosis (with a higher risk of mortality). When compared with the general population, patients with compensated cirrhosis have a 5 times increased risk of death, whereas patients with decompensated cirrhosis have a 10 times increased risk. Patients with compensated cirrhosis have a median survival of 9–12 years from diagnosis,[3,121] which falls to 2 years with the onset of hepatic decompensation.[122] In a large population-based study in Denmark, which included about 15 000 patients with predominantly alcohol-associated cirrhosis, the probability of survival in patients with cirrhosis was 66% at 1 year, 38% at 5 years, and 22% at 10 years.[123] The survival rate at 1 year in patients with compensated cirrhosis was 83%, dropping to 80% with variceal bleeding, 71% with ascites, 51% in the presence of both ascites and variceal bleeding, and 36% with hepatic encephalopathy. The annual risk of decompensation varies with disease aetiology and is 4% for patients with hepatitis C-related cirrhosis, 6–10% in those with alcohol-associated cirrhosis (higher with continued drinking), and 10% for patients with hepatitis B-related cirrhosis.[123] The risk of decompensation is associated with low serum albumin concentrations, increasing MELD score, and increased portal pressure.[14]

Survival depends not only on the severity of liver disease but also on the presence of comorbidities. As the population with cirrhosis ages and the prevalence of cirrhosis secondary to non-alcoholic fatty liver disease increases, cardiovascular disease, malignancy, diabetes, sarcopenia, and frailty are expected to become major factors contributing to negative outcomes. Portal pressure as measured by an hepatic venous pressure gradient is associated with hepatic decompensation and mortality risk, but the invasive nature and expense of the procedure make repeated measurements impractical.[124] Simple numeric scores that can be calculated at the bedside can be used to gauge mortality risk. The Child-Turcotte-Pugh score uses serum albumin, bilirubin,

prothrombin time, and the subjectively assessed parameters of ascites and hepatic encephalopathy to broadly classify patients into classes A, B, and C.[125] Patients in class A generally have compensated cirrhosis and are at low risk of mortality; such patients can undergo surgical procedures with a low risk of mortality. The MELD score uses the objective variables of serum bilirubin, international normalised ratio, and serum creatinine[126] to calculate a score ranging between 6 and 40. The higher the MELD score, the greater is the risk of mortality; for example, patients with a MELD score of 40 are unlikely to survive for more than 3 months without liver transplantation. Patients with a MELD score of up to 12 are at very low risk of mortality at 3 months, even with major surgical procedures.[127] The MELD-Na score includes serum sodium, which is an independent predictor of mortality, as a variable.[128] The MELD-Na score is used in several parts of the world to prioritise allocation of organs for liver transplantation. The relationship between MELD and MELD-Na scores and mortality can be determined by entering variables at the respective publicly available websites.[129,130] MELD scores can underestimate mortality risk in patients with acute-on-chronic liver failure, especially in the presence of circulatory or respiratory failure, in patients with hepatocellular carcinoma, and in patients with complications such as hepatopulmonary syndrome and portopulmonary hypertension.

Hepatocellular carcinoma

Hepatocellular carcinoma accounts for about 90% of all primary liver cancers and, every year, 1–4% of patients with cirrhosis will develop hepatocellular carcinoma.[14] Infection with hepatitis B (in sub-Saharan Africa and southeast Asia) and hepatitis C viruses (in the USA, Europe, and Japan) is the most important risk factor for the development of hepatocellular carcinoma, although non-alcoholic fatty liver disease is an increasingly recognised risk factor for hepatocellular carcinoma that can develop in the absence of cirrhosis.[131] Evidence of the association between metabolic syndrome, diabetes, obesity, and hepatocellular carcinoma is also accumulating.[132]

In patients with cirrhosis, surveillance for hepatocellular carcinoma is recommended every 6 months through ultrasonography. Lesions with 1 cm or more in diameter on ultrasonography are followed up by either quadruple-phase CT or dynamic contrast-enhanced MRI. On contrast imaging, hepatocellular carcinoma is brighter than the surrounding liver in the arterial phase (which is called arterial enhancement) and darker than the surrounding parenchyma in the venous and delayed phases (so-called delayed washout) with a sensitivity of 89% and a specificity of 96% for the diagnosis of hepatocellular carcinoma.

The Barcelona Clinic Liver Cancer staging system is widely used for the staging and management of hepatocellular carcinoma.[133] Hepatic resection or tumour ablation might be carried out for very early-stage hepatocellular carcinoma (stage 0 on this system), whereas liver transplantation is recommended for early-stage disease (stage A). Patients with intermediate (stage B) disease might benefit from radiology-guided regional therapy. Immune-based therapies, including the combination of atezolizumab and bevacizumab, are used for patients in the advanced stage (stage C).[134] Recent data suggest that patients with non-viral hepatocellular carcinoma (particularly non-alcoholic steatohepatitis-related hepatocellular carcinoma) might be less responsive to immunotherapy.[135] Patients with terminal (Barcelona Clinic Liver Cancer stage D) disease (class C on the Child-Turcotte-Pugh score or poor performance status) receive only supportive care.

Challenges and controversies
Role of nurses in patient care

The improvements in nursing care for the management of patients with chronic conditions, such as diabetes, arterial hypertension, heart failure, and lung diseases in the past 20 years have not been accompanied by similar developments in the field of liver diseases.[136] The need to engage nurses in the care of patients with cirrhosis has been identified as a priority by the *Lancet* Standing Commission on Liver Disease in the UK and by the LiverHope Nursing Project.[137,138] Cirrhosis constitutes an ideal area for innovations in nursing care because of the characteristics and long natural history of the disease. The care of patients with cirrhosis includes both community-based care and hospital care. Therefore, nurses not only provide a continuum of care but also facilitate patient education and responsibility for their own care, including through the application of innovative technologies such as telehealth and remote monitoring, helping patients to make informed decisions and achieve self-care to prevent complications and improve their wellbeing. Nurses in the community can also have a key role in early diagnosis of the disease, by identifying individuals at high risk of cirrhosis from among at-risk populations using diagnostic algorithms or advanced technologies, such as transient elastography.[139] Future directions include specific education of nurses involved in the care of patients with cirrhosis in these and in telehealth and remote monitoring technologies, a training that should be provided by scientific societies, universities, or nurse organisations. Specific activities that could be included in the proposed role of nurses in the care of patients with cirrhosis are shown in panel 2.

Outstanding research questions

Although the outcome of complications of cirrhosis (such as variceal bleeding, spontaneous bacterial peritonitis, and acute kidney injury–hepatorenal syndrome) has improved as a result of intensive research

in these areas, many other relevant research questions remain. For example, a very important area of research is the relationship between alterations in the intestinal microbiome and translocation of bacteria and bacterial products and hepatic and systemic inflammation and progression of cirrhosis.[59,140,141] In this regard, some studies suggest the potential benefits of statin treatment aimed at reducing systemic inflammation in patients with cirrhosis.[142,143] In the past 10 years, interest in the development of specific splanchnic vasoconstrictors that can be used for long-term therapy to reduce complications of portal hypertension (particularly refractory ascites or recurrent variceal bleeding) has been growing.[144] Although aetiology-specific therapies exist for most causes of cirrhosis (eg, antiviral drugs for cirrhosis induced by hepatitis C or hepatitis B) and can be used even in decompensated cirrhosis, there is no pharmacological therapy for patients with non-alcoholic fatty liver disease, which has become the second most common cause of cirrhosis in many countries.[29] Acute-on-chronic liver failure is the most frequent cause of death in patients with decompensated cirrhosis, and there is no effective therapy besides liver transplantation, which is not always possible and not widely available, particularly in low-income countries. Exciting experimental data indicate that liver organoids that retain most human liver cell functions and improve survival when transplanted to animals with liver failure can be engineered.[145] Finally, the issue of reversibility of cirrhosis is another important area of investigation. Although reversibility of cirrhosis and hepatic fibrosis has been reported sporadically in compensated cirrhosis after elimination of the cause,[146] the reversibility of cirrhosis in patients with decompensated disease still represents a major research challenge. Other important areas that require improvement include a multidisciplinary approach to alcohol overuse, diagnosis and management of nutrition and sarcopenia, and palliative care. Other relevant open issues regarding the management of complications in patients with decompensated cirrhosis are summarised in panel 3.

Clinical trials in cirrhosis

There is a paucity of well conducted clinical trials evaluating new or repurposed therapies for patients with decompensated cirrhosis. Many published therapeutic trials in cirrhosis are underpowered, have poorly defined populations, and evaluate soft clinical endpoints. Trials should be done in well defined populations of patients with advanced (ie, decompensated) cirrhosis, include a sufficient sample size, and use hard clinical endpoints, particularly transplant-free survival or combined endpoints of complications and patient-reported outcomes.[147] Specifically, the outcomes should reflect improvements in quality of life, in reducing or eliminating symptoms, and in enabling patients to have a healthy social and working life.

Clinical guidelines from scientific societies

Of the several clinical guidelines for the management of complications of cirrhosis published in the past 5 years, the most relevant are those from international hepatology societies (eg, the European Association for the Study of the Liver[29] and the American Association for the Study of Liver Diseases)[148] and from the Baveno Consensus Workshops.[88] In the future, guideline task force groups should ideally be co-organised by transcontinental

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Panel 2: Proposed nursing care of patients with cirrhosis according to disease stage

Patients with compensated cirrhosis
- Counselling and health education about specific causes of the disease (eg, obesity and alcohol consumption)
- Counselling on physical activity and nutrition
- Identification of patients for screening for gastro-oesophageal varices and hepatocellular carcinoma
- Nursing education of patients and caregivers regarding complications and early detection of cirrhosis, including alarm signs
- Regular follow-up with standard visits or telehealth

Patients with decompensated cirrhosis
All of the above, accompanied by:
- Control of specific complications, particularly ascites and hepatic encephalopathy
- Support of compliance with medications
- Regular assessment of quality of life and frailty indexes
- Identification of patients suitable for liver transplantation
- Remote monitoring and telehealth visits
- Palliative care for terminally ill patients

Panel 3: Some clinically relevant questions regarding the management of complications in patients with decompensated cirrhosis

- Does transjugular intrahepatic portosystemic shunt improve survival in patients with diuretic-responsive ascites without increasing the incidence of hepatic encephalopathy?
- Is long-term albumin administration effective in decreasing complications and improving survival of patients with cirrhosis and ascites?
- Is refractory ascites a contraindication for the use of β blockers in prevention of variceal bleeding?
- Is prophylactic quinolone administration for the prevention of spontaneous bacterial peritonitis associated with an increased risk of infection by multidrug-resistant bacteria?
- Are any of the treatments for complications such as variceal bleeding, ascites, and hepatic encephalopathy also associated with better quality of life and improved functioning in the community?

societies to ensure that recommendations can be universally adopted.

Cirrhosis as major public health problem

The importance of liver diseases in general—and cirrhosis specifically—as major health issues has been largely underestimated. For example, the term liver disease does not appear in the WHO list of non-communicable diseases that includes, among others, cardiovascular diseases, cerebrovascular diseases, diabetes, and chronic respiratory diseases.[149] This lack of appropriate consideration is likely to be a contributory factor to the low awareness of liver diseases, both at the public and health professional levels, and to the scarcity of appropriate campaigns against liver diseases. Efforts should be made at the national and international scales to place liver diseases at the level required to counteract the stigmatisation of the disease and initiate campaigns to promote liver health.

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