Liver Cirrhosis: Pathogenesis, Causes, Staging and management: Review Article

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Abstract:

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.

Keywords: Liver Cirrhosis, pathogenesis, causes, staging, management.

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Introduction:

Cirrhosis is a complication of liver disease involves loss of liver cells with irreversible scarring of the liver (fibrosis – nodular regeneration) that partially blocks the flow of blood through the liver and liver dysfunction **(1).**

Cirrhosis changes the structure of the liver and the blood vessels that nourish it . The disease reduces the liver's ability to manufacture proteins and process hormones, nutrients, medications, and poisons. Fibrosis describes encapsulation or replacement of injured tissue by a collagenous scar, liver fibrosis results from the perpetuation of the normal wound-healing response resulting in an abnormal continuation of fibrogenesis (connective tissue production and deposition) ,fibrosis progresses at variable rates depending on the cause of liver disease, environmental factors, and host factors **(2).**

Pathogenesis of liver cirrhosis:

Cirrhosis is the end-stage condition of many types of chronic liver diseases but the underlying mechanisms are far from being clarified . Chronic injury to the liver results in inflammation, necrosis and, eventually leads to fibrosis **(3).** Activation of hepatic stellate cells (HSCs) is a pivotal event in fibrosis (**4**). Many cytokines, reactive oxygen intermediates and other paracrine and autocrine signals activate stellate cells and fibrosis start **(5).** Kupffer cells, damaged hepatocytes and activated platelets are probably involved, the stellate cells become swollen and lose retinoids with upregulation of receptors for proliferative and fibrogenic cytokines, such as platelet derived growth factor (PDGF), and transforming growth factor α1 (TGF- α 1). In the early stage of activation , inflammatory cells contribute to fibrosis via cytokine secretion. Collagens, predominantly types 1 and 3, and fibronectin replace the normal matrix in the space of disse , subendothelial fibrosis leads to loss of the endothelial fenestrations (ports), affecting normal liver function . In liver fibrosis , tissue inhibitors of metalloproteinase (TIMPs) are increased inhibiting collagenases from degrading the newly developed collagen in the liver tissues **(6).**

Grading And Staging Of Liver Cirrhosis:

Histological subclassification of cirrhosis was determined using the Laennec fibrosis scoring system. For the Laennec system fibrosis is scored in 7 grades, with 0 indicating no definite fibrosis; 1- minimal fibrosis (no septa or rare thin septum; may have portal expansion or mild sinusoidal fibrosis); 2- mild fibrosis (occasional thin septa); 3- moderate fibrosis (moderate thin septa; up to incomplete cirrhosis); 4A- mild cirrhosis, definite or probable; 4B- moderate cirrhosis (at least 2 broad septa); 4C- severe cirrhosis (at least one very broad septum or many minute nodules).The terms 'broad septum' and 'very broad septum' were defined according to the relative comparison between the thickness of fibrous septa and the size of the nodule so, 'broad septum' was defined as septal thickness being thinner than the size of the nodule, and 'very broad septum' was defined as septal thickness being thicker than the size of the nodule (**7**).

Table (1): Laennec scoring system for staging fibrosis in liver biopsies).

Stage	Name	Septa (thickness and number)	Criteria	score
0	No definite fibrosis			0
1	Minimal fibrosis	+/−	No septa or rare thin septum; may have portal expansion or mild sinusoidal fibrosis	1
2	Mild fibrosis	+	Occasional thin septa; may have portal expansion or mild sinusoidal fibrosis	2
3	Moderate fibrosis	++	Moderate thin septa; up to incomplete cirrhosis	3
4A	Cirrhosis, mild, definite, or probable	+++	Marked septation with rounded contours or visible nodules Most septa are thin (one broad septum allowed)	4
4B	Moderate cirrhosis	++++	At least two broad septa, but no very broad septa and less than half of biopsy length composed of minute nodules	5
4C	Severe cirrhosis	+++++	At least one very broad septum or more than half of biopsy length composed of minute nodules (micronodular cirrhosis)	6

The clinical stage of cirrhosis was established by the presence or absence of varices, ascites, and bleeding, and it was classified into four stages. The stages were defined as the following: stage 1- no varices; stage 2- varices and no ascites; stage 3- ascites ± varices; stage 4 -bleeding ± ascites. Stages 1 and 2 are compatible with compensated cirrhosis whereas stages 3 and 4 with decompensated cirrhosis.**(8)**.

Causes of Liver Cirrhosis (9)

a. Infections

1. Chronic Viral hepatitis types B and C.

2. Syphilis causes cirrhosis in neonates but not in adults .

b. Toxins and drugs

1. Alcohol .

2. Methotrexate .

3. Isoniazide .

4. Hypervitaminosis A.

5. Amiodarone.

6. Perhexiline maleate .

7. α-methyl dopa .

8. Oxyphenisatin .

c. Metabolic / genetic diseases

1. Hemochromatosis .

2. Wilson's disease .

3. α_1-antitrypsin deficiency .

4. Carbohydrate disorders e.g. Fructose intolerance, galactosemia, glycogen storage disease .

5. Lipid disorders .

6. Urea cycle defects e.g. Ornithine transcarbamylase .

7. Porphyria .

8. Aminoacid disorders e.g. tyrosinosis .

d. Biliary diseases

1. Primary biliary cirrhosis .

2.Secondary " mechanical" biliary obstruction

- Primary sclerosing cholangitis .
- Neoplasm of bile ducts or pancreas .
- Iatrogenic or inflammatory biliary stricture .

3. Cystic fibrosis .

4. Biliary atresia .

5. Congenital biliary cysts .

6. Childhood biliary diseases

- Byler's disease (progressive childhood cholestasis) .
- Alagille syndrome (arteriohepatic dysplasia) .
- Aageaes syndrome (cholestasis with lymphedema) .
- Zellweger syndrome (cerebrohepatorenalsyndrome) .

e.Hepatic-venous outflow obstruction

1.Veno-occlusive disease .

2. Budd-Chiari syndrome .

3. Right-sided heart failure .

4. Tricuspid valve disease.

5.Constrictive pericarditis.

6. Pericardial effusion .

7. High inferior vena cava obstruction .

f. Disturbed immunity

1. Autoimmune hepatitis .

2. Graft-versus-host disease .

g. Miscellaneous

1. Jejunal bypass for obesity .

2. Indian childhood cirrhosis .

3. Hereditary hemorrhagic telangiectasia .

4. Nonalcoholic steatohepatitis (NASH) .

5. Polycystic liver disease .

6. Cryptogenic cirrhosis **(10).**

Classification of cirrhosis :

1-Morphological classification

Three types are recognized: micronodular, macronodular and mixed in which the liver shows both micro- and macronodular features.

However, there is no functional or prognostic value to the nodule size. **(10)**

- **Micronodular cirrhosis :**

It is characterized by thick, regular fibrous septa, by regenerating small nodules (less than 3mm) which involve every lobule. The micronodular liver may represent impaired capacity for regrowth as in alcoholism, malnutrition, old age or anemia.

- **Macronodular cirrhosis :**

It is characterized by septa and large nodules. The size of nodules are more than 3mm. **(11)**

C-**Mixed cirrhosis :**

Regeneration in a micronodular cirrhosis results in a macronodular or a mixed appearance. With time, micronodular cirrhosis often converts to macronodular.

2-Aetiological classification according to cause.

Diagnosis of Liver Cirrhosis

1.Physical examination:

- Stigmata of Chronic liver disease (Spiders, Palmar erythema…etc).
- Features of portal hypertension (Ascites, splenomegaly, caput medusa…etc).
- Features of hepatic encephalopathy (Confusion, Astrexis, Fetor hepaticus).
- Others (Jaundice,bilateral parotid enlargement, scant chest and axillary hair) **(6).**

Manifestations of liver cell failure (12).

1-Jaundice which is yellow discoloration of skin,cornea and mucous membranes due to compromised hepatocyte excretory function and occur when serum bilirubin >20mg\dl.

2-Spider angiomata which is central arteriole with tiny radiating vessels ,mainly on trunk and face due to raised oestradiol, decreased oestradiol degragation in liver.

3-Nodular liver which is irregular , hard surface on palpation due to fibrosis ,irregular regeneration.

4-Splenomegaly which is enlarged on palpation or in ultrasound due to portal hypertension ,splenic congestion.

5-Ascites which is proteinaceous fluid in the abdominal cavity due to portal hypertension.

6-Caput medusa which is prominent veins radiating from umbilicus due to portal hypertension, reopening of umbilical vein that shunt blood from portal vein.

7-Palmar erythema which is erythema sparing the central portions of the palm due to raised oestradiol,decreased oestradiol degradation in liver.

8-White nails which is horizontal white bands or proximal white nail plate due to hypoalbuminemia.

9-Gynecomastia which is benign proliferation of glandular male breast tissue due to enhanced conversion of androstendione to oesterone, and oestradiol,decreased oestradiol degradation in liver.

10-Flapping tremors which is a synchronous flapping motions of dorsiflexed hands due to disinhibitions of motor neurons .

11-Foetor hepaticus which is sweet pungent smell due to volatile dimethylsulfide especially in portosystemic shunting and liver failure.

12-Anorexia ,fatigue ,weight loss ,muscle wasting oocur in 50% of patients with cirrhosis due to catabolic metabolism by diseased liver secondary to anorexia .

13-Type 2 diabetes in 15-30% of patients with cirrhosis due to disturbed glucose use or decreased insulin removal by liver .

2.Laboratory evaluation:

- Tests of hepatocellular injury (most forms of chronic hepatitis other than alcohol have an AST/ALT ratio of less than 1; however as chronic hepatitis progresses to cirrhosis, the ratio of AST/ALT may reverse **(13).**
- Tests of cholestasis (Alkaline phosphatase, Serum bilirubin, Gamma glutamyltranspeptidase, 5'-Nucleotidase**).**
- Tests of synthetic function (Serum albumin, Prothrombin time) **(Schuppan and Afdha, 2008).**

3. Specific tests to aid in the diagnosis of aetiology:

- Viral hepatitis serology(HCV,HBV,HEV,HDV).
- PCR techniques for detecting viral RNA or DNA .
- Serum iron, total iron binding capacity (TIBC), ferritin, genetic testing for the HFE gene mutation (hemochromatosis).
- Alpha-1 antitrypsin level and protease inhibitor type.
- Serum immunoglobulins (autoimmune hepatitis).
- Autoantibodies: antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), anti-liver kidney microsomal antibodies (ALKM), anti-smooth muscle antibodies (ASMA).
- Screening test for hepatocellular carcinoma: serum alpha fetoptotein. **(12).**
- **FibroTest :**It is a biomarker test that uses the results of six blood serum tests (Alpha-2-macroglobulin, Apolipoprotein,Gamma-glutamyl-transpeptidase (GGT), Total bilirubin, and Alanine transaminase (ALT)) to generate a score that is correlated with the degree of liver damage in people with a variety of liver diseases**(14).** the following equation for calculating the FibroTest score regression coefficient:

$$z = 4.467 \times \log_{10}[\alpha 2 macroglobulin(g/L)] - 1.357 \times \log_{10}[Haptoglobin(g/L)] + 1.017 \times \log_{10}[GGT(IU/L)] + 0.0281 \times [Age(years)]$$

4. Imaging studies:

•Abdominal ultrasound:

(US) is commonly the first imaging procedure performed during the evaluation of suspected liver disease. The role of ultrasound in cirrhosis includes screening for hepatocellular carcinoma (HCC) and diagnosis of cirrhosis, portal hypertension, and HCC. Ultrasound is readily available, relatively inexpensive, radiation-free, and offers real time evaluation of the liver parenchyma, border, vascular architecture, and vascular flow (**15).**

Using ultrasound, cirrhosis is suggested by dense reflective areas of irregular distribution and increased echogenicity and portal vein flow velocity.

•Computed Tomography (CT) and Magnetic resonance imaging (MRI):

can be used to define the severity of cirrhosis e.g., by determining spleen size, ascites, and vascular collaterals but helical CT and MRI with contrast are preferred if hepatocellular carcinoma or vascular lesions are suspected **(16).** MRI has also been shown to be effective in determining hepatic iron and fat content in haemochromatosis and liver steatosis, respectively **(17).**

• Radionuclide studies:

Can visualize, assess the liver, Measure Spleen Size and Portal Hemodynamics in Portal Hypertension Due to Hepatic Cirrhosis **(18).**

•Transient Elastography:

Fibroscan is a non-invasive device that assesses the 'hardness' (or stiffness) of the liver via the technique of transient elastography.It is useful test in almost any patient in whom a clinician wishes to stage liver fibrosis. The main drawback of Fibroscan testing is that it cannot be performed in all patients. Technical limitations of the test preclude its use in patients who have ascites, individuals who are morbidly obese, and/or patients who have large amounts of chest wall fat. In these groups, either the test cannot be performed or the results are not reliable. Reliability and reproducibility have been well characterized for elastography with Fibroscan, and it is important to ensure that these technical requirements are achieved to make the scan results valid. Particularly, a valid result requires 8—10 measurements with a 60% success rate and an interquartile range less than 0.3(**19, 20**).

5. Liver biopsy:

It establishes the diagnosis of cirrhosis and may show the cause, but it is only needed when clinical observation and less invasive investigations have not established the diagnosis.**(21,22).**

6- Esophagogastroduodenoscopy to screen for gastroesophagealvarices (23).

Prognosis of liver cirrhosis:

Child-Pugh Turcotte score:

The severity of cirrhosis is commonly classified with the Child-Pugh Turcotte (CPT) score that was developed nearly 50 years ago. This score uses bilirubin, albumin, INR, presence and severity of ascites, and encephalopathy to classify patients in class A, B, or C. Class A has a favourable prognosis, while class C is at high risk of death. **(24).**

Table (2): Child-Pugh Turcotte score **(24).**

Measure	1 point	2 points	3 points
Total bilirubin, (mg/dl)	<2	2-3	>3
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Chronic liver disease is classified into Child-Pugh Turcotte score class A to C, employing the added score from above

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

One and two years survival in different classes of liver cirrhosis using CPT score is shown in the table (2) **(25).**

MELD scoring system:

More modern scores, used in the allocation of liver transplants but also in other contexts, are the Model for End-Stage Liver Disease (MELD) score and its pediatric counterpart, the Pediatric End-Stage Liver Disease (PELD) score, the hepatic venous pressure gradient, (difference in venous

pressure between afferent and efferent blood to the liver) also determines severity of cirrhosis, although hard to measure. A value of 16 mm or more means a greatly increased risk of dying (26).

Three blood tests; serum bilirubin, prothrombin time (PT) measured as international normalized ratio (INR), and serum creatinine, are used to determine this value.

The MELD score is calculated using the following equation:

MELD = 3.8 [Ln serum bilirubin (mg/dl)] + 11.2 [Ln INR] + 9.6[Ln serum creatinine (mg/dl)] + 6.4 (where Ln is the natural logarithm).

Patients may receive a MELD score of 6-40 points. The 3-month mortality statistics are associated with the following MELD scores:

- MELD score of 9 or less, 2.9% mortality.
- MELD score of 10-19, 7.7% mortality.
- MELD score of 20-29, 23.5% mortality.
- MELD score of 30-39, 60% mortality.
- MELD score of 40 or more, 81% mortality(27).

Complications of Liver Cirrhosis :

- Portal hypertension:

As portal pressure rises above 10–12 mmHg, the compliant venous system dilates and collaterals occur within the systemic venous system. The main sites of the collaterals are at the gastro-oesophageal junction, the rectum, the left renal vein, the diaphragm, the retroperitoneum and the anterior abdominal wall via the umbilical vein. The collaterals at the gastro-oesophageal junction (varices) are superficial in position and tend to rupture. Porto-systemic anastomoses at other sites seldom give rise to symptoms (28).

- Ascites:

Ascites describes collection of fluid within the peritoneal cavity. It is a common complication of cirrhosis. The accumulation of ascitic fluid represents a state of total-body sodium and water excess, but the event that initiates the unbalance is unclear. Although many pathogenic processes have been implicated in the development of abdominal ascites, about 75% likely occur as a result of portal hypertension in the setting of liver cirrhosis, with the remainder due to infective, inflammatory, and infiltrative conditions.

Three theories of ascites formation have been proposed: underfilling, overflow, and peripheral arterial vasodilatation. .(29)

The underfilling theory suggests that the primary abnormality is inappropriate sequestration of fluid within the splanchnic vascular bed due to portal hypertension and a consequent decrease in effective circulating blood volume. This activates the plasma renin, aldosterone, and sympathetic nervous system, resulting in renal sodium and water retention.

The overflow theory suggests that the primary abnormality is inappropriate renal retention of sodium and water in the absence of volume depletion. This theory was developed in accordance with the observation that patients with cirrhosis have intravascular hypervolemia rather than hypovolemia.

The most recent theory, the peripheral arterial vasodilatation hypothesis, includes components of both of the other theories. It suggests that portal hypertension leads to vasodilatation, which causes decreased effective arterial blood volume. As the natural history of the disease progresses, neurohumoral excitation increases, more renal sodium is retained, and plasma volume expands. This leads to overflow of fluid into the peritoneal cavity. The vasodilatation theory proposes that underfilling is operative early and overflow is operative late in the natural history of cirrhosis.

Regardless of the initiating event, a number of factors contribute to the accumulation of fluid in the abdominal cavity. Elevated levels of epinephrine and norepinephrine are well-documented factors. Hypoalbuminemia and reduced plasma oncotic pressure favor the extravasation of fluid from the plasma to the peritoneal fluid, and, thus, ascites is infrequent in patients with cirrhosis unless both portal hypertension and hypoalbuminemia are present. **(30)**

- **Spontaneous bacterial peritonitis (SBP):**

It is the development of infection over the existing ascites in patients with liver cirrhosis, The infection is usually due to single enteric organism ocurs in 10-15% of patients with ascites, and sometimes associated with bacteraemia.

It often presents with general malaise or fever, hypotension or hepatic encephalopathy. (S.B.P) should be suspected whenever sudden deterioration occurs in patient with ascites.**(31).**

D. Renal failure (hepatorenal syndrome):

Hepatorenal syndrome (HRS) is a life-threatening medical condition that consists of rapid deterioration in kidney functionin patients suffering from liver cirrhosis or fulminant liver failure. The kidneys themselves appear normal to the naked eye , tissue is normal when viewed under the microscope, and this type is described as 'functional'. HRS is quite common in patients with advanced cirrhosis, portal hypertension with jaundice and ascites (approximately 10% of individuals admitted to hospital with ascites have HRS) **(32).**

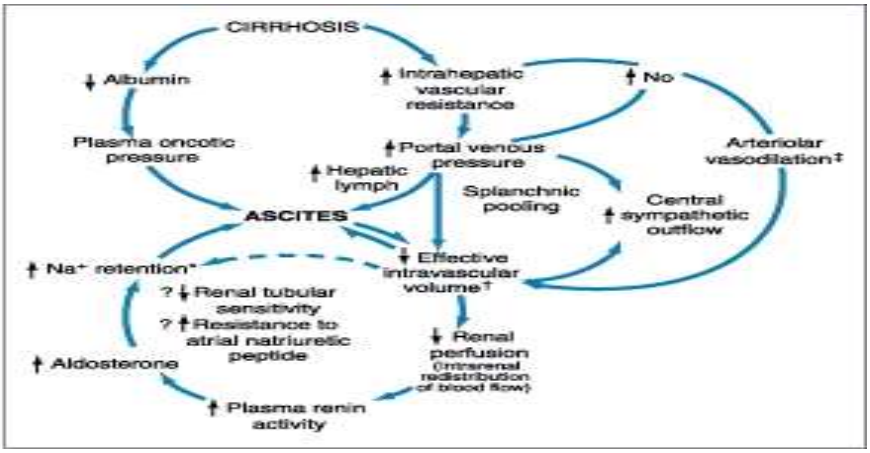

Figure (1) : Relationship between portal hypertension, ascites and Hepatorenal syndrome through changes of plasma volume and impaired water excretion **(32).**

- **Hepato pulmonary syndrome:**

This is defined as a hypoxaemia occurring in patients with advanced liver disease. It is due to intrapulmonary vascular dilatation with no evidence of primary pulmonary disease. Most patients have no respiratory symptoms, but with more severe disease, patients are breathless on standing. Transthoracic echo shows intrapulmonary shunting, and arterial blood gases confirm the arterial oxygen desaturation. These changes are improved with liver transplantation **(33).**

- **Porto-pulmonary hypertension:**

This must be distinguished from the hepatopulmonary syndrome as in this group there is pulmonary hypertension. It occurs in 1–2% of patients with cirrhosis related to portal hypertension. It may respond to medical therapy. Severe pulmonary hypertension is a contraindication for liver transplantation **(34).**

G-Hepatocellular carcinoma:

Its pathogenesis seems to arise from the development of regenerative nodules with small-cell dysplasia to invasive hepatocellular carcinoma **(35).**

Prevention and treatment of liver cirrhosis:

Prevention and therapy in the initial stages of cirrhosis, including the first decompensating event.

Population screening :

The increasing burden of liver disease and the problem of late presentation with decompensation emphasise the need for population screening to identify patients with chronic liver disease, similar to screening for cardiovascular risk factors. In the USA, screening for chronic hepatitis C is cost effective for people born between 1945 and 1965 **(36)**.Non-invasive fibrosis markers could be screening tools in primary care, especially for non-alcoholic fatty liver disease and for alcohol

misusers. The NAFLD fibrosis scores for non-alcoholic fatty liver disease (NaFlD) is based on simple indices (age, platelet count, serum albumin, aminotransferases, and diabetes) and has a negative predictive value of 96% for advanced fibrosis(37). Similarly, more complex blood tests have been used to class patients in the community into three prognostic groups to rationalise secondary referrals. Transient elastography has also been used to classify patients, although specific test cut-offs need to be established (38).

Lifestyle changes and general measures :

Lifestyle changes tend to be overlooked in the management of cirrhosis, because life expectancy is judged to be short and the benefit is difficult to measure. Although evidence comes from cohort or case-control studies, lifestyle advice should still be offered to all patients, because it is easily implemented with little risk of side-effects or cost.

Insulin resistance, Obesity, and The metabolic syndrome are pathophysiologically linked with non-alcoholic fatty liver disease, but they have deleterious effects irrespective of liver disease aetiology. Obesity is an independent predictor of cirrhosis in alcoholic liver disease, and the presence of metabolic syndrome is associated with more severe fibrosis and cirrhosis in chronic liver disease (39).In 161 patients with compensated cirrhosis who were followed up prospectively, obesity was independently associated with clinical decompensation, together with HVPG and serum albumin. Moreover, insulin resistance and metabolic syndrome were independently associated with liver-related mortality in a NHANES-III cohort of more than 2500 patients with chronic liver disease. Insulin resistance predicts the occurrence of hepatocellular carcinoma in cirrhosis, and in large cohorts, both diabetes and metabolic syndrome increased the risk of hepatocellular carcinoma(40). Overweight patients with compensated cirrhosis (clinical stages I and II) should therefore be advised to lose weight to lower their long-term risk of liver complications. In patients with decompensated cirrhosis, maintenance of adequate nutrition is important to avoid loss of muscle mass. Such patients have low tolerance to long-term fasting, with early onset of gluconeogenesis and subsequent muscle depletion, which can also contribute to development of hepatic encephalopathy. (41).

Alcohol intake is deleterious in patients with alcoholic cirrhosis but also in those with liver disease of other causes. In alcoholic cirrhosis, alcohol ingestion increases HVPG and portocollateral blood flow; these effects are likely also in cirrhosis of other causes thereby increasing the risk of variceal bleeding. Only abstinence from alcohol improves survival in alcoholic cirrhosis. In patients with chronic hepatitis C, alcohol intake increases the risk of cirrhosis and decompensated liver disease two to three times, even with moderate intake (42) .

Moreover, alcohol intake is an independent risk factor for hepatocellular carcinoma in chronic hepatitis C and non-alcoholic steatohepatitis. Therefore, all patients with cirrhosis irrespective of clinical stage should be advised to abstain from alcohol with relevant counselling if appropriate. Multidisciplinary alcohol care teams can lower the risk of acute hospital admission and improve

the quality of care. In many centres, abstinence irrespective of liver disease aetiology is mandatory for the patient to be considered for liver transplantation (43).

Vaccination against hepatitis A and B viruses, influenza virus, and pneumococcus should be offered as early as possible, because the antigenic response becomes weaker as cirrhosis progresses (44) .

Cigarette smoking is associated with more severe fibrosis in chronic hepatitis C, non-alcoholic steatohepatitis, and primary biliary cirrhosis and possibly increases the risk of hepatocellular carcinoma in chronic hepatitis B. Cannabis use worsens fibrosis in chronic hepatitis C. Smoking cessation therefore should be advocated to prevent progression of liver disease and to facilitate eligibility for liver transplantation. Smoking also increases post-transplant morbidity and mortality (45) .

Antioxidant-rich foods and drinks have a potential preventive role in cirrhosis. Coffee consumption improves all-cause mortality and is also associated with a significant reduction in fibrosis in liver disease of various causes and with reduced risk of hepatocellular carcinoma as shown in a meta-analysis including 2260 patients with hepatocellular carcinoma.(For most of the benefits described, at least two cups of coffee daily are needed) (46). In a phase 2 RCT, ingestion of dark chocolate blunted the post-prandial HVPG increase in cirrhosis by improving flow-mediated hepatic vasorelaxation and ameliorated systemic hypotension. The same effect on HVPG was noted with short-term administration of ascorbic acid. (47)

Physicians should always bear in mind drug interactions and the possible need for dose reductions when prescribing for patients with cirrhosis.(48) .

Cause-specific treatments :

Patients with cirrhosis should be treated when possible for the underlying liver disease to stop disease progression; such treatment includes immunosuppression for autoimmune hepatitis, venesection for haemochromatosis, and copper chelators or zinc for Wilson's disease (49).

Patients with viral hepatitis should be assessed for antiviral treatment. All patients with cirrhosis who are positive for HBsAg should receive oral antiviral therapy with a potent antiviral (entecavir or tenofovir) irrespective of viral load (50). Oral antiviral therapy reduces HVPG and delays clinical progression to decompensation in responders. Treatment with tenofovir for 5 years resulted in regression of cirrhosis associated with hepatitis B virus in 71 (74%) of 96 treated patients. In patients with hepatitis-C-related cirrhosis without ascites, achievement of sustained virological response significantly reduced liver-related morbidity and mortality. In a subgroup of patients, there was also regression of cirrhosis. (49) This strategy is also valid for patients with hepatitis C listed for liver transplantation because of hepatocellular carcinoma rather than complications of portal hypertension, because achievement of sustained virological response reduces post-transplant recurrence of hepatitis C, which is otherwise universal. The newly licensed direct-acting antiviral drugs boceprevir and telaprevir increase rates of sustained virological response in patients with

genotype 1 (**51**) .Supplementary strategies that can increase sustained response rates in this difficult-to-treat group of patients, as shown in cohort studies, include weight loss in obese patients, vitamin D supplementation when concentrations are low, statins in patients with diabetes, and coffee drinking **(52**). Patients with cirrhosis who respond to antiviral treatment still need regular surveillance for hepatocellular carcinoma, because the risk, although reduced, is not eliminated **(53) .**

Table (3) :Prevention and treatment for complications of cirrhosis

	Prevention	Treatment
Variceal bleeding(**54)**	Non-selective β blockers[*] Variceal band ligation	Acute: Resuscitation Vasocontrictors[‡]
		Sclerotherapy Band ligation
		TIPS Surgical shunts
		Chronic: Variceal obliteration
		TIPS Surgical shunts
Ascites(**55**)	Low sodium diet	Low sodium diet Diuretics Large volume paracentesis TIPSS (LeVeen/Denver shunts)
Renal failure(**56)**	Avoid hypovolaemia	Discontinue diuretics

		Rehydration Albumin infusion
		Hepatorenal syndrome: add terlipressin or midodrine (noradrenaline) and somatostatin (octreotide)
	Avoid precipitant	
Encephalopathy(**57**)		Treat precipitating factors: Infection Bleeding
		Electrolyte imbalance Sedatives
		High protein intake Lactulose
		Neomycin, metronidazole, rifaximin
Spontaneous bacterial peritonitis(**54**)	Treat ascites	Early diagnosic paracentesis: >250 neutrophils per mL, intravenous antibiotics (plus albumin) Secondary prophlaxis with oral antibiotics such as levofloxacin

TIPSS=transjugular intrahepatic portosystemic shunt.

*

Nadolol, propranolol.

†

Vasopressin, octreotide/somatostatin, terlipressin.

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