Overview of Complications in Cirrhosis

Madhumita Premkumar [*], Anil C. Anand [†]

[*]Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India and [†]Department of Gastroenterology and Hepatology, Kalinga Institute of Medical Sciences, Bhubaneshwar, Odisha, India

Background: **Cirrhosis is the outcome of chronic liver disease of any etiology due to progressive liver injury and fibrosis. Consequently, cirrhosis leads to portal hypertension and liver dysfunction, progressing to complications like ascites, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, cirrhotic cardiomyopathy, sarcopenia, hepatocellular carcinoma, and coagulation disorders. End-stage liver disease leads to an impaired quality of life, loss of social and economic productivity, and reduced survival.** ***Methods:*** **This narrative review explains the pathophysiology of complications of cirrhosis, the diagnostic approach and innovative management, with focus on data from India. A comprehensive literature search of the published data was performed in regard with the spectrum, diagnosis, and management of cirrhosis and its complications.** ***Results:*** **There is a change in the epidemiology of metabolic syndrome, lifestyle diseases, alcohol consumption and the spectrum of etiological diagnosis in patients with cirrhosis. With the advent of universal vaccination and efficacious long-term viral suppression agents for chronic hepatitis B, availability of direct-acting antiviral agents for chronic hepatitis C, and a booming liver transplantation programme across the country, the management of complications is essential. There are several updates in the standard of care in the management of complications of cirrhosis, such as hepatorenal syndrome, hepatocellular carcinoma, and hepatic encephalopathy, and new therapies that address supportive and palliative care in advanced cirrhosis.** ***Conclusion:*** **Prevention, early diagnosis, appropriate management of complications, timely transplantation are cornerstones in the management protocol of cirrhosis and portal hypertension. India needs improved access to care, outreach of public health programmes for viral hepatitis care, health infrastructure, and disease registries for improved healthcare outcomes. Low-cost initiatives like immunization, alcohol cessation, awareness about liver diseases, viral hepatitis elimination, and patient focused decision-making algorithms are essential to manage liver disease in India. (J Clin Exp Hepatol 2022;12:1150–1174)**

Cirrhosis-related portal hypertension (PH) leads to the formation of collateral channels and increased intermediaries like endogenous vasoconstrictors (norepinephrine, plasma renin activity, aldosterone, etc), vascular endothelial growth factor and splanchnic vasodilators like nitric oxide. PH also leads to the expansion of plasma volume due to the activation of the renin angiotensin aldosterone pathway, which increases cardiac output and alters systemic hemodynamics, which is core to the pathogenesis of several complications.[1] PH can be quantified by the measurement of the hepatic venous pressure (HVPG).[2] An HVPG of >5 mmHg is diagnostic of PH, but HVPG ≥10 mmHg is termed clinically significant PH (CSPH). The management of complications of cirrhosis implies treating the underlying causes, anticipation and prevention of complications and mitigating superimposed insults.[3,4] Patients may present for the first time with a decompensation event like ascites, acute variceal bleeding (AVB), hepatic encephalopathy (HE), or even with hepatocellular carcinoma (HCC) (Table 1). Specific therapy directed against underlying etiology, such as antiviral agents for chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, cessation of alcohol, weight loss, and obesity management, and so on, can change outcomes at the primary and secondary levels of prevention. Evidence suggesting the regression of fibrosis has been demonstrated in HBV- and HCV-related chronic viral hepatitis, autoimmune hepatitis, primary biliary cholangitis,

Keywords: cirrhosis, ascites, hepatic encephalopathy, portal hypertension, hepatocellular carcinoma
Received: 5.12.2021; *Accepted:* 30.4.2022; *Available online 14 May 2022*
Address for correspondence: Anil C Anand, M.D., D.M., Professor and Head, Department of Gastroenterology & Hepatology, Kalinga Institute of Medical Sciences, Bhubaneshwar, Odisha, India.
E-mail: anilcanand@gmail.com
Abbreviations: AIH: autoimmune hepatitis; ALP: alkaline phosphatase; AVB: acute variceal bleeding; BMI: body mass index; CLD: chronic liver disease; CSPH: clinically significant portal hypertension; CTP: Child Turcotte Pugh Score; DAAs: direct-acting antiviral agents; GGT: gamma glutamyl transpeptidase; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HE: hepatic encephalopathy; HR: hazard ratio; HRQoL: health-related quality of life; HVPG: hepatic vein pressure gradient; MELD: Model for End Stage Liver disease; MetS: metabolic syndrome; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NSBB: Non-selective beta blockers; NVHCP: National Viral Hepatitis Control programme; SAAG: Serum-ascites albumin gradient; SBP: spontaneous bacterial peritonitis; WHO: World Health Organization
https://doi.org/10.1016/j.jceh.2022.04.021

Table 1 Complications of Cirrhosis.

Complications of cirrhosis	Clinical presentation
Ascites	Ascites is the most common complication of cirrhosis.
	A diagnostic paracentesis is required in all cases of ascites
	Spontaneous bacterial peritonitis is diagnosed if the polymorphonuclear leukocyte count is ≥250 cells/mm^3
Hepatic encephalopathy (HE)	HE is a spectrum of neurological dysfunction ranging from covert encephalopathy with minimal symptoms and signs to overt HE.
Hepatic hydrothorax	Hepatic hydrothorax is a manifestation of ascites with collection of fluid in the negative pressure pleural cavity across diaphragmatic defects.
	Clinical features of hydrothorax include shortness of breath, cough, hypoxemia, and respiratory failure.
Hepatocellular carcinoma (HCC)	Patients with cirrhosis should undergo surveillance for HCC by abdominal ultrasonography every six months. The use of AFP for surveillance is controversial.
Hepatopulmonary syndrome (HPS)	Diagnosed as a trial of hypoxemia, orthodeoxia, and pulmonary arteriovenous shunting. Patients with HPS are offered MELD exception points. Clinical features include dyspnea, orthodeoxia syndrome, and hypoxemia while sleeping
Hepatorenal syndrome (HRS)	Diagnosis of exclusion in patients with renal impairment.
	Revised diagnostic criteria Increase of creatinine from baseline or estimated GFR-based criteria. • HRS-AKI • HRS-non-AKI (HRS-AKD/HRS-CKD)
	Signs include glomerular filtration rate < 40 mL/min, serum creatinine > 1.5 mg/dL, sodium excretion < 10 mmol/L, hyponatremia (<130 mmol/L), decreased diuresis (<500 mL), and greater urine vs. plasma osmolality Urine output criteria have been removed.
Porto-pulmonary hypertension	The presence of pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg) in patients with portal hypertension
Varices and/or variceal bleeding	EGD is recommended to diagnose varices in all patients with decompensated cirrhosis and in compensated cirrhosis with LSM >20 kPa with platelet count <<150 × 10^9 cells/l
	EGD should be performed when patient receives diagnosis of cirrhosis
	Patients with compensated cirrhosis and no varices: repeat EGD in 2–3 years
	Patients with small varices: repeat EGD in 1–2 years

Abbreviations: AFP, alpha feto protein; AKI, acute kidney injury; EGD, esophagogastroduodenoscopy; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; HE, Hepatic encephalopathy; HPS, hepatopulmonary syndrome; HRS, hepatorenal syndrome; HRS-AKD, HRS-acute kidney disease; HRS-CKD, HRS-chronic kidney disease; LSM, liver stiffness measurement; MELD, Model for End Stage Liver disease; PMN, polymorphonuclear; SBP, spontaneous bacterial peritonitis.

secondary biliary cirrhosis, non-alcoholic fatty liver disease (NAFLD), and hemochromatosis.

Table 2 lists the complications of chronic liver disease (CLD) covered in this review article. We hope to update the reader regarding the pathogenesis, diagnosis, and management for specific liver-related complications in India.

Changing Epidemiology of Cirrhosis

Cirrhosis- and PH-related complications contribute to the public health burden of morbidity and mortality in India. Age, gender, family income, employment status, status of residence (rural or urban), lifestyle, alcohol, smoking, nutritional status, and education may all have bearing on the etiology.[3] The prevalence of cirrhosis is as high as 4.5–9.5% based on autopsy studies. The cirrhosis attributable death rate has increased from 1.5% in 1980 to 2.4% in 2017.[5–7]

The prevalence of cirrhosis in the United States was 0.27%, corresponding to 633,323 adults, as per the National Health and Nutrition Examination Survey database between 1999 and 2000, with 69% of individuals being unaware they had the disease. The presence of diabetes mellitus, ethanol use, chronic HBV and HCV infection, male gender, and older age were independently associated with the diagnosis of cirrhosis based on aspartate transaminase-platelet ratio >2 and abnormal liver function test results.[6] More than 53.5% of cases in this database had liver disease secondary to chronic HCV infection, alcohol abuse, and diabetes, all of which

Table 2 Current Management Options of Complications of Cirrhosis.

Complication	Treatment	Dosage
Ascites	Sodium restriction, Diuretics	Maximum 2000 mg of oral Na per day– Spironolactone (Start 100 mg orally per day: maximum 400 mg orally per day) Furosemide (Start 40 mg orally per day: maximum 160 mg orally per day)[26]
	Albumin	Albumin (8–10 g IV per L of fluid (if greater than 5 L) removed for paracenteses)[28,62]
	Fluid restriction if serum Na is <120 mEq/L	In India, even patients with moderate volume paracentesis may require replacement albumin.
Spontaneous bacterial peritonitis (SBP)	Antibiotic therapy	• Cefotaxime (2 g IV q8h) • Ceftriaxone (2 g IV q12h) • Piperacillin-tazobactam (4.5 g q6-8h)
	Albumin	20% Human albumin (1.5 g per kg IV within 6 h of detection and 1 g per kg IV on day 3)
	Secondary prophylaxis Norfloxacin	400 mg orally per day for prophylaxis[33]
Hepatic encephalopathy (HE)	Lactulose	30–45 mL syrup orally titrated up to three to four times per day or 300 mL retention enema until two to four bowel movements per day and mental status improvement–
	Rifaximin	550 mg twice daily can be added to lactulose in patients who are refractory to lactulose alone.
	Oral Branched Chain amino acids	Efficacy requires further investigation
	Polyethylene glycol (PEG3350) in acute HE	Used in acute HE in patients with acute decompensation of cirrhosis and even ACLF[99]
Portal hypertension and variceal bleeding	Non-selective beta blockers	Propranolol (40–80 mg orally two times per day) Carvedilol (3.125 mg twice daily, titrate up to 25 mg qd)[75,87]
Hepatorenal syndrome (HRS)	Terlipressin Midodrine and octreotide Dopamine Noradrenaline infusion	0.5–1 mg q 6h as bolus IV with doubling of dose every 2 days to a maximum of 12 mg/day of creatinine does not decrease by >25%.[59] Treatment can be given for up to 2 weeks, but can be stopped early after complete reversal of HRS. Can be dosed as continuous infusion.[60] Dosed orally (midodrine 5–15 mg/d) and IV (octreotide 50mcg/h) to obtain a stable increase of at least 15 mm Hg in MAP. 2 to 4 mcg per kg per minute IV. Dose of 0.5–3 mg/h in combination with albumin, with a target MAP increase of 10 mmHg.

Abbreviations: ACLF, acute-on-chronic liver failure; HE, Hepatic encephalopathy; HRS, Hepatorenal syndrome; IV, intravenously; MAP, mean arterial pressure; SBP, Spontaneous bacterial peritonitis.

are treatable factors. The overall mortality in cirrhosis was 26.4% per 2-year period.[7] In India, alcohol has displaced chronic hepatitis B as the leading cause of cirrhosis in adults.[4] We lack a national disease registry for the prevalence, etiology, and complications of cirrhosis would help assess the changing epidemiology.[8,9] The rise of the metabolic syndrome pandemic has resulted in multiple risk factors for cirrhosis in an individual, such as concomitant steatohepatitis caused by obesity and NAFLD, alcohol and chronic viral hepatitis, which can be synergistic in disease progression.[5] A higher mortality has been attributed to alcohol as the etiology in several cohorts.[6,9,10]

In a large multicenter database of 13,014 patients with CLD (median age 43 years, 73% males), 33.9% presented with decompensated cirrhosis. Alcoholism (34.3% of 4413) was the commonest cause of cirrhosis while HBV (33.3%) was the predominant cause of CLD. In India, regional variations indicate a preponderance of HCV infection in the north, HBV in the southern and eastern states, and alcohol in north-east India as the predominant etiology. HBV infection (46.8%) was the most common cause of HCC in India.[11,12]

Jain *et al.* analyzed the data of 5138 patients with cirrhosis (aged 49.8 ± 14.6 years, 79.5% male, 39.5% ethanol related) who were classed as Child A, B, and C in 11.7%, 41.6%, and 46.8% cases, respectively. The median time from the diagnosis of cirrhosis to 1st hospitalization was 2 years. One third (1707 persons) of the cohort died within a year of hospitalization, 1248

(24.3%) of whom died in their primary admission, and 60% of the survivors were re-hospitalized for the same or secondary complication within a year. Patients with ethanol-related cirrhosis were more often male (97.7% vs. 67.7%; $P < 0.001$) aged between 40 and 50 years (36.2% vs. 20.2%; $P < 0.001$) with a higher incidence of sepsis (20.3% vs. 14.9%), ascites (82.2% vs. 65.9%), spontaneous bacterial peritonitis [SBP (21.8% vs. 15.7%)], HE (41.0% vs. 25.0%), AVB (32.0% vs. 23.7%), acute kidney injury [AKI (30.5% vs 19.6%)]. This sobering data suggest that a change in approach to the management of cirrhosis and prevention of complications is essential.[4]

Complications of Cirrhosis

The main complications in cirrhosis warranting periodic screening are gastrointestinal varices, ascites, and HCC.[13] In a large Asia–Pacific database, about 54.3% of global deaths attributable to cirrhosis were reported from Asia. About 72.7% of HCC-related mortality and two-third of the global burden of chronic hepatitis B and C were recorded from this region. Despite the availability of a safe and cost-effective vaccine, chronic HBV infection remains the cause of >50% of deaths attributable to cirrhosis from Asia. Alcohol (20.8%), NAFLD (12.1%), and chronic HCV infection (15.7%) are the next three etiologies. In 2015, HBV accounted for 50% of mortality due to HCC in Asia.[5]

The model for end-stage liver disease (MELD), with components being bilirubin, international normalized ratio (INR), and serum creatinine, is better than the Child Turcotte Pugh (CTP) score for predicting the short-term and intermediate-term mortality. Adding serum sodium to the MELD score (MELDNa) improves the diagnostic accuracy for short-term mortality and is now the most used risk index for transplant listing.[14] Measurement of the HVPG predicts the presence of esophageal varices (HVPG $\geq$ 12 mmHg), risk of variceal bleeding and failure to control AVB (HVPG $\geq$ 20 mmHg) or response to non-selective beta blockers (NSBB) wherein an HVPG reduction >20% of baseline or to <12 mmHg is considered a 'responder'.[15]

Comprehensive Approach to Cirrhosis and Complications

The comprehensive management of cirrhosis requires the treatment of underlying causes (viral hepatitis, obesity, alcohol, etc), early diagnosis and treatment of complications, and improving health-related quality of life outcomes. In India, specific health policy has been established for the management of chronic viral hepatitis.[16]

Universal immunization for HBV, introduced in 2004 under the aegis of the National Immunization Programme, can reduce the incidence of HBV infection with a delayed impact on disease prevalence.[17] Thus the focus of public health programmes across Asia should be on maximizing coverage of HBV vaccination.[18] The National Viral Hepatitis Control Programme was launched in India in 2018, with a focus on screening for chronic viral hepatitis, provision of free-of-charge direct-acting antiviral agents for HCV, with the expansion of immunization for HBV. We expect a reformed timeline for the elimination of viral hepatitis in India with these low-cost measures.[19,20] The health policy implementation has resulted in the improvement in blood banking, improved maternal healthcare, and biomedical waste management. In addition, NAFLD and metabolic syndrome have also gained prominence in non-communicable diseases health programmes.[4]

Ascites

Ascites is defined as the pathological accumulation of fluid in the peritoneal cavity. Ascites is caused by cirrhosis in 85% of patients, and the remaining 15% have a non-hepatic cause of fluid accumulation. Nearly 15% of patients with ascites die within one year of diagnosis and 44% may die in the next 5 years.[21] In India, a mixed etiology of ascites may be present, with cardiogenic, renal, and tubercular components, which can obfuscate the primary disease.[22]

A diagnostic abdominal paracentesis should be performed in all patients with clinically evident ascites to establish the definite etiology. The laboratory diagnosis should include a total and differential white cell count, total protein and albumin, serum-ascites albumin gradient, lactate dehydrogenase, cytology, cultures, and tests for tuberculosis, triglyceride, bilirubin, hemoglobin, amylase, and so on where clinically deemed necessary or relevant. The serum-ascites albumin gradient provides a rough estimate of portal pressure.[23] Figure 1 shows an algorithm-based diagnostic approach to ascites.

Sodium restriction is advised in all patients with portal hypertensive ascites (<88 mEq [2000 mg] daily). Adherence to fluid restriction is difficult and as such does not make clinical sense as the ascites in due to the retention of total body Na. Therefore, the goal of treatment is to increase the urinary excretion of sodium to >78 mmol/day. Fluid restriction should only be recommended in patients whose plasma sodium level is <120 mEq/L. Only 10–15% of patients with ascites can spontaneously excrete sodium >78 mmol/day and can mobilize ascites with a salt restricted diet.[24,25] Since dietary Na increases palatability of food, and patients with concomitant sarcopenia need to be encouraged to partake liver-specific nutrition, patients, and physicians prefer a combination of sodium-restricted diet and diuretics.[26] In patients with hyponatremia, the use of diuretics and sodium restriction can decrease renal perfusion pressure, leading to a vicious cycle of renal impairment. Some newer randomized

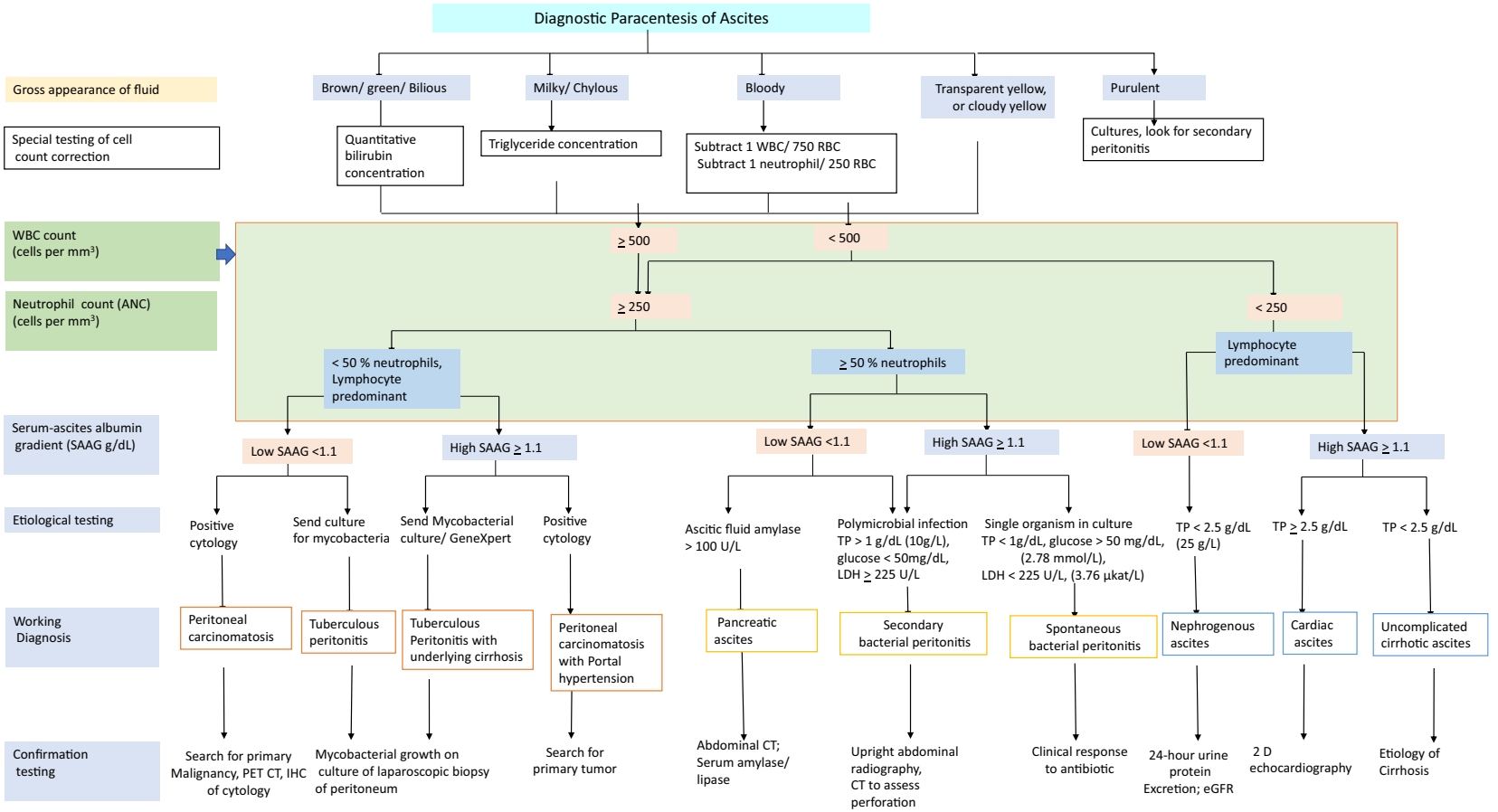

Figure 1 Diagnostic approach to ascites in patients with cirrhosis. CT, computed tomography; eGFR, estimated glomerular filtration rate; IHC, immunohistochemistry; LDH, lactate dehydrogenase; PET, positron emission tomography; RBC, red blood cells; SAAG, serum albumin ascitic gradient; TP, total protein; WBC, white blood cells.

controlled studies have suggested that excessive salt restriction may have no benefit or may even cause harm due to impaired renal hemodynamics.[27] A combination of diuretics (e.g. oral spironolactone and furosemide) prevents hypokalemia. In patients who develop painful gynecomastia because of spironolactone, the use of amiloride is a suitable replacement.[24,25] As per the guidelines of the American Association for the Study of Liver Diseases (AASLD), infusion of 8–10 g albumin per L of ascites removed is recommended in large-volume paracentesis.[23] Albumin helps in volume expansion and prevents the activation of the renin angiotensin aldosterone system that leads to increased plasma renin activity and paracentesis-induced circulatory dysfunction.[28,29] Infusion of albumin as a volume expander is deemed unnecessary for paracentesis <5L. However, recent data from a north Indian center suggest patients with ACLF and frailty are at the risk of paracentesis-induced circulatory dysfunction, even with a moderate volume paracentesis, and may need albumin support. This needs further research in India.[30]

The AASLD defines refractory ascites 'as patients who continue to have fluid accumulation despite salt restriction, maximum doses of diuretics (400 mg of spironolactone and 80 mg of frusemide) and is diagnosed in the absence of therapy with a nephrotoxic agent or NSAIDs, such patients can be managed with outpatient paracentesis, domiciliary albumin and should be offered early transplantation'.[23] The use of midodrine as adjunctive therapy to maintain mean arterial pressure and improve response to diuretics has shown promise. However, adverse events such as arterial hypertension, palpitations, and high-cost limit long-term use.[31]

Diuretic-resistant ascites is defined when at least one of the following criteria is present.

i. Failure to mobilize the ascites despite confirmed adherence to Na restriction (to <88 mEq per day, i.e. less than 2000 mg of Na per day) and the use of maximum tolerated doses of diuretics i.e. 400 mg per day of spironolactone and 160 mg per day of furosemide.
ii. Re-accumulation of ascitic fluid despite repeated therapeutic paracenteses.

The development of diuretic-related complications such as renal impairment, HE, or recurrent electrolyte imbalances would be called diuretic intractable ascites.

All patients with refractory ascites should be offered liver transplantation as the primary treatment option with the best evidence-based outcomes. Patients with refractory ascites can also be offered a transjugular intra hepatic portosystemic shunt (TIPS), as a bridge to transplantation in those with MELD < 17, in the absence of sepsis or recurrent overt HE. TIPS improves sarcopenia and the risk of bleeding but may precipitate HE or heart failure.[31] A peritoneovenous shunt can be considered in those who cannot tolerate paracenteses, or are poor candidates for transplant, or TIPS.[32] Recent data regarding the use of indwelling peritoneal catheters or automated low flow ascites pump (alfa pump) to enable the outpatient drainage of ascites has been recently proposed. However, the risk of nosocomial sepsis limits wider application.[33]

Spontaneous Bacterial Peritonitis

An ascitic fluid polymorphonuclear leucocyte (PMNL) count of ≥250 cells/mm3 is the diagnostic of SBP, and patients should be administered optimum antibiotics immediately pending culture results (e.g. ceftriaxone 2g intravenously i.v. q12h or cefotaxime 2g i.v. q8h) or based on local microorganism patterns.[25,34] In addition, albumin infusion should be given to prevent AKI.[34] An ascitic fluid PMNL count <250 cells per mm^3, and signs and symptoms of infection should also receive empiric antibiotic therapy while awaiting culture results. After recovery from SBP, patients should receive long-term antibiotic prophylaxis with norfloxacin or less commonly used sulfamethoxazole/trimethoprim. Herein, Indian data on the bacteriological spectrum of SBP are important.[33–36] On long-term norfloxacin therapy, the future risk of gram-positive organisms or atypical infections like fungal etiology needs to be ascertained. A blood culture positivity is a predictor of mortality and has a yield of 26.2% versus ascitic fluid culture positivity which has yield of 5.7%.[36] A Bayesian approach network meta-analysis tested the utility of norfloxacin and rifaximin given daily or in alternate months by calculating odds ratio (OR) and 95% credible intervals (CrI) using rank probabilities. For the primary prevention of SBP, norfloxacin daily had OR 0.061 (0.0060, 0.33) while rifaximin daily had OR 0.037 (0.00085, 0.87). For the secondary prevention of SBP, rifaximin daily had OR of 0.022 (0.00011, 0.73). This study suggests that rifaximin is useful for both primary and secondary prophylaxis of SBP.[37]

Hyponatremia in Cirrhosis

Hyponatremia occurs frequently in cirrhosis with ascites, but is largely asymptomatic, unless the serum Na concentration is <110 mmol/L or there is a rapid change in sodium levels. Severe hyponatremia warrants fluid restriction. An association with adrenal insufficiency and hypothyroidism needs to be excluded.[38] A serum sodium level < 120 mmol/L is reasonable to initiate free water restriction.[39] The accurate estimation of intravascular volume status is essential to make a diagnosis of dilutional hyponatremia and dynamic inferior vena cava indices are more accurate than central venous pressure estimation.[40]

Thuluvath et al. assessed the impact of hyponatremia in 10,187 patients and found that AKI (50.3% vs. 32.8%, P < 0.001) and sepsis (16.8% vs. 11.8%, P < 0.001) were more

common in patients with hyponatremia than those without. In addition, the prevalence of acute respiratory failure, coagulation dysfunction, SBP, acute decompensation, and HCC were more likely to be found in those with hyponatremia.[38] Praharaj et al. have described the management protocol for hyponatremia which includes the discontinuation of beta blockers, diuretics, and correct estimation of intravascular volume status. Hypothyroidism and hypocortisolism need to be excluded. Albumin infusion is the mainstay of therapy in cirrhosis with hyponatremia.[39] In patients with serum Na <110 mmol/L or when patients present with seizures or coma attributable to electrolyte imbalance, hyponatremia needs correction by administering hypertonic saline.[41] Vaptans are vasopressin receptor antagonists which have been used to treat hyponatremia in heart failure. Vaptans also correct serum Na in cirrhosis, but the recurrence of hyponatremia occurs on stopping the drug. The adverse effects of vaptans include nausea (21%), thirst (16%), dry mouth (13%), and increased urinary frequency (11%); it can also precipitate gastrointestinal bleeding in 10% of patients with cirrhosis. The aggressive correction of hyponatremia can predispose to central pontine myelinolysis if there is a Na change of >12 mEq/L per day.[42]

Cirrhosis, Inflammation, and Sepsis

The overall prevalence of bacterial infection (BIs) in patients with cirrhosis who are hospitalized, is between 33% and 47%. Recurrent SBP is associated with up to 49.5% mortality.[43] Sepsis is more likely in patients with Child C cirrhosis than Child A/B cirrhosis. Overall, 30–60% of patients with cirrhosis develop an infection, the risk being 3–5 times higher than that of the general population. The risk factors for sepsis in cirrhosis include recent variceal bleeding, alcohol abuse, steroid intake, recent hospitalization, and prior sepsis.[44]

The most common site of infection is SBP. Nosocomial sepsis can be caused by invasive interventions like placement of vascular catheters, urinary catheters endoscopic sclerotherapy variceal ligation, paracentesis, TIPS placement, and so on. After SBP, the common sites of sepsis are urinary tract (20%), pneumonia (15%), and bacteremia (12%).[45]

There are several limitations in the diagnosis of sepsis with the currently available definitions in cirrhosis. Sepsis was previously defined as systemic inflammatory response syndrome with proven infection.[46] According to the latest SEPSIS-3 guidelines, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[47] Organ dysfunction is identified by an acute change in sequential organ failure assessment score by ≥2 points. This criterion is well-validated and applicable for intensive care unit settings for patients with cirrhosis, but in view of confounding presence of organ failures, it introduces a degree of overlap in acute-on-chronic liver failure (ACLF).[44]

Multidrug Resistance

Baijal et al. showed that 25% of patients with cirrhosis had evidence of infection at presentation in a multicentric study. The common sites were SBP (31.1%), urinary tract infections (22.6%), pneumonia (11.3%), and cellulitis (11.3%). Gram negative infections (54%) were most common with multidrug resistant (MDR) organisms cultured from 41.7% of positive isolates. Severity of liver disease was an independent predictor of sepsis. Overall mortality was 7.6%, and patients with sepsis had higher mortality than those without infection (23.5% vs. 2.2%, respectively; $P < 0.001$).[48] The increased diagnosis of MDR pathogens in cirrhosis in India makes it difficult to determine the initial choice of antibiotic as most strains are increasingly resistant to cephalosporins, quinolones, and beta-lactam antibiotics. Nosocomial infections often have extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae strains, which require the use of older and potentially nephrotoxic drugs like colistin, polymyxins, and so on. This is an unaddressed and under reported problem in India. The use of these antibiotics increases the cost and duration of hospital stay and exposes the patient to drug interactions increased adverse effects like AKI, peripheral neuropathy, critical illness myopathy, electrolyte disturbances, and so on.[49] Scrupulous antibiotic pharmacovigilance is needed in hepatology practice in India. However, this may not solve the problem as new reservoirs of bacterial resistance genes have been identified globally. The spread of antibiotic resistance is also due to the increased use of drugs in the livestock and poultry sector, which poses a risk to public health and proliferation of MDR pathogens in rivers, municipal water, drinking water, milk, retail food, and so on.[50,51] This calls for global regulation of the harmful use of antibiotics with directed health policy in India as spread of these MDR infections is a public health problem.[52]

Fungal Sepsis in Cirrhosis

The incidence of fungal infections is between 4 and 15% in patients with cirrhosis. There is an apparent increase in reporting fungal infections due to changing epidemiology, use of biomarkers like β-D-glucan and galactomannan, and the extensive use of broad-spectrum antibiotics. Fungal infections are often nosocomial and significantly increase mortality in cirrhosis.[53] Nearly 45–70% of fungal infection patients have concomitant BI. Diabetes, AKI, hemodialysis, prior use of antibiotics, and admission BI are risk factors for fungal sepsis, especially in the peritransplant period.[54] spontaneous fungal peritonitis is defined as fungal infection of ascites, with fluid PMNL ≥ 250 cells/ml. Tariq et al. reported infection with mainly

Candida species [*Candida albicans* (48%–81.8%), *Candida krusei* (15%–25%), and *Candida glabrata* (6.6%–20%)], which suggests that azole antifungals or echinocandins are useful therapy. *Cryptococcus neoformans* (53.3%) was also cultured. The in-hospital mortality was 33–100% in spontaneous fungal peritonitis, and 28-day mortality was 50–73.3%.[55] The use of liposomal amphotericin B (3–5 mg/kg/day) in cirrhosis is associated with renal impairment (14–47%), hypokalemia (31–51%), and hypomagnesemia (15–50%) and should be limited to progressive and potentially fatal fungal infections.

The COVID-19 pandemic also resulted in high risk of complications like ACLF, autoimmune flare, drug induced, or hypoxia induced liver injury in cirrhosis. An increased incidence of fungal sepsis in patients with cirrhosis in the post COVID-19 phase has been reported, like the general population.[56–58]

Hepatorenal Syndrome

The criteria used to define hepatorenal syndrome were updated in 2015 by the International Club of Ascites.[59] As per their definition, HRS is further classified into two types. Type I, now called HRS-AKI is characterized by an absolute increase in serum creatinine by at least 0.3 mg/dL or 50% from baseline. The 2.5 mg/dL criterion has been removed from the older definition of type 1 HRS, as it led to delay in the identification of AKI and increased 90-day mortality. The urine output criterion has been eliminated in the revised HRS definition, as there was invariably a lower urine output at baseline due to salt and water retention, which affects response criteria.[60] The revision also defines HRS-non-AKI as functional kidney injury in cirrhosis, assessed by estimated glomerular filtration rate (eGFR) rather than serum creatinine level, which does not meet criteria for HRS-AKI.

HRS-non-AKI, in turn, is of two subcategories based on the duration of impairment. HRS-AKI is diagnosed if the eGFR is less than 60 mL/min/1.73 m2 for <3 months and HRS-chronic kidney disease if it remains <60 mL/min/m2 for more than 3 months. The first represents a loss of renal function (HRS acute kidney disease), whereas the second represents a more chronic kidney dysfunction, HRS-chronic kidney disease.[61]

The incidence of HRS at 1 and 5 years after the development of cirrhosis with ascites is 18% and 39%, respectively. HRS-AKI occurs in approximately in a fourth of patients with SBP, despite clearance of sepsis. HRS-AKI associated with SBP may be prevented by the administration of intravenous albumin in addition to antibiotic treatment than antibiotics alone and may reduce overall mortality (16% vs. 35.4%: OR 0.34, 0.19 to 0.60).[62] Albumin administration improves circulatory function, antibiotic binding capacity, ameliorates cytokine damage, and may delay renal dysfunction in SBP, but cannot prevent HRS-AKI.[28] The long-term administration of albumin may help in the management of ascites by improving response to diuretics, with improved outcomes at 18 months as shown in the ANSWER cohort.[63] Albumin also helps in the management of non-SBP infections by providing cytokine adsorption, better antibiotic binding, and preserved oncotic pressure.[64] Srivastava et al. suggested that triple therapy with dopamine (2 μg/kg/min), furosemide (0.01 mg/kg/hr), and albumin (20 g/day) vs. infusion of terlipressin (0.5 mg for every 6 h and albumin 20 g/day for 5 days) were equally effective at improving HRS type I, with lower cost when using dopamine with albumin.[65]

Hemodialysis is indicated in progressive HRS and to correct metabolic acidosis, uremia, and electrolyte imbalances. The new understanding of HRS is that it is not just a functional entity but is an inflammatory condition, with structural tubular damage due to drugs, toxins, bile salts, oxidative stress, and so on which may be irreversible. The recurrent bouts of HRS can lead to chronic tubular dysfunction. This explains the variation in responders to terlipressin and other vasoconstrictors and albumin.[66]

Gastroesophageal Varices

Screening gastroduodenoscopy is recommended in all patients with decompensated cirrhosis and compensated advanced chronic liver disease with platelet count <150 $\times$ 10^9 cells/l and high liver stiffness measurement (LSM > 20 kPa) as per the recent Baveno VII criteria.[67] Gastroesophageal varices are expected in up to 50% of patients with cirrhosis.[68] The likelihood of finding varices increases with the severity of liver disease.[69] Patients with compensated advanced chronic liver disease with a platelet count >150 $\times$ 10^9 cells/L and an LSM <20 kPa can defer endoscopy.[70,71] Gastroesophageal (GE) variceal hemorrhage is a ruinous complication in patients with cirrhosis and ACLF. The AASLD guidelines define 'AVB as bleeding from an esophageal or gastric varix at the time of endoscopy or the presence of large esophageal varices with blood in the stomach and no other recognizable source of bleeding'.[69] The annual rate of bleeding in GE varices is 10–30%, and the mortality rate of AVB is 20% at six weeks despite advanced endoscopic interventions. Size of the varix, red wale signs, and Child B/C cirrhosis are the most important predictors of bleeding.[69] The management of AVB includes early goal directed hemodynamic resuscitation, the use of vasoconstrictors like terlipressin or somatostatin within an hour of presentation and endoscopic intervention should be done as soon as possible and not more than 12 h after presentation. The prevention of re-bleeding by monitoring and appropriate restrictive patient blood management is recommended as per the AASLD guidance.[69]

If variceal ligation proves difficult (due to poor visualization in active bleeding, uncooperative patient, etc),

endoscopic sclerotherapy, and systemic use of vasoconstrictors (e.g. octreotide or terlipressin) can control bleeding.[72,73] Terlipressin acts by causing vasoconstriction of the celiac axis, and superior mesenteric artery vascular bed which reduces the splanchnic and portal pressures. At sites where HVPG measurements are not possible, the LSM has been used as a surrogate marker for predicting CSPH. An LSM >20–25 kPa, alone or combined with platelet count and spleen size or presence of portosystemic collaterals on imaging is sufficient to diagnose CSPH.[69,74] Injection of glues like cyanoacrylate or N-butyl-cyanoacrylate in gastric AVB has been reported in studies from India.[75–77] Endoscopic ultrasound assisted coil and glue injection is another technique used to control gastric variceal bleeding.[78]

Early TIPS placement (within 72 of hemorrhage) as a pre-emptive procedure can prevent rebleeding-related mortality in a selected group of patients at a high risk of failure or rebleeding (HVPG > 20 mmHg, CTP class C cirrhosis, or CTP class B with active bleeding on endoscopy) who have no contraindications for TIPS. A relative reduction of portal pressure gradient, by at least 50% from pre-TIPS baseline, may also be useful.[67,69,79]

In about 10%–20% patients, AVB cannot be controlled or reoccurs despite adequate endoscopic interventions or timely vasoconstrictor therapy.[80,81] For patients in whom an early TIPS is not performed, intravenous vasoactive drugs should be continued for 2–5 days and NSBBs initiated once vasoactive drugs are discontinued. Rescue TIPS is indicated in these patients if hemorrhage cannot be controlled or if bleeding recurs despite vasoactive drugs.[69] A Sengstaken-Blakemore tube insertion may be used as an emergency measure till definitive TIPS or surgical shunt can be done. Balloon tamponade can temporarily control bleeding in more than 80% of the patients. The use of balloon occluded retrograde transvenous obliteration, and modifications using plugs or coils, to obturate gastric varices has also been demonstrated in India.[81,82] Figure 2 shows the algorithm to manage AVB currently.

Propranolol at a dosage of 40 mg twice daily (increasing to 160 mg/d in divided doses) or a dosage titrated to a 25% reduction in heart rate is used for reducing portal pressure.[81] Carvedilol is a NSBB with more potent effect with long-term safety data.[83] Sharma et al. followed up 48 patients (25 taking carvedilol; 23 propranolol) for 6 years and showed carvedilol had better HVPG response rate when compared with propranolol (72% vs. 47.8%, P = 0.047), with comparable rebleeding rates and survival at 3 and 5 years.[84] Currently, primary prophylaxis is usually done with NSBB alone or EVL in those with contraindications to NSBB, and secondary prophylaxis done with combined EVL and NSBB.[67] Villanueva et al. demonstrated in the recent 'prevent decompensation of cirrhosis with portal hypertension (PREDESCI)' study that the risk of decompensation or death was lowered in patients with compensated cirrhosis with CSPH on NSBB therapy with 16 (16%) of 100 patients in the β blockers group vs. 27 (27%) of 101 in the placebo group (hazard ratio [HR] 0.51, 95% CI 0.26–0·97, P = 0.041) developing a decompensation event (ascites, bleeding, and encephalopathy).[85]

Portal Vein Thrombosis and Coagulation Defect in Cirrhosis

The coagulation status in cirrhosis is erroneously assumed to be of a bleeding phenotype due to the standard coagulation tests indicating thrombocytopenia or prolonged prothrombin time. However, it is now clear that patients with cirrhosis have a fine rebalance of coagulation factors (increased endothelium derived Factor VIII, vonWillebrand factor), reduced protein C and S, with a deficiency of vitamin K dependent Factors II, VII, IX, and X.[86] It is also evident that the platelet count, INR, and fibrinogen levels are not indicative of bleeding risk in cirrhosis. This state of rebalance can be upset by the onset of sepsis or any acute insult that can precipitate ACLF.[87] Patients with cirrhosis can have thrombosis at one site, e.g. portal vein or mesenteric thrombosis and have PH related variceal bleeding simultaneously. Shukla et al. have elegantly summarized the data from India and elsewhere regarding the genetic predisposition and risk factors for portal vein thrombosis.[88] The monitoring of coagulation dysfunction in cirrhosis using point-of-care viscoelastic testing, patient blood management of bleeding in or coagulation assessment during therapeutic procedures and transplantation are topics for ongoing research in India.[89]

Hepatocellular Carcinoma

The annual incidence of HCC in patients with cirrhosis is 3–5% and half a million cases of HCC are diagnosed worldwide.[90] In India, the incidence of HCC in cirrhosis is 1.6% (95% CI 0.07–3) annually with age adjusted rate as 0.7–7.5 and 0.2–2.2 per 100,000 population per year in men and women, respectively.[91] The male: female ratio of HCC is 4:1 suggesting a gender bias in propensity, etiological factors, or diagnosis rates in India. The age of presentation is between 40 and 70 years.[92] Younossi et al. reported the annual incidence of HCC was 0.44 per 1000 person-years in NAFLD, and 5.29 per 1000 person-years in NASH.[93] Surveillance for HCC in patients with NAFLD without cirrhosis is controversial due to low yield. The addition of serum alpha-fetoprotein (AFP) to ultrasound q6m increases sensitivity for HCC surveillance in NAFLD-cirrhosis but results in lower specificity and increased cost. Surveillance with AFP alone is not recommended because of low sensitivity (60%).[94]

There have been several new developments in the diagnosis and management of HCC. First, the Barcelona Clinic

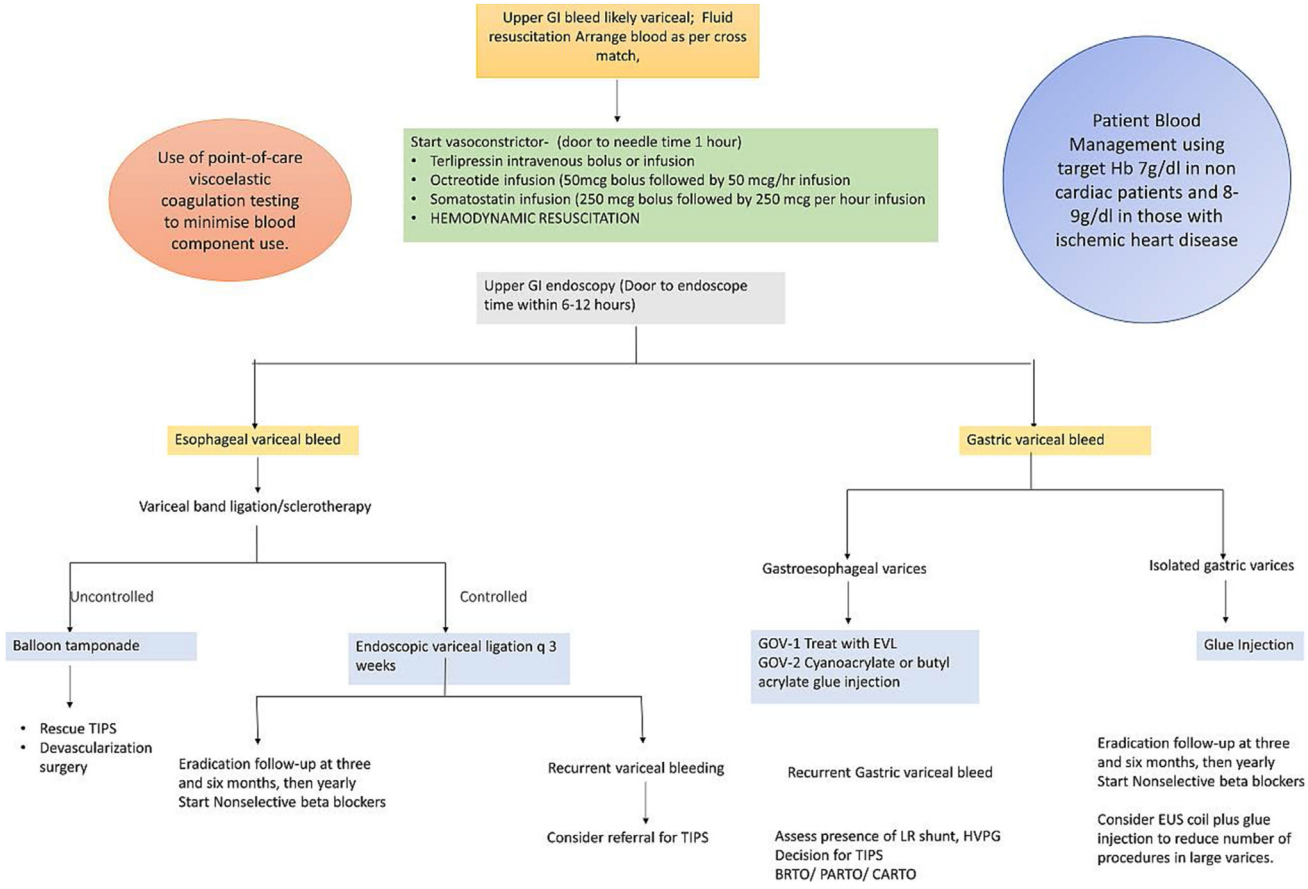

Figure 2 Management of acute variceal bleeding in cirrhosis. BRTO, balloon occluded retrograde transvenous obliteration; EUS, endoscopic ultrasound; EVL, endoscopic variceal ligation; GI, gastrointestinal; GOV, gastroesophageal varices; LR, leinorenal shunt; PARTO, plug-assisted retrograde transvenous obliteration; TIPS, transjugular intrahepatic portosystemic shunt.

Liver Cancer staging system has been updated. Changes include updating the recommended first- and second-line systemic drugs for advanced stage HCC (BCLC stage C) with addition of newer drugs like lenvatinib, atezolizumab-bevacizumab, or durvalumab-tremelimumab as first-line therapy and refining intermediate stage HCC (BCLC stage B).[95] There are several lacunae with the updated version of the system. Performance status (PS), as defined by the Eastern Cooperative Oncology Group (ECOG), plays an important and dynamic role in HCC staging and treatment recommendations, but is subjective and there is overlap between PS 0 and 1 with both physician and patient-related reporting bias.[96] In addition, re-compensation of liver disease or HCC in patients without cirrhosis (NASH or HBV related) has not been revisited in this version of the BCLC staging system. Patients with tumor rupture have undergone resection or embolization safely, even with PS1 suggesting that patients may be offered therapy based on personalized indications in real-world practice.[97] Biliary invasion and hepatic venous tumor invasion have not been addressed.[98] The system also does not consider tumor biology or role of biomarkers or liquid biopsy. Lastly, the management of HCC with stereotactic beam radiotherapy or the combination of systemic and locoregional therapy have not been addressed.

Hepatic Encephalopathy

Amodio et al. have defined hepatic (portosystemic) encephalopathy as 'a potentially reversible alteration in neuropsychiatric function in acute liver failure, cirrhosis, and ACLF, which is noted predominantly in patients with PH'.[99] The onset of HE is insidious and diagnosed by subtle fluctuating changes in memory, concentration, personality, and reaction times.[100] All other etiologies of altered mental status must be excluded before the diagnosis of HE. Despite variable evidence, lactulose remains the first-line therapy for the management of HE. PEG3350 has been used as a laxative in combination with lactulose in patients with acute HE.[101] Second-line agents include gut antibiotics like neomycin and rifaximin. An increase in the ratio of serum aromatic amino acids to branched chain amino acids in ACLF also contributes to HE. The role of systemic inflammation, neuroinflammation, bile acid metabolism, endogenous benzodiazepines, and gut dysbiosis is of

Table 3 Updates in the Therapies for Hepatic Encephalopathy.

Study	Sample Size	HE	Intervention	Mode of administration	Outcome	Ref
Sidhu SS et al, 2018	N = 193	OHE in cirrhosis	L-ornithine L aspartate vs. placebo	Intravenous infusions of LOLA (n = 98), 30 g daily, or placebo (n = 95) for 5 days	The grade of OHE was significantly lower in the LOLA group (compared to placebo) on days 1–4 but not on day 5. The mean time taken for recovery was lower in the LOLA group compared to the placebo group (1.92 ± 0.93 vs. 2.50 ± 1.03 days, P = 0.002; 95% confidence interval −0.852 to −0.202). Venous ammonia at day 5 and length of hospital stay were significantly lower in the LOLA group.	104
Jain A et al 2021	N = 140	OHE grade III-IV	Combination therapy of LOLA, rifaximin, and lactuloase	140 patients were randomized to a combination of LOLA, lactulose, and rifaximin (n = 70) or placebo, lactulose, and rifaximin (n = 70)	Improvement in grade of HE (92.5% vs. 66%, P < 0.001), lower time to recovery (2.70 ± 0.46 vs. 3.00 ± 0.87 days, P = 0.03), and lower 28-day mortality (16.4% vs. 41.8%, P = 0.001) were seen in the LOLA group compared with placebo.	105
Dhiman et al 2014	N = 66 (VSL#3) and n = 64 (Placebo)	Overt	VSL#3 (Probiotic) or placebo daily for 6 months	Oral	Reduction in the development of HE, less hospitalization, improvement in CTP & MELD, PHES, inflammation. The hazard ratio (HR) for the risk in probiotic group 0.65 (0.38–1.11; P = 0.12)	106
Sharma et al.	N = 63 (lactulose + rifaximin), n = 57 (lactulose + placebo	Overt	Lactulose + rifaximin 1200 mg/day vs. lactulose (30–60 mL/thrice/day) + placebo		A combination therapy is more effective, decreases hospital mortality, sepsis-related death, hospital stay.	107
Als-Nielsen B et al, 2004.	n = 698; 12 trials	Acute Episode of HE, Chronic HE.	Lactulose or lactitol vs. antibiotics		Lactulose 30–120 g and lactitol 30 g–60 g per day for 5–90 days. Lactulose or lactitol show significantly low treatment responses than antibiotics, lactulose or lactitol significantly higher risk of no improvement (RR 1.24, 95% CI 1.02 to 1.50)	
Gluud LL et al., 2017	16 randomized clinical trials including 827 participants	Cirrhosis with HE	With hepatic encephalopathy classed as overt (12 trials) or minimal (four trials). Eight trials assessed oral BCAA supplements and seven trials assessed intravenous BCAA		BCAA had a beneficial effect on hepatic encephalopathy (RR 0.76, 95% CI 0.63 to 0.92). Additional sensitivity analyses found no difference between BCAA and lactulose or neomycin (RR 0.66, 95% CI 0.34 to 1.30)	108,109

Table 3 (*Continued*)

Study	Sample Size	HE	Intervention	Mode of administration	Outcome	Ref
Ahmed et al., 2020	n = 29 PEG + lactulose and n = 31 to SMT	Overt	PEG (2 L q12 h) + lactulose (30 mL q8 h) or SMT, lactulose (titrated 30 mL q8 h)].	Nasogastric tube or orally	Patient treated in PEG arm vs lactulose (58.6% vs 17.1%, $P = 0.038$), early resolution of HE and reduce intensive care and hospital stay.	[101]

Abbreviations: BCAA, branched chain amino acid; CTP, Child–Turcotte Pugh; HE, Hepatic Encephalopathy; HR, hazard ratio; LOLA, L-ornithine L-aspartate; MELD, Model of End Stage Liver Disease; OHE, overt hepatic encephalopathy; PEG, Poly Ethyl Glycol; PHES, Psychometric Hepatic Encephalopathy Syndrome score; SMT, Standard Medical Therapy.

research interest for newer therapies.[102] The association of ammonia level with grade of HE and targeting ammonia reduction in therapeutic strategies has been recently challenged by emerging data.[103]

Several newer therapies have been used in the management of HE in recent years (Table 3).

Cirrhotic Cardiomyopathy

As per current definitions, cirrhotic cardiomyopathy (CCM) is defined as 'compromised cardiac function secondary to cirrhosis characterized by diastolic dysfunction, systolic dysfunction, or impaired systolic response to stress and abnormalities in electrophysiological responses in the absence of underlying primary cardiac disease'.[110,111] Cirrhosis results in the excessive release of systemic neurohormones, inflammatory mediators that cause a hyperdynamic circulatory state. Conventional electrocardiography, 2D echocardiography with tissue Doppler, or speckle tracking are diagnostic tests for CCM. The presence of CCM is associated with poor HRQoL, refractory ascites, HRS, and survival. Asymptomatic diastolic and systolic cardiac dysfunction can be unmasked by exercise, sepsis, surgery, critical illness, TIPS insertion, or transplantation. New criteria for CCM have been proposed that the use advanced cardiac imaging like magnetic resonance imaging to assess the cardiac function, dynamic changes in chamber volumes, and extracellular edema of cardiomyocytes.[112]

Porto-pulmonary Hypertension and Hepatopulmonary Syndrome

Portopulmonary hypertension (PoPH) is another underdiagnosed complication of cirrhosis. It is defined as' pulmonary hypertension (PAH) (mean pulmonary artery pressure >25 mmHg and pulmonary capillary wedge pressure <15 mmHg) in a patient with coexisting PH and no other alternative cause of PAH.[113] The triad of intrapulmonary vasodilation, impaired arterial oxygenation (hypoxemia), and hepatic dysfunction is used to characterize hepatopulmonary syndrome (HPS)'. The prevalence of HPS is between 10 and 17%, and results in poor HRQoL and increased waitlist mortality.[114] Liver transplantation can improve the five-year survival of HPS from 23 to 63%. However, poor prognostic factors, including a pre transplant PaO_2 < 50 mmHg, poor functional status despite domiciliary oxygen therapy, macroaggregated albumin shunt fraction >20%, have a mortality rate as high as 67% in the post-transplant period.[115] Therefore, the concept of a 'transplant window' has been proposed in HPS wherein patients with PaO_2 more than 60mmHg is prioritized for transplant while those with more severe hypoxemia are excluded from listing. TIPS has been used to improve gas exchange and shunt fraction in HPS in some preliminary studies. Discrete pulmonary

arteriovenous communications can be embolized using coils in patients with significant right to left shunting. Coil embolization can also be used in those with persistent hypoxemia six months after transplantation.[116]

Sarcopenia and Frailty in Cirrhosis

Muscle wasting i.e. sarcopenia and malnutrition are two sides of the same coin that affect HRQoL, survival, performance status, and tolerance for infection and surgery in cirrhosis. Nutritional assessment and tests for sarcopenia and frailty are difficult due to associated fluid retention and/or obesity due to unreliability of measures like weight, body mass index, or skin fold thickness. Obese persons with cirrhosis may have a combination of loss of skeletal muscle and increased adiposity which is termed "sarcopenic obesity." Frailty is independently associated with mortality, sepsis events, overt HE, and prolonged hospitalization after LT.[117] The assessment of sarcopenia using computed tomographic indices is a reliable measure, with age and gender-based cut offs. Cirrhosis is a state of accelerated starvation, with altered protein metabolism due to hyperammonemia, low cobalamin and vitamin D, direct effects of ethanol, systemic inflammation and cytokine abnormalities, poor oral intake, physical inactivity. Comprehensive interventions, like branched chain amino acid (BCAA) supplementation, exercise schedules, myostatin inhibitors, and so on, are under evaluation to prevent and reverse sarcopenia, in cirrhosis.[118] Handelzalts et al. have described the impact of frailty in patients with end-stage liver disease, which remains worse even after controlling for the MELD, suggesting that they remain sedentary, with fewer steps taken per day, although traditional

Table 4 Evidenced Based Interventions to Prolong Life in Decompensated Cirrhosis-evidence-based Approach.

	Strong Level Evidence	Moderate level of evidence	Low level evidence	Experimental Therapy
Prevention of Cirrhosis	Universal immunization – Hepatitis B[19,20]			
Treatment of underlying etiology	Chronic hepatitis C- direct-acting antiviral agents Chronic hepatitis B- antiviral agents[5,19]			Entry inhibitors cccDNA cleaving therapies
	Autoimmune hepatitis-steroids Alcohol-associated liver disease-Cessation of alcohol[8–10]			
	Metabolic liver disease-specific therapy for Wilson's disease, hemochromatosis etc.[31]			
Reduce portal hypertension	Beta blocker therapy Statins[3] Transjugular intrahepatic portosystemic shunt[129]	Anticoagulation in portal vein thrombosis[88] Midodrine in refractory ascites[29]		
Reduce bacterial translocation	Antibiotics to modulate microbiome[43–45] • Norfloxacin • Rifaximin[107]	Non-antibiotic therapy • Pre-biotics • Probiotics[106] • Beta Blockers	FXR agonist (Obeticholic acid)[151]	Fecal microbiota transplantation
Circulatory dysfunction	Human albumin[28,62–64] Betablockers[83,85]	Simvastatin and other statins		
Immune dysfunction	Human albumin[63]			Hematopoietic growth factors like G-CSF[130]
Sarcopenia	Nutritional interventionsg raded exercise therapy[132–134]			
Bridging therapies			Albumin dialysis[153] Plasma exchange	Stem cell therapy[154]
Definitive therapy	Liver transplantation[120–122]			

Abbreviations: cccDNA, covalently closed circular DNA of hepatitis B virus; FXR, Farnesoid X receptor; G-CSF, granulocyte colony stimulating factor.

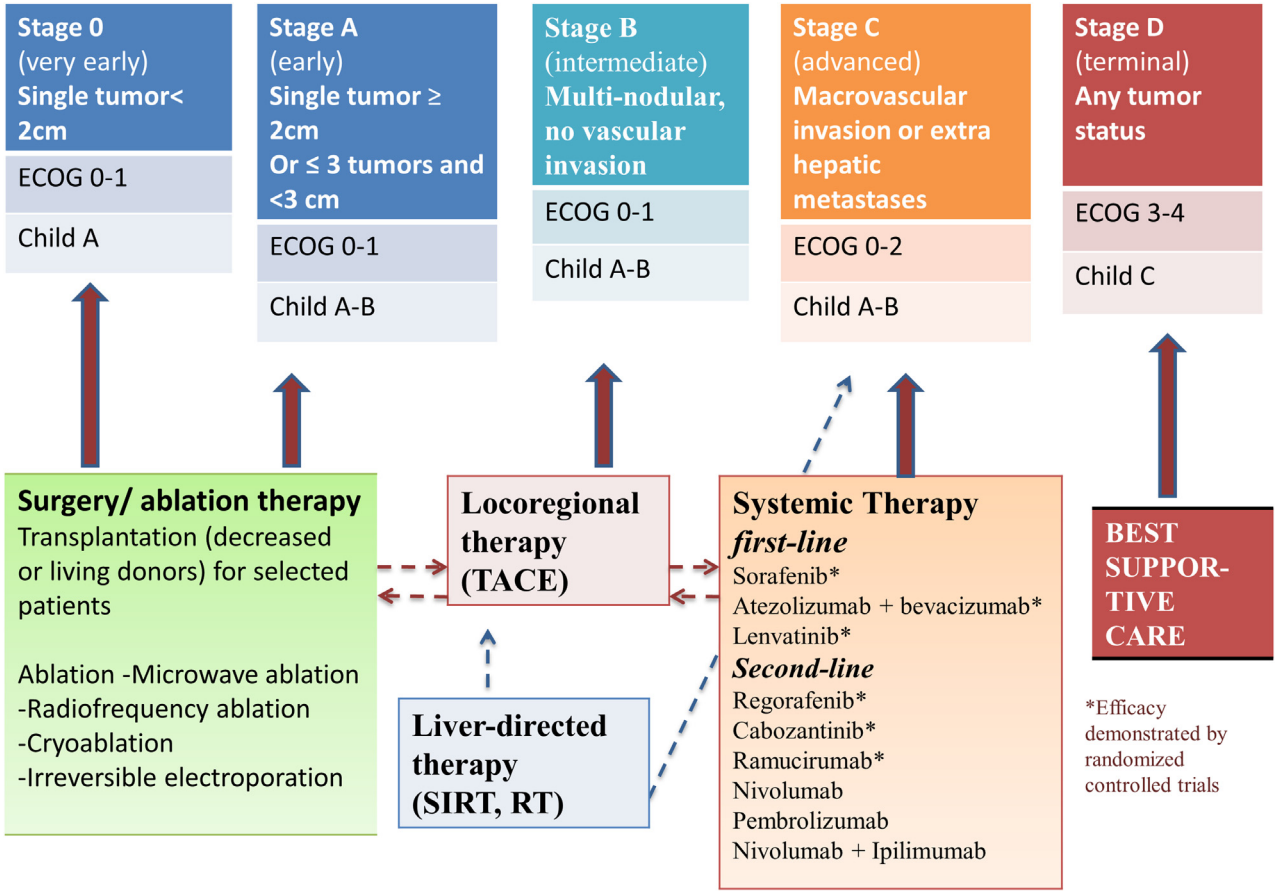

Figure 3 Update in the management of hepatocellular carcinoma.

measures like metabolic equivalent of tasks remain the same.[119]

Transplantation in Cirrhosis

Patients with cirrhosis who have decompensated with ascites, HE, or have a third complication (sepsis, recurrent AVB, or SBP) are unlikely to have good 1-year survival and should be advised early transplantation. Increasingly, the most common etiology for liver transplantation in alcohol-associated liver disease in India.[120] Timely transplantation for HCC using Milan or extended Milan criteria is curative, with good recurrence-free survival rates.[121] Mc Cabe et al. reported that among 100,618 adults listed for LT (68.8% male), patients with worse Karnofsky Performance Status Score (KPSS) were significantly more likely to have ascites, HE, and SBP at time of waitlist registration (KPSS-1 vs. KPSS-4: ascites, 66% vs. 93%; HE, 81% vs. 49%; SBP, 4% vs. 16%, $P < 0.001$ for all), which was independent of disease etiology.[122] Functional status assessment of nutrition, frailty, and sarcopenia has bearing on LT outcomes in India.[123] Expansion of the transplant programme in India brings up questions about the affordability and access to advanced care. Very few public health programmes in India offer low-cost transplantation, and most high-volume centers are managed by the private sector. Disparity in availability of hepatology care remains an issue worldwide.[124] The COVID-19 pandemic has impacted the LT programme globally but gives time to pause and assess expansion and capacity building.[125] Improvement of public health infrastructure in India, creation of more liver specific programmes and bringing affordable transplants under the ambit of national health insurance schemes may be key to ensuring the success and sustainability of LT in India.[126] In addition, over dependence on living donor programmes in India leads to questions of ethics and increases cost of LT.[127] In the future, regional organ registries and centrally regulated unbiased wait listing will be essential to ensure successful, equitable, and affordable LT.

Prolongation of Life in Cirrhosis

Table 2 summarizes the treatment of major complications in cirrhosis. First-line treatment of patients with cirrhotic ascites consists of sodium restriction, diuretics (oral spironolactone and furosemide), and nutritional interventions. The use of midodrine and domiciliary albumin infusions

Figure 4 Decline in Clinical Status guidelines. Adapted from Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD) for Hospice Determining Terminal Status (L33393) Available from https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=33393. Last accessed 23 November 2021.

has improved diuretic response.[128] TIPS may be considered as a bridge to transplant in refractory ascites, whereas peritoneovenous shunt should be considered in eligible patients are not candidates for multiple paracentesis, TIPS, or liver transplantation.[129] With increasing availability of LT, the use of these surgical shunts is limited. Patients who survive an episode of SBP should receive long-term antibiotic prophylaxis (norfloxacin) and should be listed for early LT. Patients with AVB, should be managed with vasoconstrictors like terlipressin or octreotide and specific endotherapy. They should receive antibiotics to prevent SBP. NSBBs like propranolol and carvedilol are useful for prophylaxis of variceal bleeding. The role of discontinuation of NSBB in refractory ascites or recurrent HRS is under debate. The PREDESCI study used high doses of NSBB (either propranolol up to 160 mg twice daily) vs. placebo or carvedilol ≤25 mg per day in propranolol non-responders and showed reduced risk of a new decompensation event in patients with compensated cirrhosis and CSPH.[85]

The role of oral vitamin D supplementation has been described in a recent trial wherein mean difference in BMD at lumbar spine and left hip neck did not differ after 1 year of intervention, albeit with significant improvement in vitamin D levels.[130]

Also, a Cochrane meta-analysis suggested a low level of evidence regarding prevention of liver-related morbidity or decompensation. The authors assessed the efficacy of vitamin D vs. placebo or no intervention in 27 trials with 979 participants with a mean follow-up of 7 months and showed reduced risk ratio (0.86, 95% CI 0.51 to 1.45) of all-cause mortality). They concluded that 'the effect of vitamin D versus placebo or no intervention on liver-related mortality (RR 1.62, 95% CI 0.08 to 34.66; 1 trial; 18 participants)' was unclear and serious adverse events such as hypercalcemia (RR 5.00, 95% CI 0.25 to 100.8; 1 trial; 76 participants); myocardial infarction (RR 0.75, 95% CI 0.08 to 6.81; 2 trials; 86 participants) and non-serious adverse events could not be distinguished due to

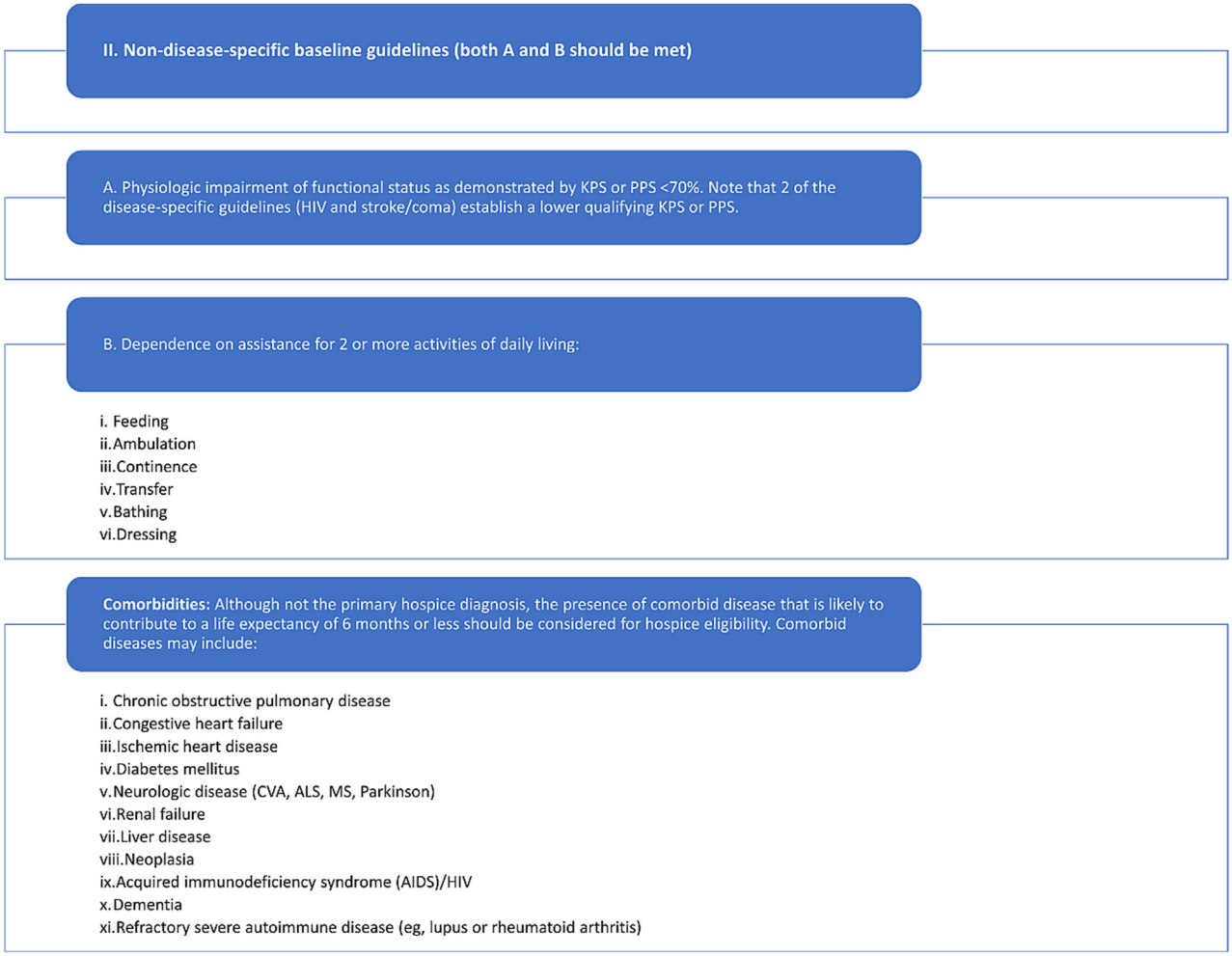

Figure 5 Decline in Clinical Status guidelines. Adapted from Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD) for Hospice Determining Terminal Status (L33393) Available from https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=33393. Last accessed 23 November 2021.

inherent bias with very low certainty of evidence for all outcomes. Trials on vitamin D supplementation have not reported on liver-related morbidity such as AVB, HE, HRS, ascites, or HCC. There were also no data on health-related quality of life.[131]

Currently, nutritional interventions and exercise therapy are underutilized as effective means of prolonging life in cirrhosis (Table 4). As per the recent Japanese Society of Hepatology guidelines in an Asian population,[31] energy intake is recommended as 25–35 kcal/kg (standard body weight)/day in the absence of glucose intolerance, and protein requirements should be 1.0–1.5 g/kg/day (including BCAA preparations) in the absence of protein intolerance.[132] Patients with BMI < 18.5 kg/m^2 are at a high-risk of protein-energy malnutrition or sarcopenia. Small frequent meals divided as 4–7 meals per day improve non-protein respiratory quotient.[133] Regular nutritional assessment, enhanced diet, and exercise in cirrhosis can improve insulin resistance, hepatic steatosis, and liver fibrosis.[134] A recent meta-analysis suggested that coffee consumption reduces liver fibrosis and risk of HCC or mortality in cirrhosis.[135,136] Kim et al. reported that statin use was associated with 46% lower risk of hepatic decompensation (4 studies; RR, 0.54; 95% CI, 0.46–0.62; moderate-quality evidence), and 46% lower mortality (5 studies; RR, 0.54; 95% CI, 0.47–0.61; moderate-quality evidence) in patients with cirrhosis.[137] Statins are reported to reduce portal pressure, improve endothelial dysfunction, decrease fibrogenesis, ameliorate endotoxin-mediated liver injury, reduce risk of ischemia reperfusion injury in liver grafts, and protect from ACLF.[138]

Role of Palliative Therapies

Hospice and palliative care models share the same principles of providing supportive care and comfort to patients

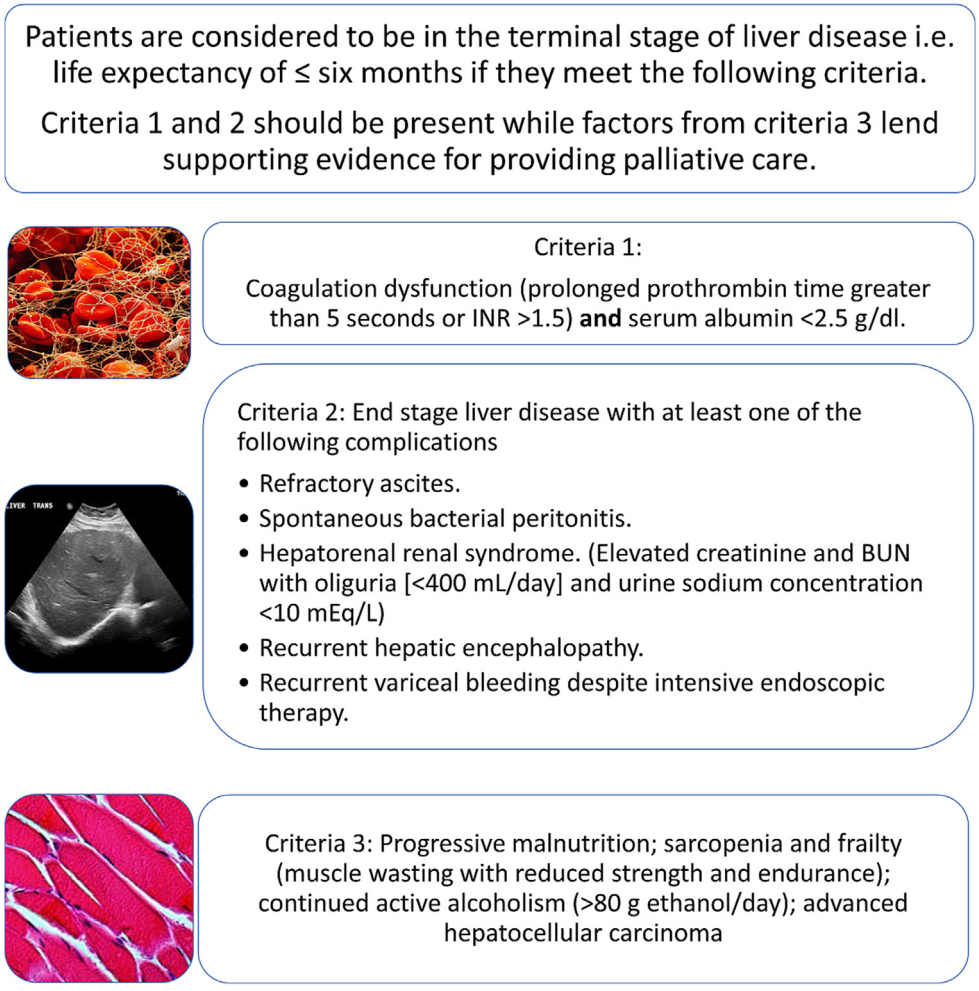

Figure 6 Diagnostic criteria for end-of-life care with life expectancy ≤6 months in patients with cirrhosis.

with advanced cirrhosis. The term hospice care is used to describe a 'model of palliative care that is offered to patients with a terminal illness, with an estimated life expectancy of six months or less or when the curative therapy or life prolonging interventions are no longer the focus of treatment'. In contrast, palliative care models should be offered to all patients with cirrhosis with complications, concurrent with disease-specific treatments like antibiotics, albumin, NSBB, and endoscopic interventions.[139]

The clinical criteria for patients with advanced liver disease include the following:

- Advanced cirrhosis with one or more of the following complications including refractory ascites, HE, HRS, recurrent SBP, and recurrent variceal bleeding.
- Serum albumin <2.5 g/dL with prolonged INR or prothrombin time.
- Advanced HCC.

As per current Medicare guidelines, patients are in the terminal stage of liver disease i.e. life expectancy of ≤6 months if they meet the following criteria. Criteria 1 and 2, pertaining to coagulation defect and PH-related complications should be present while factors from criteria 3, related to sarcopenia, frailty, alcoholism, and HCC, lend supporting evidence for providing palliative care (Figure 3). Patients should be assessed for non-disease-specific "Decline in clinical status" guidelines described in Figure 4 plus the applicable disease-specific guidelines pertaining to cirrhosis will establish the necessary expectancy.[140] It is necessary to frame such concepts for use in the Indian context (Figure 5).

Persons with cirrhosis can be considered eligible for end-of-life care if a decline in clinical status has been documented and the clinical worsening is considered irreversible. The decline in clinical status guidelines assess the progression of disease as documented by worsening clinical status signs and symptoms and laboratory results. Patients with cirrhosis can have intractable systemic infections like pneumonia, systemic sepsis, pyelonephritis, and so on. Weight loss should be

Table 5 Principles of Management and Interventions as Palliative Care in Cirrhosis.

Domain	Primary Management	Additional therapy and dose modifications	Supportive care
Ascites Management[21]	Drugs that decrease systemic blood pressure should be discontinued including ACEIs, beta blockers, ARBs, etc. NSAIDs can reduce renal perfusion and should be avoided.[27]	Midodrine is an oral vasopressor and can improved diuretic response by maintaining the mean arterial pressure. It is prescribed in a dose of 5–22.5 mg/day in 2–3 divided doses. Combination of midodrine with diuretics has been described.[29,30]	• Serial large volume paracentesis[32,129] • Domiciliary albumin infusion • Indwelling peritoneal catheter • Low flow ascitic pump.[33]
Recurrent Hepatic Encephalopathy	Precipitation of episodic HE by dehydration, dyselectrolytemia and overdiuresis can be avoided Maintenance of nutritional therapy, stool consistency and frequency by patient education.	Assessment of decision-making capacity of the patient. Provision of adequate nutrition, high value protein, exercise program and cognition support.	Caregiver assistance
Pain Management[136]	Acetaminophen is the 'safest' drug. • Tissue stores of glutathione are reduced in patients with cirrhosis or malnutrition. • Therefore, risk of formation of the toxic metabolite of acetaminophen (NAPQI) is increased • Consumption of ethanol also reduces glutathione stores • Half-life of acetaminophen is prolonged by two times in cirrhosis	Total daily dose of acetaminophen should be restricted to less than 1 g per day. Avoid frequent use or long duration of therapy. Use of acetaminophen should be avoided in advanced cirrhosis with active alcohol consumption malnutrition or concomitant drug usage which induce hepatic CYPs. Aspirin should be avoided in cirrhosis. Selective COX-2 inhibitors should also be avoided	
Opioid analgesics[155]			
	Fentanyl: Fentanyl is metabolized by CYP3A4 to inactive metabolites. Fentanyl can accumulate in tissues after repeat dosing or when administered as a continuous infusion due to protein binding. It is used as analgesia in intensive care practice	• Fentanyl is the best choice for patients with cirrhosis where opiate treatment is indicated. • It is also useful in patients with acute kidney injury • Dose adjustment is not needed for single dose of fentanyl. • However, for repeated dosing schedule the frequency and total dose should be reduced by 25–50%. • Initiate transdermal fentanyl patch at half usual dose	
	Tramadol: • This opioid analoge is metabolized to its active metabolite by CYP3A4 and CYP2D6. • However, there is unpredictable onset of action, variable efficacy, and possible accumulation of the drug in cirrhosis.	• Avoid use in patients with decompensated cirrhosis. • Avoid use in patients at risk for seizures. • Based on limited experience, a reduced dose of 25 mg every 8 h may be considered for treatment of pain in patients with advanced CLD or well-compensated cirrhosis.	

(*Continued on next page*)

Table 5 (*Continued*)

Domain	Primary Management	Additional therapy and dose modifications	Supportive care
Management of neuropathic pain[156]	Pregabalin: • Pregabalin is excreted unchanged in urine • Its excretion is dependent on renal function. • It is not metabolized in the liver nor is it bound to plasma proteins • Adverse effect effects like sedation and dizziness limits the usefulness in patients with advanced cirrhosis or hepatic encephalopathy Gabapentin • Gabapentin is excreted unchanged in the urine • Its excretion is dependent on renal function. • Adverse effects include sedation, ataxia, dizziness, and nausea which limit the tolerance of this drug in advanced cirrhosis	• Pregabalin should be initiated at the dose of 50 mg twice daily and gradually titrated over weeks. • The efficacy of pregabalin is noted only after two to three weeks, due to delayed onset of action in neuropathic pain. • The maintenance dose is dependent on renal function. Gabapentin should be initiated at a dose of 300 mg per day and gradually titrated over weeks Slow titration improves tolerability	

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor II blockers; CLD, chronic liver disease; CYP, cytochrome P450 enzyme; HE, Hepatic Encephalopathy; NSAIDs, non-steroidal anti-inflammatory drugs.

documented as loss of at least 10% of body weight in the past six months which is attributable to diabetes and has been objectively assessed by decreasing anthropomorphic measurements [midarm circumference, abdominal girth], which is not caused by depression or use of diuretics. A subjective observation of ill-fitting of clothes, decrease in skin turgor, or other subjective observations of weight loss contributes to the definition of a decline in clinical status. Decreased serum albumin or cholesterol, poor oral intake, self-imposed restriction of activity, dysphagia leading to recurrent aspiration indicated by inadequate protein calorie consumption indicate poor clinical status in cirrhosis. Other symptoms that need to be assessed in the palliative care model are dyspnea, increasing respiratory rate, intractable cough, nausea and vomiting, intractable diarrhea, and need for requiring increasing doses of analgesia to manage disease-related pain[141] (Figure 5).

Health-related Quality of Life in Cirrhosis

One of the major implications in the way patients with cirrhosis manage their clinical disease is the changes in their ability to remain working earning members of society, their state of physical, mental, and social wellbeing and the impact the disease has on the caregivers.[142] The social and economic impact of cirrhosis and its complications should be factored into any clinical decision-making with the public health burden of disease. Clinicians should be trained to assess HRQoL outcomes in cirrhosis and need to be aware of patients' preferences for care, especially for end-of-life approaches (Figure 6).

The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) reported that patients with decompensated cirrhosis report moderate to high pain scores that are like persons living with cancer.[143]

Most patients in this study expressed a preference for dying rather than living in a coma or on prolonged life support. Studies from India have also confirmed the impact of cirrhosis on patient reported outcomes such as pain, social and mental health, vitality, and functional decline with time.[144,145] Table 5 lists the interventions used in palliative care in decompensated cirrhosis.

The significant mortality while on transplant listing, suggested that waitlisted patients suffer from physical and psychological decline. More data are required from an Indian caregiver and self-financed setting rather than Western populations where most transplant programmes are on health insurance basis. Many patients remain in the transplant purgatory, with insufficient MELD to be listed for an organ, but too sick for a functional life.[146]

Nath et al. have performed a systematic review on the treatment on muscle cramps in cirrhosis. Fatigue may be defined as any transient exercise-induced decrease in

muscular force or power output, with or without task failure, that is best understood across three axes i.e., motor, cognitive, and affective.[147] The symptom of fatigue was traditionally described with autoimmune liver disease and primary biliary cholangitis but is now reported as cardinal features of alcohol-associated liver disease, chronic viral hepatitis, drug induced liver injury, and NAFLD. Patient-reported outcomes should be part of outcomes assessment in cirrhosis.[148] Experimental therapies like stem cell infusions, have yet to find wide clinical application.[149] Use of interventions like norfloxacin and rifaximin to reduce bacterial translocation and reduce risk of sepsis have been reported in the Indian context.[150] Recently, the use of obeticholic acid is diseases other than NAFLD has been described.[151] Lastly novel strategies for sarcopenia and frailty require more research to improve patient outcomes and quality of life.[152]

In conclusion, patients with cirrhosis have progressive disease and suffer from multiple complications like ascites, HE, variceal bleeding, hepatorenal syndrome, cirrhotic cardiomyopathy, pulmonary syndromes, sarcopenia, frailty, and HCC. The prevention, early diagnosis, treatment, and palliation of these complications are essential in comprehensive clinical care plans. The incorporation of patient-reported outcomes, quality of life assessment and patient driven management algorithms are the need of the hour. Importantly, access to specialized care like locoregional therapy, liver transplantation, advanced imaging and endoscopy, public health programmes for viral hepatitis, alcohol use reduction, obesity, and non-communicable disease policy frameworks can improve disease outcomes in cirrhosis. The improved understanding of pathophysiological mechanisms, availability of breakthrough drugs, like DAAs, HCC immunotherapy, and so on, generic treatments and low-cost nutritional interventions can change the natural history of disease. Lastly, understanding palliative care and end-of-life care options can improve patient centric management options.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

MP and ACA were both involved in the manuscript preparation. Both the authors have read and approved the manuscript.

CONFLICTS OF INTEREST

Both authors have none to declare.

FUNDING

None.

REFERENCES

1. Seo YS, Shah VH. Pathophysiology of portal hypertension and its clinical links. *J Clin Exp Hepatol*. 2011;1:87–93. https://doi.org/10.1016/S0973-6883(11)60127-8.
2. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. *Hepatology*. 2004;39:280–282. https://doi.org/10.1002/hep.20062.
3. Lim YS, Kim WR. The global impact of hepatic fibrosis and end-stage liver disease. *Clin Liver Dis*. 2008;12:733–746. https://doi.org/10.1016/j.cld.2008.07.007. vii.
4. Jain P, Shasthry SM, Choudhury AK, et al. Alcohol associated liver cirrhotics have higher mortality after index hospitalization: long-term data of 5,138 patients. *Clin Mol Hepatol*. 2021;27:175–185. https://doi.org/10.3350/cmh.2020.0068.
5. Sarin SK, Kumar M, Eslam M, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol*. 2020;5:167–228. https://doi.org/10.1016/S2468-1253(19)30342-5. Erratum in: Lancet Gastroenterol Hepatol. 2020;5(3): e2.
6. Scaglione S, Kliethermes S, Cao G, et al. The epidemiology of cirrhosis in the United States: a population-based study. *J Clin Gastroenterol*. 2015;49:690–696. https://doi.org/10.1097/MCG.0000000000000208.
7. Singh GK, Hoyert DL. Social epidemiology of chronic liver disease and cirrhosis mortality in the United States, 1935-1997: trends and differentials by ethnicity, socioeconomic status, and alcohol consumption. *Hum Biol*. 2000;72:801–820.
8. Lachenmeier DW, Monakhova YB, Rehm J. Influence of unrecorded alcohol consumption on liver cirrhosis mortality. *World J Gastroenterol*. 2014 Jun 21;20:7217–7222. https://doi.org/10.3748/wjg.v20.i23.7217.
9. Kim HY, Kim CW, Choi JY, et al. Complications requiring hospital admission and causes of in-hospital death overtime in alcoholic and nonalcoholic cirrhosis patients. *Gut Liver*. 2016;10:95–100.
10. Huang A, Chang B, Sun Y, et al. Disease spectrum of alcoholic liver disease in Beijing 302 hospital from 2002 to 2013: a large tertiary referral hospital experience from 7422 patients. *Medicine (Baltimore)*. 2017;96:e6163.
11. Mukherjee PS, Vishnubhatla S, Amarapurkar DN, et al. Etiology and mode of presentation of chronic liver diseases in India: a multi centric study. *PLoS One*. 2017 Oct 26;12:e0187033. https://doi.org/10.1371/journal.pone.0187033. PMID: 29073197; PMCID: PMC5658106.
12. Dhiman RK, Grover GS, Premkumar M, et al. Decentralized care with generic direct-acting antivirals in the management of chronic hepatitis C in a public health care setting. *J Hepatol*. 2019;71:1076–1085. https://doi.org/10.1016/j.jhep.2019.07.006.
13. Nusrat S, Khan MS, Fazili J, Madhoun MF. Cirrhosis and its complications: evidence-based treatment. *World J Gastroenterol*. 2014;20:5442–5460.
14. Chawla YK, Kashinath RC, Duseja A, Dhiman RK. Predicting mortality across a broad spectrum of liver disease-an assessment of model for end-stage liver disease (MELD), Child-Turcotte-Pugh (CTP), and creatinine-modified CTP scores. *J Clin Exp Hepatol*. 2011;1:161–168. https://doi.org/10.1016/S0973-6883(11)60233-8.
15. Jindal A, Bhardwaj A, Kumar G, Sarin SK. Clinical decompensation and outcomes in patients with compensated cirrhosis and a hepatic venous pressure gradient ≥20 mm Hg. *Am J Gastroenterol*. 2020;115:1624–1633. https://doi.org/10.14309/ajg.0000000000000653.
16. Dhiman RK, Premkumar M. Hepatitis C virus elimination by 2030: conquering mount improbable. *Clin Liver Dis (Hoboken)*. 2021;16:254–261. https://doi.org/10.1002/cld.978.

17. Murhekar MV, Santhosh Kumar M, Kamaraj P, et al, ICMR – Serosurvey group. Hepatitis-B virus infection in India: findings from a nationally representative serosurvey, 2017-18. *Int J Infect Dis*. 2020;100:455–460. https://doi.org/10.1016/j.ijid.2020.08.084.
18. Akbar SMF, Al Mahtab M, Begum F, et al. Implications of birth-dose vaccination against hepatitis B virus in Southeast Asia. *Vaccines (Basel)*. 2021;9:374. https://doi.org/10.3390/vaccines9040374.
19. Premkumar M, Chawla YK. Should we treat immune tolerant chronic hepatitis B? Lessons from Asia. *J Clin Exp Hepatol*. 2022 Jan-Feb;12:144–154. https://doi.org/10.1016/j.jceh.2021.08.023. Epub 2021 Aug 27. PMID: 35068795; PMCID: PMC8766700.
20. Dhiman RK, Grover GS, Premkumar M. Hepatitis C elimination: a public health perspective. *Curr Treat Options Gastroenterol*. 2019;17(3):367–377. https://doi.org/10.1007/s11938-019-00240-7.
21. Runyon BA, AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology*. 2009;49:2087–2107. https://doi.org/10.1002/hep.22853.
22. Baijal R, Praveenkumar HR, Amarapurkar DN, Nagaraj K, Jain M. Prevalence of tuberculosis in patients with cirrhosis of liver in western India. *Trop Doct*. 2010;40:163–164. https://doi.org/10.1258/td.2010.090463.
23. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018 Aug;69(2):406–460. https://doi.org/10.1016/j.jhep.2018.03.024. Epub 2018 Apr 10. Erratum in: J Hepatol. 2018 Nov;69(5):1207. PMID: 29653741.
24. Reynolds TB, Lieberman FL, Goodman AR. Advantages of treatment of ascites without sodium restriction and without complete removal of excess fluid. *Gut*. 1978;19:549–553. https://doi.org/10.1136/gut.19.6.549.
25. Runyon BA, AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology*. 2013;57:1651–1653. https://doi.org/10.1002/hep.26359.
26. Gu XB, Yang XJ, Zhu HY, Xu BY. Effect of a diet with unrestricted sodium on ascites in patients with hepatic cirrhosis. *Gut Liver*. 2012;6:355–361. https://doi.org/10.5009/gnl.2012.6.3.355.
27. Zhu YF, Gu XB, Zhu HY, Yang XJ, Wang D, Yu P. Influence of non-sodium restricted diet with diuretics on plasma rennin, renal blood flow and in patients with cirrhotic ascites. *Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi*. 2013;27:50–53.
28. Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. *J Clin Exp Hepatol*. 2014;4:302–311. https://doi.org/10.1016/j.jceh.2014.08.007.
29. Kulkarni AV, Kumar P, Sharma M, et al. Pathophysiology and prevention of paracentesis-induced circulatory dysfunction: a concise review. *J Clin Transl Hepatol*. 2020;8:42–48. https://doi.org/10.14218/JCTH.2019.00048.
30. Singh V, Dhungana SP, Singh B, et al. Midodrine in patients with cirrhosis and refractory or recurrent ascites: a randomized pilot study. *J Hepatol*. 2012;56:348–354. https://doi.org/10.1016/j.jhep.2011.04.027.
31. Yoshiji H, Nagoshi S, Akahane T, et al. Evidence-based clinical practice guidelines for Liver Cirrhosis 2020. *J Gastroenterol*. 2021;56:593–619. https://doi.org/10.1007/s00535-021-01788-x.
32. Neong SF, Adebayo D, Wong F. An update on the pathogenesis and clinical management of cirrhosis with refractory ascites. *Expert Rev Gastroenterol Hepatol*. 2019;13:293–305. https://doi.org/10.1080/17474124.2018.1555469.
33. Stirnimann G, Banz V, Storni F, De Gottardi A. Automated low-flow ascites pump for the treatment of cirrhotic patients with refractory ascites. *Therap Adv Gastroenterol*. 2017;10:283–292. https://doi.org/10.1177/1756283X16684688.
34. Jindal A, Kumar M, Bhadoria AS, Maiwall R, Sarin SK. Response to Treatment of spontaneous bacterial peritonitis: beyond the current international guidelines. *Liver Int*. 2016;36:919. https://doi.org/10.1111/liv.13074.
35. Sanglodkar U, Jain M, Vargese J, Kedarisetty C, Venkataraman J. Clinical audit to determine efficacy of daily infusion of low dose of 20% albumin in combination with antibiotics in patients with spontaneous bacterial peritonitis. *Clin Exp Hepatol*. 2019;5:301–307. https://doi.org/10.5114/ceh.2019.88774.
36. Sanglodkar U, Jain M, Venkataraman J. Predictors of immediate and short-term mortality in spontaneous bacterial peritonitis. *Indian J Gastroenterol*. 2020;39:331–337. https://doi.org/10.1007/s12664-020-01040-z.
37. Soni H, Kumar MP, Sharma V, et al. Antibiotics for prophylaxis of spontaneous bacterial peritonitis: systematic review & Bayesian network meta-analysis. *Hepatol Int*. 2020;14:399–413. https://doi.org/10.1007/s12072-020-10025-1.
38. Thuluvath PJ, Alukal JJ, Zhang T. Impact of hyponatremia on morbidity, mortality, and resource utilization in portal hypertensive ascites: a nationwide analysis. *J Clin Exp Hepatol*. 2022;12(3):871–875. https://doi.org/10.1016/j.jceh.2021.10.145.
39. Praharaj DL, Anand AC. Clinical implications, evaluation, and management of hyponatremia in cirrhosis. *J Clin Exp Hepatol*. 2022;12(2):575–594. https://doi.org/10.1016/j.jceh.2021.09.008.
40. Premkumar M, Rangegowda D, Kajal K, Khumuckham JS. Noninvasive estimation of intravascular volume status in cirrhosis by dynamic size and collapsibility indices of the inferior vena cava using bedside echocardiography. *JGH Open*. 2019;3:322–328. https://doi.org/10.1002/jgh3.12166.
41. Garg R, Kaur K, Aggarwal S, Singh N. Efficacy and safety of oral Tolvaptan therapy in hospitalized cirrhotic patients with hyponatremia. *J Assoc Phys India*. 2018;66:49–52.
42. Falleti E, Cmet S, Cussigh AR, et al. Recurrent and treatment-unresponsive spontaneous bacterial peritonitis worsens survival in decompensated liver cirrhosis. *J Clin Exp Hepatol*. 2021;11:334–342. https://doi.org/10.1016/j.jceh.2020.08.010.
43. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol*. 2014;60:1310–1324. https://doi.org/10.1016/j.jhep.2014.01.024.
44. Piano S, Singh V, Caraceni P, et al, International Club of Ascites Global Study Group. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. *Gastroenterology*. 2019;156:1368–1380.e10. https://doi.org/10.1053/j.gastro.2018.12.005.
45. Piano S, Bartoletti M, Tonon M, et al. Assessment of Sepsis-3 criteria, and quick SOFA in patients with cirrhosis and bacterial infections. *Gut*. 2018;67:1892–1899.
46. Fernández J, Prado V, Trebicka J, et al. European Foundation for the Study of Chronic Liver Failure (EF-Clif). Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. *J Hepatol*. 2019;70:398–411. https://doi.org/10.1016/j.jhep.2018.10.027.

47. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:801–810.
48. Baijal R, Amarapurkar D, Praveen Kumar HR, et al. A multicenter prospective study of infections related morbidity and mortality in cirrhosis of liver. *Indian J Gastroenterol*. 2014;33:336–342. https://doi.org/10.1007/s12664-014-0461-3.
49. Jain M, Varghese J, Michael T, et al. An insight into antibiotic resistance to bacterial infection in chronic liver disease. *J Clin Exp Hepatol*. 2017;7:305–309. https://doi.org/10.1016/j.jceh.2017.05.003.
50. Tewari R, Mitra S, Ganaie F, et al. Dissemination, and characterisation of Escherichia coli producing extended-spectrum β-lactamases, AmpC β-lactamases and metallo-β-lactamases from livestock and poultry in Northeast India: a molecular surveillance approach. *J Glob Antimicrob Resist*. 2019;17:209–215. https://doi.org/10.1016/j.jgar.2018.12.025.
51. Mills MC, Lee J. The threat of carbapenem-resistant bacteria in the environment: evidence of widespread contamination of reservoirs at a global scale. *Environ Pollut*. 2019;255(Pt 1):113143. https://doi.org/10.1016/j.envpol.2019.113143.
52. Khan AU, Maryam L, Zarrilli R. Structure, genetics and worldwide spread of New Delhi metallo-β-lactamase (NDM): a threat to public health. *BMC Microbiol*. 2017;17:101. https://doi.org/10.1186/s12866-017-1012-8.
53. Maraolo AE, Buonomo AR, Zappulo E, Scotto R, Pinchera B, Gentile I. Unsolved issues in the treatment of spontaneous peritonitis in patients with cirrhosis: nosocomial versus community-acquired infections and the role of fungi. *Rev Recent Clin Trials*. 2019;14:129–135. https://doi.org/10.2174/1574887114666181204102516.
54. Ferrarese A, Cattelan A, Cillo U, et al. Invasive fungal infection before and after liver transplantation. *World J Gastroenterol*. 2020;26:7485–7496. https://doi.org/10.3748/wjg.v26.i47.7485.
55. Tariq T, Irfan FB, Farishta M, Dykstra B, Sieloff EM, Desai AP. Spontaneous fungal peritonitis: micro-organisms, management, and mortality in liver cirrhosis-A systematic review. *World J Hepatol*. 2019;11:596–606. https://doi.org/10.4254/wjh.v11.i7.596.
56. Nori P, Cowman K, Chen V, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. *Infect Control Hosp Epidemiol*. 2021;42:84–88. https://doi.org/10.1017/ice.2020.368.
57. Kluge S, Strauß R, Kochanek M, Weigand MA, Rohde H, Lahmer T. Aspergillosis: emerging risk groups in critically ill patients. *Med Mycol*. 2021;60:myab064. https://doi.org/10.1093/mmy/myab064. PMID:34677613.
58. Menezes S, Kumar JS, Rudra OS, Nagral A. Cutaneous mucormycosis: an unusual cause of decompensation in a patient with ethanol-related cirrhosis with COVID-19 exposure. *BMJ Case Rep*. 2022;15:e247399. https://doi.org/10.1136/bcr-2021-247399. PMID: 35140094; PMCID: PMC8830195.
59. Angeli P, Gines P, Wong F, et al. International Club of Ascites. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *Gut*. 2015;64:531–537. https://doi.org/10.1136/gutjnl-2014-308874.
60. Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition, and classification of hepatorenal syndrome: a step beyond the International Club of Ascites (ICA) consensus document. *J Hepatol*. 2019;71:811–822. https://doi.org/10.1016/j.jhep.2019.07.002.
61. Simonetto DA, Gines P, Kamath PS. Hepatorenal syndrome: pathophysiology, diagnosis, and management. *BMJ*. 2020 Sep 14;370:m2687. https://doi.org/10.1136/bmj.m2687.
62. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol*. 2013;11:123–130.e1. https://doi.org/10.1016/j.cgh.2012.11.007.
63. Caraceni P, Riggio O, Angeli P, et al. ANSWER Study Investigators. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. *Lancet*. 2018;391:2417–2429. https://doi.org/10.1016/S0140-6736(18)30840-7.
64. Fernandez J, Angeli P, Trebicka J, et al. Efficacy of albumin treatment for patients with cirrhosis and infections unrelated to spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol*. 2020;18:963–973.e14. https://doi.org/10.1016/j.cgh.2019.07.055.
65. Srivastava S, Shalimar, Vishnubhatla S, et al. Randomized controlled trial comparing the efficacy of terlipressin and albumin with a combination of concurrent dopamine, furosemide, and albumin in hepatorenal syndrome. *J Clin Exp Hepatol*. 2015;5:276–285. https://doi.org/10.1016/j.jceh.2015.08.003.
66. Kulkarni AV, Arab JP, Premkumar M, et al. Terlipressin has stood the test of time: clinical overview in 2020 and future perspectives. *Liver Int*. 2020;40:2888–2905. https://doi.org/10.1111/liv.14703.
67. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VII Faculty. Baveno VII - renewing consensus in portal hypertension. *J Hepatol*. 2022;76:959–974. https://doi.org/10.1016/j.jhep.2021.12.022. Epub 2021 Dec 30. PMID: 35120736.
68. Zoli M, Merkel C, Magalotti D, et al. Natural history of cirrhotic patients with small esophageal varices: a prospective study. *Am J Gastroenterol*. 2000;95:503–508.
69. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2017;65:310–335. https://doi.org/10.1002/hep.28906. Epub 2016 Dec 1. Erratum in: Hepatology. 2017 Jul;66(1):304. PMID: 27786365.
70. D'Amico G, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology*. 2003;38:599–612.
71. Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. *Hepatology*. 2017;66:1980–1988. https://doi.org/10.1002/hep.29363.
72. Eapen CE, Kandasamy S. Improving outcomes with pharmacotherapy to treat acute esophageal variceal bleeding. *Indian J Gastroenterol*. 2018;37:279–280. https://doi.org/10.1007/s12664-018-0887-0.
73. Sharma P, Sarin SK. Improved survival with the patients with variceal bleed. *Int J Hepatol*. 2011;2011:356919. https://doi.org/10.4061/2011/356919.
74. Agarwal S, Sharma S, Anand A, Gunjan D, Saraya A. Liver stiffness assessment as an alternative to hepatic venous pressure gradient for predicting rebleed after acute variceal bleed: a proof-of-concept study. *JGH Open*. 2020;5:73–80. https://doi.org/10.1002/jgh3.12449.
75. Sharma BC, Banka AK, Rawat A, Srivastava S. Gastric varices in cirrhosis versus extrahepatic portal venous obstruction and response to endoscopic N-Butyl-2-cyanoacrylate injection. *J Clin Exp Hepatol*. 2013;3:19–23. https://doi.org/10.1016/j.jceh.2013.01.002. Epub 2013 Jan 25. PMID: 25755467; PMCID: PMC3940531.

76. Saraswat VA, Verma A. Gluing gastric varices in 2012: lessons learnt over 25 years. *J Clin Exp Hepatol*. 2012;2:55–69. https://doi.org/10.1016/S0973-6883(12)60088-7.
77. Mukkada RJ, Antony R, Chooracken MJ, et al. Endoscopic ultrasound-guided coil, or glue injection in post-cyanoacrylate gastric variceal re-bleed. *Indian J Gastroenterol*. 2018;37:153–159. https://doi.org/10.1007/s12664-018-0844-y.
78. Bhatia V. Endoscopic ultrasound (EUS) for esophageal and gastric varices: how can it improve the outcomes and reduce complications of glue injection. *J Clin Exp Hepatol*. 2012;2:70–74. https://doi.org/10.1016/S0973-6883(12)60083-8. Epub 2012 Apr 12. PMID: 25755407; PMCID: PMC3940543.
79. Lv Y, Yang Z, Liu L, et al, AVB-TIPS Study Group. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2019;4:587–598. https://doi.org/10.1016/S2468-1253(19)30090-1.
80. Rodge GA, Goenka U, Goenka M. Management of refractory variceal bleed in cirrhosis. *J Clin Exp Hepatol*. 2022;12(2):595–602. https://doi.org/10.1016/j.jceh.2021.08.030.
81. Sarin SK, Wadhawan M, Agarwal SR, Tyagi P, Sharma BC. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. *Am J Gastroenterol*. 2005;100:797–804. https://doi.org/10.1111/j.1572-0241.2005.40468.x.
82. Kumar A, Sharma P, Anikhindi SA, et al. Can non-selective beta-blockers (NSBBs) prevent enlargement of small esophageal varices in patients with cirrhosis? A meta-analysis. *J Clin Exp Hepatol*. 2017;7:275–283. https://doi.org/10.1016/j.jceh.2017.09.003.
83. Premkumar M, Rangegowda D, Vyas T, et al. Carvedilol combined with ivabradine improves left ventricular diastolic dysfunction, clinical progression, and survival in cirrhosis. *J Clin Gastroenterol*. 2020;54:561–568. https://doi.org/10.1097/MCG.0000000000001219.
84. Sharma S, Agarwal S, Gunjan D, et al. Long-term outcomes with carvedilol versus propranolol in patients with index variceal bleed: 6-year follow-up study. *J Clin Exp Hepatol*. 2021;11:343–353. https://doi.org/10.1016/j.jceh.2020.08.009.
85. Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2019;393:1597–1608. https://doi.org/10.1016/S0140-6736(18)31875-0. Epub 2019 Mar 22. Erratum in: Lancet. 2019 Jun 22; 393(10190):2492. PMID: 30910320.
86. Premkumar M, Sarin SK. Current concepts in coagulation profile in cirrhosis and acute-on-chronic liver failure. *Clin Liver Dis (Hoboken)*. 2020;16:158–167. https://doi.org/10.1002/cld.976.
87. Premkumar M, Bihari C, Saxena P, et al. Heparin-like effect associated with risk of bleeding, sepsis, and death in patients with severe alcohol-associated hepatitis. *Clin Gastroenterol Hepatol*. 2020;18:486–495.e3. https://doi.org/10.1016/j.cgh.2019.04.057.
88. Shukla A, Giri S. Portal vein thrombosis in cirrhosis. *J Clin Exp Hepatol*. 2022;12(3):965–979. https://doi.org/10.1016/j.jceh.2021.11.003.
89. Premkumar M, Kulkarni AV, Kajal K, Divyaveer SS. Principles, interpretation, and evidence-based role of viscoelastic point-of-care coagulation assays in cirrhosis and liver failure. *J Clin Exp Hepatol*. 2022;12:533–543. https://doi.org/10.1016/j.jceh.2021.05.001.
90. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention, and management. *Nat Rev Gastroenterol Hepatol*. 2019;16:589–604. https://doi.org/10.1038/s41575-019-0186-y.
91. Paul SB, Sreenivas V, Gulati MS. Incidence of hepatocellular carcinoma among Indian patients with cirrhosis of liver: an experience from tertiary care center in northern India. *Indian J Gastroenterol*. 2007;26:274–278.
92. Acharya SK. Epidemiology of hepatocellular carcinoma in India. *J Clin Exp Hepatol*. 2014;4(suppl 3):S27–S33. https://doi.org/10.1016/j.jceh.2014.05.013.
93. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatol Baltim Md*. 2016;64:73–84.
94. Kumar A, Acharya SK, Singh SP, et al. INASL Taskforce on Hepatocellular Carcinoma. 2019 update of Indian National Association for Study of the Liver Consensus on Prevention, Diagnosis, and Management of Hepatocellular Carcinoma in India: the Puri II recommendations. *J Clin Exp Hepatol*. 2020;10:43–80. https://doi.org/10.1016/j.jceh.2019.09.007.
95. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76:681–693. https://doi.org/10.1016/j.jhep.2021.11.018. Epub 2021 Nov 19. PMID: 34801630; PMCID: PMC8866082.
96. Wu H, Xing H, Liang L, et al. Real-world role of performance status in surgical resection for hepatocellular carcinoma: a multicenter study. *Eur J Surg Oncol*. 2019;45:2360–2368. https://doi.org/10.1016/j.ejso.2019.09.009. Epub 2019 Sep 12. PMID: 31543386.
97. Kim DS, Kim BW, Hatano E, et al. Surgical outcomes of hepatocellular carcinoma with bile duct tumor thrombus: a Korea-Japan multicenter study. *Ann Surg*. 2020;271:913–921. https://doi.org/10.1097/SLA.0000000000003014. PMID: 30216223.
98. Kokudo T, Hasegawa K, Matsuyama Y, et al. Liver Cancer Study Group of Japan. Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: a Japanese nationwide survey. *Hepatology*. 2017;66:510–517. https://doi.org/10.1002/hep.29225. Epub 2017 Jun 26. PMID: 28437844.
99. Amodio P. Current diagnosis and classification of hepatic encephalopathy. *J Clin Exp Hepatol*. 2018;8:432–437. https://doi.org/10.1016/j.jceh.2018.07.001.
100. Weissenborn K. Diagnosis of minimal hepatic encephalopathy. *J Clin Exp Hepatol*. 2015;5(suppl 1):S54–S59. https://doi.org/10.1016/j.jceh.2014.06.005.
101. Ahmed S, Premkumar M, Dhiman RK, et al. Combined PEG3350 plus lactulose results in early resolution of hepatic encephalopathy and improved 28-day survival in acute-on-chronic liver failure. *J Clin Gastroenterol*. 2020 Oct 13 https://doi.org/10.1097/MCG.0000000000001450.
102. Aldridge DR, Tranah EJ, Shawcross DL. Pathogenesis of hepatic encephalopathy: role of ammonia and systemic inflammation. *J Clin Exp Hepatol*. 2015;5(suppl 1):S7–S20. https://doi.org/10.1016/j.jceh.2014.06.004.
103. Haj M, Rockey DC. Ammonia levels do not guide clinical management of patients with hepatic encephalopathy caused by cirrhosis. *Am J Gastroenterol*. 2020;115:723–728. https://doi.org/10.14309/ajg.0000000000000343.
104. Sidhu SS, Sharma BC, Goyal O, Kishore H, Kaur N. L-ornithine L-aspartate in bouts of overt hepatic encephalopathy. *Hepatology*. 2018;67:700–710. https://doi.org/10.1002/hep.29410. Epub 2017 Dec 27. PMID: 28749571.
105. Jain A, Sharma BC, Mahajan B, et al. L-ornithine L-aspartate in acute treatment of severe hepatic encephalopathy: a double-blind randomized controlled trial. *Hepatology*. 2021 https://doi.

org/10.1002/hep.32255. Epub ahead of print. PMID: 34822189.
106. Dhiman RK, Rana B, Agrawal S, et al. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. *Gastroenterology*. 2014;147:1327–1337.e3. https://doi.org/10.1053/j.gastro.2014.08.031. Epub 2014 Aug 27. PMID: 25450083.
107. Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol*. 2013 Sep;108:1458–1463. https://doi.org/10.1038/ajg.2013.219. Epub 2013 Jul 23. PMID: 23877348.
108. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. *BMJ*. 2004;328:1046. https://doi.org/10.1136/bmj.38048.506134.EE. Epub 2004 Mar 30. PMID: 15054035; PMCID: PMC403844.
109. Gluud LL, Dam G, Les I, et al. Branched-chain amino acids for people with hepatic encephalopathy. *Cochrane Database Syst Rev*. 2017;5:CD001939. https://doi.org/10.1002/14651858.CD001939.pub4. PMID: 28518283; PMCID: PMC6481897.
110. Yoon KT, Liu H, Lee SS. Cirrhotic cardiomyopathy. *Curr Gastroenterol Rep*. 2020 Jul 10;22:45. https://doi.org/10.1007/s11894-020-00783-1.
111. Premkumar M, Devurgowda D, Vyas T, et al. Left ventricular diastolic dysfunction is associated with renal dysfunction, poor survival and low health related quality of life in cirrhosis. *J Clin Exp Hepatol*. 2019;9:324–333. https://doi.org/10.1016/j.jceh.2018.08.008.
112. Izzy M, VanWagner LB, Lin G, et al. Cirrhotic cardiomyopathy consortium. Redefining cirrhotic cardiomyopathy for the modern era. *Hepatology*. 2020;71:334–345. https://doi.org/10.1002/hep.30875. Erratum in: Hepatology. 2020;72(3):1161.
113. Machicao VI, Balakrishnan M, Fallon MB. Pulmonary complications in chronic liver disease. *Hepatology*. 2014;59:1627–1637. https://doi.org/10.1002/hep.26745.
114. Tumgor G. Cirrhosis and hepatopulmonary syndrome. *World J Gastroenterol*. 2014 Mar 14;20:2586–2594. https://doi.org/10.3748/wjg.v20.i10.2586.
115. Koch DG, Fallon MB. Hepatopulmonary syndrome. *Clin Liver Dis*. 2014;18:407–420. https://doi.org/10.1016/j.cld.2014.01.003.
116. Saigal S, Saraf N, Ragesh B, et al. 30 excellent outcome of living donor liver transplantation in patients with hepatopulmonary syndrome-a single center experience. *J Clin Exp Hepatol*. 2011;1:146. https://doi.org/10.1016/S0973-6883(11)60167-9.
117. Anand AC. Nutrition and muscle in cirrhosis. *J Clin Exp Hepatol*. 2017;7:340–357. https://doi.org/10.1016/j.jceh.2017.11.001.
118. Kumar V, Benjamin J, Shasthry V, et al. Sarcopenia in cirrhosis: fallout on liver transplantation. *J Clin Exp Hepatol*. 2020;10:467–476. https://doi.org/10.1016/j.jceh.2019.12.003.
119. Handelzalts S, Volk M, Zendler JD, et al. Physical activity patterns in frail and nonfrail patients with end-stage liver disease. *J Clin Exp Hepatol*. 2022;12(3):887–892. https://doi.org/10.1016/j.jceh.2021.10.013.
120. Choudhary NS, Kumar N, Saigal S, Rai R, Saraf N, Soin AS. Liver transplantation for alcohol-related liver disease. *J Clin Exp Hepatol*. 2016;6:47–53. https://doi.org/10.1016/j.jceh.2016.02.001.
121. Kumaran V. Role of liver transplantation for hepatocellular carcinoma. *J Clin Exp Hepatol*. 2014;4(suppl 3):S97–S103. https://doi.org/10.1016/j.jceh.2014.01.002.
122. McCabe P, Hirode G, Wong R. Functional status at liver transplant waitlisting correlates with greater odds of encephalopathy, ascites, and spontaneous bacterial peritonitis. *J Clin Exp Hepatol*. 2020;10:413–420. https://doi.org/10.1016/j.jceh.2020.04.015.
123. Choudhary NS, Sonavane A, Saraf N, et al. Poor performance status predicts mortality after living donor liver transplantation. *J Clin Exp Hepatol*. 2020;10:37–42. https://doi.org/10.1016/j.jceh.2019.06.006.
124. Robinson A, Hirode G, Wong RJ. Ethnicity and insurance-specific disparities in the model for end-stage liver disease score at time of liver transplant waitlist registration and its impact on mortality. *J Clin Exp Hepatol*. 2021;11:188–194. https://doi.org/10.1016/j.jceh.2020.07.011.
125. Chew CA, Iyer SG, Kow AWC, et al. An international multicenter study of protocols for liver transplantation during a pandemic: a case for quadripartite equipoise. *J Hepatol*. 2020;73:873–881. https://doi.org/10.1016/j.jhep.2020.05.023.
126. Gopichandran V. Ayushman Bharat National Health Protection Scheme: an ethical analysis. *Asian Bioeth Rev*. 2019;11:69–80. https://doi.org/10.1007/s41649-019-00083-5.
127. Silva M, Mirza DF. Live donor liver transplantation: is this really the way liver transplantation should be developed in India? *Natl Med J India*. 2004;17:61–63.
128. Kulkarni AV, Kumar P, Sharma M, et al. Midodrine improves the tolerability of diuretics in patients with acute-on-chronic liver failure-A pilot study. *J Clin Exp Hepatol*. 2021;11:573–578. https://doi.org/10.1016/j.jceh.2020.12.002. Epub 2020 Dec 17. PMID: 34511818; PMCID: PMC8414320.
129. Saab S, Nieto JM, Lewis SK, Runyon BA. TIPS versus paracentesis for cirrhotic patients with refractory ascites. *Cochrane Database Syst Rev*. 2006;2006:CD004889. https://doi.org/10.1002/14651858.CD004889.pub2. PMID: 17054221; PMCID: PMC8855742.
130. Grover I, Gunjan D, Singh N, et al. Effect of vitamin D supplementation on vitamin D level and bone mineral density in patients with cirrhosis: a randomized clinical trial. *Am J Gastroenterol*. 2021;116:2098–2104. https://doi.org/10.14309/ajg.0000000000001272. PMID: 33927126.
131. Bjelakovic M, Nikolova D, Bjelakovic G, Gluud C. Vitamin D supplementation for chronic liver diseases in adults. *Cochrane Database Syst Rev*. 2021;8:CD011564. https://doi.org/10.1002/14651858.CD011564.pub3. PMID: 34431511; PMCID: PMC8407054.
132. Fukui H, Saito H, Ueno Y, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. *J Gastroenterol*. 2016;51:629–650. https://doi.org/10.1007/s00535-016-1216-y. Epub 2016 May 31. PMID: 27246107.
133. van de Verboeket Venne WP, Westerterp KR, van Hoek B, et al. Energy expenditure and substrate metabolism in patients with cirrhosis of the liver: effects of the pattern of food intake. *Gut*. 1995;36:110–116. https://doi.org/10.1136/gut.36.1.110.
134. Rusu E, Jinga M, Enache G, et al. Effects of lifestyle changes including specific dietary intervention and physical activity in the management of patients with chronic hepatitis C–a randomized trial. *Nutr J*. 2013;12:119. https://doi.org/10.1186/1475-2891-12-119.
135. Kennedy OJ, Roderick P, Buchanan R, et al. Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis. *Aliment Pharmacol Ther*. 2016;43:562–574. https://doi.org/10.1111/apt.13523.
136. Bravi F, Bosetti C, Tavani A, et al. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11:e1.

137. Kim RG, Loomba R, Prokop LJ, Singh S. Statin use and risk of cirrhosis and related complications in patients with chronic liver diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2017;15:1521–1530.e8. https://doi.org/10.1016/j.cgh.2017.04.039. Epub 2017 May 4. PMID: 28479502; PMCID: PMC5605397.
138. Bosch J, Gracia-Sancho J, Abraldes JG. Cirrhosis as new indication for statins. *Gut*. 2020;69:953–962. https://doi.org/10.1136/gutjnl-2019-318237. Epub 2020 Mar 5. PMID: 32139553.
139. Mazzarelli C, Prentice WM, Heneghan MA, Belli LS, Agarwal K, Cannon MD. Palliative care in end-stage liver disease: time to do better? *Liver Transpl*. 2018;24:961–968. https://doi.org/10.1002/lt.25193.
140. Plunkett A, Mortimore M, Good P. Palliative care in cirrhosis with decompensation. *Intern Med J*. 2019;49:904–908. https://doi.org/10.1111/imj.14348.
141. Centers for Medicare & Medicaid Services. *Local Coverage Determination (LCD) for Hospice Determining Terminal Status (L33393)*; 2021. Available from: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=33393.
142. Low JTS, Rohde G, Pittordou K, et al. Supportive and palliative care in people with cirrhosis: International systematic review of the perspective of patients, family members and health professionals. *J Hepatol*. 2018;69:1260–1273. https://doi.org/10.1016/j.jhep.2018.08.028.
143. Roth K, Lynn J, Zhong Z, Borum M, Dawson NV. Dying with end stage liver disease with cirrhosis: insights from SUPPORT. Study to understand prognoses and preferences for outcomes and risks of treatment. *J Am Geriatr Soc*. 2000;48:S122–S130.
144. Poonja Z, Brisebois A, van Zanten SV, Tandon P, Meeberg G, Karvellas CJ. Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. *Clin Gastroenterol Hepatol*. 2014;12:692–698. https://doi.org/10.1016/j.cgh.2013.08.027.
145. Janani K, Varghese J, Jain M, et al. HRQOL using SF36 (generic specific) in liver cirrhosis. *Indian J Gastroenterol*. 2017;36:313–317. https://doi.org/10.1007/s12664-017-0773-1.
146. Patel AA, Woodrell C, Ufere NN, et al, Palliative Care Education, Advocacy, and Research in Liver Disease (PEARL) workgroup and the AASLD Public Health/Healthcare Delivery Special Interest Group (SIG). Developing priorities for palliative care research in advanced liver disease: a multidisciplinary approach. *Hepatol Commun*. 2021;5:1469–1480. https://doi.org/10.1002/hep4.1743.
147. Kalia S, Nath P, Pathak M, Anand AC. Treatment of muscle cramps inpatients with cirrhosis of liver: A systematic review. *J Clin Exp Hepatol*. 2022;12:980–992. https://doi.org/10.1016/j.jceh.2021.10.147.
148. Bhandari K, Kapoor D. Fatigue in cirrhosis. *J Clin Exp Hepatol*. 2022;12(2):617–624. https://doi.org/10.1016/j.jceh.2021.08.028.
149. Sharma M, Kulkarni A, Sasikala M, et al. Long-term outcome of autologous hematopoietic stem cell infusion in cirrhosis: waning effect over time. *J Clin Transl Hepatol*. 2020;8:385–390. https://doi.org/10.14218/JCTH.2020.00052.
150. Praharaj DL, Premkumar M, Roy A, et al. Rifaximin vs. norfloxacin for spontaneous bacterial peritonitis prophylaxis: a randomized controlled trial. *J Clin Exp Hepatol*. 2022;12(2):336–342. https://doi.org/10.1016/j.jceh.2021.08.010.
151. Kulkarni AV, Tevethia HV, Arab JP, et al. Efficacy and safety of obeticholic acid in liver disease-A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol*. 2021;45:101675. https://doi.org/10.1016/j.clinre.2021.101675.
152. Gnanadeepam S, Janeela AM, Zachariah U, et al. Sarcopenia is closely associated with frailty in decompensated cirrhosis. *J Clin Exp Hepatol*. 2022;12(1):237–238. https://doi.org/10.1016/j.jceh.2021.09.021.
153. Camus C, Locher C, Saliba F, et al. Outcome of patients treated with molecular adsorbent recirculating system albumin dialysis: a national multicenter study. *JGH Open*. 2020 May 17;4:757–763. https://doi.org/10.1002/jgh3.12359.
154. Watanabe Y, Tsuchiya A, Terai S. The development of mesenchymal stem cell therapy in the present, and the perspective of cell-free therapy in the future. *Clin Mol Hepatol*. 2021;27:70–80. https://doi.org/10.3350/cmh.2020.0194.
155. Dwyer JP, Jayasekera C, Nicoll A. Analgesia for the cirrhotic patient: a literature review and recommendations. *J Gastroenterol Hepatol*. 2014;29:1356–1360. https://doi.org/10.1111/jgh.12560.
156. Serag Eldin M, Mahmoud F, El Hassan R, et al. Intravenous patient-controlled fentanyl with and without transversus abdominis plane block in cirrhotic patients post liver resection. *Local Reg Anesth*. 2014;7:27–37. https://doi.org/10.2147/LRA.S60966.