Journal of Clinical and Translational Hepatology **2021** vol. 9(4) | 576–586
DOI: 10.14218/JCTH.2020.00110

Review Article

Critically Ill COVID-19 Patient with Chronic Liver Disease - Insights into a Comprehensive Liver Intensive Care

Cyriac Abby Philips[1*], Kamna Kakkar[2], Moby Joseph[3], Praveen Kumar Yerol[4], Rizwan Ahamed[5], Sasidharan Rajesh[6] and Philip Augustine[5]

[1]Department of Clinical Hepatology, The Liver Institute, Center of Excellence in GI Sciences, Rajagiri Hospital, Chunangamvely, Aluva, Ernakulam, Kerala, India; [2]Department of Pulmonary and Critical Care Medicine, Pt. B. D. Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India; [3]Great Western Hospitals, NHS Foundation Trust, Swindon, United Kingdom; [4]Department of Gastroenterology, State Government Medicine College and Hospital, Thrissur, Kerala, India; [5]Gastroenterology and Advanced G.I Endoscopy, Center of Excellence in GI Sciences, Rajagiri Hospital, Chunangamvely, Aluva, Ernakulam, Kerala, India; [6]Interventional Hepatobiliary Radiology, The Liver Institute, Center of Excellence in GI Sciences, Rajagiri Hospital, Chunangamvely, Aluva, Ernakulam, Kerala, India

Received: 12 November 2020 | **Revised:** 7 March 2021 | **Accepted:** 7 April 2021 | **Published:** 28 April 2021

Abstract

The novel coronavirus-related coronavirus disease 2019 (COVID-19) pandemic has been relentless in disrupting and overwhelming healthcare the world over. Clinical outcomes of COVID-19 in patients with chronic comorbidities, especially in those with metabolic syndrome, are well documented. Chronic liver disease and cirrhosis patients are a special subgroup, among whom the management of COVID-19 is challenging. Understanding the pathophysiology of COVID-19 in patients with cirrhosis and portal hypertension improves our identification of at-risk patients for disease progression that will further help compartmentalize generalized and specialized treatment options in this special patient group. In this exhaustive review, we critically review the impact of COVID-19 on the liver and in chronic liver disease and cirrhosis patients. We further discuss common features associated with the pathophysiology of COVID-19 and cirrhosis, based on the renin-angiotensin system and deliberate current literature on guidelines for the treatment of COVID-19 and extrapolate the same to the cirrhosis population to provide a concise and stepwise, evidence-based management for cirrhosis patients with severe and critical COVID-19. There are no specific management guidelines for cirrhosis patients with COVID-19 and current recommendations for treatment are as per guidelines for general population. Nevertheless, specific issues like avoiding corticosteroids in decompensated patients with variceal bleeding, suspected sepsis, high grade hepatic encephalopathy and acute kidney injury, use of early mechanical ventilation strategies in those with severe ascites and hepatopulmonary syndrome, avoidance of remdesivir in advanced liver disease, and application of liver-specific severity scores for prognostication and identification of futility need to be highlighted.

Citation of this article: Philips CA, Kakkar K, Joseph M, Yerol PK, Ahamed R, Rajesh S, *et al*. Critically ill COVID-19 patient with chronic liver disease - Insights into a comprehensive liver intensive care. J Clin Transl Hepatol 2021;9(4):576–586. doi: 10.14218/JCTH.2020.00110.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped, positive single-stranded large RNA virus belonging to the beta-CoV family, is the causative agent of the current pandemic, the coronavirus disease 2019 (COVID-19), that has affected developed and developing countries worldwide. Even though the well-described and reported initial clinical sign of COVID-19 is pneumonia (fever, cough, and shortness of breath), further studies have shed light on the variable presentations and clinical outcomes in affected patients. This spectrum was found to include asymptomatic carriers, patients with gastrointestinal system predominant symptoms (nausea, diarrhea), those with anosmia and dysgeusia, and symptomatic hypercoagulable states affecting multiple organs and immune-mediated organ involvement such as vasculitis-like syndromes.[1] The majority of transmissions occur via coughing and sneezing, through respiratory droplets with particle size >5–10 μm, and through the fecal-oral route. Asymptomatic COVID-19 contributes up to 80% of trans-

Keywords: SARS-CoV-2; Coronavirus; Pandemic; ACLF; Decompensation; Portal hypertension; Sepsis.

Abbreviations: ACE2, angiotensin-converting enzyme receptor type 2; ACLF, acute-on-chronic liver failure; ACTT, adaptive covid-19 treatment trial; Ang I, angiotensin I; Ang II, angiotensin II; AT1, angiotensin II type 1 receptor; ARDS, acute respiratory distress syndrome; CLIF-C, chronic liver failure-consortium; CLD, chronic liver disease; COVID-19, novel coronavirus-related coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IV, intravenously; MELD, model for end stage liver disease; NAFLD, non-alcoholic fatty liver disease; NIH, national institutes of health; NO, nitric oxide; RAS, renin-angiotensin system; RECOVERY, randomised evaluation of covid-19 therapy; ROTEM, rotational thromboelastometry; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBECD, sulfobutylether-β-cyclodextrin; TEG, thromboelastography; TNF, tumor necrosis factor; WHO, world health organization.

[*]**Correspondence to:** Cyriac Abby Philips, Department of Clinical Hepatology, The Liver Institute, Center of Excellence in GI Sciences, Rajagiri Hospital, Chunangamvely, Aluva, Ernakulam, Kerala 683112, India. ORCID: https://orcid.org/0000-0002-9587-336X. Tel: +91-484-2905000, Fax: +91-484-7184000, E-mail: abbyphilips@gmail.com

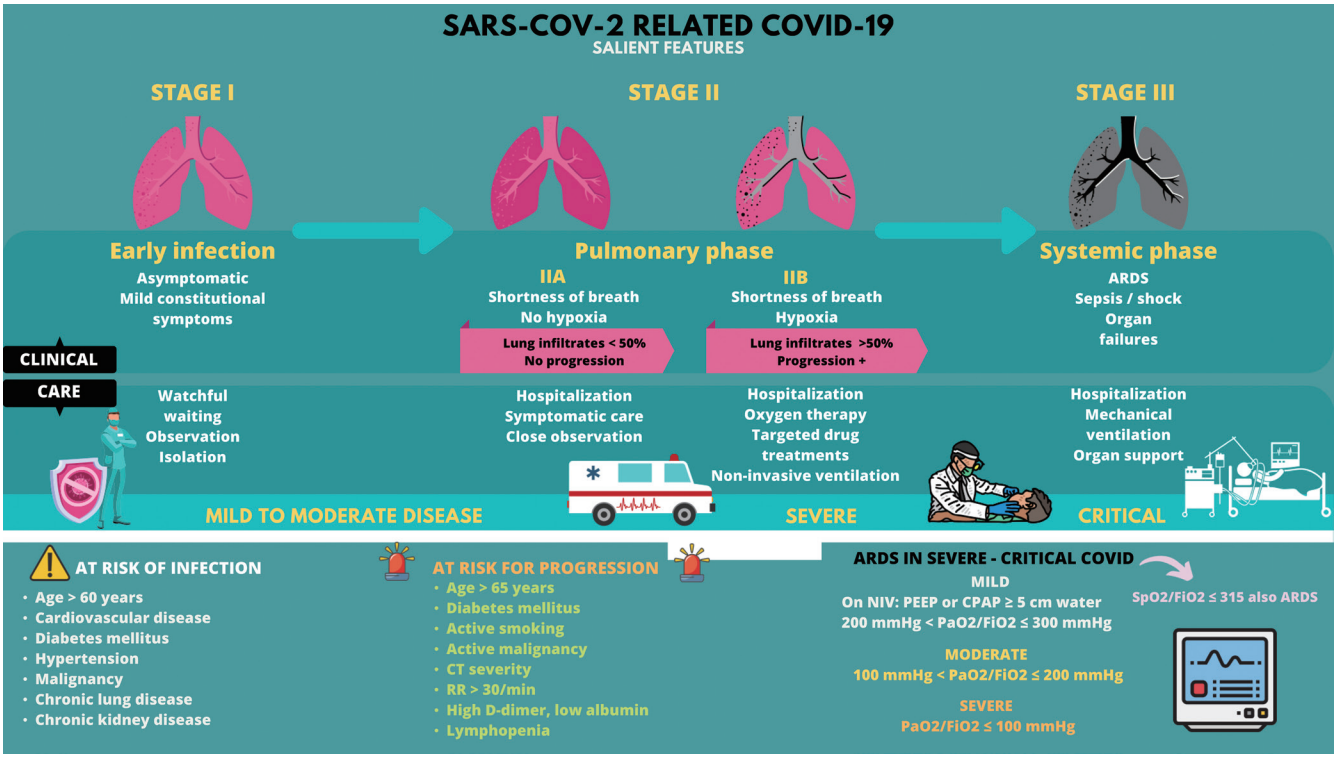

Fig. 1. Salient features of SARS-CoV-2-related COVID-19. CT, computed tomography; CPAP, continuous positive airway pressure; FiO2, fraction of inspired oxygen; NIV, non-invasive ventilation; PaO2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; RR, respiratory rate; SpO2, saturation of peripheral oxygen.

mission, primarily limited to family members, healthcare professionals, and others with close contacts (6 feet, 1.8 meters) within closed-space public gatherings.[2] Initial studies have shown that the incubation time is between 3 to 7 days and the basic reproduction number (R0 or R naught) is 2.2.[3] The viral infection starts with the glycoprotein spike receptor-binding protein, which allows viral attachment to the angiotensin-converting enzyme receptor type 2 (ACE2) in the lungs and other tissues as well. A polybasic amino acid site in the spike protein is functionally processed by the human protease enzyme furin, which further allows exposure of the integrated sequences, resulting in a fusion of the viral and cell membranes and subsequent virus passage into the primary cell.[4]

Around 97.5% of symptomatic presentations will occur within 11.5 days of infection and the median time from symptom onset to hospital admission is 7 days. The median age of hospitalized patients varies between 47 and 73 years, with male preponderance. Overall, a quarter of infected patients have comorbidities but among hospitalized COVID-19 patients, approximately 60% to 90% have comorbidities.[5,6] The most common chronic conditions include hypertension and cardiovascular disease, diabetes, chronic kidney disease, and chronic lung disease. Clinical complications leading to morbidity and mortality include hypoxemic lung failure, myocarditis, cardiomyopathy, ventricular arrhythmias, and hemodynamic instability, stroke and rarely encephalitis, secondary bacterial sepsis, and arterial and venous thromboembolic events, the latter notable in up to 60% of those admitted to the intensive care unit (ICU).[4–7]

In this review, we discuss the impact of COVID-19 on the liver, focus on key aspects of disease pathogenesis and outcomes in patients with pre-existing liver disease, and discuss current evidence-based treatment protocols and exhaustive algorithms for the management of COVID-19 in cirrhosis.

COVID-19 and the liver

The Chinese Centers for Disease Control described three clinical classifications of COVID-19 based on pulmonary symptoms, classified as mild to moderate, severe, and critical disease. Patients with severe pneumonia can develop acute respiratory distress syndrome (ARDS) classified as mild, moderate, and severe depending on clinical and ventilatory criteria. Severe disease is also identified when computed tomography of the chest reveals lung infiltrates >50% within 24 to 48 h, or in the presence of septic shock or multiple organ failure (Fig. 1). ACE2, the host cell receptor for SARS-CoV-2, is present on type 2 alveolar cells and in the gastrointestinal tract and the liver. In the liver, ACE2 is highly expressed in the endothelial layer of small blood vessels and absent in the sinusoidal endothelium and is also expressed greater in cholangiocytes than in hepatocytes.[4]

Multiple studies have shown that index presentation with gastrointestinal symptoms was notable in approximately 19.6% to 73.0% of patients with SARS-CoV. Similarly, 3% to 79% of those with SARS-CoV-2 infection presented gastrointestinal predominant symptoms in various studies.[8–11] Abnormal liver tests have been reported in approximately 19–76% of patients with COVID-19. It is now clear that elevated liver biochemistries are predominantly associated with severe and critical COVID-19 due to multifactorial reasons, such as drug-induced liver test abnormalities, liver involvement in critical illness, and hypoxic insults.[12–15] Even though ACE2 receptors are more greatly expressed in cholangiocytes, the principal pattern of liver test abnormality demonstrated in COVID-19 is of the hepatocellular type, with elevation in aminotransferases rarely above 5-times the upper limit of normal in those with and without pre-existing liver disease.[16,17]

Direct cytopathic effects of SARS-CoV-2 on hepatocytes

remain unconfirmed, and liver test abnormalities are mostly related to multisystem involvement associated with severe disease, multifactorial, and secondary to systemic inflammation, immune-mediated injury, microvascular thrombosis, drug toxicity, hepatic congestion, and intercurrent sepsis.[18,19] Post-mortem liver biopsy studies have shown non-specific features, such as focal or mild to moderate macro/microvesicular steatosis, mild portal and lobular inflammation, and sinusoidal dilatation. The direct viral cytopathic effect, viral nucleic acid, or demonstrable replication has not been demonstrated consistently across studies. Acute liver failure due to COVID-19 is not described. However, concomitant hepatotoxic drug use, including complementary and alternative medications in patients with COVID-19 with a predisposition to acute severe liver injury, could lead to acute liver failure, independent of the primary infection, and should be kept in mind with patients presenting with liver failure.[20,21]

COVID-19 and chronic liver disease (CLD)

To understand the outcomes associated with COVID-19 in patients with CLD, an understanding of the common pathophysiology that plays an important role in the causation and progression of these conditions, attributable to the renin-angiotensin system (RAS), is pertinent. RAS activity starts with the breakdown of angiotensinogen (derived from the liver) by circulating renin (from the juxtaglomerular apparatus of the kidney) to form angiotensin I (Ang I). In the classical pathway, ACE in pulmonary capillaries converts Ang I to angiotensin II (Ang II), which then binds to angiotensin II type 1 receptor (AT1) that, in effect, causes vasoconstriction, is trophic, enhances fibrogenesis, increases sodium reabsorption, and is pro-inflammatory and prothrombotic. In the alternate RAS, ACE2 degrades Ang II to the peptide Ang1-7, which then acts through the *mas* receptor that promotes vasodilation, is anti-trophic and anti-fibrotic, promotes natriuresis, and is anti-inflammatory and anti-thrombotic.[22]

In CLD, the classical pathway and its activation contributes to inflammation and fibrosis, while the alternative pathway is up-regulated to counterbalance the harmful effects. As fibrosis worsens, ACE levels and AT1 gene expressions rise, coinciding with an up-regulation in ACE2 and *mas* expression, increasing in both Ang 1-7 and Ang II. Cirrhotic livers have enhanced capacity to convert Ang II to Ang 1-7, which has been shown to have beneficial effects on liver fibrosis and inflammation. In late-stage cirrhosis, sympathetic nervous system activation, acetylcholine-mediated vasodilation, increased production of dysfunctional nitric oxide (NO), secretion of antidiuretic hormone, central hypovolemic status, and worsening peripheral and splanchnic vasodilation due to high Ang 1-7 renders early beneficial effects of the alternate RAS pathway redundant.[23–25] In chronic inflammation, Ang II expression activates hepatic stellate cells that drive the pathogenesis of portal hypertension. With cirrhosis progression, intrahepatic resistance increases, leading to systemic and splanchnic vasodilation and hypo-responsiveness to vasoconstrictors.[26] Thus, there is a clear change in modus operandi in the RAS-mediated pathophysiology of cirrhosis and its progression.

In patients with cirrhosis and COVID-19, SARS-CoV-2 overwhelms the ACE2 receptors, resulting in the functional inhibition of the alternate RAS pathway, leading to reduced expression of Ang 1-7 (increasing proinflammatory cytokines such as interleukin (IL)-6, IL-1β and tumor necrosis factor-alpha (TNF-α) and paving the way for harmful consequences via the AT1 receptor) within the liver microenvironment and other systems.[27,28] However, in stable cirrhosis, in the presence of highly up-regulated ACE2 receptors and higher expression of Ang 1-7, SARS-CoV-2 infection may not be uncontrollably detrimental and could be associated with better outcomes.[29] In decompensated cirrhosis, chronic activation of RAS and sympathetic nervous system activation and secretion of antidiuretic hormones occur in the presence of persistent arterial hypotension.

COVID-19 can worsen the already perturbed portosystemic hemodynamics through the overwhelming use of ACE2 receptors, increasing Ang 1-7, which leads to worsening systemic and splanchnic vasodilation. Furthermore, cirrhosis is a state of chronic systemic inflammation, immunomodulation, endotoxemia, and hemodynamic alterations that promote subclinical dysfunction in most organ systems that worsen with increasing cirrhosis stages.[30–33] Hence, from our understanding of pathophysiology, it is safe to assume that COVID-19 in cirrhosis is associated with different clinical outcomes, depending on the stages of liver disease and degree of portal hypertension (Fig. 2).

Worsening of pre-existing liver injury is an important clinical aspect of COVID-19. In this regard, new-onset or worsening thrombocytopenia, coagulation tests, and hypoproteinemia or low albumin could be considered part of progression in the multisystem involvement of the primary infection or worsening of the pre-existing liver disease.[34–36] The novel coronavirus itself does not cause acute severe liver injury or trigger liver failure.[20,21] Nonetheless, COVID-19 in patients with pre-existing liver disease, such as alcohol-related or nonalcohol-related fatty liver, early and advanced hepatic fibrosis (CLD), cirrhosis with or without portal hypertension (clinically significant [defined as hepatic venous pressure gradient ≥10 mmHg] or otherwise) can present with acute hepatitis with or without jaundice and rarely cholestatic liver injury, acute decompensation of cirrhosis and acute-on-chronic liver failure (ACLF) due to severity of infection and subsequent treatment interventions.

Impact of COVID-19 in patients with CLD and cirrhosis

A recent meta-analysis on 2,034 adult individuals with a median age of 49 years found that the overall prevalence of CLD at admission was 3%.[37] In a narrative review, Garrido and colleagues,[38] based on published evidence, presumed that patients with CLD were not at greater risk for acquiring the infection. Still, those with compensated advanced and decompensated cirrhosis, hepatocellular carcinoma, nonalcoholic fatty liver disease (due to associated metabolic syndrome), autoimmune liver diseases, or a liver transplant may have a greater risk for severe COVID-19. In a small series of patients with liver disease, Ji *et al*.[39] showed that disease progression was higher in COVID-19 patients with CLD than in those without CLD, with the risk of developing ACLF that portend a worse prognosis. In a retrospective study from Wuhan, China, investigators found that COVID-19 patients with CLD had a longer length of stay in hospital but with mild liver injuries and higher mortality (in the presence of decompensation) than in those without CLD. The neutrophil-to-lymphocyte ratio significantly predicted in-hospital death.[40]

Another systematic review and meta-analysis that included 74 clinical studies demonstrated that the prevalence of CLD among all COVID-19 patients was approximately 3%. This proportion was similar in COVID-19-positive and -negative population, but CLD was significantly associated with more severe COVID-19 infection and overall mortality.[41] In Italian multicenter retrospective studies, Iavarone *et al*.[42,43] showed that COVID-19 was associated with deterioration in liver function and increased mortality in the elderly with cirrhosis compared to a historically-matched group of patients with bacterial sepsis. The severity of lung and liver disease scores according to the Chronic Liver Failure-Consortium

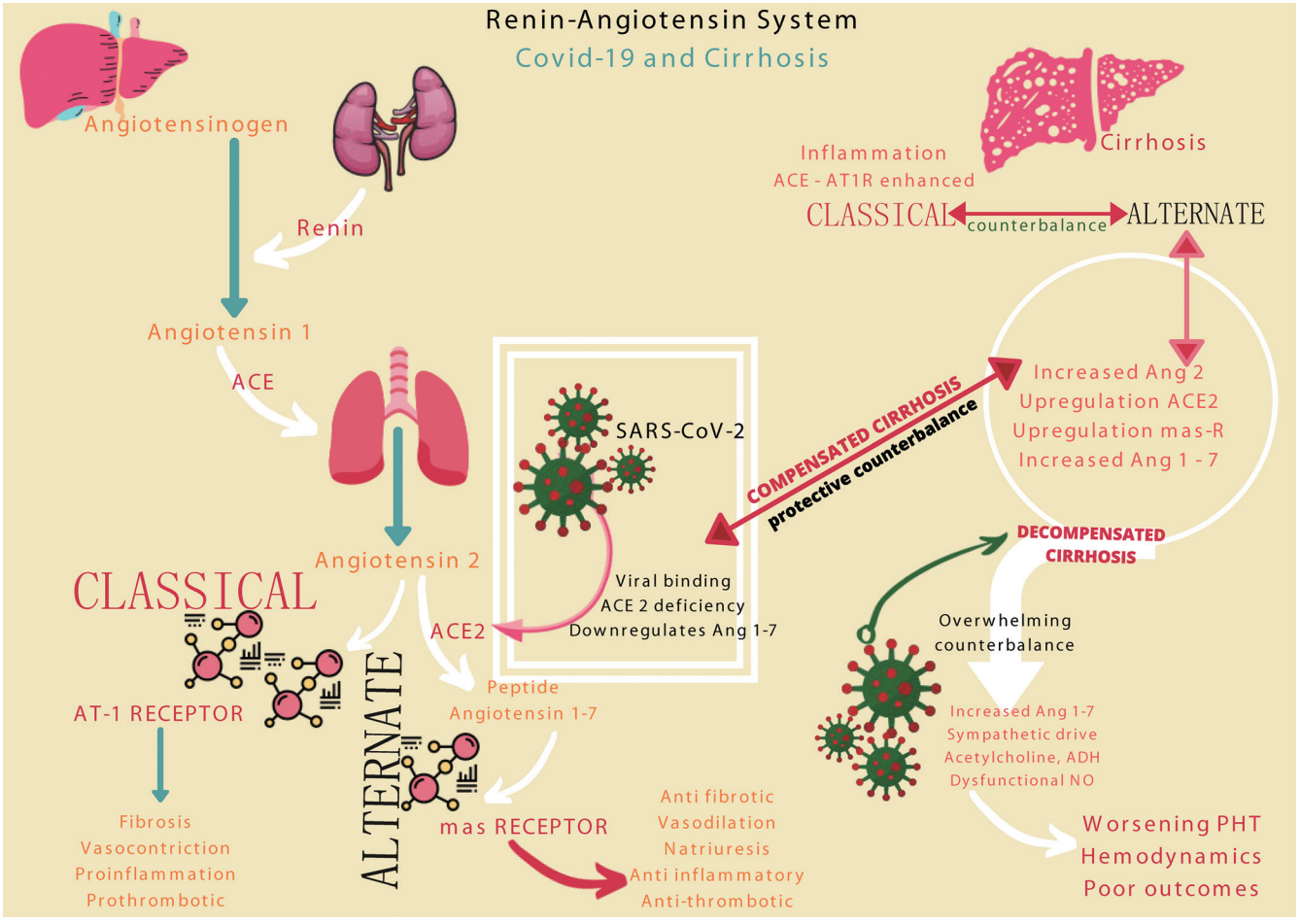

Fig. 2. RAS and its central role in pathophysiology of COVID-19 and cirrhosis. ACE, angiotensin-converting enzyme; ADH, antidiuretic hormone; Ang 1-7, angiotensin peptide 1-7; mas-R, mas receptor; PHT, portal hypertension

(commonly known as CLIF-C)-Organ Failure (>9), CLIF-C-ACLF ≥70 and Model for End-stage Liver Disease (commonly known as MELD; >15) independently predicted mortality. Notably, ACLF was not the cause of death in most patients but respiratory failure was in 71%.[42,43]

An international registry's preliminary results included 103 cirrhosis patients from 21 countries and four continents (60% male, median age 61 years, most common liver etiology being non-alcoholic fatty liver disease or NAFLD). Among patients analyzed from combined registries, 38% decompensated during their disease course (worsening ascites, encephalopathy, or acute kidney injury) due to COVID-19. Mortality in this group was far more than that noted with cirrhosis in the pre-COVID-19 era. However, the cause of death was lung failure in approximately 80% and liver-related in 12% (CLD without cirrhosis 12.2%, <Child class A cirrhosis 23.9%, <Child class B cirrhosis 43.3%, <Child class C 63%). This meant that deaths and liver and portal hypertension-related new onset or worsening of events were seen among those with advanced liver cirrhosis.[44] Marjot *et al*.[45] found that baseline liver disease stage and alcohol-related liver disease were independent risk factors for death from COVID-19. The APCOLIS study from the Asian Pacific region showed that SARS-CoV-2 infection caused a significant liver injury in CLD patients, decompensating one-fifth of cirrhosis, and worsening the clinical status of those already decompensated. The number of cirrhosis patients with symptomatic COVID-19 in that study was less at baseline, showing the lower prevalence of infection associated with early cirrhosis. The authors concluded that CLD patients with diabetes and obesity were more vulnerable to disease risk and progression.[46] A position paper from Europe stated that CLD patients did not *per se* appear to be over-represented in cohorts with COVID-19 and were not at increased risk of contracting SARS-CoV-2. However, the risk of infection and the risk of a severe course of COVID-19 may be different, depending on the nature of the CLD and the presence of advanced fibrosis or cirrhosis and MELD score ≥15.[47]

In a North American multicenter contemporaneously enrolled study, age and sex-matched patients with cirrhosis and COVID-19 had similar mortality compared with cirrhosis patients alone but was higher than among patients with COVID-19 alone. ACLF rates were similar between groups. Nevertheless, Charlson Comorbidity Index scores and lactate levels were worse among cirrhosis patients who were COVID-19-positive. At present, evidence for a strong conclusion that COVID-19 increases the risk for development of ACLF or mortality in patients with cirrhosis (other than in Child class C) more than other etiologies for new-onset or worsening decompensation is lacking.[48] The salient features of pertinent recent studies on patient characteristics and impact of COVID-19 in liver disease are shown in Table 1.[37–45,48]

Current treatments for hospitalized COVID-19 patients and impact in cirrhosis

According to the National Institutes of Health (NIH, which does not consider cirrhosis as a high-risk comorbid condition), in patients with COVID-19 who are hospitalized with moderate disease (clinical or radiographic evidence of lower respiratory tract infection, respiratory rate <24 breaths/m and SpO_2 ≥94% on room air at sea level) but do not require supplemental oxygen, dexamethasone is not recommended, while remdesivir may be considered in those at high risk for clinical deterioration.[49]

Dexamethasone use was associated with the absence of survival benefit in patients who did not require supplemental oxygen at enrolment and lead to a slightly higher 28-day mortality when used in this group of patients, as demonstrated in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, open-label trial in the UK.[50] The use of remdesivir was not associated with clinical benefit in patients with mild to moderate disease in the multinational, randomized controlled Adaptive COVID-19 Treatment Trial (ACTT-1).[51]

For hospitalized patients with COVID-19 who require only supplemental oxygen, the NIH recommends the use of remdesivir at 200 mg intravenously (IV) for 1 day, followed by 100 mg intravenous once daily for 4 days (which can be extended up to 10 days if no clinical improvement is noted on the 5th day) or until hospital discharge, whichever comes first. Alternatively, a combination regimen (yet to be studied in rigorous clinical trials) of remdesivir and dexamethasone at 6 mg intravenous or orally for up to 10 days or until hospital discharge, or if remdesivir cannot be used (especially in resource-poor countries like India), dexamethasone alone is recommended for use. The final analysis of the ACTT-1 trial showed that remdesivir was associated with improved time to recovery in a subgroup. On post hoc analysis of deaths by Day 29, it appeared to provide a substantial survival benefit. The RECOVERY trial showed that COVID-19 patients who required supplemental oxygen, but not those on mechanical ventilation, received survival benefit from using dexamethasone. The use of only dexamethasone would dampen viral clearance by reducing inflammatory responses, and hence concomitant use of an antiviral for improving outcomes has been hypothesized. For hospitalized patients with COVID-19 who require oxygen delivery through a high-flow device or noninvasive ventilation, both remdesivir and steroid use were advocated. In these patients, the ACTT-1 study did not show the clinical benefit of using remdesivir alone. Only early dexamethasone use has been shown to improve outcomes in ventilated patients for those who require invasive mechanical ventilation or extracorporeal membrane oxygenation.[52]

The World Health Organization (commonly known as WHO) recommends the use of systemic corticosteroids for severe and critical cases of COVID-19 but do not recommend the use of remdesivir or other repurposed drugs, such as hydroxychloroquine, lopinavir (fixed-dose combination with ritonavir), and interferon-β1a with or without lopinavir at any stage of the disease due to absence of clinical benefit on early recovery and mortality, as demonstrated in the SOLIDARITY trial. Except for the use of remdesivir, the WHO guidelines are in tune with the NIH guidelines concerning other antiviral use in COVID-19.[53,54] Remdesivir was developed by Gilead® Sciences with collaboration between the USA Centers for Disease Control and the USA Army Medical Research Institute of Infectious Diseases. It is a monophosphate nucleoside analog with broad activity against RNA viruses, targeting the divergent RNA-dependent RNA polymerase through the misintegration of an active nucleoside triphosphate form, which has been shown to reduce viral load in *in vitro* and *in vivo* studies and also in non-human primate models of severe acute respirator syndrome, Middle East respiratory syndrome and Ebola virus infection.[55] Liver toxicity is a rare but potentially severe side effect of remdesivir. A compassionate use study revealed that hepatic enzyme increases were by far the most common adverse event, occurring in 23% of patients, while infusion-related hypotension was seen in 8%.[56] Liver enzyme increases observed in the Gilead®-run SIMPLE trial involved 7% of patients with grade 3 or higher alanine aminotransferase elevations and 3% who stopped the drug over elevated liver enzymes. In a Chinese trial, alanine aminotransferase elevation led to treatment discontinuation in one patient, and acute kidney injury prompted it in another.[57]

In the ACTT-1 study, serious adverse events were reported in 24.6% of patients who received remdesivir. Serious respiratory failure as an adverse event was noted in 8.8% of patients in the remdesivir group, which included acute respiratory failure and the need for endotracheal intubation. Grade 3 or 4 adverse events occurred on or before day 29 in 51.3% in the remdesivir group, of which 41 events were judged by the investigators to be related to remdesivir. The most common nonserious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin level, and decreased lymphocyte count. Nonetheless, the incidence of these adverse events was generally similar in the remdesivir and placebo groups.[51] Infusion-related reactions were noted as potential side effects, along with increased liver enzymes in the USA Food and Drug Administration's guideline for remdesivir use. The efficacy and safety of remdesivir have not been studied in patients with liver impairment or CLD. In such clinical situations, current knowledge demands that remdesivir only be used if the potential benefit outweighs the potential risk. The European Medicines Agency summary warned against use in patients with concomitant hepatotoxic drugs and liver enzymes 5 or more times the upper limit of normal. In abnormal liver tests that occur after remdesivir initiation, especially at high levels, adverse drug reactions need to be considered, and drug discontinuation is required. Zampino *et al*.[58] showed that remdesivir might cause hepatocellular injury in those without CLD without progression to severe liver damage or liver failure. In 4/5 patients treated with the antiviral, baseline normal liver tests worsened, suggesting a direct role of remdesivir in hepatocellular toxicity. The authors suggested that remdesivir be used with close monitoring of liver function tests and with caution in subjects with prior liver disease.

Leegwater and colleagues[59] reported the case of a man with COVID-19 who developed acute hepatotoxicity related to remdesivir with potential interaction of P-glycoprotein inhibitors, such as chloroquine or amiodarone, that increased intracellular levels of active drug metabolite within the hepatocytes. Similarly, in those with acute and CLD, potential nephrotoxicity could be due to direct effects or the accumulation of sulfobutylether-β-cyclodextrin (also known as SBECD) carrier, the latter used due to limited water solubility.[60] Animal studies have shown that SBECD accumulation can potentiate liver cell necrosis and renal tubular damage. Remdesivir is not recommended in adults and pediatric patients (>28 days-old) with estimated glomerular filtration rate <30 mL/m or with serum creatinine ≥1 mg/dL, unless the potential benefit outweighs the potential risk.[60,61] Thus, remdesivir has the potential to cause pulmonary, hepatic, and renal toxicity in predisposed individuals.

WHO pharmacovigilance noted a disproportionately high number of reports of liver injuries and renal toxicities among patients receiving remdesivir compared with that among patients receiving other drugs for COVID-19, and the European Medicines Agency initiated a review of patients on remdesivir with acute kidney injuries.[61,62] On the

Table 1. Salient features of pertinent recent studies on impact of COVID-19 in patients with CLD

Author	Type of study	Patients	Outcomes	Comments
Ji *et al*.[39]	Retrospective observational	*n*=22/140; Cirrhosis=3; CLD (HBV, NAFLD)=19	None had decompensation at admission. 13/22 (59%) had COVID-19 disease progression. One patient developed ACLF	Risk of disease progression as high among CLD patients (NAFLD over-represented). Possible that metabolic syndrome was related to poor outcomes
Li *et al*.[40]	Retrospective observational	CLD, *n*=52/104	CLD with COVID-19 had longer hospital stay, but mild liver injury, even though the mortality was higher compared with the non-CLD group	Neutrophil-lymphocyte ratio predictor of mortality in CLD with COVID-19. Liver failure was not a cause for mortality, but progression of disease and lung failure were
Iavarone *et al*.[42,43]	Multicenter retrospective observational	Cirrhosis, *n*=50	Overall, 30-day mortality of 34%. Mortality high in those with respiratory failure	Cirrhosis with presumed underlying risk factors may increase risk of disease progression, rather than cirrhosis alone. Comparison group was cirrhosis with bacterial infection (soft end-points). NAFLD was under-represented; presence of multiple comorbid (obesity) and associated risk factors (smoking) among cirrhosis patients needs further review
Moon *et al*.[44]	Multicenter international observational cohort study	CLD, *n*=152; Cirrhosis=103; CLD non cirrhosis=49; Common – alcohol, NAFLD	Decompensation in 37% during disease course. 24% with new decompensation had no respiratory symptoms. Death in 40%. Cause of death was lung failure in 78.7%; only 12.2% died of liver-related causes	Advanced age, obesity, renal impairment, heart disease, and DM were over-represented among those who died. Child-Pugh B and C were significant predictors of mortality
Marjot *et al*.[45]	Multinational multicenter cohort study	*n*=745; CLD with cirrhosis, 386; CLD non-cirrhosis, 359; NAFLD 43%, ALD 24%; HTN 41%, DM 37%, obesity 28%	Overall death 20%, 8% CLD without cirrhosis and 32% among those with cirrhosis. Acute decompensation in only 1% without cirrhosis, 30% Child-Pugh A; 179 decompensated total, of which 50% met ACLF criteria (EASL, no APASL)	71% died due to COVID-19 lung disease; 19% due to liver disease progression. Case fatality rate lowest in CLD; no cirrhosis and highest in cirrhosis with Child C status at admission. Alcohol-related CLD was an independent risk factor for COVID-19 death
Sarin *et al*.	Multinational multicenter cohort study	*n*=228, CLD without cirrhosis in 185 and cirrhosis in 43; NAFLD in 61%; 43% CLD without cirrhosis had acute liver injury; ACLF in 11% and AD in 9%	Worsening liver disease in those with severe liver disease at baseline. Progression of liver disease in 57% and overall 43% mortality	Higher mortality in this cohort could be due to over-representation of NAFLD, metabolic syndrome, obesity and other well-known associated risk factors and not cirrhosis per say
Bajaj *et al*.[48]	Multicenter in-patient observational cohort	Cirrhosis plus COVID-19 (*n*=37) compared with age/ sex-matched patients with COVID-19 alone (*n*=108) and cirrhosis alone (*n*=127)	Risk of mortality in hospitalized patients with cirrhosis plus COVID-19 was not significantly higher than those hospitalized with cirrhosis but without COVID-19. Patients with cirrhosis developed complications related to the viral infection rather than cirrhosis	Active smoking and alcohol use were higher among those with cirrhosis. Charlson Comorbidity Index was the only independent predictor of death among those with cirrhosis. Cirrhosis may not be a risk factor, but advanced cirrhosis may be a risk factor for progression of COVID-19
Mantovani *et al*.[37]	Meta-analysis	CLD: *n*=62/2,034	Abnormal liver tests in only severe COVID-19	Prevalence of CLD in COVID-19 patients was low, at 3%
Kovalic *et al*.[41]	Meta-analysis	CLD: *n*=729/24,299	Prevalence of CLD among COVID-19 was 3%. Severe and critical illness and mortality were greater in the CLD group. No differences in rate of ICU admission and invasive ventilation between the CLD and non-CLD groups	Need prospective case-controlled studies to truly determine outcomes in CLD with COVID-19. Speculation that decompensation precipitated by COVID-19 in those with advanced cirrhosis or perhaps due to comorbidities among CLD patients
Garrido *et al*.[38]	Literature review	Incidence across studies 0.6% to 37.6%	Decompensated cirrhosis patients did not have COVID-19 with precautionary measures. Chronic HBV-related CLD did not show poor outcomes with COVID-19	CLD and cirrhosis are 'expected' to be risk factors for COVID-19

AD, acute decompensation; APASL, Asia-Pacific Association for the Study of Liver; DM, diabetes mellitus; EASL, European Association for the Study of Liver; HBV, hepatitis B virus; HTN, hypertension.

other hand, short courses of corticosteroids, including dexamethasone, are safe and efficacious in acute and chronic hepatocellular or cholestatic inflammatory diseases of the liver, including reactivation of viral hepatitis, severe drug-induced liver injury, ACLF, severe alcohol-related hepatitis and also in advanced decompensation associated with relative adrenal insufficiency.[63–65] However, one must be cautious in patients with decompensated cirrhosis and those with advanced liver failure, such as higher grades of ACLF and CLD patients with uncontrolled metabolic syndrome, in whom steroid use can lead to *de novo* or worsening bacterial or fungal infections. Hydrocortisone use in the non-cirrhosis septic shock population has been shown to improve short outcomes, such as shorter vasopressor therapy, mechanical ventilation, and length of ICU stay.[66] Higher and longer duration of steroid use can also lead to delirium and precipitate hepatic encephalopathy in patients with multiple decompensations at baseline or those who develop decompensation during COVID-19.[67–69]

Current adjuvant treatments for hospitalized COVID-19 patients and impact on cirrhosis

Guidelines at the national level from different regions/countries recommend using multiple other drugs in tandem with a universally-accepted protocol for COVID-19 treatment. However, the evidence to use these medications and adjuvant treatments is currently lacking in literature or has been confirmed to have no benefit and is not recommended for use in the treatment of COVID-19. These include hydroxychloroquine or chloroquine with or without azithromycin, ivermectin, lopinavir/ritonavir, and other protease inhibitors, favipiravir, interferon therapy, interleukin inhibitors (tocilizumab and tocilizumab), kinase inhibitors, COVID-19 convalescent plasma, intravenous immunoglobulin G specific and non-specific to SARS-Cov-2, mesenchymal stem cells, vitamin C and zinc.[70–74]

Chloroquine/hydroxychloroquine have likelihood score D for liver toxicity and are possible rare causes of clinically apparent liver injury. In patients with porphyria cutanea tarda, high doses of hydroxychloroquine can trigger an acute hepatic injury associated with marked serum enzyme elevations resulting from an increased excretion of porphyrins. Both, but more commonly chloroquine, have been associated with life-threatening cardiac events, including arrhythmias and conduction disorders, such as QT prolongation. A majority of cirrhosis patients have subclinical cardiomyopathy.[75–77] Hence, the use of chloroquine derivatives needs caution, especially when combined with another drug, such as fluoroquinolones that may precipitate adverse cardiac events. Azithromycin is well known to cause clinically apparent liver injury in the form of acute, transient, or asymptomatic elevation in serum aminotransferases, which occurs in 1% to 2% of patients treated for short periods.[78] High-dose vitamin C resulting in high circulating concentrations, may affect the accuracy of point-of-care glucometers in assessing glycemic status in the ICU.[79] Interferons are unsafe in advanced cirrhosis, and portal hypertension and interleukin inhibitors are not well studied in cirrhosis, and hence their use should be strictly compartmentalized to research protocols.

Even though zinc supplementation has not been shown to have beneficial disease-modifying properties in COVID-19, a recent meta-analysis demonstrated mild benefits in reducing hepatic encephalopathy. It may be considered an adjuvant to the standard of care in patients with cirrhosis and COVID-19 with hepatic encephalopathy.[80] Plasma and other blood product transfusions have detrimental effects in patients with cirrhosis and portal hypertension. Hence, transfusions must be curtailed in the absence of evidentiary proof for utility.[81] The benefits of vitamin D supplementation in COVID-19 patients remain to be determined. However, in those with insufficient levels (such as cirrhosis), supplementation therapy can be considered as per recommended guidelines. Nonetheless, whether this would benefit clinical outcomes in COVID-19 warrants further study.[82] A large body of published evidence suggests thrombotic events' central role in negative outcomes in patients with severe and critical COVID-19. In this regard, current recommendations for venous thromboembolism prophylaxis should be followed as per the standard of care for hospitalized adults. However, in cirrhosis, in those who have bled from varices or have variceal bleeding or are at high risk for variceal bleeding, anticoagulation use needs caution and must be tailored on a case basis. In this regard, newer diagnostic point-of-care modalities to assess the coagulation state, such as thromboelastography (i.e. TEG™) or rotational thromboelastometry (i.e. ROTEM®), could help guide prophylactic anticoagulation in patients with cirrhosis.[83–86]

Supportive treatment for severe or critically ill COVID-19 patients with cirrhosis

Norepinephrine is the first-choice vasopressor for cirrhosis patients with shock, as per standard recommendations followed in patients with septic shock. Additionally, terlipressin may be considered as it has shown benefits for acute variceal bleeding and kidney injury. The use of dopamine in cirrhosis is not recommended, due to the high risk of inducing arrhythmias, and dobutamine is recommended only in patients with clinically significant myocardial dysfunction. Applications of intravenous human albumin in cirrhosis with sepsis, acute kidney injury, hepatic encephalopathy, and hypotension have been well documented in the literature. Adjuvant use of intravenous human albumin is recommended in severe and critically ill cirrhosis patients, in the absence of absolute contraindications for use. In cirrhosis, profound distributive shock leads to the development of refractoriness towards inotropes and pressors. In such a situation, the use of methylene blue has been shown to reduce the requirement of inotropes and could potentially be used as a salvage option. Methylene blue has also been hypothesized as an inhibitor of NO with antagonistic effects on bradykinin that could improve oxygenation at the pulmonary level in patients with COVID-19. However, with regards to methylene blue, further clinical studies are required to confirm this proposal.[70,71,87–90]

For patients with acute hypoxemic respiratory failure despite conventional oxygen therapy, high-flow nasal cannula oxygen is preferred over noninvasive positive pressure ventilation. However, in patients with severe hepatopulmonary syndrome, the latter may be considered in a well-controlled environment.[91] With high-flow nasal cannula, to optimize the alveolar recruitment, improve dead-space carbon dioxide washout as well as the positive end-expiratory pressure or to reduce airway resistance, it is prudent to initiate flow at 60 L/m, especially in situations of acute respiratory failure. In patients with hypoxemic respiratory failure and those with hypercapnia, targeted oxygen saturation should be in the range of 94–98% in the former and 88–92% in the latter. Cirrhosis patients with overt hepatic encephalopathy with a high risk of aspiration and those with hemodynamic instability should be excluded from high-flow nasal cannula use as risks outweigh benefits, including delay in early intubation.[92] For COVID-19 patients with persistent hypoxemia despite incremental oxygen supplementation, endotracheal intubation is not otherwise indicated; a trial of awake prone positioning to improve oxygenation is recommended. However, this strategy can be difficult to pursue in decompensated cirrho-

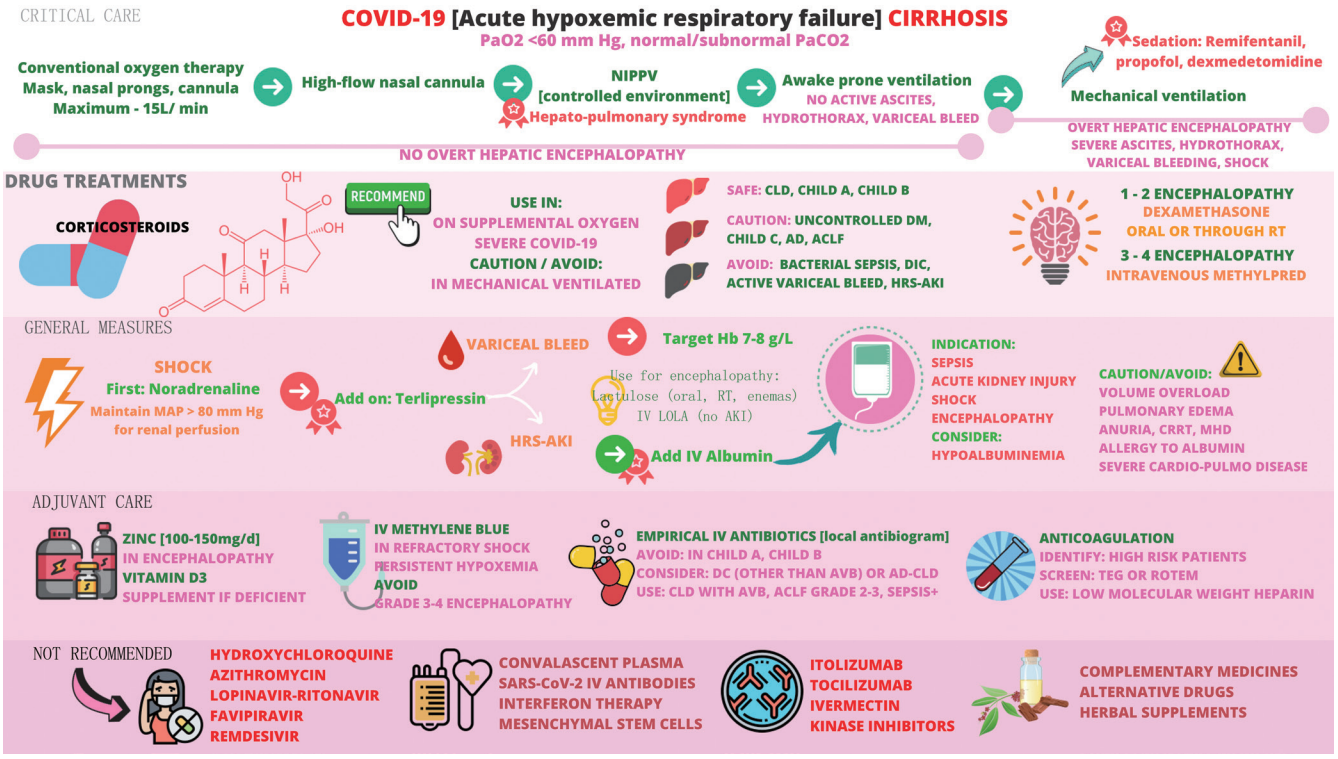

Fig. 3. Summary of proposed management of COVID-19 in patients with cirrhosis. AD, acute decompensation; AKI, acute kidney injury; AVB, acute variceal bleeding; CRRT, continuous renal replacement therapy; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; Hb, hemoglobin; HRS, hepatorenal syndrome; LOLA, L-ornithine L-aspartate; MAP, mean arterial pressure; MHD, maintenance hemodialysis; NIPPV, non-invasive positive pressure ventilation; PaCO2, partial pressure of arterial carbon dioxide; PaO2, partial pressure of arterial oxygen; RT, Ryle's tube; red ribbon logo denotes specific interventions related to cirrhosis.

sis patients who have ascites or hydrothorax. Awake prone positioning as rescue therapy for refractory hypoxemia to avoid intubation is not recommended, and early intubation should be considered in such situations, especially in cirrhosis. In cirrhosis, sedation choice in such circumstances should ideally include medications with short half-lives, such as propofol and remifentanil, with avoidance of benzodiazepines. Dexmedetomidine was well tolerated in patients with liver disease who received the medication for more than 48 h. Nonetheless, patients with liver disease required more time before extubation after drug discontinuation.[93]

For mechanically ventilated adults with COVID-19 and ARDS, low tidal volume ventilation (4–8 mL/kg of predicted body weight) is recommended. In those with refractory hypoxemia, despite optimized ventilation, prone positioning for 12 to 16 h per day is suggested. Inhaled pulmonary vasodilator as rescue therapy if no rapid improvement in oxygenation is suggested if optimized ventilation and other rescue strategies do not resolve hypoxemia. The routine use of extracorporeal membrane oxygenation (ECMO) for patients with COVID-19 and refractory hypoxemia in this situation is controversial, and no recommendation can be made. In patients with cirrhosis and ARDS with life-threatening hypoxemia and hepatopulmonary syndrome, anecdotal reports have shown the benefits of using ECMO, even as a bridge to liver transplantation. Nonetheless, liver tests, especially bilirubin and alkaline phosphatase levels, were found to predict poor outcomes post-ECMO in cardiac surgery patients. Hence, advanced cirrhosis patients may not be ideal candidates for ECMO in critical COVID-19. The use of ECMO also can lead to an elevation in liver enzymes. Further to this, a nationwide population-based cohort study on the outcome of ECMO support in patients with liver cirrhosis showed that its utility for cirrhosis patients, especially when >2 risk factors (age ≥65 years, those with underlying respiratory disease, hypoalbuminemia, and liver transplant receipt) have been identified, was deleterious on clinical outcomes.[94–97] In case staged upgraded medical interventions fail to improve hypoxemic respiratory failure, then ECMO may be considered on a case-by-case basis and following inclusion as per EOLIA trial criteria, which include one of the following: a ratio of the partial pressure of arterial oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of less than 50 mmHg for more than 3 h or Pao2:Fio2 of less than 80 mmHg for more than 6 h or an arterial blood pH of less than 7.25 with a partial pressure of arterial carbon dioxide of at least 60 mmHg for more than 6 h.

Even though the early use of ECMO does not significantly improve mortality at 60 days in patients with severe ARDS, it might help improve short-term survival when used as a rescue modality.[98] For critically ill patients with COVID-19 who have acute kidney injury and develop indications for renal replacement therapy, continuous renal replacement therapy is recommended. In its absence, prolonged intermittent renal replacement therapy holds for those with cirrhosis and advanced liver failure.[99,100] At present, for patients with COVID-19 and severe or critical illness, empiric broad-spectrum antimicrobial therapy in the absence of another indication is not recommended. However, in the cirrhotic population, especially among those with decompensation such as variceal bleeding or those with ACLF, early empirical antibiotics may be considered since the patients are at high risk of developing hospital-acquired infections and secondary bacteremia.[101–103] An exhaustive algorithm for the management of cirrhosis patients with COVID-19 is shown in Figure 3.

Conclusions

The incidence of COVID-19 among patients with cirrhosis may be low but further studies are required to address this topic clearly. The novel coronavirus does not cause direct liver injury or promote liver failure, but severe infections can result in unstable decompensation of cirrhosis and ACLF. COVID-19 in decompensated cirrhosis and in conditions that lead to ACLF are associated with poor clinical outcomes, even though the most common cause for mortality is lung failure and not progressive liver dysfunction. Current recommended treatment guidelines, such as use of corticosteroids appear to be safe in patients with stable cirrhosis, while caution must be exerted towards experimental and nonevidence-based treatments in this special patient population, especially in patients with decompensated cirrhosis with secondary sepsis and those with ACLF. Physician-driven use of experimental methods or therapeutics within clinical research must be guided by its safety in the liver disease population. Critical care management of severe COVID-19 in cirrhosis should be on similar lines as in the general patient population but with the use of specific therapies beneficial in cirrhosis, such as intravenous human albumin and terlipressin. Early recognition of those at risk for worse outcomes is imperative for imparting beneficial critical care management in cirrhosis.

Funding

None to declare.

Conflict of interest

Cyriac Abby Philips is an editorial member, academic editor and guest editor of the special issue on COVID-19 and the Liver in the *Journal of Clinical and Translational Hepatology*. The other authors have no conflict of interests related to this publication.

Author contributions

Study conception and design (CAP, PA, PKY), drafting of the manuscript (CAP, KK, MJ), critical revision of the manuscript for important intellectual content (SR, RA, PA, KK, MJ, PKY), and technical, or material support, study supervision (PA, PKY, MJ).

References

[1] Philips CA, Mohan N, Ahamed R, Kumbar S, Rajesh S, George T, *et al*. One disease, many faces-typical and atypical presentations of SARS-CoV-2 infection-related COVID-19 disease. World J Clin Cases 2020;8(18):3956–3970. doi:10.12998/wjcc.v8.i18.3956.
[2] Shi Y, Wang G, Cai XP, Deng JW, Zheng L, Zhu HH, *et al*. An overview of COVID-19. J Zhejiang Univ Sci B 2020;21(5):343–360. doi:10.1631/jzus.B2000083.
[3] Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med 2020;27(2):taaa021. doi:10.1093/jtm/taaa021.
[4] Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, *et al*. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol 2020;251(3):228–248. doi:10.1002/path.5471.
[5] Chilamakuri R, Agarwal S. COVID-19: Characteristics and therapeutics. Cells 2021;10(2):206. doi:10.3390/cells10020206.
[6] Griffin DO, Brennan-Rieder D, Ngo B, Kory P, Confalonieri M, Shapiro L, *et al*. The importance of understanding the stages of COVID-19 in treatment and trials. AIDS Rev 2021;23(1):40–47. doi:10.24875/AIDSRev.200001261.
[7] García LF. Immune response, inflammation, and the clinical spectrum of COVID-19. Front Immunol 2020;11:1441. doi:10.3389/fimmu.2020.01441.
[8] Cevik M, Bamford CGG, Ho A. COVID-19 pandemic-a focused review for clinicians. Clin Microbiol Infect 2020;26(7):842–847. doi:10.1016/j.cmi.2020.04.023.
[9] Tay SW, Teh KKJ, Wang LM, Ang TL. Impact of COVID-19: perspectives from gastroenterology. Singapore Med J 2020;61(9):460–462. doi:10.11622/smedj.2020051.
[10] Qureshi H. The digestive system and the COVID-19. J Pak Med Assoc 2020;20(5 Suppl 3):S98–S100. doi:10.5455/JPMA.19.
[11] Ng SC, Tilg H. COVID-19 and the gastrointestinal tract: more than meets the eye. Gut 2020;69(6):973–974. doi:10.1136/gutjnl-2020-321195.
[12] Kulkarni AV, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, *et al*. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. Aliment Pharmacol Ther 2020;52(4):584–599. doi:10.1111/apt.15916.
[13] Metawea MI, Yousif WI, Moheb I. COVID 19 and liver: An A-Z literature review. Dig Liver Dis 2021;53(2):146–152. doi:10.1016/j.dld.2020.09.010.
[14] Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol 2020;5(6):529–530. doi:10.1016/S2468-1253(20)30084-4.
[15] Cheong J, Bartell N, Peeraphatdit T, Mosli M, Al-Judaibi B. Gastrointestinal and liver manifestations of COVID-19. Saudi J Gastroenterol 2020;26(5):226–232. doi:10.4103/sjg.SJG_147_20.
[16] Tang D, Comish P, Kang R. The hallmarks of COVID-19 disease. PLoS Pathog 2020;16(5):e1008536. doi:10.1371/journal.ppat.1008536.
[17] Bertolini A, van de Peppel IP, Bodewes FAJA, Moshage H, Fantin A, Farinati F, *et al*. Abnormal liver function tests in patients with COVID-19: Relevance and potential pathogenesis. Hepatology 2020;72(5):1864–1872. doi:10.1002/hep.31480.
[18] Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, *et al*. COVID-19 and liver dysfunction: Current insights and emergent therapeutic strategies. J Clin Transl Hepatol 2020;8(1):18–24. doi:10.14218/JCTH.2020.00018.
[19] Ridruejo E, Soza A. The liver in times of COVID-19: What hepatologists should know. Ann Hepatol 2020;19(4):353–358. doi:10.1016/j.aohep.2020.05.001.
[20] Philips CA, Ahamed R, Augustine P. SARS-CoV-2 related liver impairment - perception may not be the reality. J Hepatol 2020;73(4):991–992. doi:10.1016/j.jhep.2020.05.025.
[21] Philips CA, Ahamed R, Augustine P. Letter to the Editor: Coronavirus disease 2019-related liver injury and clinical outcomes: Does it really exist? Hepatology 2021;73(1):469–470. doi:10.1002/hep.31447.
[22] Alqahtani SA, Schattenberg JM. Liver injury in COVID-19: The current evidence. United European Gastroenterol J 2020;8(5):509–519. doi:10.1177/2050640620924157.
[23] Bolognesi M, Di Pascoli M, Verardo A, Gatta A. Splanchnic vasodilation and hyperdynamic circulatory syndrome in cirrhosis. World J Gastroenterol 2014;20(10):2555–2563. doi:10.3748/wjg.v20.i10.2555.
[24] Iwakiri Y, Shah V, Rockey DC. Vascular pathobiology in chronic liver disease and cirrhosis - current status and future directions. J Hepatol 2014;61(4):912–924. doi:10.1016/j.jhep.2014.05.047.
[25] Martell M, Coll M, Ezkurdia N, Raurell I, Genescà J. Physiopathology of splanchnic vasodilation in portal hypertension. World J Hepatol 2010;2(6):208–220. doi:10.4254/wjh.v2.i6.208.
[26] Téllez L, Martín Mateos RM. COVID-19 and liver disease: An update. Gastroenterol Hepatol 2020;43(8):472–480. doi:10.1016/j.gastrohep.2020.06.006.
[27] Wiese OJ, Allwood BW, Zemlin AE. COVID-19 and the renin-angiotensin system (RAS): A spark that sets the forest alight? Med Hypotheses 2020;144:110231. doi:10.1016/j.mehy.2020.110231.
[28] Lanza K, Perez LG, Costa LB, Cordeiro TM, Palmeira VA, Ribeiro VT, *et al*. Covid-19: the renin-angiotensin system imbalance hypothesis. Clin Sci (Lond) 2020;134(11):1259–1264. doi:10.1042/CS20200492.
[29] Novaes Rocha V. Viral replication of SARS-CoV-2 could be self-limitative - The role of the renin-angiotensin system on COVID-19 pathophysiology. Med Hypotheses 2020;145:110330. doi:10.1016/j.mehy.2020.110330.
[30] Dalan R, Bornstein SR, El-Armouche A, Rodionov RN, Markov A, Wielockx B, *et al*. The ACE-2 in COVID-19: Foe or friend? Horm Metab Res 2020;52(5):257–263. doi:10.1055/a-1155-0501.
[31] Lubel JS, Herath CB, Burrell LM, Angus PW. Liver disease and the renin-angiotensin system: recent discoveries and clinical implications. J Gastroenterol Hepatol 2008;23(9):1327–1338. doi:10.1111/j.1440-1746.2008.05461.x.
[32] Simões E Silva AC, Miranda AS, Rocha NP, Teixeira AL. Renin angiotensin system in liver diseases: Friend or foe? World J Gastroenterol 2017;23(19):3396–3406. doi:10.3748/wjg.v23.i19.3396.
[33] Shim KY, Eom YW, Kim MY, Kang SH, Baik SK. Role of the renin-angiotensin system in hepatic fibrosis and portal hypertension. Korean J Intern Med 2018;33(3):453–461. doi:10.3904/kjim.2017.317.
[34] Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. Nat Rev Dis Primers 2016;2:16045. doi:10.1038/nrdp.2016.45.
[35] Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet 2018;392(10141):75–87. doi:10.1016/S0140-6736(18)30696-2.
[36] Gustot T, Moreau R. Acute-on-chronic liver failure vs. traditional acute decompensation of cirrhosis. J Hepatol 2018;69(6):1384–1393. doi:10.1016/j.jhep.2018.08.024.
[37] Mantovani A, Beatrice G, Dalbeni A. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. Liver Int 2020;40(6):1316–1320. doi:10.1111/liv.14465.
[38] Garrido I, Liberal R, Macedo G. Review article: COVID-19 and liver disease-

what we know on 1st May 2020. Aliment Pharmacol Ther 2020;52(2):267–275. doi:10.1111/apt.15813.
[39] Ji D, Zhang D, Yang T, Mu J, Zhao P, Xu J, *et al*. Effect of COVID-19 on patients with compensated chronic liver diseases. Hepatol Int 2020; 14(5):701–710. doi:10.1007/s12072-020-10058-6.
[40] Li C, Chen Q, Wang J, Lin H, Lin Y, Lin J, *et al*. Clinical characteristics of chronic liver disease with coronavirus disease 2019 (COVID-19): a cohort study in Wuhan, China. Aging (Albany NY) 2020;12(16):15938–15945. doi:10.18632/aging.103632.
[41] Kovalic AJ, Satapathy SK, Thuluvath PJ. Prevalence of chronic liver disease in patients with COVID-19 and their clinical outcomes: a systematic review and meta-analysis. Hepatol Int 2020;14(5):612–620. doi:10.1007/s12072-020-10078-2.
[42] Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, *et al*. High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol 2020;73(5):1063–1071. doi:10.1016/j.jhep.2020.06.001.
[43] Iavarone M, D'Ambrosio R, Lampertico P. Reply to: Correspondence on "High rates of 30-day mortality in patients with cirrhosis and COVID-19". J Hepatol 2020;73(6):1570–1571. doi:10.1016/j.jhep.2020.08.001.
[44] Moon AM, Webb GJ, Aloman C, Armstrong MJ, Cargill T, Dhanasekaran R, *et al*. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry. J Hepatol 2020;73(3):705–708. doi:10.1016/j.jhep.2020.05.013.
[45] Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, *et al*. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. J Hepatol 2021;74(3):567–577. doi:10.1016/j.jhep.2020.09.024.
[46] Sarin SK, Choudhury A, Lau GK, Zheng MH, Ji D, Abd-Elsalam S, *et al*. Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). Hepatol Int 2020;14(5):690–700. doi:10.1007/s12072-020-10072-8.
[47] Boettler T, Marjot T, Newsome PN, Mondelli MU, Maticic M, Cordero E, *et al*. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. JHEP Rep 2020;2(5):100169. doi:10.1016/j.jhepr.2020.100169.
[48] Bajaj JS, Garcia-Tsao G, Biggins SW, Kamath PS, Wong F, McGeorge S, *et al*. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. Gut 2021;70(3):531–536. doi:10.1136/gutjnl-2020-322118.
[49] Therapeutic management of adults with COVID-19. Available from: https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/.
[50] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, *et al*. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384(8):693–704. doi:10.1056/NEJMoa2021436.
[51] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, *et al*. Remdesivir for the treatment of Covid-19 - Final report. N Engl J Med 2020;383(19):1813–1826. doi:10.1056/NEJMoa2007764.
[52] Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, *et al*. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA 2020;324(13):1330–1341. doi:10.1001/jama.2020.17023.
[53] World Health Organization. Corticosteroids for COVID-19. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1.
[54] Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, *et al*. Repurposed antiviral drugs for Covid-19 - Interim WHO solidarity trial results. N Engl J Med 2021;384(6):497–511. doi:10.1056/NEJMoa2023184.
[55] Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, *et al*. Remdesivir: A review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Cent Sci 2020;6(5):672–683. doi:10.1021/acscentsci.0c00489.
[56] Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, *et al*. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med 2020;382(24):2327–2336. doi:10.1056/NEJMoa2007016.
[57] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, *et al*. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236):1569–1578. doi:10.1016/S0140-6736(20)31022-9.
[58] Zampino R, Mele F, Florio LL, Bertolino L, Andini R, Galdo M, *et al*. Liver injury in remdesivir-treated COVID-19 patients. Hepatol Int 2020;14(5):881–883. doi:10.1007/s12072-020-10077-3.
[59] Leegwater E, Strik A, Wilms EB, Bosma LBE, Burger DM, Ottens TH, *et al*. Drug-induced liver injury in a patient with coronavirus disease 2019: Potential interaction of remdesivir with P-Glycoprotein inhibitors. Clin Infect Dis 2021;72(7):1256–1258. doi:10.1093/cid/ciaa883.
[60] Adamsick ML, Gandhi RG, Bidell MR, Elshabourey RH, Bhattacharyya RP, Kim AY, *et al*. Remdesivir in patients with acute or chronic kidney disease and COVID-19. J Am Soc Nephrol 2020;31(7):1384–1386. doi:10.1681/ASN.2020050589.
[61] World Health Organization. Descriptive analysis of COVID-19-related spontaneous reports from VigiBase: interim results. Available from: https://www.who.int/medicines/regulation/medicines-safety/COVID19-PV-update11.pdf.
[62] European Medicines Agency. Veklury. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/veklury.
[63] Xue R, Meng Q. The management of glucocorticoid therapy in liver failure. Front Immunol 2019;10:2490. doi:10.3389/fimmu.2019.02490.
[64] Kim H, Kwon JH, Kim YH, Nam SW, Lee JY, Jang JW. Favorable effect of corticosteroids in treating acute-on-chronic liver failure underlying chronic hepatitis B. Clin Mol Hepatol 2018;24(4):430–435. doi:10.3350/cmh.2017.0016.
[65] Philips CA, Augustine P, Yerol PK, Rajesh S, Mahadevan P. Severe alcoholic hepatitis: current perspectives. Hepat Med 2019;11:97–108. doi:10.2147/HMER.S197933.
[66] Briegel J, Huge V, Möhnle P. Hydrocortisone in septic shock: all the questions answered? J Thorac Dis 2018;10(Suppl 17):S1962–S1965. doi:10.21037/jtd.2018.04.120.
[67] Gustot T, Fernandez J, Szabo G, Albillos A, Louvet A, Jalan R, *et al*. Sepsis in alcohol-related liver disease. J Hepatol 2017;67(5):1031–1050. doi:10.1016/j.jhep.2017.06.013.
[68] Woods CP, Hazlehurst JM, Tomlinson JW. Glucocorticoids and non-alcoholic fatty liver disease. J Steroid Biochem Mol Biol 2015;154:94–103. doi:10.1016/j.jsbmb.2015.07.020.
[69] Philips CA, Ahamed R, Rajesh S, George T, Mohanan M, Augustine P. Update on diagnosis and management of sepsis in cirrhosis: Current advances. World J Hepatol 2020;12(8):451–474. doi:10.4254/wjh.v12.i8.451.
[70] COVID-19 treatment guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov/whats-new/.
[71] Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
[72] Lam S, Lombardi A, Ouanounou A. COVID-19: A review of the proposed pharmacological treatments. Eur J Pharmacol 2020;886:173451. doi:10.1016/j.ejphar.2020.173451.
[73] Florindo HF, Kleiner R, Vaskovich-Koubi D, Acúrcio RC, Carreira B, Yeini E, *et al*. Immune-mediated approaches against COVID-19. Nat Nanotechnol 2020;15(8):630–645. doi:10.1038/s41565-020-0732-3.
[74] Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020;371:m3939. doi:10.1136/bmj.m3939.
[75] Liu H, Lee SS. Cardiopulmonary dysfunction in cirrhosis. J Gastroenterol Hepatol 1999;14(6):600–608. doi:10.1046/j.1440-1746.1999.01920.x.
[76] Mocarzel LOC, Rossi MM, Miliosse BM, Lanzieri PG, Gismondi RA. Cirrhotic cardiomyopathy: A new clinical phenotype. Arq Bras Cardiol 2017; 108(6):564–568. doi:10.5935/abc.20170066.
[77] Izzy M, VanWagner LB, Lin G, Altieri M, Findlay JY, Oh JK, *et al*. Redefining cirrhotic cardiomyopathy for the modern era. Hepatology 2020;71(1):334–345. doi:10.1002/hep.30875.
[78] Hydroxychloroquine. In: LiverTox: Clinical and research information on drug-induced liver injury [Internet]; 2012. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. March 25, 2018.
[79] Sartor Z, Kesey J, Dissanaike S. The effects of intravenous vitamin C on point-of-care glucose monitoring. J Burn Care Res 2015;36(1):50–56. doi: 10.1097/BCR.0000000000000142.
[80] Diglio DC, Fernandes SA, Stein J, Azeredo-da-Silva A, de Mattos AA, Tovo CV. Role of zinc supplementation in the management of chronic liver diseases: A systematic review and meta-analysis. Ann Hepatol 2020;19(2):190–196. doi:10.1016/j.aohep.2019.08.011.
[81] Liu P, Hum J, Jou J, Scanlan RM, Shatzel J. Transfusion strategies in patients with cirrhosis. Eur J Haematol 2020;104(1):15–25. doi:10.1111/ejh.13342.
[82] Triantos C, Kalafateli M, Aggeletopoulou I, Diamantopoulou G, Spantidea PI, Michalaki M, *et al*. Vitamin D-related immunomodulation in patients with liver cirrhosis. Eur J Gastroenterol Hepatol 2020;32(7):867–876. doi: 10.1097/MEG.0000000000001597.
[83] Tal S, Spectre G, Kornowski R, Perl L. Venous thromboembolism complicated with COVID-19: What do we know so far? Acta Haematol 2020;143(5):417–424. doi:10.1159/000508233.
[84] Thai C, Oben C, Wagener G. Coagulation, hemostasis, and transfusion during liver transplantation. Best Pract Res Clin Anaesthesiol 2020;34(1):79–87. doi:10.1016/j.bpa.2020.03.002.
[85] Seeßle J, Löhr J, Kirchner M, Michaelis J, Merle U. Rotational thrombelastometry (ROTEM) improves hemostasis assessment compared to conventional coagulation test in ACLF and Non-ACLF patients. BMC Gastroenterol 2020;20(1):271. doi:10.1186/s12876-020-01413-w.
[86] Raeven P, Baron-Stefaniak J, Simbrunner B, Stadlmann A, Schwabl P, Scheiner B, *et al*. Thromboelastometry in patients with advanced chronic liver disease stratified by severity of portal hypertension. Hepatol Int 2020;14(6):1083–1092. doi:10.1007/s12072-020-10093-3.
[87] Care of critically ill patients with COVID-19. Available from: https://www.covid19treatmentguidelines.nih.gov/critical-care/.
[88] Choudhury A, Kedarisetty CK, Vashishtha C, Saini D, Kumar S, Maiwall R, *et al*. A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int 2017;37(4):552–561. doi:10.1111/liv.13252.
[89] Arora V, Maiwall R, Rajan V, Jindal A, Muralikrishna Shasthry S, Kumar G, *et al*. Terlipressin is superior to noradrenaline in the management of acute kidney injury in acute on chronic liver failure. Hepatology 2020;71(2):600–610. doi:10.1002/hep.30208.
[90] Alamdari DH, Moghaddam AB, Amini S, Keramati MR, Zarmehri AM, Alamdari AH, *et al*. Application of methylene blue -vitamin C -N-acetyl cysteine for treatment of critically ill COVID-19 patients, report of a phase-I clinical trial. Eur J Pharmacol 2020;885:173494. doi:10.1016/j.ejphar.2020.173494.
[91] Chihara Y, Egawa H, Tsuboi T, Oga T, Handa T, Yamamoto K, *et al*. Immediate noninvasive ventilation may improve mortality in patients with hepatopulmonary syndrome after liver transplantation. Liver Transpl

2011;17(2):144–148. doi:10.1002/lt.22207.
[92] Drake MG. High-flow nasal cannula oxygen in adults: An evidence-based assessment. Ann Am Thorac Soc 2018;15(2):145–155. doi:10.1513/AnnalsATS.201707-548FR.
[93] Bateman RM, Sharpe MD, Jagger JE, Ellis CG, Solé-Violán J, López-Rodríguez M, *et al*. 36th International Symposium on Intensive Care and Emergency Medicine : Brussels, Belgium. 15-18 March 2016. Crit Care 2016;20(Suppl 2):94. doi:10.1186/s13054-016-1208-6.
[94] Roth C, Schrutka L, Binder C, Kriechbaumer L, Heinz G, Lang IM, *et al*. Liver function predicts survival in patients undergoing extracorporeal membrane oxygenation following cardiovascular surgery. Crit Care 2016;20:57. doi:10.1186/s13054-016-1242-4.
[95] Monsel A, Mal H, Brisson H, Luo R, Eyraud D, Vézinet C, *et al*. Extracorporeal membrane oxygenation as a bridge to liver transplantation for acute respiratory distress syndrome-induced life-threatening hypoxaemia aggravated by hepatopulmonary syndrome. Crit Care 2011;15(5):R234. doi:10.1186/cc10476.
[96] Blandino Ortiz A, Lamanna I, Antonucci E, Pozzebon S, Dell'anna AM, Vincent JL, *et al*. Altered liver function in patients undergoing veno-arterial extracorporeal membrane oxygenation (ECMO) therapy. Minerva Anestesiol 2017;83(3):255–265. doi:10.23736/S0375-9393.16.11442-7.
[97] Chou AH, Wu VC, Chen DY, Hung KC, Chang SH, Chu PH, *et al*. Outcome of extracorporeal membrane oxygenation support in patients with liver cirrhosis: a nationwide population-based cohort study. Eur J Cardiothorac Surg 2020;58(3):519–527. doi:10.1093/ejcts/ezaa089.
[98] Sameed M, Meng Z, Marciniak ET. EOLIA trial: the future of extracorporeal membrane oxygenation in acute respiratory distress syndrome therapy? Breathe (Sheff) 2019;15(3):244–246. doi:10.1183/20734735.0363-2018.
[99] Allegretti AS, Parada XV, Eneanya ND, Gilligan H, Xu D, Zhao S, *et al*. Prognosis of patients with cirrhosis and aki who initiate RRT. Clin J Am Soc Nephrol 2018;13(1):16–25. doi:10.2215/CJN.03610417.
[100] Saraiva IE, Ortiz-Soriano VM, Mei X, Gianella FG, Woc WS, Zamudio R, *et al*. Continuous renal replacement therapy in critically ill patients with acute on chronic liver failure and acute kidney injury: A retrospective cohort study. Clin Nephrol 2020;93(4):187–194. doi:10.5414/CN109983.
[101] Fernández J, Tandon P, Mensa J, Garcia-Tsao G. Antibiotic prophylaxis in cirrhosis: Good and bad. Hepatology 2016;63(6):2019–2031. doi:10.1002/hep.28330.
[102] Garcia-Tsao G. Prophylactic antibiotics in cirrhosis: Are they promoting or preventing infections? Clin Liver Dis (Hoboken) 2019;14(3):98–102. doi:10.1002/cld.819.
[103] Haussner F, Chakraborty S, Halbgebauer R, Huber-Lang M. Challenge to the intestinal mucosa during sepsis. Front Immunol 2019;10:891. doi:10.3389/fimmu.2019.00891.