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Review Article

Critical Update on the Diagnosis and Management of COVID-19 in Advanced Cirrhosis and Liver Transplant Recipients

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Abstract

The novel coronavirus disease 2019 (COVID-19) pandemic has impacted health care worldwide, with specific patient populations, such as those with diabetes, cardiovascular disease, and chronic lung disease, at higher risk of infection and others at higher risk of disease progression. Patients with decompensated cirrhosis fall into the latter category and are a unique group that require specific treatment and management decisions because they can develop acute-on-chronic liver failure. In liver transplant recipients, the atypical immunity profile due to immunosuppression protects against downstream inflammatory responses triggered by COVID-19. This exhaustive review discusses the outcomes associated with COVID-19 in patients with advanced cirrhosis and in liver transplant recipients. We focus on the immunopathogenesis of COVID-19, its correlation with the pathogenesis of advanced liver disease, and the effect of immunosuppression in liver transplant recipients to provide insight into the outcomes of this unique patient population.

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Keywords: Coronavirus; Cirrhosis; Portal hypertension; Acute-on-chronic liver failure; Sepsis; Hepatic encephalopathy; Multiple-organ failure; Critical care.

Abbreviations: ACLF, acute on chronic liver failure; ARDS, acute respiratory distress syndrome; CAID, cirrhosis-associated immune dysfunction; CD, cluster of differentiation; CLD, chronic liver disease; COVID-19, novel coronavirus disease; IFN, interferon; IL, interleukin; NF-kB, nuclear factor-kappa B; NK, natural killer; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; STAT3, signal transducer and activator of transcription 3; TLR, toll-like receptors; TNF, tumour necrosis factor.

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Introduction

The novel coronavirus

On January 30, 2020, the World Health Organization (WHO) declared severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)-related disease (named coronavirus disease 2019 [COVID-19] on February 11, 2020) a Public Health Emergency of International Concern and later declared it a pandemic.[1] The incubation period is 3–5 days, with some cases presenting 24 days after exposure. The expected number of cases directly generated by one case in a population where all individuals are susceptible to infection (R_0) is 4.7–6.6, and the mortality rate is approximately 2%. The main clinical features of COVID-19 include fever in approximately 90%, cough in 75%, and dyspnea in up to 50% of symptomatic patients. Additional symptoms include myalgia, severe headache, pharyngitis, nausea, and vomiting. A small but significant group of patients also present with atypical symptoms, such as diarrhea (approximately 7%) or hyposmia/anosmia and ageusia. Patients with severe disease develop rapid-onset acute respiratory distress syndrome (ARDS), sepsis (due to overwhelming viral infection and systemic inflammation as well as superadded bacterial infection), shock, coagulation failure featuring both thrombotic and bleeding events, and multiple organ failure.[2]

Diagnosing SARS-CoV-2 and COVID-19

A combination of clinical history, clinical manifestations, supportive laboratory tests, and radiological findings are crucial to accurately diagnose COVID-19. The gold standard for diagnosis is identifying SARS-CoV-2 viral particles by electron microscopy or intracellular viral inclusions by light microscopy. Active viral replication in tissue cultures is also considered direct evidence of viral infection. At the population level and commercially, laboratories generally utilize enzyme immunoassays or agglutination tests to de-

tect the viral antigens or nucleic acid amplification tests to detect viral genetic material. The immune response to the virus occurs primarily due to innate immunity, particularly the action of natural killer (NK) cells, and cellular immunity, contributed by cytotoxic T ($CD8^+$) cells.[3]

The most common modality used for etiologic diagnosis is the identification of SARS-CoV-2 genetic material by real-time polymerase chain reaction (RT-PCR), whereby viral RNA is reverse transcribed to complementary DNA (cDNA) followed by amplification of specific cDNA regions. In SARS-CoV-2 detection, these regions include the genes for RNA-dependent RNA polymerase (*RdRp*), the virus envelope (*E*) and nucleocapsid (*N*), and open reading frames 1a and 1b (*ORF1ab*). Multiple protocols exist for sequential probe and primer applications for different genetic targets. Although the Charité-Berlin protocol for *RdRp*, *E*, and *N* shows good sensitivity and specificity,[4] the sensitivity and specificity of commercial RT-PCR kits are not 100%.

Personnel who perform testing for COVID-19 must be familiar with the various important measures and protocols that help to confirm a diagnosis of COVID-19. The sensitivity and specificity of the best kits currently available are approximately 75% and 95%, respectively. This is partly due to multiple factors, such as the collection method, symptom duration (low yield before day 3 or beyond day 7 of symptom onset), collection site (nasopharyngeal swabs are better than oropharyngeal swabs), disease severity, and sampling expertise, all of which also contribute to material adequacy and viral yield. Furthermore, viral mutations produce false-negative results, leading to new waves of infection clusters due to inadequate identification of positive cases. Ideally, to avoid false-negative results, more than one region of the virus genome should be amplified to reduce the chances of probe and primmer mismatch.[5,6] The swab material must be Dacron or polyester and should be immediately immersed in a refrigerated storage medium after sample collection and transported to the laboratory. Bronchoalveolar lavage specimens have the highest positivity, followed by sputum, nasopharyngeal swabs (not oropharyngeal swabs), and nasal swabs. Viral genetic material, but not the infecting virus, has been identified in feces. In emergency situations, such as liver transplantation for acute liver failure, where immediate viral detection results are warranted, the Cepheid GeneXpert platform, which has a turnaround time of 45 m and performs the amplification process within a cartridge, is used for the qualitative detection of E and N protein genes.[5–7] The detection of viral genetic material does not always correlate with infectivity. Immunoglobulin (Ig) M is detectable from day 5 and is significant from day 8 after symptom onset, while IgG is the most significant from day 14 onwards. Nonetheless, although these are inappropriate for early diagnosis of COVID-19, they are relevant in patients who have symptoms strongly suggestive of SARS-CoV-2 infection with RT-PCR negative results and in those with severe inflammatory syndromes associated with COVID-19.[8,9]

Laboratory tests are not useful to confirm COVID-19, but they help to assess illness severity and progression. Typical findings, including lymphopenia, a neutrophil to lymphocyte ratio ≥3.13, thrombocytopenia (higher risk for myocardial involvement), C-reactive protein, ferritin, D-dimer, and interleukin (IL)-6, indicate severe systemic inflammation, and high levels of alanine transaminase (ALT) indicate liver abnormalities in more severe disease.[10–12] Plain chest X-rays are less sensitive than computed tomography (CT) scans. The latter demonstrates bilateral, multifocal subpleural or peripheral ground-glass opacities (GGOs) with a predisposition to the lower lobes in the presence or absence of consolidations. These may be evident with or without the classical halo or inverted halo (GGOs surrounded by consolidation/condensation). Bedside lung ultrasonography shows good sensitivity for diagnosing pneumonia, characterized by B-lines, pleural thickening, and consolidations, and is recommended for unstable patients and those who cannot be moved for CT scans (especially critical patients with cirrhosis).[13,14]

Immune signatures and pathogenesis

COVID-19

SARS-CoV-2 disrupts the innate immune system by perturbing normal immune responses, causing uncontrolled systemic inflammation in the host and leading to organ damage and critical illness. Innate immune sensing is the first line of defense against viral infection. Innate signaling and downstream actions are activated by pattern-recognition receptors (PRRs) on the RNA virus, through the cytosolic retinoic acid-inducible gene I-like receptors and toll-like receptors (TLRs). Signal activation triggers the secretion of interferon (IFN) types I and III, the most critical cytokines in antiviral defense, which induce pathways in the target cells that promote adaptive immune responses.[15–17]

SARS-CoV-2 dysregulates the IFN-I response via degradation and phosphorylation pathways to escape immune sensing by preventing downstream signaling and inhibiting early induction of the IFN pathway. This promotes the activation of other cytokine signaling pathways, such as the induction of IL-6 and IL-8 by the SARS-CoV-2 proteins NSP9 and NSP10.[16,17] Such proinflammatory processes contribute to the cytokine storm observed in COVID-19 patients, which sheds light on the role of targeted immunosuppressive treatment regimens.[17,18]

The major immunopathologic features associated with COVID-19 include lymphopenia and lymphocyte dysfunction, T cell activation, granulocyte and monocyte abnormalities, increased cytokine production, and increased antibody generation.[17,19,20] Dysregulated myeloid responses drive the hallmark syndromes of COVID-19, such as ARDS, cytokine release syndrome, and lymphopenia.[18,19] Flow cytometry analysis of peripheral blood mononuclear cells from symptomatic COVID-19 patients show significantly increased levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), producing activated $CD4^+$ T cells, inflammatory monocytes (and derived macrophages), and IFN-mitogen-activated protein kinase-driven adaptive immune responses, which lead to clinical progression.[20] Increased levels of polyclonal $GM\text{-}CSF^+$ $CD4^+$ T cells, which promote IL-6 and IFN-γ production, are notable in critically ill patients with COVID-19. Furthermore, high levels of $GM\text{-}CSF^+$ $CD4^+$ T cells have been associated with poor sepsis outcomes.[19–21]

Regarding the innate lymphoid cells (NK cells and the noncytotoxic helper cells) in COVID-19, the levels of circulating NK cells are reduced in peripheral blood, partly because the chemokine receptor CXCR3 pathway facilitates NK cell recruitment from the blood to infected lung tissue.[22] Triggering NK cell activation not only contributes to infection resolution but also to the cytokine storm. Increased immune checkpoints on NK cells contribute to viral escape. The high IL-6 levels in COVID-19 also correlate with lower numbers of NK cells and impaired cytolytic function. Furthermore, a marked reduction in T cells, especially $CD8^+$ T cells, and B cells occurs in COVID-19.[22,23] Elevated levels of IL-2 or its receptor in patients with COVID-19 are directly proportional to the disease severity. IL-1β, IL-6, IL-10, IL-2, IL-7, and tumor necrosis factor (TNF)-α are the cytokines that are most elevated in COVID-19 and are associated with severe and critical illness.[21,23] Lymphocyte dysfunction in

the form of exhaustion phenotypes with upregulated programmed cell death protein 1, increased expression of T cell Ig domain and mucin domain 3, and killer cell lectin-like receptor subfamily C member 1 (NKG2A) are notable in patients with COVID-19.[24] The immune checkpoint NKG2A is increased on NK cells and $CD8^+$ T cells in patients with COVID-19.[23,24]

Similarly, regulatory T cells (Tregs) are reduced in severe COVID-19. Tregs help to resolve ARDS inflammation, and their reduction results in the development of COVID-19 immunopathology.[18,20] Neutrophil levels are higher, while the proportions of eosinophils, basophils, and monocytes are reduced. Although the number of B cells usually falls within the normal range,[25] COVID-19 patients with B cell activation, higher total antibody titers, and relatively high B cell levels have poor survival.[25,26] In COVID-19, the monocyte-macrophage activation markers, such as soluble CD14 and CD163, are increased and correlate with other inflammatory markers associated with hospital admission.[27]

The series of events that culminate in the immunopathologic picture of COVID-19 can be briefly summarized. First, SARS-CoV-2 enters host cells that express angiotensin-converting enzyme (ACE) 2 receptors, mainly via TLR-7 present in endosomes, and utilizes transmembrane protease serine 2 and the endosomal cysteine proteases cathepsin B and L for priming.[18–20] Once SARS-CoV-2 overwhelms the ACE2 receptors, functional inhibition of the alternative renin-angiotensin system (RAS) pathway occurs, leading to reduced expression of angiotensin (Ang) 1-7, which increases proinflammatory cytokines, resulting in systemic inflammation through the angiotensin 1 receptors.[28] This causes a concomitant increase in inflammatory cytokine levels, promoting pulmonary damage and ARDS. Furthermore, T cell depletion and exhaustion results in lymphopenia and the generation of dysfunctional lymphocytes, which is further worsened by direct damage to the lymphatic organs by the virus.[28,29] Hyperactivation of the nuclear factor-kappa B (NF-κB) pathway is involved in local and systemic inflammation. A major pathway for NF-κB activation following coronavirus infection is the MyD88 pathway through PRRs, leading to the induction of proinflammatory cytokines. The Ang II/I receptor axis activates NF-κB, which generates epidermal growth factor receptor ligands and TNF-α, which also stimulates NF-κB. Signal transducer and activator of transcription 3 (STAT3) is required to fully activate the NF-κB pathway, and the main stimulator of STAT3 is IL-6. Therefore, SARS-CoV-2 infection in the respiratory system activates NF-κB and STAT3, leading to NF-κB hyperactivation by STAT3.[25,30]

In cases of severe COVID-19, increases in blood lactic acid levels inhibit the proliferation and promote the dysfunction of lymphocytes. This leads to further activation and recruitment of dysfunctional neutrophils, increasing the risk of secondary infections.[30,31] An overwhelming SARS-CoV-2 infection also promotes a cytokine storm, initiated by activating $CD4^+$ T cells into T helper (Th)-1 cells that secrete GM-CSF, inducing $CD14^+CD16^+$ and $CD14^+IL\text{-}1\beta^+$ monocytes and the secretion of high levels of IL-6 and IL-1β.[31] Eosinophil recruitment and proliferation occur in severe disease, enhancing IL-6 secretion and promoting end-organ damage and multiple organ failure.

Advanced cirrhosis

Cirrhosis-associated immune dysfunction (CAID) occurs due to alterations in acquired innate and adaptive immunity during chronic liver disease (CLD) progression. CAID predisposes the patient to enhanced susceptibility toward severe systemic inflammatory conditions and a grave state of immune exhaustion, leading to sepsis and organ failure. CAID shadows both acute and chronic liver function deterioration.[32] PRR (of both tissue-specific and circulating soluble forms) expression and downstream functions are altered in patients with cirrhosis. Furthermore, PRRs, such as CD14, macrophage scavenger receptor, C-type lectin receptors, and soluble CD163, are dysregulated in CAID.[32,33]

M1 macrophages, neutrophils, Th17 cells, $CD8^+$ T cells, and NK cells promote fibrosis in CLD by secreting proinflammatory cytokines and mediators that activate hepatic stellate cells. On the other hand, IL-10, IL-22, IFN-γ, and TNF related apoptosis-inducing ligand secretion by M2 macrophages, Tregs, and NK cells ameliorate fibrogenic activity.[34,35] Depending on the stage of liver disease, NK cell-mediated downstream action can reduce or promote fibrogenic potential in the liver microenvironment. In advanced liver disease, the capacity of resident hepatic macrophages, such as Kupffer cells, to ameliorate local inflammation is reduced due to suppressed lipopolysaccharide (LPS) scavenging, albumin oxidation, and reduced secretion of high-density lipoprotein. Continuous LPS exposure leads to tolerance, further associated with a reduction in nuclear translocation of NF-κB due to an altered TLR-4 signaling pathway. Interestingly, lactate negatively regulates TLR induction of the NLRP3 inflammasome and reduces IL-1β production in patients with acute liver injury.[35,36] However, NF-κB acts as a double-edged sword in liver disease because its inhibition may not only exert beneficial effects but also negatively impact hepatocyte viability, especially when the inhibition is pronounced.

In early cirrhosis, NF-κB plays a protective role against hepatocyte death. In contrast, NF-κB inhibition in advanced cirrhosis leads to worsening inflammation due to unchecked induction of c-Jun N-terminal kinases and caspases mediated by the TNF-α signaling pathway.[37,38] Similarly, functional impairment of TLR2 and TLR4 (most important for bacterial recognition) heightens the risk of sepsis in cirrhosis. However, the virus-recognizing TLR7/8 and TLR3 remain unaffected in patients with cirrhosis. Interestingly, the etiology of CLD in hepatitis C and B virus infection is associated with virus-specific inhibition of TLR7 and TLR3, resulting in the persistence of viral replication and reduction in viral clearance, which may translate to lower severity of COVID-19 in patients with chronic viral hepatitis.[35,37–39]

Impaired monocyte function in CAID results in dysfunctional chemotaxis, phagocytosis, and superoxide generation. This progresses to a state of immune paralysis in patients with advanced cirrhosis, characterized by decreased human leucocyte antigen (HLA)-DR-related expression of monocytes. In immune paralysis, there is an increase in anti-inflammatory cytokines, such as IL-6 (myokine fraction), and IL-10-related suppression of proinflammatory cytokines, such as IL-1 and TNF-α.[32,34]

Blood monocytes in humans are broadly classified into three subsets based on CD14 and CD16 expression: classical $CD14^{high}/CD16^-$ monocytes (comprising □80% of peripheral blood monocytes) expressing high levels of chemokine receptor CCR2, nonclassical $CD14^+CD16^+$ monocytes (proinflammatory) expressing the chemokine receptor CX3CR-1, and intermediate (CD14 and CD16] monocytes.[40] There is a marked increase in nonclassical subsets in CLD, and a low lymphocyte to monocyte ratio is an independent prognostic marker in advanced cirrhosis. Regarding the adaptive immunity associated with CAID, Th1 cells express antifibrotic cytokines, and Th2 cells express profibrotic cytokines. $CD8^+$ T cells are elevated in cirrhosis, and the $CD4^+/CD8^+$ T cell ratio is reduced, favoring the fibrogenic process.[40,41] The prolonged activation of T lymphocytes resulting from long-standing systemic inflammation and antigenic stimulus leads to decreased T cell proliferation that defines immuno-

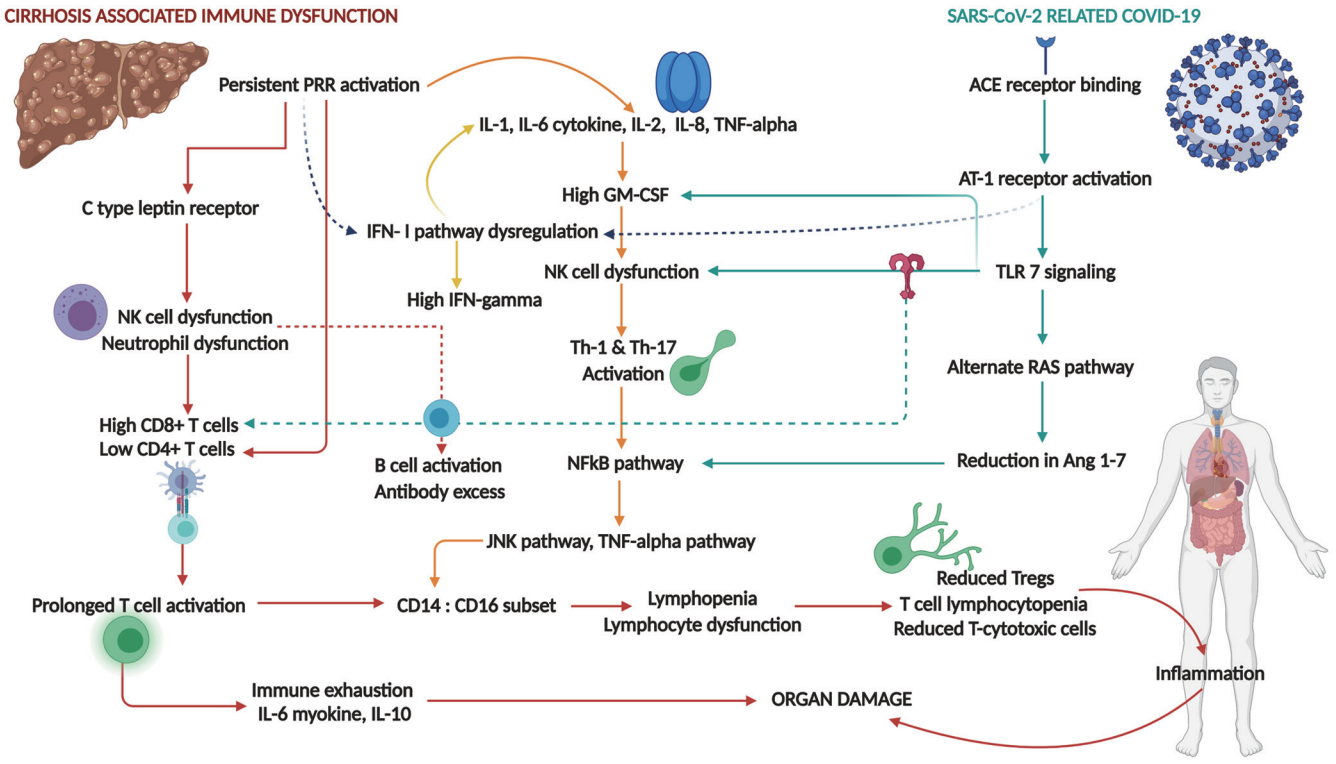

Fig. 1. Schematic diagram showing common components and pathways driving cirrhosis-associated immune dysfunction and novel coronavirus-related disease. In cirrhosis, persistent PRR activation leads to upregulation and downstream signaling of various cytokine pathways, such as the interferon pathway, proinflammatory interleukins, growth factor-mediated signaling, NF-kB and JNK pathway as TNF-a signaling, which are also common to inflammatory downstream activation associated with COVID-19. The innate and adaptive cellular responses leading to immune exhaustion is also common to both cirrhosis and COVID-19 which worsens organ damage. AT, angiotensin; JNK, Janus-kinase pathway.

suppression (IS) due to exhaustion of the adaptive immune response in advanced cirrhosis. T cell lymphopenia is common in cirrhosis and affects Th and cytotoxic T cells. T cell depletion is more pronounced in naïve than in compartmentalized memory cells, regardless of disease etiology.[40–42]

Excessively oxidized albumin is associated with unfavorable clinical outcomes in patients with cirrhosis. Cirrhosis progression leads to greater anti-albumin immune responses, favoring predominant systemic inflammation.[43] Thus, inflammatory cytokine production, macrophages, dendritic cell (antigen-presenting cells) activation, neutrophil activation with dysfunctionality, and T cell activation with functionally inert but inflammatory subtypes lead to a state of continuous systemic inflammation with the predominance of indolent immune exhaustion in cirrhosis.[43,44] In contrast, patients with acute-on-chronic liver failure (ACLF) show an exaggerated combination of immune paresis (hyporesponsive monocytes, reduced inflammatory cytokines, impaired macrophage and neutrophil phagocytosis, impaired antibody responses, and increased susceptibility to opportunistic infections), and excessive inflammatory responses predominate.[44–46]

The classical RAS components contribute to inflammation and fibrosis in CLD, while the alternative RAS pathway is upregulated to counteract its damage.[47] ACE levels and Ang 1 gene expressions increase as fibrosis worsens, leading to increased Ang 1-7 and Ang II levels. Cirrhotic livers have an enhanced capacity to convert Ang II to Ang 1-7, which has beneficial effects on liver fibrosis and inflammation.[47,48] In late-stage cirrhosis, with the onset of additional sympathetic nervous system activation in the presence of worsening portal hypertension, increased production of dysfunctional nitric oxide and acetylcholine-mediated vasodilation intervene, leading to central hypovolemia and worsening peripheral and splanchnic vasodilation due to unregulated high Ang 1-7, which negates the initial beneficial effects of the alternative RAS pathway.[47–49] This probably promotes worse outcomes in cases of advanced cirrhosis with COVID-19, in contrast to a lesser risk of disease progression in cases of stable cirrhosis. Therefore, there is evidence of commonality in the immunopathology of COVID-19 and advanced cirrhosis, which determines clinical outcomes when both are present in the same host (Fig. 1).

Liver transplant recipients

After liver transplantation, alloantigens from the transplanted organ are recognized by the host lymphocytes within the secondary lymphoid organs. Dendritic cells, macrophages, B cells and endothelial cells act as antigen-presenting cells. Non-self-recognition occurs through three main pathways: (1) T cell receptors on host T cells directly interact with the HLA molecules on the surface of donor antigen-presenting cells; (2) host antigen-presenting cells process donor peptides derived from donor HLAs, thereby activating host T cells; and (3) membrane exchange occurs between donor and host cells or extracellular vesicles.[50] Following T cell activation after antigen presentation, two additional signals intervene: (1) T cell receptor interaction occurs when costimulatory molecules bind to T cells (CD40 and CD28) and their corresponding ligands to antigen-presenting cells (CD40L, CD80, and CD86); and (2) the presence of T cell stimulatory cytokines in the microenvironment results in T

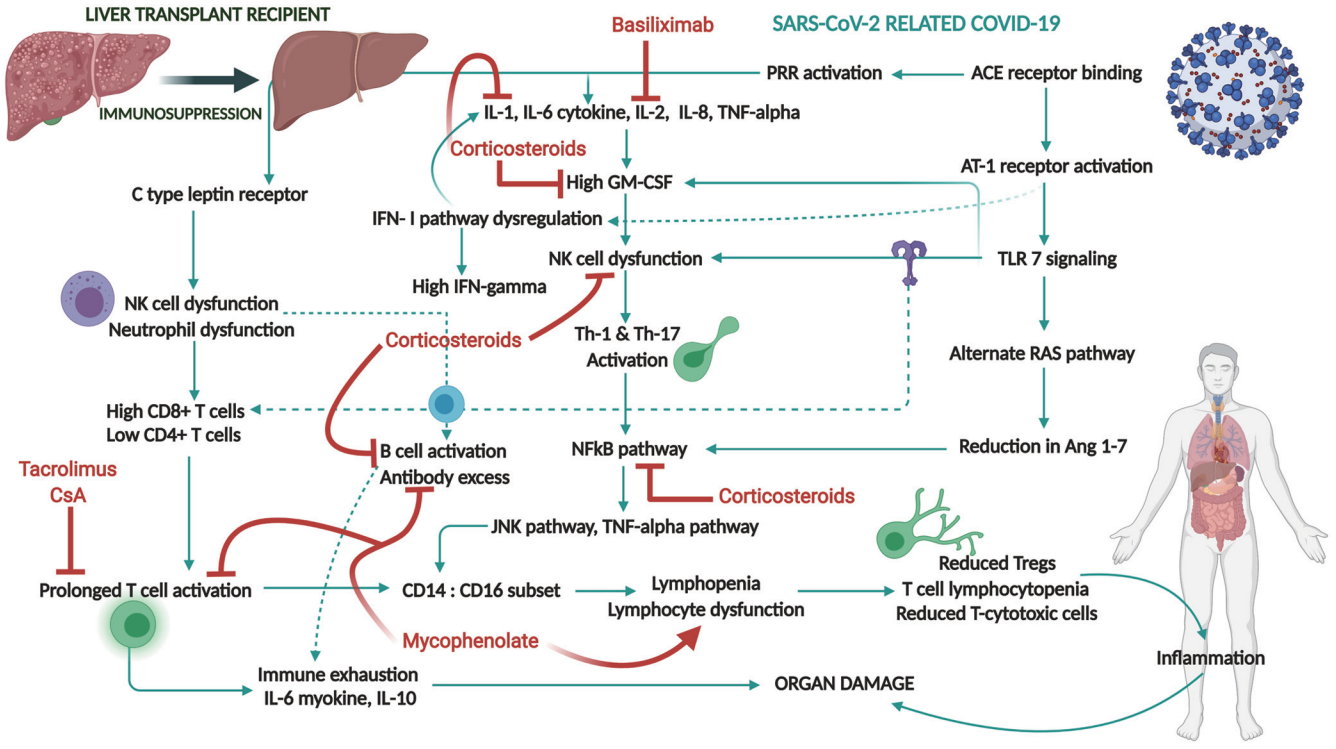

Fig. 2. Schematic diagram showing immunopathogenesis of COVID-19 and immunology of liver transplant recipients and pathways affected by IS that contribute to disease progression or reduction in clinical severity. In the liver transplant recipient, IS drugs downregulate certain specific inflammatory pathways, such as basiliximab on IL-6, corticosteroid action on NK cells, B cell activation and ILs, and tacrolimus on prolonged T cell activation. These inflammatory pathways are the very same which are highly activated through novel coronavirus receptor binding. In the presence of IS and amelioration of inflammatory signaling, COVID-19 activity and clinical outcomes could remain asymptomatic or mild among this special group of patients. CsA, cyclosporine A.

cell proliferation. In effect, IS in liver transplant recipients ameliorates T cell function and cytokine-based inflammation at both local and systemic levels.[50]

As discussed in the preceding sections, activation of the T cell innate immune response (increased concentration of highly proinflammatory CCR6$^+$ Th17 in CD4$^+$ T cells) and downstream cytokine signaling is the hallmark of COVID-19. Although immunosuppressed liver transplant recipients could be more susceptible to severe clinical COVID-19, the anti-inflammatory effects of immunosuppressants probably diminish the clinical expression of disease in this unique group of patients.[51,52]

The immunosuppressive and immunomodulatory drugs used in liver transplant recipients act on at least one of three signals of T cell activation and proliferation:

- Signal 1 features antigen-presenting cells, such as macrophages and dendritic cells, which activate T cell receptors that relay signals through the T cell receptor/CD3 complex transduction pathway.
- Signal 2 is a nonantigen-specific costimulatory signal resulting from the binding of peripheral membrane protein B7 of the activated antigen-presenting cells to CD28 on T cells. This activates the calcium-calcineurin, mitogen-activated protein, and NF-κB signal transduction pathways.
- These signals lead to increased IL-2 expression, which activates the cell cycle (signal 3). Thus, IS is ultimately attained via depletion of lymphocytes, diversion of lymphocyte traffic, or blockade of the lymphocyte response pathways.[53,54]

Basiliximab, a chimeric monoclonal antibody to the IL-2 receptor, is often used as an IS induction agent in the perioperative period of liver transplantation. This antagonist ameliorates the entire T cell activation process required to activate calcineurin-mediated stimulation of the transcription, translation and secretion of IL-2, the key autocrine growth factor that induces T cell proliferation. IL-2 blockade and the subsequent offset of downstream pathways reduce the severity of COVID-19 infection.[55] Glucocorticosteroids have a multipronged action on the immune system and stop NF-κB activation, thereby halting downstream proinflammatory signaling.[56] B cell-mediated antibody production is also reduced, and macrophage-mediated IFN release is reduced with an increase in IL-4, curbing NK cell-mediated cytotoxicity. Thus, corticosteroids are an important intervention to prevent cytokine release syndrome and protect patients from developing downstream proinflammation.[56–58] Tacrolimus and cyclosporine lessen the production of IL-2, which regulates the proliferation, survival, and maturation of all T cell subsets. Furthermore, tacrolimus and mycophenolic acid inhibit IL-17 production, inhibiting Th-17 activation. Mycophenolate depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation, suppressing cell-mediated immune responses and antibody formation.[52–54,57] Additionally, cyclophilins, the binding proteins of cyclosporine, catalyze the cis/trans isomerization of propyl peptide bonds, an essential step in correcting the folding of viral proteins. This function of cyclophilin A is essential for SARS-CoV-2 replication, which is inhibited in the presence of cyclosporine. Mycophenolic acid-related inhibition of SARS-CoV-2 replication *in vitro* has also been demonstrated.[53,54,57] Thus, it is plausible that the chronic use of immunosuppressive drugs could exert a protective function against severe clinical manifestations of COVID-19 in the post-liver transplant period (Fig. 2).

Impact of COVID-19 in patients with cirrhosis and liver transplant

COVID-19 in patients with advanced cirrhosis

Patients with CLD do not appear to be at greater risk of acquiring COVID-19 than other individuals in the general population. The outcome of COVID-19 in patients with decompensated cirrhosis is dismal, especially if ACLF develops.[59–61] Large single-center series and multinational studies have shown that disease progression is significantly higher in COVID-19 patients with CLD than those without CLD. In CLD patients, additional risk factors, such as active decompensation, metabolic syndrome, obesity, older age, alcoholic liver disease, the active drinking of alcohol, and hepatocellular carcinoma, were significant drivers of disease progression and not independent drivers of CLD. ACLF development was higher in cases of decompensated cirrhosis, which was dependent on COVID-19 severity. The cause of mortality was primarily progressive lung disease leading to multiple organ failure.[62–64] Combined analysis of the COVID-HEP and SECURE-Cirrhosis registries analyzing COVID-19 outcomes among patients with cirrhosis revealed that 38% of patients showed decompensation during the disease course in the form of worsening ascites, encephalopathy, or acute kidney injury. It is well known that infection or sepsis in patients with reduced liver reserves leads to new-onset or worsening decompensation due to significant cytokine activation, cytokine-induced hepatocyte apoptosis, and necrosis. In these patients, further categorization into ACLF, stable decompensation, or unstable decompensation as per the PREDICT criteria helps stratification for transplant listing once the infection is controlled.[65,66]

A prospective multicenter study found that the rates of mortality or transfer to hospice care in patients with cirrhosis and COVID-19 were higher than those with COVID-19 alone, but there was no significant difference compared with those with cirrhosis alone. The proportion of patients developing ACLF and mortality due to ACLF were also similar in the cirrhosis groups. In patients with COVID-19, mortality was markedly greater in cirrhosis patients than in those without cirrhosis.[67] In a national study of >80,000 USA veterans with SARS-CoV-2 infection, older age (≥50 years) was the most significant risk factor associated with hospitalization, mechanical ventilation, and mortality. Other risk factors for mortality included preexisting comorbidities, such as heart failure, chronic kidney disease, and cirrhosis.[68] Nonetheless, in another large study performed by the author-group, patients with cirrhosis were less likely to test positive for COVID-19 than patients without cirrhosis. The 30-day mortality and ventilation rates were highest in patients with COVID-19 and cirrhosis compared with those with COVID-19 only. Cirrhosis patients with COVID-19 were 4.1 times more likely to undergo mechanical ventilation and 3.5 times more likely to die than those who tested negative. In those with cirrhosis and COVID-19, significant predictors of mortality were advanced age, decompensation, and a high model for end-stage liver disease (MELD) score. These findings revealed that cirrhosis was not a risk factor for SARS-CoV-2 infection but was a risk for disease progression in the presence of advanced liver disease and age.[69] A summary of pertinent studies of patients with cirrhosis and COVID-19 is presented in Table 1.[61,64,65,67,68,70–76]

COVID-19 in liver transplant recipients

In a single-center report from King's College Hospital, UK, liver transplant recipients appeared to have a low incidence of COVID-19, with less severe symptoms than expected, as compared with the general population and transplant recipients of other solid organs.[77] IS drugs, such as cyclosporine and tacrolimus, could reduce the viral load by inhibiting viral replication via immunophilin pathway suppression, but confirmation studies in clinical settings are pending. Thus, the lower incidence of symptomatic presentation in liver transplant recipients could be due to amelioration of the systemic inflammatory response brought on by COVID-19.[78,79] A report from Lombardy, Italy, showed that death among liver transplant recipients with COVID-19 was very low and mainly driven by the presence of associated metabolic syndrome comorbidities.[80] Another series of COVID-19 cases in liver transplant recipients had death in only four patients (median age <65 years) who had received their transplant within the past 2 years. Over one-third of these patients suffered from metabolic syndrome. In contrast, the comorbidity frequencies were not significantly different between fatal and nonfatal cases of COVID-19 in the study cohort, but this could have been due to the small sample size.[81] Data from the European Liver and Intestine Transplant Association/European Liver Transplant Registry COVID-19 registry suggests that mortality in liver transplant recipients is higher in older recipients and increases in long-term transplant recipients.[82]

Analysis of liver disease patients at a transplant center in India revealed that outcomes after liver transplant in the COVID era were similar to that in non-COVID times.[83] A prospective nationwide study including a consecutive cohort of liver transplant recipients with COVID-19 recruited during the Spanish outbreak after a median follow-up of 23 days revealed that of the 86.5% who were hospitalized, 19.8% required respiratory support, with a mortality rate of 18%, which was lower than that of a matched general population. It was concluded that because liver transplant recipients were chronically immunosuppressed, they had an increased risk of acquiring SARS-CoV-2 infection; however, their mortality rates were lower than those of a matched general population.[84] A prospective multicenter study in a European liver transplant recipient cohort showed that COVID-19 was associated with overall and in-hospital fatality rates of 12% and 17%, respectively, with notably poorer outcomes among those with a history of cancer.[85] In contrast, the initial experience among liver transplant recipients from a USA COVID-19 epicenter revealed that approximately 33% of hospitalized patients required mechanical ventilation. Only a quarter of them survived, with a high proportion presenting with acute kidney injury. Mortality was high in the short- and long-term post-transplant period and was associated with IS reduction.[86] In another study, adjusted analyses revealed that transplant recipients had a significantly higher risk of hospitalization but not a higher risk of mortality, thrombosis, or intensive care requirement compared with controls. Furthermore, transplant recipients had a higher incidence of acute kidney injury than nontransplant COVID-19 patients.[87] A large meta-analysis of patients with solid organ transplantation in the COVID-19 era demonstrated that patients with COVID-19 who were kidney transplant recipients had a higher mortality rate compared with those who were liver transplant recipients (pooled incidence of all-cause mortality 22% vs. 11%, respectively). Similar COVID-19 mortality outcomes among liver transplant recipients were also reported in other systematic reviews (13.6%).[88,89] The pertinent studies on COVID-19 in liver transplant recipients are summarized in Table 2.[81,82,84,120–124]

Treatment and management

COVID-19 treatment in advanced cirrhosis, including liver transplant-listed patients

Asymptomatic and mild COVID-19 infections are managed

Table 1. Summary of pertinent studies on COVID-19 in cirrhosis

Study	Design/Patients	Clinical outcomes	Major comments
Jeon *et al*. (2020)[70]	Korean national cohort, propensity score matching, *n*=67 (cirrhosis+COVID-19)	Variceal bleeding 3%; Ascites 3%; HE 4.5%; Mortality 9%	Older age, hypertension, cancer, chronic obstructive pulmonary disease and higher Charlson comorbidity index associated with higher risk of severe complications. Cirrhosis was not independently associated with the development of severe complications, including mortality, in patients with COVID-19
Shalimar *et al*. (2020)[61]	Single center from India, case control study, *n*=28 (cirrhosis+COVID-19)	ACLF 34.6%; Acute decompensation 61.5%; Variceal bleeding 30.8%; Ascites 7.7%; Mortality 42.3%	COVID-19 was associated with poor outcomes in patients with cirrhosis especially in those developing ACLF. Mechanical ventilation was associated with a poor outcome
Kim *et al*. (2020)[64]	Multicenter, observational cohort study from USA, *n*=227 (cirrhosis+COVID-19)	Acute decompensation 29.5%; Variceal bleeding 3.1%; HE 10.1%; Ascites 4.8%; Mortality 25%	Independent risk for death - alcohol etiology, decompensated cirrhosis and hepatocellular carcinoma. Risk for severe COVID-19-decompensated cirrhosis and Hispanic ethnicity
Lee *et al*. (2020)[71]	Multicenter South Korean cohort study, *n*=14 (cirrhosis+COVID-19)	Child-Pugh class A 64.3%; Child-Pugh class B 35.7%; Secondary bacterial infection 7.1%; Mortality 28.6%	Higher proportion with cirrhosis required oxygen therapy, intensive unit admission, had septic shock and lung and renal failure. Overall survival rate significantly lower in patients with liver cirrhosis
Moon *et al*. (2020)[72]	International reporting registries (COVID-Hep.net and COVIDCirrhosis.org), *n*=103 (cirrhosis+COVID-19)	Decompensation 36.9%; Variceal bleeding 1%; Ascites 27.2%; SBP 2.9%; Mortality 39.8%	Cause of death in patients with cirrhosis was lung disease in 78.7%. Mortality correlated strongly with baseline Child-Pugh B/C class and MELD
Sarin *et al*. (2020)[73]	Data from 13 Asian countries, *n*=43 (cirrhosis+COVID-19)	ACLF 11.6%; Acute decompensation 9.3%; Variceal bleeding 9.3%; HE 7%; SBP 7%; Mortality 16.3%	Liver related complications increased with stage of liver disease. Child-Pugh score ≥9 at presentation predicted high mortality. In decompensated cirrhotics, the liver injury was progressive in 57% patients, with 43% mortality. Rising bilirubin and AST/ALT ratio predicted mortality among cirrhosis patients. SARS-CoV-2 infection causes significant liver injury in cirrhosis, decompensating one-fifth affected
Iavarone *et al*. (2020)[74]	Italian multicenter retrospective study, *n*=50 (cirrhosis+COVID-19)	ACLF 28%; HE 22%; Mortality 34%	30-day-mortality rate 34%. Severity of lung and liver as per CLIF-C/OF scores independently predicted mortality. In patients with cirrhosis, mortality was significantly higher in those with COVID-19 than in those hospitalized for bacterial infections
Clift *et al*. (2020)[75]	Population-based cohort study using electronic health record data, *n*=11,865 with cirrhosis	106 hospitalizations with COVID-19 in patients with cirrhosis; 37 deaths from COVID-19 in patients with cirrhosis	QCOVID population-based risk algorithm model. Since the chance of being hospitalized or dying from COVID-19 is critically dependent on factors that the authors did not include in their model, the algorithm does not know who actually was exposed to or was infected by the virus
Ioannou *et al*. (2020)[68]	Veterans Affairs national health care system cirrhosis population study, *n*=305 (cirrhosis+COVID-19)	Patients with cirrhosis were less likely to test positive than patients without cirrhosis; Cirrhosis+COVID-19 were 4.1-times more likely to undergo mechanical ventilation	Most important predictors of mortality were advanced age, cirrhosis decompensation, and high MELD score. COVID-19 was associated with a 3.5-fold increase in mortality in patients with cirrhosis. Cirrhosis was associated with a 1.7-fold increase in mortality in patients with COVID-19
Qi *et al*. (2021)[76]	Chinese retrospective multicenter study (COVID-Cirrhosis-CHESS), *n*=21 (cirrhosis+COVID-19)	ACLF 4.8%; Variceal bleeding 19%; Ascites 5.9%; Mortality 23.8%	Small size and narrow composition of study population. Cause of death in most patients was respiratory failure rather than progression of liver disease. Lower lymphocyte and platelet counts, and higher direct bilirubin level are poor prognostic indicators

(continued)

Table 1. *(continued)*

Study	Design/Patients	Clinical outcomes	Major comments
Bajaj *et al*. (2021)[67]	North American multicenter study, *n*=37 (cirrhosis+COVID-19)	ACLF 30%; Variceal bleeding 14%; HE 14%; Mortality 30%	Cirrhosis+COVID-19 had worse Charlson Comorbidity Index, higher lactate. Age/gender-matched patients with cirrhosis+COVID-19 had similar mortality compared with patients with cirrhosis alone but higher than patients with COVID-19 alone
Marjot *et al*. (2021)[65]	Multicenter international registries case control study, *n*=386 (cirrhosis+COVID-19)	ACLF 23%; Acute decompensation 46%; Variceal bleeding 3%; HE 27%; SBP 3%; Mortality 32%	Compared to patients without CLD significant increases in mortality in those with Child-Pugh B and C notable. 21% with acute decompensation had no respiratory symptoms. Half of those with hepatic decompensation developed ACLF. Baseline liver disease stage and alcohol-related liver disease are independent risk factors for death from COVID-19

MELD, model for end stage liver disease; HE, hepatic encephalopathy; ACLF, acute on chronic liver failure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SBP, spontaneous bacterial peritonitis.

at home with isolation, close monitoring for clinical worsening, and symptomatic treatment, including acetaminophen (not nonsteroidal anti-inflammatory drugs) and antipyretics for fever, headache, and myalgia. Although short-term acute pain can be treated with 3-4 g of acetaminophen daily, a maximum daily dose of 2–3 g in patients with al-

Table 2. Summary of pertinent studies on COVID-19 in liver transplant recipients

Study	Design/Patients	Clinical outcomes	Major comments
Kates *et al*. (2020)[120]	Multicenter prospective cohort study, *n*=73	28-day mortality 21% in whole solid organ transplant cohort (*n*=482); LT not independently associated with death	Age >65 years, congestive heart failure, chronic lung disease, obesity, lymphopenia, abnormal chest imaging independently associated with mortality. Multiple measures of IS intensity not associated with mortality
Ravanan *et al*. (2020)[121]	Multicenter national cohort study, *n*=64	Overall mortality 23%; Reduced risk of COVID-19 in transplanted patients	Increasing recipient age was the only variable independently associated with death
Colmenero *et al*. (2020)[84]	Prospective multicenter cohort study, *n*=111 (LT recipients with COVID-19), *n*=13,000 (LT recipients without COVID-19)	Mortality in LT recipients 18%, which was lower than the matched general population; Chronic IS increases the risk of acquiring COVID-19 but could reduce disease severity	Baseline mycophenolate independent risk factor for severe COVID-19 (ICU, IPPV or death) particularly at doses higher than 1,000 mg/day. Deleterious effect not observed with calcineurin inhibitors or everolimus. Complete IS withdrawal showed no benefit
Webb *et al*. (2020)[81]	Multinational registry study, *n*=151	Overall mortality 19%; LT did not significantly increase the risk of death	Risk factors for mortality within LT recipients included age, renal function (serum creatinine) and non-liver cancer
Rabiee *et al*. (2020)[122]	Multicenter retrospective cohort study, *n*=112	Overall mortality (22%); No independent risk factors for death identified	Incidence of acute liver injury lower in LT recipients. Factors associated with liver injury - younger age, Hispanic ethnicity, antibiotic use and metabolic syndrome. Reduction in IS not associated with liver injury or mortality
Belli *et al*. (2020)[82]	European registry study, ELITA/ELTR Multicenter cohort, *n*=243	Overall mortality 20%; Risk factors for mortality include age, diabetes and chronic kidney disease	Tacrolimus had positive independent effect of survival. Increasing age, renal impairment and diabetes associated with higher mortality
Webb *et al*. (2021)[123]	Combined analysis from a multinational cohort, *n*=258	Overall mortality 18–19%	Age and Charlson Comorbidity Index independently associated with death. No association with type of IS regime
Fraser *et al*. (2021)[124]	Systematic review and quantitative analysis, *n*=223	36% had severe COVID-19; Dyspnea on presentation, diabetes mellitus, and age ≥60 years significantly associated with increased mortality	LT recipients with severe COVID-19 are overrepresented with regard to severe disease and hospitalizations. Older liver transplant patients with diabetes mellitus or hypertension on maintenance corticosteroids are at high risk of death

LT, liver transplantation; ICU, intensive care unit; IPPV, invasive positive pressure ventilation.

cohol-associated cirrhosis may be a safer recommendation if analgesia is required for >14 days. Furthermore, acetaminophen use of 2–3 g/day for an average of 2–3 days or 1 g/day for up to 3 weeks in patients with cirrhosis was not associated with an increased risk of hospitalization for acute liver decompensation.[90,91] For the home care of decompensated cirrhosis patients, telehealth visits can be scheduled on days 4, 7, and 10 following the onset of clinical illness. It appears prudent to schedule the first follow-up telehealth visit within 24 h for patients at high risk of disease progression, including those aged ≥65 years who have one or more established (liver cancer, chronic kidney disease, chronic lung disease, obesity, coronary artery disease, active smoking, alcohol use disorder, and type 2 diabetes mellitus) or possible (moderate to severe airway disease and systemic hypertension) risk factors, any patient with moderate dyspnea at the time of initial evaluation, and those who may not reliably report symptom deterioration. If these patients remain clinically stable, subsequent telehealth visits can be reduced to once every other day. Patients must avoid nebulized medications at home to prevent potential aerosolization of SARS-CoV-2 and should use a metered-dose inhaler preparation if already using such medications or for COVID-19 symptom treatment, when possible. They must also avoid herbal supplements, advertised but untested traditional, complementary, and alternative methods of immune-boosting, and associated therapeutic practices for asymptomatic and mild infections while at home. For example, fenugreek extracts and concoctions have been shown to worsen coagulation failure in patients with cirrhosis, and the use of ashwagandha, turmeric, or curcumin supplements have been associated with severe liver injury and dose-dependent hepatotoxicity.[92–95]

Hospital admission for further treatment, monitoring, and care is advised for patients with decompensated cirrhosis who develop unstable decompensation and those with moderate to severe COVID-19. Screening for bacterial sepsis is mandatory for all decompensated cirrhosis patients with moderate to severe COVID-19 upon admission. In patients who have been symptomatic for >7 days and require supplemental oxygen or mechanical ventilation, dexamethasone (6 mg daily for up to 10 days) or equivalent doses of prednisone, methylprednisolone, or hydrocortisone should be considered if the sepsis screen is negative and there is an absence of active variceal bleeding, acute kidney injury, or a higher grade of hepatic encephalopathy.[96]

Effectiveness of the antiviral drug remdesivir in patients with severe and mild COVID-19 remains ill-defined. Randomized trials have not demonstrated a clear, significant clinical benefit of remdesivir administration among hospitalized patients, and a meta-analysis of four trials of >7,000 patients with COVID-19 on remdesivir did not demonstrate reduced mortality or the need for mechanical ventilation compared with the standard of care or placebo.[97,98] Remdesivir should be avoided in COVID-19 patients on mechanical ventilation or extracorporeal membrane oxygenation (ECMO). The vehicle for remdesivir administration is cyclodextrin, which accumulates in patients with renal impairment, resulting in renal and hepatic toxicity. Thus, it is not recommended in patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2, especially in decompensated cirrhosis patients with acute kidney injury and those with acute hepatitis. Liver test abnormalities are not uncommon with remdesivir use, and administration should be discontinued in patients with ALT elevations >10 times the upper limit of normal.[98,99]

There is no substantial evidence for using other agents, such as the Janus kinase inhibitor baricitinib, lopinavir-ritonavir, favipiravir, ivermectin, hydroxychloroquine, azithromycin, IFNs, IL-6 pathway inhibitors (e.g., itolizumab), various monoclonal antibodies, and convalescent plasma in patients with cirrhosis.[99] Nonetheless, the recent metanalysis from the WHO Living Guidelines strongly recommends treatment with monoclonal antibody IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical COVID-19 infection in combination with corticosteroids; although, it was reported that secondary infections occurred in 21.9% of patients treated with IL-6 antagonists vs. 17.6% of patients treated with the standard of care or placebo at 28 days.[100] Although specific data on the use of IL-6 blockers in patients with cirrhosis are lacking, cautious and reasonable use in stable patients with cirrhosis and liver transplant recipients may be warranted with close monitoring for acute decompensation events, sepsis episodes, cellular rejection, or opportunistic infections. No other monoclonal antibodies are currently recommended for use in patients with COVID-19, pending further assimilation of data from larger replication studies. A very recent systematic review and metanalysis showed that treatment with convalescent plasma compared with placebo or the standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes. Hence, this therapy modality must be avoided entirely in patients with and without cirrhosis who have COVID-19.[101]

Empirical antibiotic treatment should only be considered in decompensated patients with acute variceal bleeding and a strong clinical suspicion of active bacterial sepsis who are at high risk for developing intercurrent secondary infections, such as those with acute kidney injury or overt hepatic encephalopathy.[102] In those with acute variceal bleeding, endoscopy must be performed at the bedside and in a dedicated COVID-19 unit following universal precautions and the wearing of personal protective equipment. If possible, a gastrointestinal bleed unit/room dedicated for COVID-19 patients should be prepared for the purpose of this invasive, specialized treatment. The personnel, including the endoscope operator, anesthetist, and assisting nursing and technical staff, must be kept to a minimum. A recent metanalysis and a randomized trial showed that endoscopy could be safely deferred for up to 24 h in acute variceal bleeding.[103,104]

Routine use of anticoagulation therapy is not recommended in patients with severe or critical COVID-19, particularly in those with cirrhosis, because it worsens bleeding events and does not improve clinical outcomes.[105] Intravenous human albumin should be considered for all patients with moderate to severe COVID-19 who have decompensated cirrhosis. Complications include volume overload, and it is contraindicated in cases of pulmonary edema, severe ARDS, and acute kidney injury requiring renal replacement therapy.[106]

Adjuvant treatments for admitted patients with decompensated cirrhosis and COVID-19 should be as per the recommendations of relevant societies and guidelines. They should include screening and correction of dyselectrolytemia, ammonia-lowering therapies, such as intravenous infusion of L-ornithine-L-aspartate or the oral or rectal administration of lactulose formulations, and terlipressin for acute kidney injury. All critically ill patients with COVID-19 and cirrhosis can be considered to have ACLF and must be managed as per the general rules and recommendations for ACLF inclusive of specific considerations for COVID-19 treatment.[107,108] Generally, as per current evidence, the following measures are advisable for critically ill patients with cirrhosis and COVID-19:[109–112]

The lowest possible fraction of inspired oxygen should ideally target a peripheral oxygen saturation level of 90–96%, even in those with hepatopulmonary syndrome.

- Noninvasive measures should be initiated, such as

high-flow nasal cannula (HFNC) oxygen therapy and noninvasive ventilation (NIV) for acute hypoxemic respiratory failure that does not improve with low-flow oxygen, rather than directly intubating.
- NIV may be appropriate in patients with indications that have proven efficacy, such as acute hypercapnic respiratory failure from an acute exacerbation of chronic obstructive pulmonary disease, acute cardiogenic pulmonary edema, and sleep-disordered breathing.
- Patients on HFNC or NIV require frequent clinical and arterial blood gas evaluation every 1–2 h to ensure efficacy and safe ventilation.
- In the absence of overt hepatic encephalopathy and severe ascites, encouraging prone positioning seems appropriate; however, the threshold for intubating such patients should be kept low (e.g., rapid progression over a few hours, failure to improve despite HFNC >50 L/min and FiO_2 >0.6, hypercapnia and hemodynamic instability, or multiorgan failure).
- Low tidal volume ventilation (LTVV) of ≤6 mL/kg predicted body weight with plateau pressure ≤30 cm water and graded positive end-expiratory pressure should be utilized, for an oxygenation goal of PaO_2 levels of 55–80 mmHg or SpO_2 levels of 88–95%. Propofol or remifentanil should be the sedating agent of choice to lower the risk for encephalopathy precipitation.
- Dopamine must be avoided in critically ill patients with decompensated cirrhosis, and fluid management should include a combination of crystalloids and human albumin.
- In those patients where LTVV fails, prone ventilation is the preferred next step, and finally, continuous renal replacement therapy and ECMO must be considered in critically ill patients who can be salvaged, optimized, and bridged to liver transplantation because the development of ARDS in ACLF rapidity progresses to multiorgan failure, in which case treatment is futile.

COVID-19 treatment in liver transplant recipients

The major international liver societies recommend limiting liver transplants to patients with high MELD scores or hepatocellular carcinoma progression during the current pandemic. Nasopharyngeal swabs of all potential donors are screened using an RT-PCR assay and a chest CT scan, and those who are positive by RT-PCR or chest CT should be rejected. The American Association for the Study of Liver Diseases does not recommend transplantation in patients with COVID-19. Nonetheless, liver transplantation can proceed 3 weeks after symptom resolution and negative diagnostic tests in patients with advanced cirrhosis.[113] A small case series on liver transplantation in SARS-CoV-2-positive recipients showed favorable clinical outcomes.[114]

The standard management of mild, moderate, and severe COVID-19 can be safely extrapolated to liver transplant recipients with caveats. IS dosing should not be modified, unless there is severe progressive disease. Drugs such as statins, ACE inhibitors, and angiotensin receptor blockers should be continued.[115,116] For those receiving supplemental oxygen, HFNC, or NIV, dexamethasone is recommended. For those requiring mechanical ventilation or ECMO, low-dose dexamethasone but not remdesivir is suggested. No other COVID-19 therapies, including convalescent plasma, are recommended in the post-liver transplant period.[115–117] Apart from these standards of care, specific treatment and management considerations need to be exercised in liver transplant recipients. This includes stopping mycophenolate mofetil in those with documented lymphopenia (a marker of severe and progressive disease or a drug-induced adverse event). Because SARS-CoV-2 activates innate immunity and proinflammation to promote organ damage, IS may be protective or promote reduced disease severity. Nonetheless, immunosuppressed transplant recipients who develop COVID-19 may have prolonged viral shedding.[118] IS should be started in all liver transplant recipients, even in those with COVID-19, without compromising institutional transplant drug protocols. Reduction or modification of IS regimens must be considered in liver transplant recipients with cytopenia, secondary bacterial or fungal sepsis (reduce calcineurin inhibitors and stop azathioprine and mycophenolate), and severe/critical COVID-19 with a high risk for opportunistic infections. For transplant recipients who develop progressive GGOs and are receiving mammalian target of rapamycin (mTOR) inhibitors, switching to calcineurin inhibitors may be ideal, with the immediate benefit of the doubt given to the former causing mTOR-induced pneumonitis. Liver transplant recipients with COVID-19 who develop kidney injury should be maintained on higher doses of prednisolone with the reduction or stoppage of calcineurin inhibitors until recovery. In summary, IS modifications in the post-transplant period are advisable in cases of severe and critical COVID-19 with specific considerations for those with cytopenia, drug-related adverse events/interactions, and secondary bacterial or fungal sepsis.[118,119] The general and specific schematic of managing COVID-19 in advanced cirrhosis and liver transplant recipients is shown in Figure 3.

Conclusion

COVID-19 affects liver disease patients differently than other patient populations. In those with advanced cirrhosis, depending on the severity of liver disease, the underlying systemic inflammation plausibly worsens in the presence of SARS-CoV-2 infection, leading to new-onset or aggravation of decompensation, sometimes resulting in ACLF, which may carry a poor prognosis. In the post-liver transplant scenario, even though the risk of infection seems high, changes in innate and adaptive immunity promoted by immunosuppressants cause the severity of COVID-19 to remain low, with the probable exception of patients who are long-term transplant recipients who develop the chronic metabolic disease, in whom diabetes or renal disease promotes infection susceptibility and poor outcomes.

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Conflict of interest

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Author contributions

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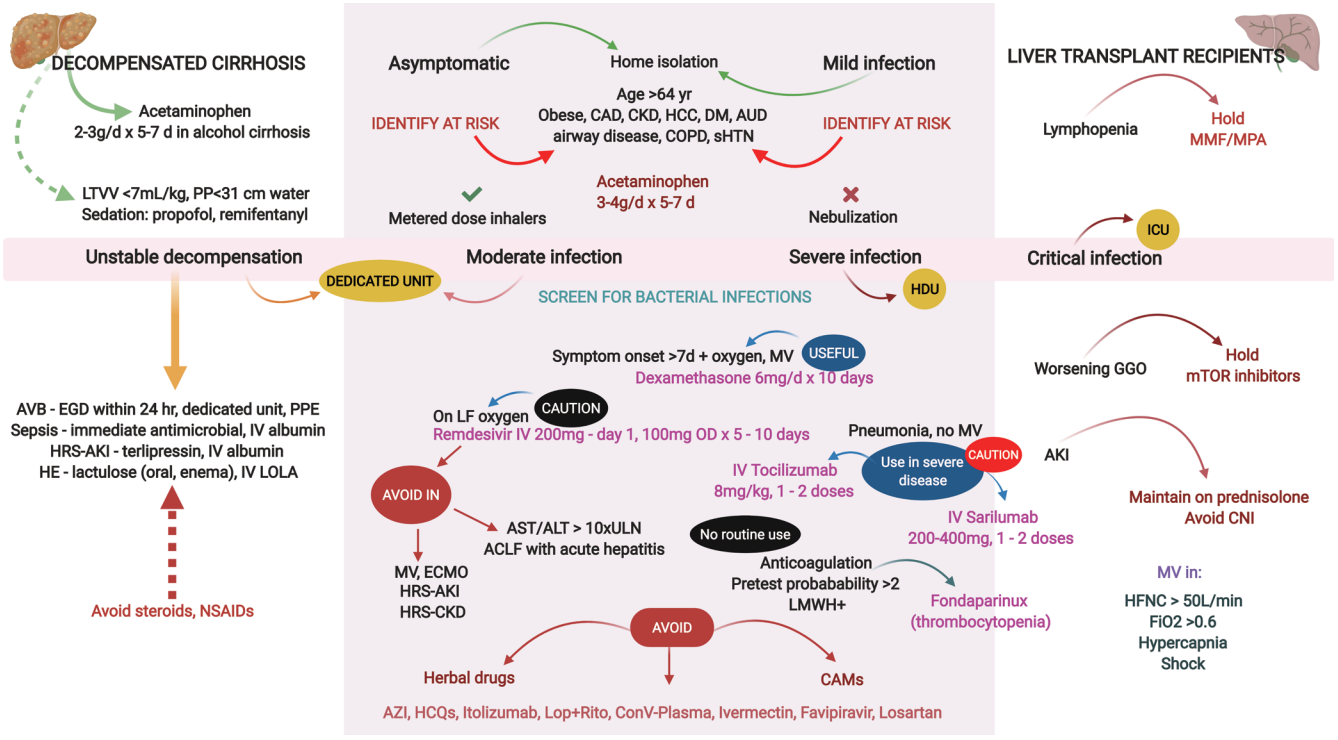

Fig. 3. Current updates in the management of COVID-19 in patients with decompensated cirrhosis and liver transplant recipients. As per published literature, the general management of COVID-19 is shown in the middle panel, while specific considerations for the management of decompensated cirrhosis patients and liver transplant recipients is shown in the left and right panels, respectively. It is pertinent to note that the use of remdesivir for COVID-19 is not recommended by the WHO or real-world data, but feature in guidelines released by certain governments and its use is subject to treating physician discretion. AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; AVB, acute variceal bleeding; AZI, azithromycin; CAD, coronary artery disease; CAM, complementary and alternative medicines; CKD, chronic kidney disease; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; EGD, esophago-gastro-duodenoscopy; FiO2, fraction of inspired oxygen; GGO, ground glass opacity; LOLA, L-ornithine-L-aspartate; HCC, hepatocellular carcinoma; HCQs, hydroxychloroquine; HDU, high-dependency unit; HE, hepatic encephalopathy; HFNC, high-flow nasal cannula; HRS, hepatorenal syndrome; ICU, intensive care unit; IV, intravenous; LF, low-flow; LMWH, low molecular weight heparin; Lop, lopinavir; MMF, mycophenolate mofetil; mono-Abs, monoclonal antibodies; MPA, mycophenolic acid; mTOR, mechanistic target of rapamycin; MV, mechanical ventilation; NSAIDS, non-steroidal anti-inflammatory drugs; PP, partial pressure; Rito, ritonavir; sHTN, systemic hypertension; ULN, upper limit of normal.

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