

# Liver Disease and Coronavirus Disease 2019: From Pathogenesis to Clinical Care

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Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus that emerged in late 2019, is posing an unprecedented challenge to global health. Coronavirus disease 2019 (COVID-19), the clinical disease caused by SARS-CoV-2, has a variable presentation ranging from asymptomatic infection to life-threatening acute respiratory distress syndrome and multiorgan failure. Liver involvement is common during COVID-19 and exhibits a spectrum of clinical manifestations from asymptomatic elevations of liver function tests to hepatic decompensation. The presence of abnormal liver tests has been associated with a more severe presentation of COVID-19 disease and overall mortality. Although SARS-CoV-2 RNA has been detected in the liver of patients with COVID-19, it remains unclear whether SARS-CoV-2 productively infects and replicates in liver cells and has a direct liver-pathogenic effect. The cause of liver injury in COVID-19 can be attributed to multiple factors, including virus-induced systemic inflammation, hypoxia, hepatic congestion, and drug-induced liver disease. Among patients with cirrhosis, COVID-19 has been associated with hepatic decompensation and liver-related mortality. Additionally, COVID-19's impact on health care resources can adversely affect delivery of care and outcomes of patients with chronic liver disease. Understanding the underlying mechanisms of liver injury during COVID-19 will be important in the management of patients with COVID-19, especially those with advanced liver disease. This review summarizes our current knowledge of SARS-CoV-2 virus-host interactions in the liver as well the clinical impact of liver disease in COVID-19. (HEPATOLOGY 2021;0:1-13).

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was officially declared a pandemic by the World Health Organization in March 2020. COVID-19 has a variable presentation ranging from an asymptomatic illness to severe pneumonia with acute respiratory distress syndrome, accompanied by multiorgan failure, shock, and severe thromboembolic events. The most common clinical features reported among patients who were symptomatic include fever, dry cough, shortness of breath, anosmia and ageusia, and diarrhea.

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses belonging to the *Coronaviridae*

family, responsible for mild upper respiratory and gastrointestinal tract infections in humans. Two emerging members of the *Coronaviridae* family were previously demonstrated to pose a major public health threat, namely the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle Eastern respiratory syndrome coronavirus (MERS)-CoV. In December 2019, the first cases of viral pneumonia caused by a novel coronavirus (SARS-CoV-2) was reported. Over the ensuing months, the virus has rapidly spread globally, resulting in over 50 million infected persons and one million deaths, exceeding other major infectious causes of death worldwide.

*Abbreviations: ACE2, angiotensin-converting enzyme 2; ACLF, acute-on-chronic liver failure; AST, aspartate aminotransferase; CLD, chronic liver disease; COVID-19, coronavirus disease 2019; E, envelope; ER, endoplasmic reticulum; FDA, U.S. Food and Drug Administration; ICU, intensive care unit; LFT, liver function test; M, membrane; nsp, nonstructural protein; ORF, open reading frame; S, spike; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane protease serine subtype 2.*

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Considering the worldwide spread, high mortality rate, and reports of long-term sequelae, such as persistent organ damage (in particular cardiac, renal, and neurological), among recovered individuals, there is an urgent need for an effective vaccine and efficient antiviral therapies. Here, we provide a state-of-the-art review of virus-host cell interactions in the liver, liver manifestations in COVID-19 disease, mechanisms of COVID-19-related liver injury, and perspectives for potential intervention.

## SARS-CoV-2 Virus-Host Cell Interactions and the Human Liver

SARS-CoV-2 is an enveloped, positive-sense RNA virus with a large genome of about 30 kbp coding for 16 nonstructural proteins (nsp) and 4 structural proteins. The main surface glycoprotein, the spike (S) protein, is responsible for the interaction with the primary host receptor, the angiotensin-converting enzyme 2 (ACE2)<sup>(1,2)</sup> (Fig. 1-1) and the recently identified coreceptor neuropilin-1.<sup>(3,4)</sup> Together with the transmembrane protease serine subtype 2 (TMPRSS2), which primes the S-protein for virus-host cell fusion

(Fig. 1-2), these proteins are thought to be responsible for SARS-CoV-2 cell tropism.<sup>(1)</sup> Additionally, as the main surface glycoprotein, the S-protein is also the primary target for neutralizing antibodies<sup>(5)</sup> and presents an attractive target for vaccines and antiviral strategies (Fig. 1).

Following viral cell entry (Fig. 1-3) either at the plasma membrane or via the endosomal route, the viral genome is released into the cytoplasm and can directly serve as a template for protein translation (Fig. 1-4). About two-thirds of the 30 kbp genome are encompassed by the first 2 open reading frames (ORFs) coding for 2 large polyproteins that are post-translationally cleaved into the 16 nsp that form the viral replication complex (Fig. 1-4 and 1-5). The last third of the genome encodes the four main structural proteins, including the S-protein, envelope (E), nucleocapsid (N), and membrane (M) proteins, and several accessory proteins whose functions are potentially involved in immune modulation.<sup>(6)</sup> Three of the four structural proteins, S, M, and E are translated into the endoplasmic reticulum (ER), whereas the N protein is translated in the cytoplasm, where it interacts with the viral genomic RNA to form the viral ribonucleoprotein (vRNP) (Fig. 1-7). The vRNPs and the other three structural proteins, S, M, and E, autoassemble into viral particles at the ER-Golgi-intermediate-complex

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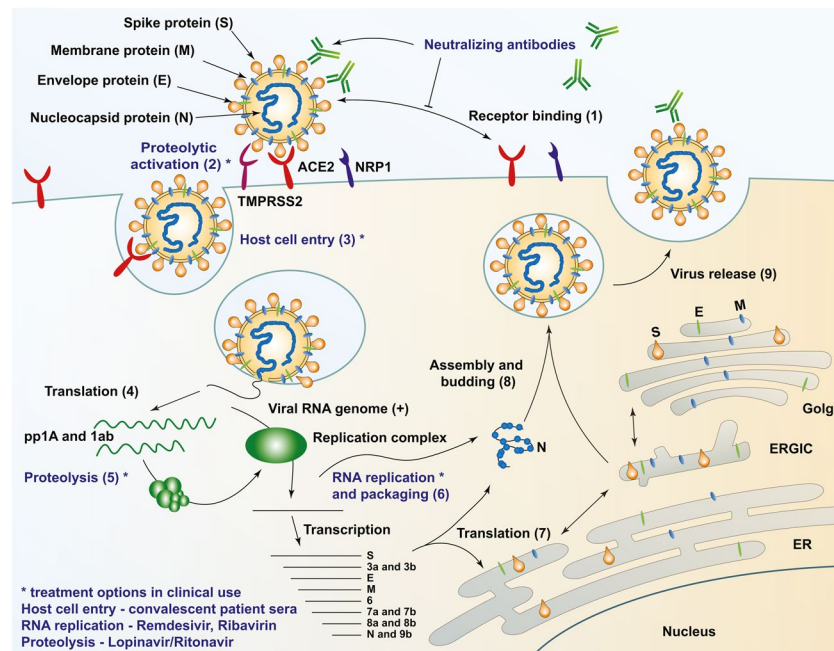
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**FIG. 1.** Model of the SARS-CoV-2 life cycle in infected host cells of human patients. Following binding to the ACE2 receptor and the coreceptor (1) neuropilin-1 (NRP1) and priming by (2) TMPRSS2, SARS-CoV-2 enters the host cell, where (3) the viral RNA is released into the cytoplasm. ORFs 1a and 1ab are then directly translated into (4) large polyproteins, which, following (5) proteolytic cleavage, form the replication complex. (6) A negative-sense viral RNA is synthesized and used as template to form the positive-sense viral genome and the individual mRNAs. (7) The nucleocapsid protein is translated in the cytoplasm, whereas spike, membrane, and envelope proteins are translated in the ER and transported to the Golgi. Viral particles containing RNA-nucleocapsid complexes, spike, and envelope proteins (8) assemble at the ERGIC and (9) are subsequently released from the host cells. Current treatment options target different stages of the viral life cycle. Virus entry can be blocked by the recently FDA-approved therapy with convalescent patient sera. Proteolysis of the viral polyproteins is inhibited by the HIV-protease inhibitors lopinavir/ritonavir, whereas replication can be targeted by the nucleotide-analogue remdesivir. Targets and compounds for antiviral therapy are marked in blue. Abbreviations: ERGIC, ER-Golgi-intermediate-complex; pp, polyprotein.

(Fig. 1-8) and are subsequently released from the cells (Fig. 1-9).

Replication of the SARS-CoV-2 genome by the viral replication complex is carried out using a negative sense template and a double-strand intermediate, similarly to other positive-sense viruses (Fig. 1). Viral replication takes place in double membrane vesicles (DMVs) derived from the ER.<sup>(7)</sup> These DMVs are largely devoid of pattern recognition receptors, such as retinoic acid inducible gene I (RIG-I), nucleotide-binding oligomerization domain-containing proteins (NOD)s, and C-type lectin receptors, which might shield the viral RNA from detection by the innate immune system.<sup>(8)</sup> Additionally, several proteins of SARS-CoV, including nsp1, nsp3, ORF3b, ORF6, and ORF9, have been shown to directly counteract the innate immune response by several different mechanisms,<sup>(9)</sup> facilitating viral replication during

early stages of COVID-19. It is of interest to note that many of these processes are similarly used by other viruses and therefore provide targets for approved antiviral therapies against other viruses. An example is the proteolytic cleavage of the polyproteins targeted by the HIV protease inhibitors lopinavir and ritonavir (Fig. 1). Additionally, viral replication appears to be inhibited by remdesivir, which is a prodrug that is intracellularly transformed into a ribonucleotide inhibitor of the viral RNA polymerase. Following extensive clinical testing with more than 70,000 patients, treatment with convalescent patient plasma targeting the viral envelope has received emergency use authorization for clinical use as a COVID-19 treatment by the U.S. Food and Drug Administration (FDA) (<https://www.fda.gov/media/141480/download>) and is currently in use for severe forms of COVID-19. The FDA also issued emergency use authorizations

for bamlanivimab (<https://www.fda.gov/media/143602/download>), and the combination of casirivimab and imdevimab (<https://www.fda.gov/media/143891/download>), neutralizing monoclonal antibodies targeting the receptor binding domain of the S-protein.

The primary point of entry for SARS-CoV-2 infection is the respiratory tract. The main cells infected by SARS-CoV-2 infection are nasal goblet cells and type II pneumocytes.<sup>(10)</sup> However, the SARS-CoV-2 receptor, ACE2, is also expressed in epithelial cells of the small and large intestine, arterial and venous endothelial cells, cardiomyocytes, and arterial smooth muscle cells.<sup>(10)</sup> Indeed, viral RNA has been detected by *in situ* hybridization in different tissues outside of the respiratory tract, including heart, kidney, liver, gut, brain, and blood, which coincides with host factor expression.<sup>(11)</sup> Additionally, viral RNA has been isolated from saliva and stool.<sup>(12)</sup> These findings together with the clinical manifestations suggest that SARS-CoV-2 also infects cells outside the respiratory tract.

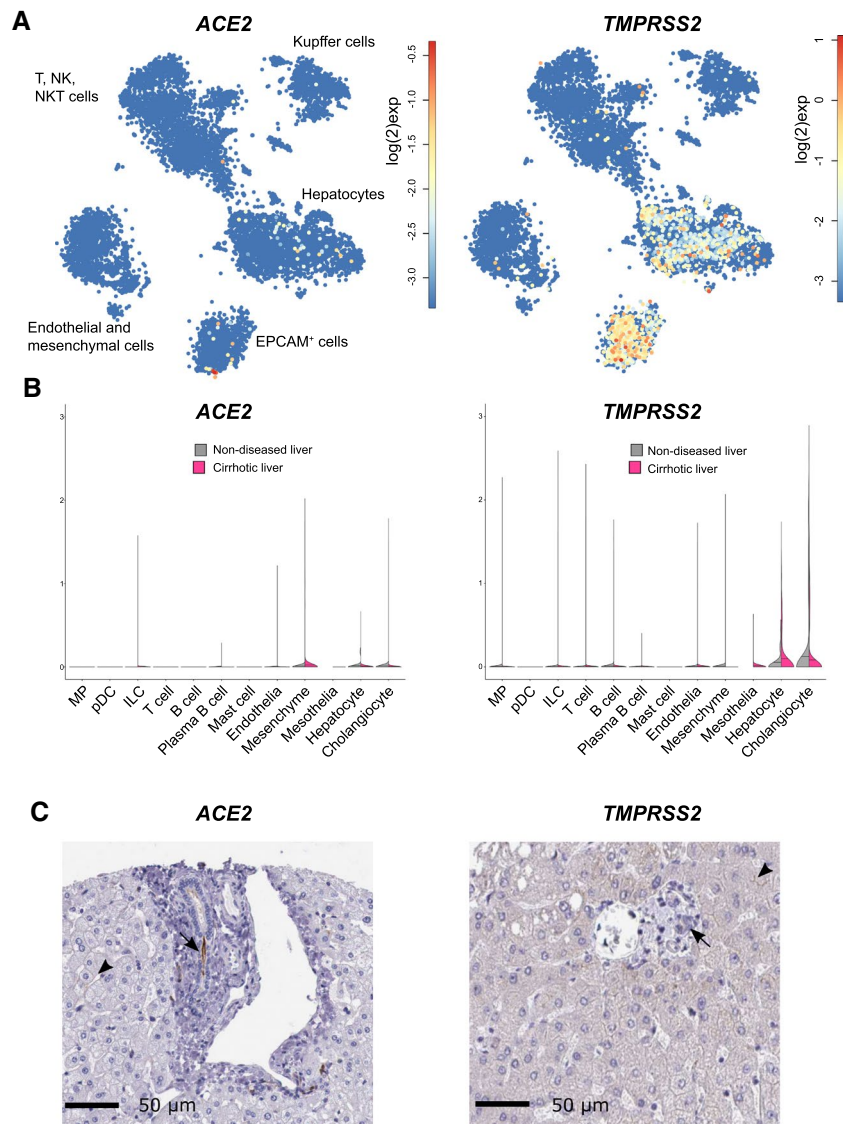
COVID-19 can rapidly progress to multiorgan dysfunction or failure with high fatality rates. The progression from mild to severe forms of COVID-19 is associated with a dysregulated immune response, responsible for uncontrolled viral replication and cellular damage leading to additional inflammation and immune-mediated damage of tissues and organs. Many of the released inflammatory cytokines are known to be key players of inflammation related injury of other organs, including the liver. Furthermore, anti-SARS-CoV-2-S IgGs from patients who are severely ill with COVID-19 have been shown to induce macrophage hyperinflammatory responses,<sup>(13)</sup> and anti-SARS-CoV-S antibodies were shown to cause acute lung injury in mice by skewing macrophage responses during acute infection.<sup>(14)</sup> However, it is not clear whether these findings are clinically relevant, given the encouraging results of convalescent plasma therapy.<sup>(15)</sup> The inflammatory responses in these cases were mediated via FcγRII and FcγRIII receptors,<sup>(13)</sup> which are present on nonpulmonary macrophages, such as liver-resident Kupffer cells, providing another route by which the immune system might contribute to COVID-19 pathogenesis of the lung and other organs.

Whether the SARS-CoV-2 productively infects liver cells remains to be determined. Several studies

observed the presence of viral RNA in the liver of severe COVID-19 cases.<sup>(11)</sup> Expression data in the human liver cell atlas<sup>(16)</sup> demonstrated that the ACE2 receptor and TMPRSS2 protease are expressed in the liver, mainly on cholangiocytes and at lower levels on hepatocytes, indicating that SARS-CoV-2 may enter into parenchymal cells (Fig. 2). Supporting this concept, SARS-CoV-2 can enter and replicate in liver organoids<sup>(17)</sup> and in the HCC cell line Huh7.<sup>(18)</sup> However, although viral particles and viral RNA have been detected within hepatocytes,<sup>(19)</sup> the bona fide proof for productive infection of primary liver cells by SARS-CoV-2 via remains to be demonstrated.

## Prevalence and Manifestations of Liver Injury in COVID-19

Liver injury as defined by elevated serum aminotransferase levels has been reported following infection with other coronaviruses, such as severe acute respiratory syndrome and MERS.<sup>(20,21)</sup> Among patients who are hospitalized with symptomatic COVID-19 disease, abnormal liver function tests (LFTs) are common, ranging from 14% to 53%. The most common observed abnormalities are hypoalbuminemia, elevated  $\gamma$ -glutamyltransferase ( $\gamma$ GT), mild elevation of aminotransferases, and hyperbilirubinemia.<sup>(22-26)</sup> Multiple studies have reported a correlation between COVID-19 severity and LFT abnormalities, with elevated aminotransferase levels being more frequent in intensive care unit (ICU) inpatients and patients requiring ventilation.<sup>(27-29)</sup> The pattern of liver injury is typically hepatocellular rather than cholestatic.<sup>(30,31)</sup> The aspartate aminotransferase (AST) levels correlate highly with alanine aminotransferase levels throughout the course of the illness, suggesting a hepatocellular origin.<sup>(32)</sup> Notably, the prevalence of elevated AST was substantially higher among patients with severe COVID-19 disease (45.5%) compared with those with mild disease (15.0%). In severe COVID-19 cases, hypoalbuminemia is common and correlates with worse patient outcomes.<sup>(25)</sup> Additionally, increased bilirubin levels and liver stiffness measured by transient



**FIG. 2.** Expression of SARS-CoV-2 cell entry factors ACE2 and TMPRSS2 in the human liver assessed by single-cell RNA sequencing (RNASeq) and immunohistochemistry. (A) Expression t-distributed stochastic neighbor embedding (t-SNE) maps of ACE2 and TMPRSS2 in the nondiseased human liver. The color bar indicates log<sub>2</sub> normalized expression (n = 10,372 cells) retrieved by data processing from the human liver cell atlas.<sup>(16)</sup> The y-axis shows log<sub>2</sub> normalized expression. (B) Violin plots of scaled gene expression data of ACE2 and TMPRSS2 in liver cell subsets of patients with and without cirrhosis from <https://www.livercellatlas.mvm.ed.ac.uk/>.<sup>(73)</sup> (C) Immunohistochemistry staining of ACE2 and TMPRSS2 of nondiseased livers showing protein expression in cholangiocytes (arrows) and hepatocytes (arrowheads). Data and images from <https://www.proteinatlas.org/>.<sup>(74)</sup> Abbreviations: EPCAM, epithelial cell adhesion module; ILC, innate lymphoid cell; NK, natural killer cell; NKT, natural killer T cell; NP, mononuclear phagocytic cell; pDC, plasmacytoid dendritic cell.

elastography were found to be associated with more severe outcomes.<sup>(33,34)</sup>

Although informative, these studies were limited by the fact that LFT abnormalities were not consistently reported across studies and the proportion of patients with underlying chronic liver diseases (CLD) was rarely provided. Although LFT abnormalities are frequently observed and shown to correlate with

mortality, acute liver failure is extremely rare among patients with COVID-19 without underlying CLD and is more typically associated with severe pneumonia and multiorgan dysfunction.<sup>(35,36)</sup> The prevalence of abnormal LFTs among asymptomatic patients with SARS-CoV-2 infection is unknown.

The liver plays an important role in regulating immune homeostasis. Patients with CLD,

particularly those with cirrhosis, may have dysregulated innate and acquired immunity and may therefore be at higher risk of acquiring SARS-CoV-2, COVID-19–related complications, and death.<sup>(37)</sup> However, current evidence shows no enrichment of patients with CLD, the prevalence being 3%, suggesting no increased susceptibility to infection in this population.<sup>(38)</sup> Nevertheless, patients with CLD may be at higher risk of developing more severe COVID-19 and higher mortality compared with those without CLD. Indeed, a large study including 2,780 patients with COVID-19 that compared the outcomes among those with and without CLD reported that patients with CLD were at ~3-fold higher risk for mortality compared with patients without CLD, and this risk was markedly higher in patients with cirrhosis (~5-fold).<sup>(39)</sup>

## Histopathological Findings

The most common histopathological findings observed on liver biopsies from patients with COVID-19 are moderate macrovesicular steatosis and mild lobular and portal inflammation.<sup>(40,41)</sup> Features of acute hepatitis, defined as presence of lobular inflammation, were present in 50% of cases but were generally mild. No bile duct or vascular injury was noted, and liver tissue showed mostly chronic changes associated with patients' pre-existing comorbidities and a variable degree of acute congestion. Interestingly, viral RNA by PCR was found in the liver in up to 55% of cases.<sup>(41,42)</sup> In a series of 48 postmortem wedge biopsies of patients who died of severe pulmonary COVID-19, partial or complete sinusoidal thrombosis was also observed.<sup>(43)</sup> Finally, electron microscopy of two postmortem liver samples identified coronavirus-like particles in hepatocytes together with mitochondrial swelling, ER dilatation, and massive hepatic apoptosis.<sup>(19)</sup> However, no immunolabeling of these particles was performed, raising concerns as to the specificity of these particles in postmortem autolyzed samples.<sup>(44)</sup> In summary, based on current knowledge, most liver-related pathological findings appear to be related to underlying comorbidities such as NAFLD or ICU care rather than because of SARS-CoV-2.

# COVID-19 in Special Populations With Liver Disease

## CIRRHOSIS

Patients with cirrhosis have an increased risk of liver decompensation and acute-on-chronic liver failure (ACLF) following viral infection, such as influenza.<sup>(45)</sup> Whether the same is true for patients with cirrhosis with SARS-CoV-2 remains to be determined. SARS-CoV-2 infection in patients with cirrhosis was associated with worsening Model for End-Stage Liver Disease (MELD) score, ACLF, and death.<sup>(46)</sup> A study comparing hepatic liver-related outcomes between 185 patients without cirrhosis but with CLD and 43 patients with cirrhosis of mostly metabolic and viral etiology observed a higher rate of severe liver injury and death with more advanced stage of liver disease following SARS-CoV-2 infection, especially in patients with Child-Pugh score of  $\geq 9$ .<sup>(47)</sup> Twenty percent of patients with cirrhosis developed either ACLF or acute decompensation. Moreover, mortality was significantly higher among patients with cirrhosis with COVID-19 compared with a control group with cirrhosis who were admitted for bacterial infections.<sup>(46,48)</sup> However, a U.S. multicenter study that compared inpatient mortality among patients with cirrhosis with or without COVID-19 with a matched control group with COVID-19 without cirrhosis also reported a higher mortality among patients with COVID-19 with underlying cirrhosis compared with those without cirrhosis (30% vs 13%, respectively) but similar mortality between the two groups with cirrhosis (30% vs. 20%, respectively).<sup>(49)</sup> Interestingly, the Charlson Comorbidity Index, a score of prognostic comorbidities, was the only independent mortality predictor in patients with cirrhosis, suggesting an important role of multiple comorbidities in determining the severity of COVID-19.<sup>(49)</sup> Thus, patients with cirrhosis who contract SARS-CoV-2 infection may be at greater risk for COVID-19 and liver-related mortality, but it remains to be determined if their mortality is higher compared with patients with cirrhosis who acquire other viral or bacterial infections. Initial data on patients with COVID-19 and cirrhosis from the COVID-Hep (<https://covid-hep.net>)

registry showed that lung disease and liver-related death accounted respectively for 78.7% and 12.2% of causes.<sup>(46)</sup> Mortality strongly correlated with baseline liver function and was up to 43.3% in patients with Child-Pugh class B cirrhosis and 63% in patients with Child-Pugh class C.<sup>(46)</sup>

## HEPATITIS B

Lymphopenia induced by SARS-CoV-2 may trigger HBV reactivation in patients who are coinfecting with SARS-CoV-2/HBV. However, this appears to be rare occurrence, with only a single case report of a patient with possible HBV reactivation.<sup>(50)</sup> The limited evidence suggests that chronic HBV infection is not associated with worse outcomes compared with those without HBV infection.<sup>(51,52)</sup>

## NAFLD

NAFLD has been reported to be associated with more severe COVID-19 disease (~4-fold increased risk) and prolonged duration of viral shedding.<sup>(53)</sup> A multicenter retrospective study from the United States reported a higher risk of ICU admission and need for mechanical ventilation but not overall mortality among patients with CLD primarily caused by NAFLD.<sup>(54)</sup> In addition, among younger patients (<60 years), the presence of NAFLD was shown to be associated with >2-fold higher prevalence of severe illness.<sup>(55,56)</sup> The risk of severe COVID-19 increases with the number of metabolic risk factors present, such as obesity or diabetes. Although obesity, arterial hypertension, diabetes, and cardiovascular diseases are common in patients with NAFLD, they are also independent risk factors for severe COVID-19 disease.<sup>(29,56,57)</sup> It has been challenging to separate NAFLD from these known metabolic risk factors for severe COVID-19; however, the available evidence suggests that NAFLD is an independent risk factor for severe COVID-19. Most studies have not distinguished between NAFLD and its more severe form, NASH. Thus, whether the more severe outcomes are predominantly in patients with NASH remains to be determined.

## LIVER TRANSPLANTATION

Liver transplant recipients are also a special population who may have an increased risk for COVID-19 and a more severe clinical course because of the need

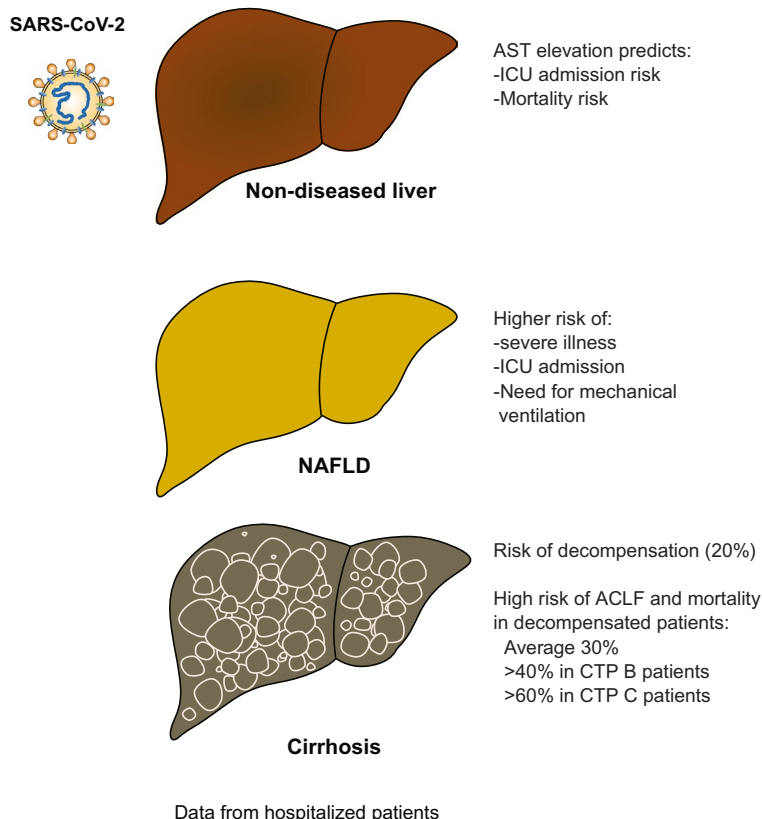
for immunosuppressive medications. An Italian study reported a negative impact of COVID-19 on the postoperative transplant course, especially in patients who are older or obese with comorbidities.<sup>(58)</sup> A prospective study from Spain observed that recipients of liver transplants have an increased risk of SARS-CoV-2 infection but lower mortality compared with a matched general population.<sup>(2)</sup> Among immunosuppressive treatments, only mycophenolate treatment was an independent risk factor for severe COVID-19 (almost 4-fold increased risk).<sup>(2)</sup> However, because of the small number of patients included in these studies, further analyses are needed to determine the impact of COVID-19 on the outcome of liver transplantations.

In summary, chronic comorbidities, such as cardiovascular diseases, kidney diseases, diabetes, and cirrhosis, are associated with higher mortality and more severe course of COVID-19.<sup>(59)</sup> Despite the low quality of the data (retrospective studies), the heterogeneous prevalence of cirrhosis, type of CLD (i.e., higher or lower prevalence of NAFLD), and the cohort type (patients who are outpatient, inpatient, or in ICU), data on patients with CLD suggest that patients with NAFLD have an increased risk of severe COVID-19, a risk that is independent from features of the metabolic syndrome. Importantly, patients with cirrhosis have a high risk of mortality and ACLF even though the mortality rate of patients with COVID-19 and cirrhosis appears to be comparable with patients with cirrhosis with any other systemic infection (Fig. 3).

# Mechanisms of Liver Injury in COVID-19

## DIRECT CYTOTOXICITY

Current data suggest that liver injury in COVID-19 is most likely mediated by systemic inflammation rather than direct cytopathic effect of viral infection of liver cells. Although viral particles and RNA can be detected in liver tissue of patients with COVID-19, productive infection of primary liver cells has yet to be demonstrated. The low prevalence of clinically significant liver injury in patients without CLD suggests that direct infection of hepatocytes or cholangiocytes is unlikely to be a major mechanism of liver injury.



**FIG. 3.** COVID-19–related liver injury and mortality in patients who were hospitalized with and without chronic liver disease (CLD). Patients without CLD usually present with AST elevation, which correlates with ICU admission and mortality. Among patients with CLD, NAFLD has the highest risk of severe illness, ICU admission, and need for mechanical ventilation.<sup>(54,56)</sup> Patients with cirrhosis are at risk for decompensation, and patients who are decompensated have a high risk of acute-on-chronic liver failure (ACLF) and mortality.<sup>(46-49)</sup> Abbreviations: CTP, Child-Turcotte-Pugh; ICU, intensive care unit.

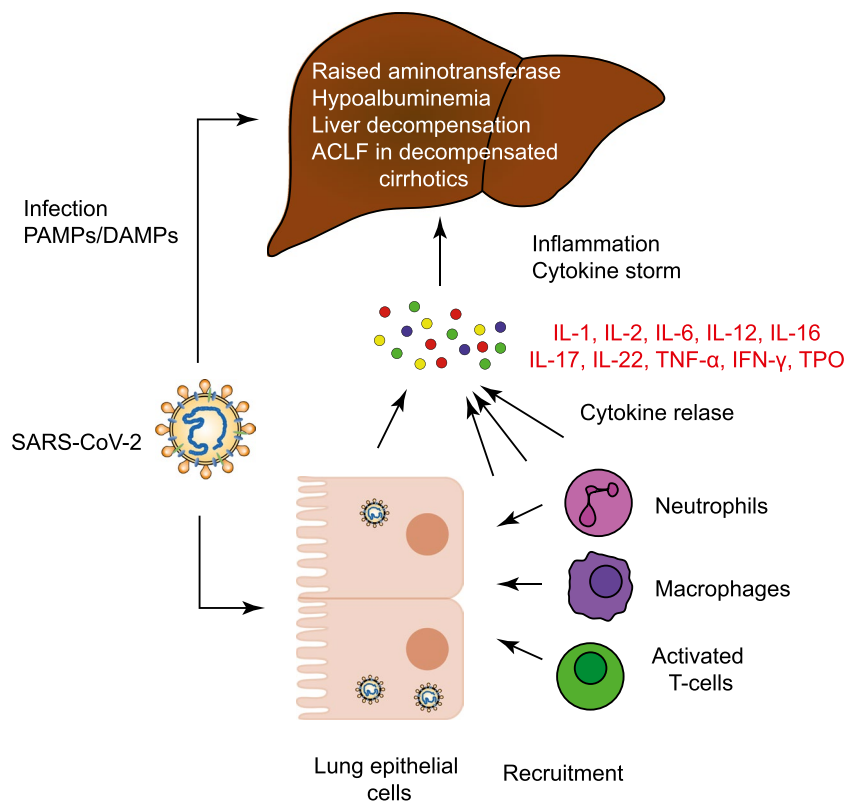
## IMMUNE-MEDIATED LIVER INJURY

Liver injury is more common in severe forms of COVID-19. The human antiviral response is mediated by the innate and acquired immune systems, which recognize pathogen-associated molecular patterns and specific viral antigens, release inflammatory molecules, such as cytokines and chemokines, and activate macrophages and T cells to clear the virus and kill virus-infected cells.<sup>(60)</sup> In all patients with COVID-19, higher levels of several inflammatory cytokines have been observed.<sup>(61,62)</sup> Severe forms of COVID-19 and worse outcomes are more common in patients with early cytokine elevation that does not decline over the course of the disease.<sup>(61)</sup> Patients with severe COVID-19 had lower

levels of stromal growth factors (e.g., EGF) mediating tissue healing and repair and higher levels of proinflammatory type 1 cytokines, type 2 cytokines mediating antihelminthic effects, and type 3 cytokines activating mononuclear macrophages, recruiting neutrophils, and inducing epithelial antimicrobial responses.<sup>(61)</sup> Patients with the worst outcomes exhibited increased levels of interferon- $\lambda$ , TGF- $\alpha$ , thymic stromal lymphopoietin (TSLP), IL-16, IL-23, and IL-33, and markers linked to coagulopathy, such as thrombopoietin.<sup>(61)</sup>

In summary, severe COVID-19 and ACLF in patients with cirrhosis share similar pathophysiological mechanisms involving systemic inflammation and early massive cytokine release that do not regress over the disease course and trigger multiorgan failure (Fig. 4).





**FIG. 4.** Current understanding of mechanisms of liver injury in COVID-19. Following SARS-CoV-2 infection of lung epithelial cells, immune cells such as T cells, macrophages, and neutrophils are recruited to the site of infection and cause local inflammation. In severe cases, local inflammation can spill over to global circulation, inducing a massive release of cytokines that can affect other organs, including the liver. Additionally, SARS-CoV-2 can potentially induce local inflammation in the liver, either by activating liver-resident immune cells or by directly infecting hepatocytes and other liver cells. Mostly, COVID-19 only results in raised aminotransferases and in some cases mild hypoalbuminemia, but in the most severe cases, it can lead to liver decompensation, which can result in potentially fatal ACLF.<sup>(22,36,47,75)</sup> Abbreviations: ACLF, acute-on-chronic liver failure; DAMP, damage-associated molecular pattern; IFN, interferon; PAMP, pathogen-associated molecular pattern; TPO, thrombopoietin.

## LIVER INJURY RELATED TO COVID-19 CLINICAL CARE

### Hypoxic Liver Injury/Hepatic Congestion

Patients with severe forms of COVID-19 are frequently admitted to the ICU and require mechanical ventilation and/or vasopressor support, which alters liver hemodynamics and adversely affects hepatic function by decreasing cardiac output, increasing hepatic vascular resistance and portal vein pressure, and reducing portal and arterial blood flow. This may result in acute liver injury and/or cholestasis.

### Drug-Induced Liver Disease

DILI is likely an important cause of liver injury in patients who are hospitalized with COVID-19.

A recent meta-analysis reported a pooled incidence of DILI of 25.4% in patients with COVID-19.<sup>(24)</sup> DILI was reported in 15.2% of patients treated with remdesivir and in 37.2% of patients treated with lopinavir/ritonavir.<sup>(24)</sup> Furthermore, immunosuppressive drugs, such as tocilizumab, tofacitinib, and dexamethasone, used for the treatment of severe COVID-19 can potentially induce liver injury via HBV reactivation in patients with occult infections.<sup>(63,64)</sup> Despite these concerns, randomized controlled clinical trials testing the safety and efficacy of remdesivir and tocilizumab in patients with COVID-19 did not reveal any significant difference in the prevalence of liver injury in the treatment compared with the placebo groups.<sup>(65,66)</sup> Finally, antibiotics and nonsteroidal anti-inflammatory drugs, which are the most common causes of DILI in the general population, can also contribute to

liver damage in patients with COVID-19 when used to treat bacterial superinfection, myalgias, or fever.

## IMPACT OF REALLOCATION OF HEALTH CARE RESOURCES

The ongoing COVID-19 pandemic has placed replace with substantial strain on health care services worldwide. Social distancing, city lockdowns, limited access to both primary and tertiary health care centers, and the postponement of all nonurgent diagnostic tests or treatments will have a long-term impact on liver disease mortality. Data from Iran during the first SARS-CoV-2 outbreak (first quarter of 2020) showed a reduced rate of hospital admission for liver-related morbidities, with admitted patients presenting with higher MELD scores and longer hospital stays as compared with 2019.<sup>(67)</sup> This observation suggests that patients with CLD had reduced access to hospital care, which was mostly restricted to those with more advanced liver disease. HCC screening in patients with cirrhosis is associated with reduction in HCC mortality.<sup>(68)</sup> Restricted access to health care services during the SARS-CoV-2 pandemic might lead to excess HCC mortality in the next future.<sup>(69)</sup> Endoscopic procedures are considered high risk for SARS-CoV-2 transmission, leading to deferral of prophylactic screening and treatment of esophageal varices, which could result in higher risk of variceal bleeding. Social distancing and lockdown strategies have had an impact on patients' mental health and resulted in alcohol abuse and relapse of alcohol addiction. This can induce or aggravate alcohol use disorders and alcohol-associated CLD and liver failure and can restrict access to liver transplantation.<sup>(70)</sup> The SARS-CoV-2 pandemic has led to a significant contraction in organ donation and liver transplantations performed ranging from 25% in the United States, to 80% in the United Kingdom, and India during the first infection wave.<sup>(71)</sup> Last but not least, the COVID-19 pandemic is also impacting the efforts to eliminate viral hepatitis worldwide. Mathematical models estimate an excess mortality of 44,800 for HCC and 72,300 for liver-related deaths with a 1-year delay of HCV treatment administration.<sup>(72)</sup>

## Summary and Conclusions

The presence of liver injury is a surrogate marker for more severe disease and higher mortality in patients with COVID-19. An elevated AST level is the most robust predictor of poor outcome. Although SARS-CoV-2 particles and RNA have been detected in tissue samples from patients with COVID-19 and viral entry factors are expressed on hepatocytes and cholangiocytes in the liver, it remains unclear whether the virus can productively infect liver cells. Rather, liver injury and mortality in COVID-19 are likely multifactorial, driven by a sustained and excessive systemic release of proinflammatory and prothrombotic cytokines following SARS-CoV-2 infection, iatrogenic injury caused by DILI, hemodynamic changes associated with mechanical ventilation or vasopressor use, and worsening of underlying liver injury in those with CLD. Risk of *de novo* liver injury appears limited in patients without CLD, and only rare cases of COVID-19-related ACLF were observed. Among patients with CLD, those with NAFLD show an increased risk of severe illness, ICU admission, and need of mechanical ventilation independently of other comorbidities, such as hypertension, obesity, diabetes, and cardiovascular diseases. Patients with cirrhosis and COVID-19 and especially patients with decompensated cirrhosis experienced a high mortality (up to 60%) comparable with patients with cirrhosis and ACLF mediated by infection or systemic inflammation (Fig. 3). Importantly, although patients with liver transplantations have higher risk of contracting the disease, the mortality is lower as compared with the general population, even though mycophenolate treatment has been suggested as an independent risk factor for severe COVID-19. Finally, health care providers should be aware that the SARS-CoV-2 pandemic may have profound, unexpected short- and long-term effects on mortality from liver disease by limited access to health care services for HCV treatment, limited HCC screening, limited endoscopic management of esophageal varices, decreased liver transplant donor pool, and increased alcohol-associated liver disease caused by the psychological effects of social distancing and isolation resulting from efforts to prevent virus transmission.

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