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# COVID-19-induced liver injury in adult patients: a brief overview

COVID-19-induced liver injury

Martina Grando, Massimiliano Balbi, Marco Zeppieri

**Abstract**

Coronavirus disease has spread worldwide since 2019, causing important pandemic issues and various social health problems to date. Little is known about the origin of this virus and the effects it has on extra-pulmonary organs. The different mechanisms of the virus and influence it has on humans are still being studied in order to find a cure for the disease and the pathologies associated with the infection. Liver damage caused by coronavirus 2019 (COVID-19) is an element that is sometimes underestimated and has been of important clinical interest in the past few years. Hepatic dysfunctions can manifest in different forms, which can sometimes be mild and not have non-specific signs or symptoms or be severe with important clinical implications. There are several studies that have tried to explain the mechanism of entry (hepatotropism) of the virus into hepatocytes and the effects the virus has on this important organ. What clearly emerges from current literature is that hepatic injury represents an important clinical aspect in the management of patients infected with COVID-19, especially in frail patients and those with comorbidities. The aim of our brief overview is to summarize the current literature regarding the forms of hepatic damage, complications, mechanisms of pathology, clinical features of liver injury, influence of comorbidities and treatment in patients with COVID-19 infection.

**Key Words:** Coronavirus 2019 **(**COVID-19); Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Hepatotropism; Hepatic injury; Cirrhosis; Cytokine storm; Angiotensin-Converting Enzyme 2 (ACE2)

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**Core Tip:** Liver damage can occur in patients infected by COVID-19. The organ damage can be due to various mechanisms such as direct infection, immune injury, drug-induced, hypoxia, or inflammation response. It is of clinical importance to manage

hepatic damage in COVID-19-positive patients. Patient outcomes, the success of therapy, prevention of life-threatening complications, and management of existing comorbidities depend on proper organ functioning.

## INTRODUCTION

In December of 2019, a new RNA virus in humans was reported in China, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This viral infection has spread quickly throughout the world ever since the first outbreak. The virus causes coronavirus disease 2019 (COVID-19), which has had a great global impact on health worldwide [1]. SARS-CoV-2 started as a zoonotic infection, but currently also affect humans. The disease propagates quickly between humans via air droplets, sneezing, and coughing, especially amongst people that are in close contact with each other. Studies have also shown the possibility of fecal-oral transmission [2]. The majority of SARS-CoV-2 infected patients can be without symptoms or present with mild disturbances, which range from coughing, fever, headache, anosmia, etc. About 15% of cases, however, can show severe pulmonary disease leading to respiratory compromise which can progress to multiorgan failure, coagulopathy, and death [3-5]. Common risk factors for severe disease progression include male gender, the elderly, and coexisting comorbidity that range from heart disease, tumors, diabetes, hypertension, etc [6,7].

The hepatic involvement has been recognized in two recent types of pathogenic Coronaviruses, which include SARS-CoV-2 and MERS CoV (Middle East Respiratory Syndrome Coronavirus). These two viruses show striking genetic similarity, therefore hepatic involvement in this is not entirely unexpected [8]. COVID-19 patients showing injury of the liver can present with altered liver biochemical indicators such as elevated levels of ALT, AST, and total bilirubin (TBIL), in addition to lower levels of albumin [9,10]. The mechanisms involved with viral infections include the possibility of a direct effect of the virus on hepatocytes or biliary epithelium, liver injury related to accentuated immune response (cytokine storm) and immune-mediated damage, drug toxicity and ischemic hepatitis. These complications can occur in patients having

multiorgan dysfunction including hemodynamic instability [11]. Moreover, COVID-19 can give rise to worsening of existing chronic liver disease, which can lead to higher mortality due to acute-on chronic liver failure and hepatic decompensation.

Our overview provides a brief summary (Table 1) based on the various forms of hepatic damage, complications, occurrence, mechanisms, clinical features of liver injury, influence of comorbidities and treatment in patients with infection of SARS-CoV-2.

**TABLE 1: Summary**

**Mechanism and hepatotropism of SARS-CoV-2**

**Clinical presentation**

**Prognosis**

**Hepatic damage**

**a. Direct damage**

**b. Systemic inflammatory response syndrome (SIRS) and cytokine storm**

**c. Ischemia and reperfusion injury**

**d. Antibody-dependent enhancement (ADE)**

**e. Drug induced injury**

**f. Other mechanisms**

**Aggravation or recurrence of existing liver disease**

**1. Cirrhosis**

**2. Non-alcoholic fatty liver disease (NAFLD)**

**3. Immune hepatitis, viral chronic hepatitis**

**4. Liver transplant (LT)**

**Treatment**

**CONCLUSIONS**

## MATERIAL AND METHODS

We conducted a search of the literature published between January 1, 2011, to June 1, 2022, using PubMed (https://pubmed.ncbi.nlm.nih.gov) and Reference Citation Analysis (https://www.referencecitationanalysis.com). The database was first searched

using the key words "SARS-CoV-2 AND hepatic injury, hepatic damage AND therapy". We considered only studies in English and those referring to humans and with abstract, thus reducing the count to 350 papers. The reference lists of all retrieved articles were assessed to identify additional relevant studies. Only articles with abstract were considered. Each study was independently assessed by at least two reviewers (GM and BM), and rating decisions were based on the consensus of the reviewing authors. Our manuscript was based on the most relevant and pertinent studies, which included 66 references listed in the paper.

**Mechanism and hepatotropism of SARS-CoV-2**

Angiotensin-Converting Enzyme 2 (ACE2), which is expressed in about 80% of pulmonary alveolar cells, seems to be a susceptible receptor for SARS-CoV-2. In vitro studies from the SARS epidemic identified ACE2 as the host receptor for viral entry [12]. Furin and transmembrane serine protease 2 (TMPRSS2) have shown to play an important role in infection. Cells expressing these specific receptors can be indicative of putative hepatic permissive cells [13].

Hepatic distribution of ACE2 is peculiar. Single-cell RNA sequencing analyzed from livers from normal patients have shown higher levels of gene expression in cholangiocytes, followed in turn by sinusoidal endothelial cells and hepatocytes [14,15]. The ACE2 expression levels in cholangiocytes are similar to those found in pulmonary type 2 alveolar cells of the lungs, thus indicating that the liver could be a potential target for SARS-CoV-2 [16]. In addition, studies have reported that furin and TMPRSS2 have shown a broad gene expression profile in many types of liver cell [14]. In three single-cell RNA combined analysis from sequencing obtained from healthy liver tissue, only a few hepatocytes, however, co-expressed ACE2 and TMPRSS2 [17]. Zhao *et al* conducted studies on liver ductal organoids that expressed ACE2- and TMPRSS2, which were shown to recapitulate infection of SARS-CoV-2 [18], indicative that the epithelium of bile duct may support entry of pseudoparticles. Elevated cholangiocytes viral permissibility and high SARS-CoV-2 entry receptor expression is at odds liver

biochemistry showing a non-cholestatic pattern, which is commonly seen in patients with COVID-19. The exact reasons for to explain these findings are not known. It may be possible, however, that the virus may show low levels of replication in cholangiocytes *in vivo* in the absence of cell death.

The effects of coexisting liver disease and injury on SARS-CoV-2 hepatotropism is still not known. Studies performed before COVID-19 have reported an increase in liver ACE2 expression in patients with cirrhosis due to hepatitis virus C when compared with normal patients [19]. Moreover, liver mRNA TMPRSS2 and ACE2 expression have shown to be upregulated in non-infected obese individuals and non-alcoholic steatohepatitis patients, however, not in the presence of individuals only with steatosis [20]. Studies based on liver injury in animal models using ligation of the bile ducts have shown elevated expression and activity of hepatic ACE2 in in addition to hypoxia markers[19, 21]. Inflammation and injury of the liver may potentially enhance hepatotropism of SARS-CoV-2 by influencing the expression of viral receptors, with ACE2 shown as an interferon-inducible gene in the epithelia of the respiratory system in humans [22,23]. While the tissue specific factors involved in the infection of SARS-CoV-2 are not completely known, the importance of accessory receptors like the receptor B type 1 high-density lipoprotein scavenger (SR-B1) can help better understand *in vitro* facilitated coronavirus attachment [24].

**Clinical presentation**

Liver biochemistries abnormalities in are frequent in COVID-19 patients, which has been reported to be seen in 15-65%of individuals infected with SARS-CoV-2 [13]. Liver biochemistry abnormalities are generally characterized by mild to moderate elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, accompanied by a slight increase in bilirubin levels [25] and gamma-glutamyl transferase (GGT). Hypoalbuminemia, a typical manifestation of a hepatic synthetic dysfunction, has been reported to be associated with worsening COVID-19 outcomes [26-28]. Interestingly, despite the presence of ACE2 in cholangiocytes, more patients have

shown raised levels of transaminases. Several studies, however, have reported the development of cholangiopathy after severe COVID-19, characterized by marked elevation in serum alkaline phosphatase (ALP) accompanied by evidence of bile duct injury on imaging. ALP peaks may be seen in patients with worse prognosis. AST elevations can also be seen as a result of myositis [29]. Studies showed that levels of AST at admission tended to correlate with ferritin [30]. Further studies are needed to determine whether or not COVID-19 aggravates cholestasis in individuals with primary sclerosing cholangitis and primary biliary cholangitis [31,32]. The clinical manifestation [10, 13, 28, 32] of signs and symptoms can include gastrointestinal alterations, like nausea, anorexia, vomiting, diarrhea, *etc.* The patient can also complain of abdominal pain, especially in the right upper quadrant region.

**Prognosis**

The prognostic significance of elevated liver enzymes in COVID-19 patients is currently debatable. Unpublished data from Wuhan, China showed increased GGT levels in severe case of COVID-19 [33]. Moreover, some reports have demonstrated that high levels of AST and ALT can be associated with negative outcomes, including mechanical ventilation and management in an intensive care unit (ICU) [34-37]. A review showed that the pooled frequency of elevations of ALT and AST was similar in the overall COVID-19 cases, but interestingly, the prevalence of AST elevations was more than ALT in the severe COVID-19 disease [38]. It is possible to suppose that increased liver enzymes tend to be seen in patients needing severe critical care. Studies have reported raised AST in 62% patients in the ICU compared to 25% in the non-ICU setting [39]. The current literature available may be prone to bias considering that infected individuals with severe health issues tend to undergo more laboratory testing than patients with mild symptoms. The influence of liver enzymes on mortality is debatable. Several studies have stated that there are no apparent associations between mortality rates and elevations in levels of liver enzymes [34, 40], whereas different studies have reported elevated levels of liver enzymes (i.e. AST and ALT elevations higher than five times

normal ranges) in patients with greater risk of mortality [41,42]. Studies have suggested that indicators based on liver biochemical levels can be useful predictors of prognosis and severity in COVID-19 individuals, however, it is important to note that the prognostic significance could also be due to enhanced host response and therapies that could be more aggressive in patients with important signs and symptoms [43].

**Hepatic damage**

The complex mechanisms of liver injury during SARS-CoV-2 infection is of important clinical importance and to date, is still under investigation. The hepatic damage could be related to the direct cytopathic effect of the virus. Huang *et al* [44], however, found that liver injury as the first manifestation in COVID-19 patients was very rare, and that hepatic damage in COVID-19 patients appeared mostly due to secondary liver injury. Numerous studies have speculated that in addition to the virus itself causing initial liver injury, other factors involved that could cause secondary liver injury in patients with COVID-19 include an uncontrolled immune reaction or systemic inflammatory response syndrome (SIRS), ischemia and reperfusion, cytokine storm injury, and/or liver injury induced by drugs [39, 43, 45].

**a. Direct damage**

Liver injury in patients with COVID-19 could be partially caused by the direct SARS-CoV-2 viral invasion and hepatocyte destruction. Several studies [45, 46] have reported hepatic necrosis foci located near peri-portal areas and terminal hepatic veins, without signs of surrounding inflammatory cellular infiltration, which tend to be consistent with acute liver injury patterns. Amongst hospitalized patients with COVID-19, elevations of serum AST levels have been shown to be positively correlated with levels of ALT, which was not reported with markers of systemic inflammation like ferritin and C-reactive protein (CRP) [47]. Increased liver enzymes levels in COVID-19 patients could possibly be due to direct hepatic injury. Bile duct epithelium shows ACE2 expression, which tends to be much greater than that seen in hepatocytes. Compensatory

proliferation in parenchymal cells of the liver arising from cells of the bile duct may lead to the upregulation of ACE2 expression in the liver that could be an important mechanism involved in SARS-CoV-2 induced liver injury.

The direct hepatic damage caused by the virus is still a hypothesis, especially considering the low number of autopsies performed in COVID-19 patients and the relatively low ACE2 expression in the liver. The direct toxic attack of SARS-CoV-2 on the liver is still questionable and remains debatable. Moreover, biomarkers for cholangiocyte injury, such as GGT and alkaline phosphatase (ALP) have also been seen in some patients [40], and consistent with injury to biliary epithelial cells. COVID-19 patients can show elevated total bilirubin levels. These results could be indicative that SARS-CoV-2 might directly bind to cholangiocytes expressing ACE2, thus giving rise to cholangiocytes injury. Further clinical and histopathological studies are needed to confirm these hypothetical mechanisms.

**b. Systemic inflammatory response syndrome (SIRS) and cytokine storm**

Similar to numerous other diseases, SARS-CoV-2 is associated with systemic inflammation, which could cause elevations in biochemistries in the liver due to the release of cytokine [48]. Individuals with relatively high serum ALT levels tend to show elevated levels of CRP, D-dimer, ferritin and IL6 [49]. Studies have shown elevated serum levels of interleukin (IL) IL2 receptor and IL6 in COVID-19 individuals, which tend to correlate with the severity of the disease [50] Moreover, other cytokines such us tumor necrosis factor (TNF), IL18, IL4, IL 10 have shown to be increased, as do peripheral blood pro-inflammatory CCR4+ CCR6+ Th17 cells [51]. After being infected, a large number of immune cells may be overactivated and induced to secret excessive cytokines and chemokines that can lead to acute respiratory syndrome and SIRS, which can give rise to cell damage and necrosis.

**c. Ischemia and reperfusion injury**

Individuals with COVID-19 tend to show different degrees of hypoxemia. Systemic hypoxia might also have a contributory role. Studies have shown raised AST levels with other viral pneumonias, including influenza A H1N1 infection [52]. With hypoxia and ischemia, glycogen consumption, lipid accumulation and adenosine triphosphate depletion of hepatocytes may inhibit cell survival signal transduction, which can lead to hepatocyte death. It is important to note that Hepatic Ischemia-Reperfusion Injury (HIRI) is considered as a normal pathophysiological process. The mechanism behind this injury is closely related to neutrophils, Kupffer cells, reactive oxygen species, and calcium overload. HIRI can induce neutrophils, Kupffer cells, and platelets, which induce destructive cellular processes that can cause inflammation and injury to cells [53]. Ischemia and hypoxia could surely be involved in the mechanisms of liver damage in patients with severe and critical COVID-19 disease.

Histological studies have showed altered intrahepatic blood vessel derangement, coagulopathy, antiphospholipid antibodies and abnormal hepatic perfusion, which could be indicative of micro thrombotic disease [54,55].

**d. Antibody-dependent enhancement (ADE)**

ADE involves the interaction between the Fc receptor and/or complement receptor with the virus-specific antibody to enhance the virus ability to enter granulocytes, macrophages, and monocytes. Studies have shown that antibodies against the SARS-CoV-2 spike protein trigger ADE causing the virus to enter immune cells that do not express ACE2 [56-58]. The liver has numerous immune-response cells. ADE could also mediate SARS-CoV-2 in immune cell infection by a pathway not dependent on ACE2 and be involved in injury to the liver.

**e. Drug induced injury**

Drug-induced liver injury may have been more common during the initial periods of the pandemic, which could have been favored by the use of experimental therapies [57]. It is also important to note that the common symptom in COVID-19 patients is fever,

which may lead to the abundant use of antipyretic agents that contain acetaminophen, which is known to cause liver damage when excessively used without prescription in certain patients. Antiviral drugs currently available have not proven to be very effective in controlling the disease. During the outbreak, patients were given ritonavir, lopinavir, oseltamivir, etc. Raised hepatic enzyme levels have been reported in patients receiving lopinavir/ritonavir therapy (56.1% *vs* 25%) [58,59]. Remdesivir is also an antiviral drug that is used to inhibit the replication of SARS-CoV-2 virus, and studies have shown increased levels of blood creatinine, acute kidney injury and higher levels of liver enzymes in patients using the drug [60]. A study published in 2019 [61] showed that CYP3A4 may have an important role in hepatotoxicity mediated by ritonavir and the that oxygen free radical can be produced by the CYP3A4 metabolic pathways. Covalent binding could occur with substances found in the cells of the liver, which can cause peroxidation of membrane lipid, damage the integrity and ca2+-ATPase pathway of the membrane, influence the homeostasis of external and internal cell levels of Ca2+, and impair the function of critical organelles within the liver cells that can eventually lead to tissue damage and cell death. In addition, the overuse of ritonavir and lopinavir could activate the endoplasmatic reticulum stress pathway, induce apoptosis, inhibit the replication of hepatocytes, induce inflammatory reactions, and accelerate liver injury by aggravating oxidative stress [53]. Drug-induced damage needs to be included in the differential diagnosis, which requires a thorough and accurate medical history and pertinent examinations and tests to exclude other forms of liver injury and diseases.

**f. Other mechanisms**

There are several other potential contributors that have been reported to be important in understanding abnormal liver biochemistries in COVID-19. Current literature also describes COVID-19 as a vascular disease, in which endothelial cells can be infected and thereby causing endothelitis. Subsequent microvascular dysfunction leads to hypercoagulability, tissue edema and organ ischemia [62]. Moreover, some studies have shown that AST levels can exceed ALT during the disease, which would not be typical

for a classic hepatocellular pattern of liver injury. This is commonly seen in alcohol-related liver disease and cirrhosis. These alternative factors that may play a role in hepatic damage in COVID-19 patients remain unknown and require future clinical and histological studies. The mechanisms may include mitochondrial dysfunction related to COVID-19 [63] and hepatic steatosis induced by SARS-CoV-2.

**Aggravation or recurrence of existing liver disease**

Patients with pre-existing chronic liver disease (CLD) can undergo COVID-19. Whether or not CLD patients tend to be more susceptible to infection of SARS-CoV-2 has been the aim of several studies, which still needs to be meticulously evaluated. Data from large case series using health records do not suggest that these patients are over-represented [64]. CLD patients tend to have immune disfunction due to the disease and/or to long-term immunosuppressants treatments (as in immune hepatitis). These chronic patients have been reported to have worse clinical outcomes when compared to patients without underlying liver diseases, with preliminary studies reporting a potentially higher mortality rate and a more severe disease course, however, further studies with large cohorts are needed [65-67].

**1. Cirrhosis**

Acute hepatic decompensation (AHD) is typical in individuals with COVID-19 and cirrhosis. Studies have reported 47% of patients with cirrhosis and COVID-19 [66] show AHD, which typically manifests as worsening ascites and encephalopathy. Amongst COVID-19 infected patients with cirrhosis, studies have shown an increase in mortality and morbidity with increasing disease severity based on the Child-Pugh class. The number of hospitalized individuals reported in COVID-Hep the SECURE-Cirrhosis registries showed no significant differences amongst patients with CLD and CP classes A, B and C [67]. Studies however, have showed an increase in the number of admissions in the ICU, patients needing renal replacement therapy, individuals using mechanical ventilation, and mortality. SARS-CoV-2 infection does not seem to cause the

progression of liver disease beyond the natural clinical course of cirrhosis. The composition of the gut microbiota may play an important role in regulating disease severity and host immune responses. Considering that cirrhosis can induce changes in the function and composition of the gut microbiota, in addition to influencing the intestinal permeability, gut–liver axis alterations may play a role in the clinical severity in this patient COVID-19 group [13].

## 2. Non-alcoholic fatty liver disease (NAFLD)

The influence (NAFLD) on COVID-19 infected individuals is debatable. Studies have reported that it may be difficult to identify the effects of NAFLD from other metabolic conditions and viral-induced steatosis. A retrospective series on about 200 SARS-CoV-2 patients showed NAFLD to be a risk factor in COVID-19 infection severity, elevated levels of liver enzyme and longer shedding times of the virus [13].

## 3. Immune hepatitis, viral chronic hepatitis

Studies have reported that individuals with autoimmune hepatitis tend to show COVID-19-related mortality rates similar normal matched-individuals of the population [68] and that the immunosuppression use does not seem to be an independent mortality risk factor. With regards to chronic hepatitis B individuals in the phase of immune tolerance, studies still need to be performed to show if these individuals have persistent liver injury after infection. Studied based on guidelines from the Chinese Medical Association reported that for hepatitis-B individuals using antiviral drugs, discontinuation of anti-HBV therapy could favor replication and reactivation of HBV after high-dose hormone therapy (i.e. estrogens, estradiol, progesterone, ethisterone, medroxyprogesterone, norethindrone, cyproterone, norgestrel, clomiphene, *etc.*) during SARS-CoV-2 infection [69]. Clinicians who deal with autoimmune liver disease know that an unspecific infection may induce a flare of these diseases. Besides, SARS-Cov2 can indeed induce several types of autoimmune disease or autoimmune phenomena.

## 4. Liver transplant (LT)

Is not yet clear if LT recipients are more susceptible to COVID-19. A prospective study based on more than 100 individuals [70] showed that patients that underwent liver transplantation had an increased risk of SARS-CoV-2 infection probably due to the chronic immunosuppression therapy (liver transplant patients were excluded from this cohort). Moreover, data from the United Kingdom and Spain have shown that SARS-CoV-2 diagnoses tend to be greater in LT patients when compared to normal individuals. Biases in data could be present, however, considering the increased testing and intense management in LT patients [71, 72]. Studies have reported that LT recipients tended to be more likely to present gastrointestinal symptoms when compared to non-LT patients [73]. Clinical data incorporating adjustments for concurrent comorbidity suggest that LT individuals do not seem to be at greater risk of COVID-19 severity or mortality when compared to normal individuals [71,72].

**Treatment**

In the presence of acute liver injury, the clinicians should first assess the probable causes of injury, and then take the applicable measures. Although liver injury is a normal complication of COVID-19 infection, the majority of infected individuals show mild abnormalities in liver function that are not permanent and tend to resolve without therapy [39]. COVID-19 individuals showing liver damage can be treated with anti-jaundice, hepatoprotective, or anti-inflammatory drugs (i.e. glycyrrhizic acid, polyene phosphatidylcholine, adenosylmethionine, and ursodeoxycholic acid) [74]. Hepatoprotective drugs should be administered prudently. It is preferable to avoid administering more than 2 types of these drugs at the same time. For individuals with critical and severe COVID-19 disease with liver injury, the clinician should consider carefully managing the respiratory and circulatory support. Xu *et al* [75] showed that an artificial liver blood purification system may be beneficial in severe patients due to the rapid removal of inflammatory mediators, thus limiting cytokine storms, and enhancing

the balance of water–electrolytes. In COVID-19 individuals with suspect liver damage caused by drugs, clinicians should consider dose reduction or suspension. Acetaminophen (paracetamol) can be useful in patients with COVI-19, however, dosing (preferably not exceeding 2000 mg in a 24-hour period) must be carefully monitored [67]. Future studies in large cohorts having long-follow-ups are needed in determining the long-term effects of COVID-19 induced liver injury.

## CONCLUSION

Liver damage caused by COVID-19 is very common, especially in individuals with severe or critical disease. This aspect is also more relevant in patients with pre-existing chronic liver disease. The damage can be caused due to various mechanisms such as direct infection, immune injury, drug induced, hypoxia, or inflammation response. Further studies, however, are needed to understand the pathogenic mechanisms that lead to this damage and the hepatotropic mechanism of the virus. It is of utmost importance to monitor and treat abnormal liver function in COVID-19 positive patients, considering that success of therapy, prevention of life-threatening complications and worsening of comorbidities also depends on proper hepatic functioning in the global management of these patients.

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