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Review Article

COVID-19 and Indirect Liver Injury: A Narrative Synthesis of the Evidence

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Abstract

The liver is frequently affected by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection. The most common manifestations are mildly elevated alanine aminotransferase and aspartate aminotransferase, with a prevalence of 16-53% among patients. Cases with severe coronavirus disease 2019 (COVID-19) seem to have higher rates of acute liver dysfunction, and the presence of abnormal liver tests at admission signifies a higher risk of severe disease during hospitalization. Patients with chronic liver diseases also have a higher risk of severe disease and mortality (mainly seen in patients with metabolic-associated fatty liver disease). Several pathways of damage have been proposed in the liver involvement of COVID-19 patients; although, the end-cause is most likely multifactorial. Abnormal liver tests have been attributed to the expression of angiotensin-converting enzyme 2 receptors in SARS-CoV-2 infection. This enzyme is expressed widely in cholangiocytes and less in hepatocytes. Other factors attributed to liver damage include drug-induced liver injury, uncontrolled release of proinflammatory molecules ("cytokine storm"), pneumonia-associated hypoxia, and direct damage by the infection. Hepatic steatosis, vascular thrombosis, fibrosis, and inflammatory features (including Kupffer cell hyperplasia) are the most common liver histopathological findings in deceased COVID-19 patients, suggesting important indirect mechanisms of liver damage. In this translational medicine-based narrative review, we summarize the current data on the possible indirect mechanisms involved in liver damage due to COVID-19, the histopathological findings, and the impact of these mechanisms in patients with chronic liver disease.

Keywords: COVID-19; SARS-CoV-2; Liver hepatitis; Liver injury; Novel coronavirus.

Abbreviations: ACE2, angiotensin-converting enzyme 2; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; DILI, drug-induced liver injury; FIB-4, fibrosis-4 score; GGT, gamma-glutamyl transferase; GM-CSF, granulocyte-macrophage colony-stimulating factor; HBV, hepatitis B virus; IFN, interferon; IL, interleukin; LPV/R, lopinavir/ritonavir; MAFLD, metabolic-associated fatty liver disease; MERS, Middle East respiratory syndrome; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PSI, pneumonia severity index; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor.

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Introduction

The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection and related coronavirus disease 2019 (COVID-19) was first described in December 2019 in patients with severe pneumonia in Wuhan, Hubei Province, China.[1] In less than 3 months, SARS-CoV-2 infections had spread rapidly from Wuhan city to the entire country, and then on to more than 191 countries worldwide. The World Health Organization declared COVID-19 a global pandemic in March 2020.[2] The disease quickly became a great burden for health systems and focused worldwide research on therapies against this disease.[3,4] To date, SARS-CoV-2 has infected more than 60 million individuals and caused 1.4 million deaths worldwide. Patients with COVID-19 usually present with fever and respiratory symptoms.[5–9] However, patients can either behave asymptomatically[10,11] or have extrapulmonary involvement, even multiorgan failure. Gastrointestinal symptoms are evident in 11.4–18% of patients[12,13] and are associated with a potential higher risk of hospitalization.[14] These include anorexia, diarrhea (13%), nausea/vomiting (10%), and abdominal pain (8%). In some patients, it may even be their chief complaint.[13–15]

The liver is the second most common organ affected in COVID-19, after the lung. The most frequent manifestation is a mildly elevated alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST). Elevation of alkaline phosphatase, gamma-glutamyl transferase (GGT), and hepatic steatosis is also commonly observed in patients who tested positive for SARS-CoV-2.[16–18] Several pathways have been proposed as a cause of liver involvement in COVID-19. SARS-CoV-2 activates angiotensin-converting enzyme 2 (ACE2) receptors; therefore, abnormal liver tests could be explained by the presence of ACE2 in endothelial cells of the liver and the biliary epithelium.[19–21] Other mechanisms include drug-induced liver injury (DILI), cytokine storm, pneumonia-associated hypoxia, and even direct damage by the infection.[22,23] This review aimed to summarize the current data on the possible indirect mechanisms involved in liver damage due to COVID-19.

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General mechanisms of damage in COVID-19

The pathogenic process in COVID-19 begins when the virus binding to ACE2 in the target cell via receptor in the viral capsule,[19,24,25] allowing inoculation and multiplication. ACE2 is expressed mainly in the lung's epithelia; however, it is also present in the liver, gastrointestinal tract, and vascular endothelium.[26] Usually, the inoculation of the virus in the pulmonary epithelium leads to severe pulmonary, and later, systemic inflammation. On the other hand, some patients will develop a systemic inflammatory response syndrome (SIRS), which is characterized by a "cytokine storm" (an uncontrolled release of proinflammatory molecules). These patients have increased levels of tumor necrosis factor (TNF)-α, interleukin (IL)-2, IL-6, IL-7, and IL-10. There is also an increase in other inflammatory biomarkers, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, inducible protein-10, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1-α. Patients also present lymphopenia (mainly CD4+ and CD8+ T cells),[9,27,28] altered coagulation, and an increase of D-dimer, troponin, and N-terminal pro-B-type natriuretic peptide serum levels.[29–31] Some of these dysfunctions have been associated with significantly increased mortality.

Liver and COVID-19

In the liver, ACE2 is expressed mainly in cholangiocytes and less in hepatocytes.[26] However, bile duct injury has been reported, albeit rarely, in COVID-19 patients. In contrast, elevated ALT and AST levels have been extensively reported. Abnormal liver enzymes were first reported by Chen *et al*.[6] in Wuhan. In that descriptive study, a total of 43 out of 99 (43.4%) cases had mildly increased ALT and AST serum levels, with only 1 case having high levels of aminotransferases (ALT of 7,590 U/L and AST of 1,445 U/L). Several subsequent studies described the prevalence of high ALT and AST serum levels as being between 16–53% for all patients.[32]

Also, patients with severe COVID-19 seem to have higher liver dysfunction rates, and patients with abnormal liver tests at admission have a higher risk of progressing to severe disease during hospitalization.[21] In a large study by Chuan *et al*.,[5] conducted in China and including 1,099 patients from 552 different hospitals in 30 provinces, AST/ALT was elevated in 18.2–19.8% of patients with mild disease and 28.1–39.4% with severe disease. Similarly, Huang *et al*.[9] demonstrated an elevated AST in 62% of patients in intensive care units compared with 25% of non-intensive care unit patients.[15,21,33] In a study from New York by Richardson *et al*.,[34] 2.1% (56/5,700) of patients developed acute hepatic injury (defined as an elevation in AST or ALT of >15 times the upper limit of normal), which correlated with older patients and higher mortality (53 of them died). In contrast, in patients with subclinical disease, abnormal liver tests are rare (AST 8.7% and ALT 8.9% of patients).[35] Despite being frequent, changes in liver enzymes are usually mild, transitory, and do not impact the majority of patients.[16]

Liver damage indirectly related to COVID-19

Several liver damage mechanisms in patients with COVID-19 have been proposed, although the end-cause is most likely multifactorial. While the increase in liver enzymes could be the consequence of COVID-19 binding to ACE2 in the liver's endothelial cells and the biliary epithelium,[19–21] liver involvement is likely due to other, more indirect, pathways such as DILI, "cytokine storm", and pneumonia-associated hypoxia.[22,23]

SIRS

SIRS can be caused by infection, drugs, and other factors and is characterized by an acute and uncontrolled increase in the level of a large number of proinflammatory cytokines, also called the "cytokine storm". Many of which are produced by the liver. These inflammatory mediators in severe cytokine storms usually include IFNs, TNFs, ILs, and chemokines.[36] Among these, IL-6 is one of the critical components in SIRS,[37] as it is a multi-effective cytokine taking part in different signal transduction pathways, including classical signal transduction, trans-signal transduction, trans-presentation, and the JAK-STATA, RAS-RAF, SRC-YAP-NOTCH, and AKT-PI3K pathways. Thereby, IL-6 can promote T cell population expansion, activation, and differentiation of B cells, which increases antibodies consequently. It also regulates the acute phase response and has a hormone-like effect on lipid metabolism, insulin resistance, mitochondrial activity, and regulates the neuroendocrine system. This contributes to essential biological functions, including immune regulation.[38] In hepatocytes, IL-6 is a potent inducer of acute-phase reactive proteins. It can induce hepatocytes to synthesize acute-phase reactive protein at the gene transcription level, especially serum amyloid A and C-reactive protein.

Equally owing to its unique anatomical location, the liver is highly exposed to circulating antigens, endotoxins, inflammatory signals, and viral particles, which reach the liver either from the systemic circulation via arterial blood or the gastrointestinal tract through the portal vein.

SARS-CoV-2 binds to pulmonary epithelial cells and can directly induce multiple proinflammatory signals via Toll-like receptors and activation of cytotoxic T cells (powerfully activating the natural and cellular immunity).[39,40] After SARS-CoV-2 infection, cytotoxic T cells are rapidly activated, producing GM-CSF, IL-6, and other proinflammatory factors. Later GM-CSF activates CD14+/CD16+ inflammatory monocytes, which produce more IL-6 and other proinflammatory factors (Fig. 1). On the other hand, viral-specific CD8+ T cells, generated in response to a viral infection restricted to sites outside the liver (as in COVID-19), can trigger T cell-mediated hepatitis in the absence of viral antigens in the liver via activation of Kupffer cells. The recruitment of CD8+ effector T cells to the liver in response to the viral infection may be part of the liver damage's pathophysiology during cytokine storm.[41]

Huang *et al*.,[9] in a study of 41 hospitalized patients in China, described high levels of proinflammatory cytokines, including IL-2, IL-6, IL-7, G-CSF, inducible protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1-α, and TNFα in severe COVID-19 cases. Likewise, lymphopenia has been described in patients with COVID-19, particularly in severe cases.[42,43] These findings suggested a relationship between lymphopenia and "cytokine storm" in the pathogenesis of COVID-19, as previously described in SARS and Middle East respiratory syndrome (MERS).[44–46] In patients with COVID-19, the presence of lymphopenia, increased neutrophil count, and higher plasma levels of many innate cytokines have been associated with a higher risk of severe COVID-19.[9,42,47]

This excessive or uncontrolled release of proinflammatory molecules ("cytokine storm") leads to immune damage to other organs, acute respiratory distress syndrome,[34] respiratory failure, shock, and multiple organ failure.[48,49] The apoptosis and necrosis release damage-associated mo-

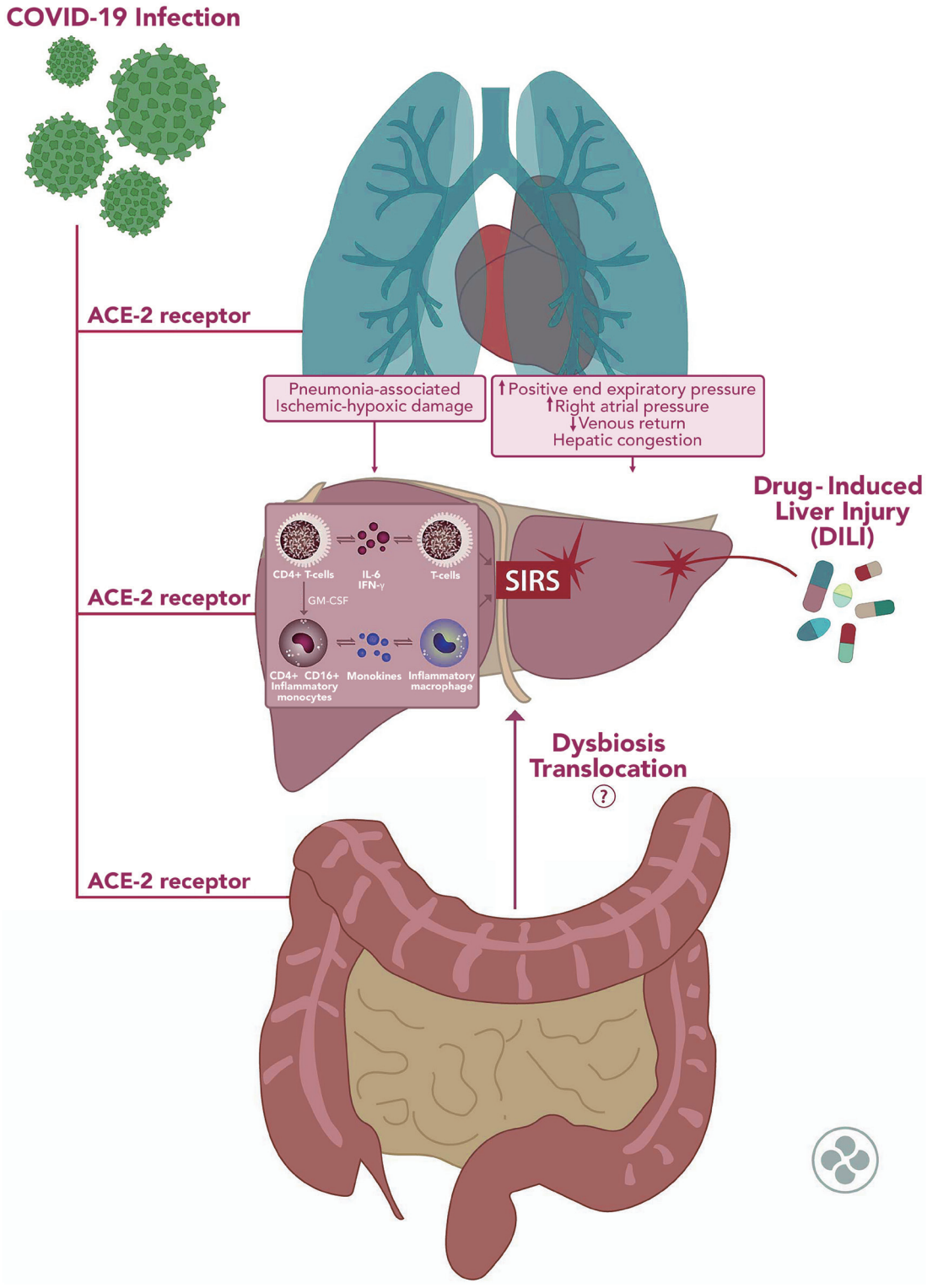

Fig. 1. Mechanisms involved in the pathogenesis of liver damage in patients with COVID-19 infection. The pathogenic process in COVID-19 begins when the virus binding to ACE2 in the target cell via receptor in the viral capsule. Some patients develop SIRS characterized by a "cytokine storm". The activated T cells produced GM-CSF, IL-6, and other proinflammatory factors. The inflammatory monocytes CD14+CD16+ respond to GM-CSF, producing a larger amount of IL-6 and other proinflammatory factors. Other factors such as hepatic ischemia, hypoxia-reperfusion dysfunction, and DILI probably perpetuate and induce more significant damage. Other mechanisms of damage, including intestinal abnormalities, have been raised (abnormal permeability, dysbiosis, viral translocation); however, without clear evidence yet. ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; DILI, drug-induced liver injury; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin.

lecular patterns and inflammatory signals can interact with Toll-like receptors, increasing the inflammatory response. Also, the T lymphocyte depletion cannot control the viral infections, activating multiple inflammatory signaling pathways, macrophage activation, and more secondary inflammatory reactions.[39,40] In severely ill COVID-19 patients, this mechanism of damage has been proposed as vital in the disease's evolution and mortality. This also explains why immunosuppressive therapies (such as corticosteroids or monoclonal antibodies) have been proposed. Tocilizumab (a humanized monoclonal antibody that targets IL-6) has been proposed as a possible specific treatment for cytokine storm in COVID-19. However, to date, this therapy has not demonstrated clinical benefit.[50]

Two other studies using artificial liver support systems (consisting of plasma exchange, plasma adsorption, blood/plasma filtration, and other blood purification modules) has been used to treat patients with COVID-19, with positive results. In one retrospective study, 23 patients with COVID-19 on corporeal extracorporeal membrane oxygenation were examined and found to have lower levels of IL-6 post treatment.[51] Interestingly, the results exhibited that the levels of IL-10 were not significantly reduced after treatment. This is important, as IL-10 is produced by many different cell populations including hepatocytes, sinusoidal endothelial cells, Kupffer cells, hepatic stellate cells and liver associated lymphocytes.[52] This cytokine has immunoregulatory functions and improved levels of IL-10 exert protective effects on the hepatocyte.[53] Changes of inflammation-related indicators, including white blood cell count, neutrophil count, lymphocyte count, C-reactive protein, and procalcitonin, showed a downward trend after artificial liver support treatment. Conversely, the lymphocyte count was reversely increased. In another study by Guo *et al*.[54] of 12 patients, the use of artificial liver blood purification systems was also associated with lower and sustained decrease of cytokines. However, it did not correlate with a significant improvement of liver enzymes. It is of note that in both of these studies, the decrease in cytokines was associated with improvement of clinical parameters such as APACHE II, Pneumonia Severity Index (PSI), sequential organ failure assessment and oxygenation index.

There is a direct link between COVID-19 and cytokine storms (an uncontrolled release of proinflammatory signals), which could correlate to disease severity. This phenomenon has multiple effects on immune regulation and may cause multiple organ failure, including the liver. This could also be worsened by the inability to mount a contra-inflammatory response by the liver. The use of artificial liver blood purification systems could have a positive impact in severe cases.

Hypoxia-reperfusion injury

As stated before, COVID-19 primarily affects the lungs, and many patients present with hypoxia. In newer studies, hemoglobinopathy and cell iron overload might additionally have a possible role. Two potential pathophysiological mechanisms have been proposed: acute respiratory distress syndrome[34] caused by SARS-CoV-2 and its interaction with hemoglobin through CD147, CD26, and other receptors located on erythrocyte or blood cell precursors. Hepcidin-mimetic action of a viral spike protein can also induce ferroportin blockage.[55] Other mechanisms, such as hypoperfusion caused by hemodynamic changes, may cause hepatic ischemia and hypoxia-reperfusion injury.[23,56,57]

In patients with acute cardiac failure, the decrease in systemic arterial pressure leads to an acute reduction in hepatic arterial perfusion, producing hepatocellular hypoxia.[58] Hepatic venous congestion resulting from heart failure can also cause hypoxic damage to the hepatocyte.[59] In mechanically ventilated patients (where high positive end-respiratory pressure is used), similar hemodynamic alterations have been described, mainly due to increased intra-abdominal pressure.[60,61] Studies in this context show abnormal liver enzymes, but their meaning is unclear.[61]

The hepatic ischemia and hypoxia-reperfusion dysfunction lead to lipid accumulation in hepatocytes until cell death. Hypoxia also induces an increase in reactive oxygen species, and their peroxidation products act as a second messenger activating redox-sensitive transcription factors and amplifying the release of multiple proinflammatory cytokines.[62] Mitochondrial damage probably also has a role in liver damage.[63,64]

DILI

In addition to the indirect mechanisms already exposed, DILI likely has an important role in liver injury in patients with COVID-19. Some findings show that DILI may be present in patients with COVID-19 during autopsy examinations (described as moderate microvascular steatosis and hepatic inflammation).[65] This finding could be due to the widespread use of hepatotoxic drugs in patients with COVID-19, such as acetaminophen, antivirals (i.e. oseltamivir, abidol, and lopinavir/ritonavir), corticosteroids, immunemodulators, and antibiotics.[32,66,67] Acetaminophen has been widely used to manage symptoms, and its hepatotoxic effects are well-known; however, no studies have assessed its role in liver damage in COVID-19 patients.

In a study of the incidence of adverse drug reactions in COVID-19 patients in China, based on a Hospital Pharmacovigilance System, the prevalence was 37.8%. The most prominent was drug-induced gastrointestinal disorders (23%) and liver system disorders (13.8%). Length of stay (odds ratio (OR): 2.02), number of drugs used in the hospital (OR: 3.17), and underlying diseases (OR: 2.07) were independent risk factors for having an adverse reaction. In this study, these were mainly associated with lopinavir/ritonavir (LPV/R) (63.8%) and umifenovir (18.1%).[68]

In a meta-analysis by Kulkarni *et al*.,[65] which included 107 articles (20,874 patients), the global incidence of DILI in COVID-19 patients was 25.4%. The highest incidence of DILI was associated with patients using remdesivir (15.2%) and LPV/R (37.2%).[69]

Remdesivir, a nucleotide analog prodrug that inhibits viral RNA polymerases, has shown *in vitro* activity against SARS-CoV-2 and had promising results in some clinical studies.[70] In a multicenter study of 53 individuals that received remdesivir, 23% (12/53) of patients developed elevated aminotransferases, and two discontinued the drug due to the same reason.[70] In another double-blind, placebo-controlled, multicenter trial in Hubei, China, that included 158 patients using remdesivir, the total incidence of adverse effects was reported at 66%. This included hyperbilirubinemia (10%) and AST elevation (5%). Remdesivir was stopped early because of adverse events in 18 patients (12%).[71] Nevertheless, recent studies have determined that remdesivir use was not associated with statistically significant clinical benefits.[72]

LPV/R are combined protease inhibitors approved for use against human immunodeficiency virus infection that has also been used in COVID-19 patients. The most frequently reported adverse effects of LPV/R is hyperbilirubinemia, followed by elevated aminotransferases.[21,73,74] A retrospective, single-center study of 148 patients with confirmed SARS CoV-2 in Shanghai found that 48% of them had developed abnormal liver biochemistries a week after admission. Of

those, 58% had received LPV/R. In a retrospective study of 417 patients with confirmed COVID-19 in Shenzhen, China, the use of LPV/R was associated with an increase of liver injury (7 times higher odds of abnormal liver biochemistries).[21] In another retrospective cohort study of patients treated with oral arbidol and LPV/R, 68.7% of them showed elevated bilirubin levels (mean of top bilirubin was 25.26 μmol/L). Interestingly, some studies have reported a similar prevalence of patient adverse drug reaction using placebo vs. LPV/R.[73,75] Similar to that described in remdesivir, the use of LPV/R has not shown to have a clinical benefit.[73]

Hydroxychloroquine has been linked to arrhythmias due to QTc prolongation,[76] but preliminary data did not associate this treatment with significant liver abnormalities. A probable benefit was reported in patients with COVID-19. However, recent reports have shown that hydroxychloroquine does not reduce the viral load of the virus nor does it have any clinical benefit.[77,78] In a systematic review including four randomized controlled trials, ten cohort studies, and nine case series, liver injury was not reported.[79] Similar results were observed in a double-blind, randomized, phase IIb clinical trial with 81 adult hospitalized patients.[76] Despite this, hydroxychloroquine has significant drug-drug interactions, particularly with anti-rejection immunosuppressants.[22]

Other drugs such as tocilizumab commonly produce liver enzyme elevation but are only rarely linked with severe liver injury.[22] Nevertheless, tocilizumab treatment has been associated with an increased risk of hepatitis B virus (HBV) reactivation. A prospective study of patients with rheumatoid arthritis treated with tocilizumab combined with conventional synthetic disease-modifying drugs showed an increased risk of HBV reactivation.[80]

It is important to consider that antibiotics are the most common type of drugs that have been reported as a cause of DILI. In severe COVID-19 patients, antibiotics are widely used and probably have an essential role in liver injury.[81]

Other mechanisms of liver damage

As previously stated, the main target of SARS-CoV-2 is the lung via ACE2 receptors, which are also present in cholangiocytes and hepatocytes,[26,82] meaning that during a SARS-CoV-2 infection, the liver could also be directly targeted. It is notable that despite the extensive ACE2 expression of cholangiocytes, specific abnormalities of bile duct chemistries are rare.[5] However, cholestasis has been observed. In a recent case report, three young adults without preexisting chronic liver disease underwent liver biopsies due to prolonged and severe cholestasis during recovery from critical COVID-19 that required mechanical ventilation. Of note, each patient had severe but acute aminotransferase elevations, in line with previously stated biochemical alterations common in COVID-19 patients. After cardiopulmonary and renal recovery, they developed persistent cholestasis associated with jaundice. Their biopsies exhibited moderate portal and periportal fibrosis, with focal fibrotic obliteration of terminal hepatic veins in one case. All three cases showed extensive degenerative cholangiocyte injury, including necrosis. Furthermore, there was necrosis of the cholangiocyte epithelial layer of terminal bile ducts and marginal ductules and microvascular changes. These changes are similar to secondary sclerosing cholangitis of the critically ill patient that could be superimposed due to direct injury to cholangiocytes after exposure to SARS-CoV-2. Although further evidence is needed (as *in situ* hybridization and immunohistochemistry for SARS-CoV-2 was negative in two of the three patients), these findings point to the unique susceptibility of the liver to COVID-19.[83]

Recent studies have observed SARS-CoV-2 viral particles in the cytoplasm of hepatocytes. The majority of viral particles were noted to harbor a complete envelope with corona-like spikes, suggesting that SARS-CoV-2 can enter and replicate in hepatocytes.[84] This may drive hepatocyte apoptosis[85] via caspase-dependent pathways,[86] and translocation from the gut lumen into the liver via portal flow.[23] These findings were also described in the SARS and MERS diseases.[32]

Pathological findings of COVID-19 disease

Several reports have described multiple liver histopathological findings in COVID-19 patients, including hepatic steatosis, congestion of hepatic sinuses, and inflammatory features. A recent systematic review of autopsies from patients with COVID-19 reported that the most frequent histopathological features were hepatic steatosis (55.1%), venous outflow obstruction (36.4%), congestion of hepatic sinuses (34.7%), vascular thrombosis (29.4%), fibrosis (20.5%), necrosis (15.4%), Kupffer cell hyperplasia (13.5%), portal inflammation (13.2%), and lobular inflammation (11.6%).[87]

The high prevalence of steatosis can be partially explained by the population's baseline characteristics (risk factors of severe COVID-19 are similar to the risk factors associated with steatosis).[88] Also, metabolic-associated fatty liver disease (MAFLD) is independently associated with more severe COVID-19 disease. DILI and cytokine storm can also contribute to the development of hepatic steatosis.[89] Vascular thrombosis was frequently observed due to endothelial dysfunction (endotheliitis), a procoagulant state, and direct vascular injury of the disease, all mechanisms described as part of the pathophysiology of severe COVID-19 disease.[65,84,90–98]

Congestion and necrosis may be explained by circulatory dysfunction, heart failure, and ischemia due to multiorgan failure. Finally, some of these findings have also been described in SARS and MERS patients and may be related to the ongoing systemic inflammatory process and sepsis, affecting the liver (portal inflammation, lobular inflammation, and Kupffer cell hyperplasia or proliferation).[85,91–95] To date, no specific histologic indicator of direct infection in the liver tissue (i.e. viral cytopathic effect) has been reported.

Liver damage in pre-existing liver disease

Patients with pre-existing liver disorders, such as liver cirrhosis and hepatocellular carcinoma, are considered to have a higher susceptibility for any kind of infection and sepsis secondary to impaired host defense. The prevalence of chronic liver diseases is between 0.6% and 1.4% in patients hospitalized for COVID-19.[34,99,100] These patients are at high risk of severe disease (up to 60% develop a severe disease) and higher mortality (even reaching 18%).[101] Also, SARS-CoV-2 infection causes higher liver injury in chronic liver disease patients, decompensation in 20% of cases with cirrhosis, and worsening clinical outcomes of already unstable patients.[102]

Among cases with chronic liver diseases and COVID-19, the relationship between MAFLD and COVID-19 has been the most studied. The first evidence was established by Qian *et al*.,[103] in an early study in China that included 324 COVID-19 patients, 21.6% of the subjects had MAFLD (diagnosed by computed tomography scan), and the prevalence of MAFLD was higher among patients with severe COVID-19. Later Ji *et al*.[104] studied 202 patients admitted for COVID-19 and with the diagnosis of MAFLD (established through hepatic steatosis index >36 points and/or by abdominal ultrasound).

They concluded that patients with MAFLD had a higher risk of disease progression, a higher likelihood of abnormal liver function from admission to discharge, and longer viral shedding time than patients without MAFLD. Subsequently, other studies have described similar results with higher mortality in patients with MAFLD, obesity, and those over 60 years of age.[88] Similarly, a multicenter retrospective study by Zheng *et al*.[105] further validated this information.

Furthermore, patients with MALFD had an OR for severe COVID-19 of 2.3, and for obese patients with MALFD it was an OR of 6.32 compared to non-obese patients. This is believed to be caused by liver fat, and associated inflammation could exacerbate the virus-associated cytokine storm, leading to worsening COVID-19. Other studies found that increasing liver fibrosis measured by NAFLD Fibrosis Score and Fibrosis-4 (FIB-4) scores was linked to increased severity of disease in COVID-19 patients. Moreover, liver fat has been independently linked with an increased risk of testing positive for COVID-19.[106]

Likely, the presence of already activated inflammatory pathways in patients with MAFLD is associated with more severe SIRS development when they are infected with SARS-CoV-2.[107] The increased ACE2 expression on hepatocytes of patients with MAFLD[108] and paired hepatic innate immune system in these patients are potential mechanisms that would explain the increased risk of severe COVID-19 in patients with MAFLD.[109]

Autoimmune liver disease, treated with immunomodulatory or immunosuppressive drugs, could increase the risk of complications associated with COVID-19. In an Italian study based on 148 clinical telephone interviews, the incidence of SARS-CoV-2 infection in patients with autoimmune hepatitis was similar to the general population, and the prevalence of severe COVID-19 was low.[110] Since there are no adequate studies to define the real risk, the patients with autoimmune hepatitis on immunosuppressive treatment should be considered at high risk for severe COVID-19.[36,111]

Finally, according to initial reports concerning co-infection with COVID-19 and other viruses, chronic infection with HBV does not seem to confer a worse prognosis in patients with SARS-CoV-2.[5] However, it is necessary to pay carefully attention to the use of immunosuppressors (high-dose glucocorticoids or tocilizumab) as therapy for COVID-19, due to the possible risk of virus reactivation.[112]

Management

Although we aimed to review the mechanism of liver damage in COVID-19, it is important to mention how current guidelines have addressed this issue and the implications of COVID-19 for patients with previous liver diseases. Due to the pandemic's novel nature, there is still little evidence regarding this topic, and most recommendations are based on expert consensus.[113] These include recommending that patients with cirrhosis or other liver diseases minimize their risk of contracting COVID-19 through general preventive measures, such as hand hygiene, social distancing, use of telemedicine visits for ongoing disease management, and reducing exposure to health services if possible. It is also recommended that clinicians decrease routine laboratory and imaging surveillance frequency when the associated risk is deemed to be low and delay non-urgent procedures. As the pandemic prolongs in time, this recommendation must be addressed more fully in newer updates and the impact on mortality on patients isolated from care studied. On the other hand, early admission for patients with COVID-19 who also have advanced liver disease, especially with other risk factors, is recommended.[36,114] Another important topic will be to assess the effectiveness and security of the available vaccines against SARS-CoV-2 in this particular population.

As discussed above, there are few drugs with clinically significant impact against COVID-19. To date, remdesivir is the only approved medical treatment for COVID-19 as of October 2020. Elevated liver biochemistries are not currently a contraindication for its use, although it is not recommended in patients with an ALT ≥5 times the upper limit of normal. The Federal Drug Administration in the USA also suggests that clinicians should perform hepatic laboratory testing in all patients before and while receiving remdesevir and consider discontinuing if ALT levels increase to greater than 10 times the upper limit of normal or is accompanied by signs or symptoms of liver inflammation.[72,115,116] As stated above, there is consensus that more research is needed to validate remdesivir as an effective treatment against COVID-19. Furthermore, current studies have shown that it may lead to DILI. Therefore, it is unclear whether there is clinical benefit in the use remdesivir to prevent or treat direct liver damage due to SARs-Cov-2 and more studies are necessary.[117]

Other data from randomized trials overall support the role of glucocorticoids for severe COVID-19. In a meta-analysis of seven trials that included 1,703 critically ill patients with COVID-19, glucocorticoids reduced 28-day mortality compared with standard care or placebo (32 vs. 40 percent, OR: 0.66, 95% confidence interval: 0.53–0.82) and were not associated with an increased risk of severe adverse events.[118] For patients on glucocorticoids, such as patients with autoimmune hepatitis, therapy should not be abruptly discontinued but should be used at the lowest dose possible to control the underlying disease, regardless of COVID-19 exposure or infection status.[119] This is why guidelines suggest an individualized approach in patients with autoimmune hepatitis and COVID-19, based on the severity of infection, patient comorbidities, the severity of liver disease, and the existing medication regimen. The goal of medication adjustment is to reduce immunosuppression during active viral replication, so as to lower the risk of COVID-19-related complications while balancing the risk of disease flare.[36] The general strategy includes maintaining treatment in asymptomatic patients and dose reduction in moderate to severe COVID-19. This must be balanced with the possible benefits of dexamethasone for moderate to severe COVID-19.

As previously mentioned, reactivation of HBV infection has been observed in patients treated with glucocorticoids and tocilizumab. Thus, HBV prophylaxis may be indicated when initiating these therapies. Certain antiviral therapies have shown a greater risk for developing DILI. However, there are no contraindications to initiating or continuing specific antiviral therapy for HBV or HCV infection in patients with or without COVID-19.[36]

Due to the pandemic, transplant programs worldwide have been severely impacted, with fewer number of transplantations performed. There is also conflicting data regarding the risk of severe COVID-19 in recipients.[120,121] Furthermore, there is insufficient data as to how immunosuppressive medications should be adjusted. SARS-CoV-2 infections have been reported in patients receiving different types of antirejection therapy.[122] Guidelines have extrapolated from their practices of managing other viruses, such as Epstein-Barr virus, cytomegalovirus, and BK viruses. This follows that for transplant recipients without COVID-19, maintenance immunosuppression is continued without adjustment or in some patients reduces the antimetabolite component of immunosuppression (e.g., mycophenolate or azathioprine), although clear guidelines must be issued. For patients with acute T cell-mediated (cellular) rejection of the liver allograft, the approach to management, including high-dose glucocorticoids for patients with moderate to

severe rejection, has not changed.[36] In transplant recipients with COVID-19, adjustments to immunosuppression are individualized, based on COVID-19 severity, the specific regimen used, time post-transplant, and allograft rejection risk. Experts recommend reducing immunosuppression in patients with moderate to severe COVID-19 (e.g., those requiring hospitalization).

Finally, specific management in scenarios like an acute liver failure in critically ill patients or hepatic carcinoma and other issues such as when to suspend or resume chronic therapies escape the scope of this review. It is of note that the indirect impact of the pandemic on patients isolated from their healthcare providers is yet unknown.

Conclusions

The liver is the second most common organ affected in COVID-19. Liver injury caused during COVID-19 infection is likely multifactorial, such as the use of potentially hepatotoxic drugs, systemic inflammatory response, respiratory distress syndrome-induced hypoxia, and direct damage. Indirect damage probably plays a prominent role in seriously ill patients and patients with chronic liver disease.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

FI, GA, JPA and LAD conceived and designed the review, all authors collected the data and contributed to the interpretation. All the authors participated in drafting the article and revising it critically for important intellectual content, and all the authors gave final approval of the version submitted.

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