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Review article

Liver and SARS-CoV-2: Literature key aspects

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Abstract

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a virus that has spread around the world, causes an acute respiratory infection and it may also cause death. The damage that can cause in other organs is frequent. Many studies had also shown alterations in liver function tests, that are then related to serious illness and with hospitalization requirements. Moreover, in patients infected with the virus that had underlying liver disease, a significant increase in the level of aminotransferases was observed in the course of the disease. A greater risk of serious illness was also detected. The pathophysiological explanation of liver injury in those patients covers the direct cytopathic effect produced by binding the virus, the angiotensin-converting enzyme (ACE2) to the hepatocytes and the cholangiocytes, excessive immune response, and in some cases, drug-induced hepatotoxicity.

Keywords

SARS-CoV-2, Coronavirus transaminases, Hepatic failure, Hepatocyte.

INTRODUCTION

Severe acute respiratory syndrome type 2 (SARS-CoV-2) is a new coronavirus whose initial cases were reported in the population of Wuhan, China[(1)]. This new betacoronavirus, like severe acute respiratory syndrome type 1 (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV), produces mainly mild alterations in the respiratory tract; however, it can also trigger respiratory distress syndrome and disturbances in other systems[(1)].

In this regard, gastrointestinal symptoms and abnormalities in liver injury tests have been described[(2)]. This review outlines the prominent abnormalities in liver function tests, possible pathophysiological pathways, and potential therapeutic approaches for this clinical event.

SARS-CoV-2: BASIC VIROLOGY

Coronaviruses belong to the genus *Betacoronavirus* of the *Coronavirinae* subfamily under the *Coronaviridae* family. SARS-CoV-2 is a positive single-stranded ribonucleic acid (RNA) virus; its genome size is approximately 29.9 kb, and its diameter is 65–125 nm[(3-5)]. SARS-CoV-2 shares the genetic sequence with SARS-CoV (79%) and MERS-CoV (50%)[(6)].

The SARS-CoV-2 genome comprises 14 open reading frames (ORF), two-thirds of which encode 16 non-structural proteins (NSP; 1–16), and the remaining third encode nine accessory proteins and four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) [3,5,6]. The M protein determines the shape of the virus, the E protein plays a role in the assembly and release of the virus into the host cell, and the N protein maintains the stability of the viral genome[7]. The importance of S protein lies in that it mediates the process of entry of the virus into the host cell since it binds to the receptor for angiotensin-converting enzyme II (ACE-II) in the host cell through its receptor-binding domain (S1 subunit). In addition, the S2 subunit of the S protein is responsible for fusing the membranes of the virus and the host cell[4,6]. The cleavage of S protein by cellular proteases such as cathepsin L and transmembrane serine protease 2 (TMPRSS2) is also an essential step for fusing cell and viral membranes[8,9].

Once the genome is released into the host cell, viral replicase is translated, and RNA-dependent RNA polymerase is formed; subsequently, this replication/transcription complex reorganizes the endoplasmic reticulum into double-membrane vesicles, facilitating the replication of viral RNA and the translation of structural and accessory proteins that ultimately form viral particles[3,4,9].

EPIDEMIOLOGY

At the end of 2019 in China, specifically in Wuhan, capital of the Hubei province, an outbreak of pneumonia of unknown etiology was reported, capable of producing severe respiratory distress syndrome[1]. On January 12, 2020, the genomic sequence of the coronavirus was identified and made public by China[10].

The spread of SARS-CoV-2 continued to be reported massively: on January 13, Thailand reported the first confirmed case of coronavirus disease of 2019 (COVID-19) in a country other than China. It arrived in Colombia on March 6, 2020, when it was identified in a 19-year-old girl from Italy[10,11]. On March 11 of the same year, due to concerns about the high propagation rate, the World Health Organization (WHO) declared the COVID-19 disease as pandemic[10].

At present, infections reach 126 million worldwide and 2.76 million deaths. In Colombia, infections rise to 2,359,942 and 62,519 deaths, maintaining a mortality rate like the global one, between 2% and 3%[12].

COVID-19 is highly contagious; however, most cases are reported asymptomatic or with mild symptoms. Severe cases are not limited to pulmonary manifestations since multiple organs can be affected, including the liver[1].

LIVER DAMAGE IN INFECTION WITH SARS-CoV-2 AND OTHER CORONAVIRUSES

Histopathological changes

Different types of coronaviruses are known. SARS-CoV-2, responsible for the current pandemic, is part of the betacoronavirus family. Previous outbreaks were due to SARS and MERS, whose incidence peaks occurred in 2003 and 2012, respectively[13].

In some patients infected by coronaviruses such as SARS-CoV or MERS-CoV, alterations were found in liver injury tests[14,15]. On the one hand, autopsies of patients with SARS-CoV-1 detected viral particles in the parenchyma and vascular endothelium of the liver; liver biopsies reported mitotic cells increased with eosinophilic infiltrates and hepatocyte ballooning, showing the apoptosis capacity of the virus in liver cells[14]. It is known that SARS-CoV uses ACE-II for viral entry into tissue; studies have found its genome in liver cells using real-time polymerase chain reaction (RT-PCR), which could explain liver involvement. Another pathophysiological pathway proposes that the expression of the SARS-CoV virus protein 7a produces apoptosis in different tissues, including the lung, kidney, and liver, through the caspase-dependent pathway[14]. On the other hand, MERS-CoV enters the body through dipeptidyl peptidase 4 (DPP-4). DPP-4 is highly expressed in liver cells, explaining liver abnormalities[14].

Pathophysiological mechanisms

Currently, cohorts of COVID-19 patients develop liver damage during the disease, especially in severe cases; nonetheless, the pathophysiological mechanisms are still not precise, but various hypotheses have been formulated that could account for this event[15-17].

The liver injury could be explained by the direct cytopathic effect of SARS-CoV-2[17] due to its binding to ACE-II, playing the role of the receptor by binding to the S proteins of the virus. It is then processed by TMPRSS2 in the liver cell, breaking the binding of the virus with its receptor, thus facilitating cell infection[18]. ACE-II shows variable heterogeneity and is expressed in various human body tissues, mainly type II epithelial cells of the lung and, to a lesser extent, enterocytes, hepatocytes, and cholangiocytes. Due to the role played by ACE-II in the entry of the virus into different tissues, the presence of the enzyme could elucidate the manifestations and liver involvement of this new disease due to direct viral replication in hepatocytes[14-17,19,20].

However, Chai *et al* used RNA sequence from a single cell from healthy liver tissue to identify which cell type

expressed ACE-II. The results demonstrated high expression in cholangiocytes, 20-fold lower expression in hepatocytes, and no ACE-II in Kupffer cells or liver endothelial cells. Accordingly, the liver does not appear to be a target organ for SARS-CoV-2, or at least it does not use ACE-II to induce direct cytopathic damage; rather, the capacity for liver regeneration, the immune response of cholangiocytes, and viral invasion on them could explicate liver damage[21]. For their part, Seow *et al* also used a single-cell RNA sequence from human liver tissue obtained from patients with hepatocellular carcinoma (taking a sample of neoplastic tissue and normal adjacent tissue) to determine which cell type expressed ACE-II and TMPRSS2 and prove whether they were involved in viral entry into liver tissue[18]. The tumor-associated calcium signal transducer 2 (Trop-2) indicates the fate of hepatic epithelial progenitor cells: A low expression of Trop-2 indicates the fate in hepatocytes and a high expression in cholangiocytes[18]. The study results identified the expression of ACE-II and TMPRSS2 in a Trop-2 positive liver progenitor population. Thus, it was deduced that it could alter the liver's ability to regenerate cholangiocytes, explaining liver damage[18].

Consequently, liver involvement is attributed to bile duct injury and not to direct infection of the liver parenchyma[14-17,20]. Nevertheless, increased levels of alkaline phosphatase or γ-glutamyltransferase are not significant, and biopsies do not show reasonable damage to the bile ducts, so other hypotheses are considered a possible etiology of liver damage[16].

Drug toxicity theory

Drug-induced hepatotoxicity is another theory of SARS-CoV-2 liver involvement since the liver is the organ in charge of drug biotransformation processes. The treatments proposed to combat the virus, such as hydroxychloroquine, oseltamivir, tocilizumab, umifenovir, acetaminophen, antibiotics (macrolides, quinolones), steroids, among others, could contribute to liver damage[15-17,19,20,37]. In a retrospective study of patients with SARS-CoV-2 and impaired liver tests, Fan *et al* found that this damage could result from the use of lopinavir/ritonavir[22]. Similarly, another study that described the first 12 patients with COVID-19 in the United States found three patients who received remdesivir and had elevated liver tests[23]. The administration of drugs such as tocilizumab or baricitinib in the presence of preexisting chronic viral hepatitis caused by hepatitis B virus (HBV) or hepatitis C virus (HCV)[20,24] can reactivate the disease and cause hepatic injury[20]. In addition, autopsy liver biopsies have shown moderate microvesicular steatosis with mild lobular and portal activity, findings attributed to medications[14,15,20,24]. This possibility should be further studied since alterations in liver tests have been observed before pharmacological management[24].

Meanwhile, high levels of positive end-expiratory pressure (PEEP) with mechanical ventilation (MV) may result in congestion of the liver tissue that increases the pressure in the right atrium and hinders venous return, contributing to liver injury[17,24]. However, the veracity of this pathophysiological process has not been proven since there have been patients with alterations in liver function tests not subjected to this type of assisted ventilation[24]. Liver damage could even be caused by the same respiratory failure—a characteristic of this disease—giving rise to hypoxic hepatitis, mainly in severe cases[20].

Disorderly activation of the immune system and the expression of cytotoxic T cells that attack infected cells producing apoptosis and necrosis may play an essential role in SARS-CoV-2 liver injury[16,24]. Lymphocytes alone cannot control infection and, through signaling pathways, activate macrophages and stimulate cytokine synthesis, causing further tissue damage. This process occurs in severely ill patients and is known as an *inflammatory storm*, resulting primarily in lung injury and later in a state of multiple organ dysfunction (MOD), including liver tissue[16,20].

Among the released substances that favor MOD are interleukin (IL) IL-6, IL-10, IL-2, and interferon-gamma (IFN-γ) mainly, other substances such as CRP, ferritin, lactate dehydrogenase (LDH), D-dimer, T helper 17 (Th17) cell levels, cluster of differentiation antigen 8 (CD8), IL-7, tumor necrosis factor-alpha (TNF-α), granulocyte colony-stimulating factor, interferon-inducible protein-10, monocyte chemotactic protein-1, macrophage inflammatory protein, and protein 1α[15,20].

The gut-liver axis regulates immune tolerance in the body. Still, in some situations (such as SARS-CoV-2 infection), this tolerance is adversely affected and contributes more to the release of pro-inflammatory substances. It can also be associated with hypoxia, Kupffer cell overstimulation, oxidative stress, and stimulation of the sympathetic and adrenal nervous systems[15].

LIVER FUNCTION TESTS AND COVID-19

The clinical manifestations of COVID-19 include fever, cough with or without expectoration, and dyspnea with the possibility of progressing to greater pulmonary involvement. The finding of ground-glass opacity is frequent on radiological imaging[22,25].

The liver appears to be another target in SARS-CoV-2 disease. A broad spectrum of event manifestations has been

described, ranging from mild elevations in transaminases to liver failure and intrahepatic cholestasis complications. The latter two are more frequent in patients with pre-existing liver diseases[15].

Liver test abnormalities have been relatively common in COVID-19 patients. In a study by Cai *et al*, laboratory studies related to liver function and injury in 417 patients were analyzed; 76.3% were altered and 21.5% developed liver injury after admission, increasing the risk of severe disease by nine times (odds ratio [*OR*] = 9.04; 95% confidence interval [*CI*]: 3.19–25.6; $p < 0.001$)[2]. These results are like those found by Mao *et al*, who conducted a meta-analysis that included 35 studies and more than 6,000 patients. They found a 15% prevalence of gastrointestinal manifestations and 19% liver test abnormalities. Severe cases were associated with a higher rate of gastrointestinal symptoms and liver test abnormalities than non-severe cases[26].

Omrani-Nava V *et al*, through a case-control study of 93 patients with COVID-19 and 186 healthy people, evaluated hospital stay, mortality, and prognosis associated with liver test abnormalities and found a significant elevation of aspartate-aminotransferase (AST) ($p < 0.001$), alanine-aminotransferase (ALT) ($p < 0.001$), and alkaline phosphatase ($p = 0.004$) in infected patients compared to controls. The elevation of indirect bilirubin and AST had a sensitivity of 71.4% and specificity of 68.5% for transfer to the intensive care unit (ICU). Similarly, AST levels were also associated with mortality in these patients ($p = 0.023$)[27].

Nonetheless, given the presence of this enzyme in other tissues, it is possible that its elevation reflects the systemic involvement of SARS-CoV-2 and is not necessarily a marker of liver dysfunction[15,27]. In a retrospective study carried out by Xie *et al*, prolonged hospitalization was noted in patients with liver damage who exhibited an increase in leukocytes, neutrophils, CRP, and greater pulmonary involvement in the CAT ($p < 0.05$)[28].

Other alterations in paraclinical tests were reported in the study by Li *et al.* On the one hand, they found a higher elevation of lactic acid ($p = 0.037$), neutrophilia ($p = 0.006$), myoglobin ($p = 0.001$), and decreased lymphocytes and albumin ($p = 0.000$) in the group with liver injury. Lymphopenia ($p = 0.005$) and CRP levels > 20 mg/L ($p = 0.014$) were independent risk factors for developing liver damage[29]. On the other hand, patients treated with antiviral drugs such as lopinavir/ritonavir were more prone to developing a liver injury, so cautious administration of these antivirals is advisable[2].

In conclusion, the evidence suggests that, for the time being, the alteration of liver tests during SARS-CoV-2 infection behaves like a poor prognostic marker that probably reflects the systemic involvement of the virus and that the appearance of severe liver complications during infection is infrequent.

CLINICAL MANIFESTATIONS IN PATIENTS WITH PREVIOUS LIVER DISEASE AND LIVER TRANSPLANT

According to statistics from China, where the COVID-19 pandemic began, 2%–11% of patients with SARS-CoV-2 infection had liver comorbidities, and 14%–53% showed alterations of aminotransferases during the disease[1].

One of the comorbidities present in patients with COVID-19 is liver cirrhosis. A recent study carried out in Wuhan, China, with a sample of 111 patients with decompensated cirrhosis, revealed that when precautionary and isolation measures were taken, there were no suspected or confirmed cases of COVID-19, while in a similar population with the same diagnosis of 101 patients treated in other hospitals where these measures were not adopted, the incidence was 17%[30].

Generally, patients with comorbidities such as type 2 diabetes mellitus (DM2) or cardiovascular disease are at high risk for developing severe disease from COVID-19 and non-alcoholic fatty liver disease (NAFLD), making them more susceptible to liver compromise[17]. In a study to evaluate the rate of confirmed patients for COVID-19 and NAFLD, liver damage was observed in 50% during admission and 75% during the hospital stay. The majority had hepatocellular alterations due to elevated aminotransferases[31]. The same study found that patients with NAFLD had a higher risk of disease progression, a greater probability of impaired liver function upon admission, and prolonged viral shedding than patients without NAFLD[31]. This association may be mediated by the high presence of diabetes mellitus, hypertension, dyslipidemia, and obesity, known risk factors for NAFLD and the progression of SARS-CoV-2 infection. In fact, the relationship between obesity, NAFLD, and COVID-19 has been studied. The results of the study published by Zheng *et al* state that obesity in patients with NAFLD was associated with a six-fold increased risk of severe COVID-19[32].

Additionally, in patients with a history of liver transplantation and SARS-CoV-2 infection, there is a risk of transmission from donors to recipients; furthermore, when the recipient develops the disease, it can produce more significant viral load and spread, increasing the potential for contagion to other individuals[33]. So far, several case reports evidence the clinical course and outcomes of patients with a history of liver transplantation and COVID-19 (**Table 1**). It should be mentioned that, in all cases, the diagnosis was made by RT-PCR, diminishing immunosuppressive management during the disease. In a case series from Italy,

Table 1. Characteristics of the subjects in the case report of patients diagnosed with COVID-19 and a history of liver transplantation

Author	Age	Sex	History	Transplant date	Treatment	Oxygen therapy	Final condition
Qin *et al* [36]	37	M	Hepatocellular carcinoma, HBV infection	January 2020	- Oseltamivir - rhG-CSF - IVIG	High flow nasal cannula	Alive
Lui *et al* [37]	50	M	Liver cirrhosis, HBV infection	July 2017	- Umifenovir - Lopinavir/ritonavir - Methylprednisolone - IVIG - Cefoperazone - IFN-α	Nasal cannula	Alive
Huang *et al* [38]	59	M	Hepatocellular carcinoma, HBV infection	May 2017	- Umifenovir - Lopinavir/ritonavir - IFN-α Piperacillin/tazobactam	Invasive ventilation	Dead

IVIG: Intravenous immunoglobulin; rhG-CSF: Recombinant Human Granulocyte Colony-Stimulating Factor.

three patients died from SARS-CoV-2 infection, although they had undergone the transplant more than ten years ago. These patients shared age > 65 years, hypertension, overweight, diabetes mellitus, and dyslipidemia. Therefore, this outcome seems to be more related to these comorbidities than a direct complication of the transplant[34]. In this type of patient, strategies are aimed at prevention such as social isolation, avoiding unnecessary trips, telemedicine, hand hygiene, constant temperature checks, and early attendance at a health center in case of symptoms associated with SARS-Cov-2 infection[35].

TREATMENT

For those patients who develop liver disease due to SARS-CoV-2, management is not well defined and is based on standard guidelines[1,16]. Regarding treatment, the administration of various medications (remdesivir, lopinavir, ritonavir, hydroxychloroquine, azithromycin, umifenovir, among others) has been studied. However, in patients with pre-existing liver disease or those who develop it during infection, the risk of hepatotoxicity, drug interactions, and recommendations for use should be evaluated (**Table 2**) to avoid worsening the clinical picture[1,39].

For patients with pre-existing liver disease infected with SARS-CoV-2, there is more significant evidence of management depending on the entity they exhibit (**Table 3**). Generally, hospitalization in case of risk factors that may result in a severe event (hypertension, diabetes, obesity, cirrhosis, hepatocellular carcinoma, or liver transplant), incorporating antiviral treatments, following the management guidelines for liver disease, and preventing acetaminophen overdose with doses of 2–3g/day are recommended[39].

CONCLUSIONS

SARS-CoV-2 mainly affects the respiratory system and is the primary concern of the health sector worldwide. Nevertheless, the involvement of different organs and systems has been frequent in infected patients during this pandemic, making it necessary to consider extrapulmonary symptoms as atypical manifestations of the disease. The alteration of liver biochemistry seems to be a poor prognostic factor in these patients. Although there is no specific treatment for liver complications, recommendations have been made to mitigate the damage in patients with pre-existing liver disease or those who develop it during the infection aimed at the rational use of specific drugs for the liver or treatments against SARS-CoV-2 with potential hepatotoxicity.

Table 2. Drug interactions, liver involvement, and recommendations in pre-existing liver disease for drugs used in the treatment of SARS-CoV-2[39]

Drug	Adverse effects, recommendation, or drug interaction
Remdesivir	- Safe in HBV and HCV (nucleotide analog) - Hepatotoxicity (increased ALT) may occur - No significant drug interactions
Hydroxychloroquine/azithromycin	- Exclude G6PD deficiency before starting - Drug interaction with immunosuppressants - Null or mild hepatotoxicity
Lopinavir/ritonavir	- Drug interaction with immunosuppressants - Contraindicated in patients taking mTOR inhibitors - Low risk of hepatotoxicity
Tocilizumab	- Elevation of ALT is common - Not recommended in patients with decompensated cirrhosis - Could reactivate HBV
Glucocorticoids	- Increases the risk of developing other infections (spontaneous bacterial peritonitis) - Increases viral shedding in patients with decompensated cirrhosis - Antimicrobial prophylaxis should be performed - Could reactivate HBV
Umifenovir (Arbidol)	- Drug interaction with inhibitors and inducers of CYP3A4 - Metabolism is potentially hepatic
Favipiravir/favilavir	- Liver metabolism (aldehyde oxidase and xanthine oxidase) - Elevation of ALT and rarely of AST
Sofosbuvir/ribavirin	- Good result in patients with HCV and decompensated cirrhosis - Ribavirin can cause hemolytic anemia
Baricitinib	- Mild and transient increase in ALT - Do not administer in decompensated cirrhosis
Emapalumab	- Mild and transient increase in ALT weeks after initiation of treatment - Could reactivate TB, *Pneumocystis jirovecii*, shingles, and HBV
Anakinra	- Low liver metabolism

CYP3A4: Cytochrome P450 3A4; G6PD: Glucose-6 phosphate dehydrogenase; mTOR: Mammalian target of rapamycin; TB: tuberculosis. Adapted from: Boettler T *et al* JHEP Rep. 2020;2(3):100113.

Table 3. Recommendations in managing patients with pre-existing liver disease and SARS-CoV-2[39]

Liver disease or involvement	Recommendation
All patients with pre-existing liver disease	- Hospitalize if there are risk factors - Start management with antivirals - Acetaminophen, maximum dose 2–3 g/day
Decompensated cirrhosis or portal hypertension	- Do not administer NSAIDs - Continue with the pharmacological management of the disease to avoid complications
Chronic HBV with low viral load	- Nucleotide analog treatment
Autoimmune hepatitis	- Management with glucocorticoids (there is no evidence of prognosis in these patients)
Hepatocellular carcinoma	- Regional and checkpoint inhibitor therapies should be postponed - The use of kinase inhibitors should be agreed with the specialist in patients with non-severe COVID-19
Liver transplant	- Adjust doses of calcineurinics and mTOR inhibitors according to antiviral therapy

NSAIDs: Non-steroidal anti-inflammatory drugs. Adapted from: Boettler T *et al* JHEP Rep. 2020;2(3):100113.

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