

Liver dysfunction and SARS-CoV-2 infection

Abraham Edgar Gracia-Ramos, Joel Omar Jaquez-Quintana, Raúl Contreras-Omaña, Moises Auron

ORCID number: Abraham Edgar Gracia-Ramos 0000-0003-1842-2554; Joel Omar Jaquez-Quintana 0000-0002-0990-8571; Raúl Contreras-Omaña 0000-0003-0062-5919; Moises Auron 0000-0001-6398-6047.

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Abraham Edgar Gracia-Ramos, Department of Internal Medicine, General Hospital, National Medical Center "La Raza", Instituto Mexicano del Seguro Social, Mexico City 02990, Mexico

Joel Omar Jaquez-Quintana, Gastroenterology Service and Department of Internal Medicine, Faculty of Medicine, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo León, Monterrey 64460, Mexico

Raúl Contreras-Omaña, Centro de Estudio e Investigación en Enfermedades Hepáticas y Toxicológicas (CEIHET), Pachuca 42184, Mexico

Moises Auron, Departments of Hospital Medicine and Pediatric Hospital Medicine, Cleveland Clinic, Cleveland, OH 44195, United States

Corresponding author: Abraham Edgar Gracia-Ramos, MD, MSc, Department of Internal Medicine, General Hospital, National Medical Center "La Raza", Instituto Mexicano del Seguro Social, Av. Jacaranda S/N, Col. La Raza, Del. Azcapotzalco, C.P., Mexico City 02990, Mexico. dr.gracia.dmm@gmail.com

Abstract

Severe acute respiratory syndrome coronavirus 2 infection is the cause of coronavirus disease 2019 (COVID-19), which predominantly affects the respiratory system; it also causes systemic and multi-organ disease. Liver damage is among the main extrapulmonary manifestations. COVID-19-associated liver injury is defined as any liver damage occurring during the disease course and treatment of COVID-19 in patients with or without pre-existing liver disease, and occurs in approximately one in five patients. Abnormal liver test results have been associated with a more severe course of COVID-19 and other complications, including death. Mechanisms linking COVID-19 to liver injury are diverse. Particular consideration should be made for patients with pre-existing liver disease, such as metabolic dysfunction-associated fatty liver disease, chronic liver disease due to viral or autoimmune disease, liver transplant carriers, or cirrhosis, given the risk for more severe outcomes. This manuscript summarizes the current lines of evidence on COVID-19-associated liver injury regarding pathophysiology, clinical significance, and management in both patients with or without pre-existing liver disease, to facilitate clinicians' access to updated information and patient care. Finally, we mention the ideas and recommendations to be considered for future research.

Key Words: SARS-CoV-2; Coronavirus; COVID-19; Liver; Liver diseases; Liver failure; Liver injury; Cirrhosis

and hepatology

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Core Tip: Coronavirus disease 2019 (COVID-19)-associated liver injury is defined as any liver damage occurring during the disease course and treatment of COVID-19 in patients with or without pre-existing liver disease, with an observed ratio of 1:5. The presence of abnormal liver biochemical parameters has been associated with a severe course of severe acute respiratory syndrome coronavirus 2 infection and other complications, including death. Pathophysiology of COVID-19-induced liver injury is complex. Also, special consideration should be made in patients with pre-existing liver disease, such as metabolic dysfunction-associated fatty liver disease, chronic liver disease due to viral or autoimmune disease, liver transplant carriers, or cirrhosis.

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INTRODUCTION

In December 2019, multiple cases of unexplained pneumonia were reported in Wuhan, China[1]. The etiology of the outbreak was attributed to a newly identified coronavirus, initially named '2019-nCoV' (human), and subsequently renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was denominated coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO)[1,2]. Due to the constantly increasing number of cases worldwide, on March 11, 2020, the WHO formally declared the COVID-19 outbreak as a pandemic[3]. More than a year after its appearance, SARS-CoV-2 has infected almost 10 million people worldwide and caused more than 2 million deaths[4].

Coronaviruses are members of the subfamily Coronavirinae in the family Coronaviridae and the order Nidovirales (International Committee on Taxonomy of Viruses). This subfamily consists of four genera (*Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*)[5]. The *Betacoronavirus* include the Middle East respiratory syndrome (MERS) coronavirus, SARS-CoV, and SARS-CoV-2. These viruses have a positive-sense single-stranded RNA genome[6]. The angiotensin-converting enzyme 2 (ACE2) has been identified as the main viral receptor for SARS-CoV and SARS-CoV-2[5,7]. ACE2 is ubiquitously and widely expressed in many organs and systems, including the lungs, cardiovascular system, kidneys, pancreas, intestines, liver, adipose tissue, and muscular and nervous systems[8]. Another cellular protein, the transmembrane protease serine 2 (*i.e.*, TMPRSS2), facilitates viral entry into the host cells through plasma membrane surface interaction[9].

SARS-CoV-2 could be transmitted from person to person through close contact, respiratory droplets, and aerosol[10]. The manifestations of COVID-19 represent a wide clinical spectrum, which ranges from asymptomatic individuals or mild respiratory symptoms to severe-critical illness; overall, it is categorized as a mild, severe, or critical illness[11]. Although SARS-CoV-2 predominantly causes respiratory symptoms, it can also result in extrapulmonary disease, including thrombotic complications, myocardial damage, acute kidney failure, gastrointestinal symptoms, hepatocellular injury, hyperglycemia and ketosis, neurologic illnesses, ocular symptoms, and dermatologic manifestations[12,13]. These manifestations can occur in subjects without identified pre-existing organic disease, as well as in individuals with comorbidities, such as patients with hypertension, obesity, and chronic liver disease, among others.

The objective of this review is to discuss and show current data regarding liver dysfunction caused by SARS-CoV-2 infection in patients with or without pre-existing liver disease, its pathophysiology and management, as well as the prospects for future research.

SARS-COV-2 INFECTION AND LIVER DYSFUNCTION IN PATIENTS WITH NO PREVIOUS LIVER DISEASE

Epidemiology

COVID-19-associated liver injury is defined as any liver damage occurring during disease course and treatment of COVID-19 in patients with or without pre-existing liver disease[14]. A summary of the principal studies about liver damage in COVID-19 patients is showed in Table 1. Studies have shown that one in five patients with COVID-19 develop abnormalities in liver function tests[15]. A large systematic review that included 64 studies with 11245 patients with SARS-CoV-2 infection showed the following prevalence of abnormal liver function parameters: Elevated aspartate aminotransferase (AST) in 23.2%; alanine aminotransferase (ALT) in 21.2%; elevated total bilirubin in 9.7%; increased gamma-glutamyltransferase (GGT) in 15.0%; and increased alkaline phosphatase in 4.0%[16]. The presentation of liver injury during COVID-19 infection occurs mostly during the acute hospitalization period and it is associated with increased length of hospital stay, worse pulmonary score on computed tomography (commonly referred to as CT), overall severity of disease, and increased mortality.

In a single-center retrospective study that described temporal variations of liver injury during hospitalization due to SARS-CoV-2 infection, the percent of subjects with elevated aminotransferases (transaminitis) in mild cases was 12.6% *vs* 46.2% in severe cases. Most of the patients presented ALT elevations between days 4 and 17 of their hospitalization, with a mean of 10.7 d and 7.3 d in mild and severe cases, respectively. During treatment, increases in liver function test parameters were predominantly mild and elevations in ALT and AST were largely isolated, occurring in 19% of patients. The majority of patients were discharged with normal liver function parameters[17]. A large retrospective multicenter cohort study that included 5771 patients with COVID-19 pneumonia determined the distribution and temporal patterns of liver injury indicators in these patients; an initial elevation of AST, followed by ALT in severe patients, and mild fluctuation in total bilirubin levels in both non-severe and severe disease were found[18]. Another study of 79 in-patients with COVID-19 found that the extent of pulmonary lesions observed on CT was predictive of liver function damage [19]. In a systematic review that included 45 studies, abnormal liver biochemical indicators were detected at admission in 27.2% of cases, which increased to 36% during hospitalization, and there was a higher incidence of severe and/or critical cases [20]. Another meta-analysis revealed that, among 15407 patients with SARS-CoV-2 infection, the incidence of elevated liver chemistries was 23.1% at early presentation and 24.4% throughout the course of illness[21]. A prospective cohort study in 1611 hospitalized patients from 11 Latin American countries found abnormal liver tests on admission in 45.2% and that such was independently associated with death [odds ratio (OR): 1.5, 95% confidence interval (CI): 1.1-2.0] and severe COVID-19 (OR: 2.6, 95% CI: 2.0-3.3)[22]. A systematic review of 24 studies (5961 subjects) found that, among COVID-19 patients who were critically ill, the OR of hypoalbuminemia was 7.1, of AST elevation was 3.4, of ALT elevation was 2.5, and of hyperbilirubinemia was 1.7[23]. Systematic reviews with meta-analyses showed that patients with prolonged prothrombin time had a higher odds for progression to severe disease (OR: 1.82) and intensive care unit (ICU) admission (OR: 2.18)[24,25]. A synthesis of the literature that compared survivors and non-survivors with severe COVID-19 patients showed an OR of 1.98 (95% CI: 1.39-2.82) for liver dysfunction and mortality[26]. Similarly, previous investigations have shown that liver injury was common among patients infected by SARS-CoV and MERS coronavirus, and associated with the severity of diseases[27].

In patients with SARS-CoV-2 infection, the degree of transaminitis is generally mild [22,23], defined as less than 5 times the upper reference limit, and severe liver failure occurs infrequently[28]. In a cohort of 5700 patients from New York, United States, AST and ALT were both commonly increased (58.4% and 39.0% of subjects, respectively). In this same study, 56 (2.1%) patients had developed severe acute liver injury (defined as an increase in ALT or AST of > 15 times the upper limit of normal) and an association with mortality was found in 95%[29]. Finally, abnormal liver function test has been observed in patients with subclinical disease (elevated AST in 8.7% and elevated ALT in 8.9%)[30].

Pathophysiology

The mechanisms of liver injury in patients with SARS-CoV-2 infection are diverse. It has been postulated that SARS-CoV-2 may cause cytopathic effects due to viral replication after entrance into the liver and bile duct cells *via* interaction with ACE2

Table 1 Principal studies about liver damage in coronavirus disease 2019 patients

Ref.	Study	Findings
Mao <i>et al</i> [15]	SR (35 studies, <i>n</i> = 6686)	The prevalence of abnormal liver functions was 19% (CI: 9-32). Patients with severe COVID-19 had higher rates of abnormal liver function including increased ALT (OR: 1.89, CI: 1.30-2.76) and increased AST (OR: 3.08, CI: 2.14-4.42) compared with those with non-severe disease
Wijarnpreecha <i>et al</i> [16]	SR (64 studies, <i>n</i> = 11245)	The prevalence of elevated AST, ALT, total bilirubin, GGT, and alkaline phosphatase was 23.2%, 21.2%, 9.7%, 15.0%, and 4.0%, respectively. The prevalence of elevated AST was higher among those with severe cases (45.5%) compared to non-severe cases (15.0%). Co-existing CLD presented in up to 37.6% of patients with COVID-19
Wang <i>et al</i> [17]	Single-center retrospective study (<i>n</i> = 105)	Fifty-six percent of the patients had abnormal ALT, AST, or total bilirubin during the illness (91.4% cases were \leq 3 fold of the ULN). The percentage of patients with elevated both ALT and AST was 12.7% in mild cases vs 46.2% in severe cases. One third of patients with severe disease started to have abnormal ALT after admission, and 73.3% of all patients had normal ALT before discharge
Lei <i>et al</i> [18]	Multicenter retrospective cohort study (<i>n</i> = 5771)	The distributional and temporal patterns of liver injury indicators were following: AST elevated first, followed by ALT, in severe patients. Alkaline phosphatase modestly increased during hospitalization and largely remained in the normal range. The fluctuation in total bilirubin levels was mild in the non-severe and severe groups
Xie <i>et al</i> [19]	Retrospective study (<i>n</i> = 79)	Logistic regression analyses suggested that the extent of pulmonary lesions on CT was a predictor of liver function damage
Wu <i>et al</i> [20]	SR (45 studies, <i>n</i> = 7228)	The incidence of any abnormal liver biochemical indicator at admission and during hospitalization was 27.2% and 36%, respectively
Kulkarni <i>et al</i> [21]	SR (107 studies, <i>n</i> = 20874)	The prevalence of CLD was 3.6% (CI: 2.5-5.1). The incidence of elevated liver chemistries was 23.1% (CI: 19.3-27.3) at initial presentation and 24.4% (CI: 13.5-40) during the illness. The incidence of DILI was 25.4% (CI: 14.2-41.4). The prevalence of CLD among 1587 severely infected patients was 3.9% (3%-5.2%). CLD was not associated with the developing severe COVID-19 (OR: 0.81, CI: 0.31-2.09) compared to non-CLD patients. COVID-19 patients with elevated liver chemistries had an increased risk of mortality (OR: 3.46 CI: 2.42-4.95) and severe disease (OR: 2.87, CI: 2.29-3.6) compared to patients without
Mendizabal <i>et al</i> [22]	Multicenter prospective cohort study (<i>n</i> = 1611)	Abnormal liver tests on admission were present on 45.2% and were independently associated with death (OR: 1.5, CI: 1.1-2.0), and severe COVID-19 (OR: 2.6, CI: 2.0-3.3). The prevalence of CLD was 8.5%
Wong <i>et al</i> [23]	SR (24 studies, <i>n</i> = 5961)	In subjects with critical COVID-19, the OR of hypoalbuminemia was 7.1 (CI: 2.1-24.1), of AST elevation was 3.4 (CI: 2.3-5.0), of ALT elevation was 2.5 (CI: 1.6-3.7), and of hyperbilirubinemia was 1.7 (CI: 1.2-2.5)
Zhu <i>et al</i> [24]	SR (34 studies, <i>n</i> = 6492)	Patients with severe COVID-19 showed significantly longer PT, and a longer PT was associated with a higher risk to die
Eshazli <i>et al</i> [25]	SR (52 studies, <i>n</i> = 6320)	Prolonged PT was associated with a higher risk of progression to severe COVID-19 (OR: 1.82) and ICU admission (OR: 2.18)
Wu and Yang [26]	SR (13 studies, <i>n</i> = 3722)	The comparison between survivors and non-survivors with severe COVID-19 patients showed an OR of 1.98 (CI: 1.39-2.82) for liver dysfunction and mortality
Richardson <i>et al</i> [29]	Multicenter prospective cohort study (<i>n</i> = 5700)	In hospitalized COVID-19 patients, AST and ALT were both commonly increased (58.4% and 39.0% of patients, respectively). Fifty-six (2.1%) subjects developed a severe acute liver injury with a mortality of 95%
Shi <i>et al</i> [30]	Two-center retrospective study (<i>n</i> = 81)	Abnormal liver function test was found in patients with subclinical disease (elevated AST in 8.7% and elevated ALT in 8.9%)
Sultan <i>et al</i> [58]	SR (47 studies, <i>n</i> = 10980)	The prevalence estimates of elevated liver abnormalities were as follows: AST 15.0% (CI: 13.6-16.5), ALT 15.0% (CI: 13.6-16.4), and abnormal bilirubin 16.7% (CI: 15.0-18.5)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CI: Confidence interval; CLD: Chronic liver disease; COVID-19: Coronavirus disease 2019; CT: Computed tomography; DILI: Drug-induced liver injury; GGT: Gamma-glutamyltransferase; ICU: Intensive care unit; PT: Prothrombin time; OR: Odds ratio; SR: Systematic review; ULN: Upper limit of normal.

and TMPRSS2[31]. ACE2 expression is considerably higher in cholangiocytes (59.7%) than in hepatocytes (2.6%)[32]. Cholangiocytes have an important role in immune response, inflammation, and liver regeneration[33]. Furthermore, the expression of ACE2 in hepatocytes increases in cases of liver injury[34]. In postmortem liver biopsies from two patients who died from COVID-19, typical coronavirus particles were identified in the cytoplasm of hepatocytes, with cytopathic damage characterized by mitochondrial swelling, endoplasmic reticulum dilatation, and glycogen granule decrease[35]. These findings support the hypothesis of virus-related hepatic damage. However, other liver biopsy specimens of a patient who died from COVID-19 showed moderate microvesicular steatosis and mild lobular and portal activity, which are not specific and could have been caused by the viral infection, drug-induced liver injury (DILI), or nonalcoholic fatty liver disease (NAFLD)[36,37]. In addition, viral inclusion

bodies were not detected in liver tissue[37]. Another postmortem liver histopathologic study also reported microvesicular steatosis, accompanied by overactivation of T cells, suggesting a component of immune-mediated liver injury[38]. SARS-CoV-2 could also cause liver damage through the generation of endothelitis[39]. Endothelial cells are involved in ischemia-reperfusion liver damage and promote oxidative stress through reactive oxygen species and derivatives of nitric oxide[40]. Post-mortem wedge liver biopsies from 48 patients who died from severe COVID-19 disease showed vascular alterations characterized by an increased number of portal vein branches associated with massive lumen dilatation, partial or complete luminal thrombosis of portal and sinusoidal vessels, and marked focal enlargement and fibrosis of the portal tract[41]. In addition, transaminitis has been reported in some cases of portal thrombosis due to SARS-CoV-2 infection[42,43].

The immune overactivation associated with SARS-CoV-2 infection may also be involved in liver injury. Prominent elevations in serum inflammatory cytokine levels, such as interferon- γ , interleukin (IL)-1 β , IL-6, IL-10, soluble IL-2 receptor α , and tumor necrosis factor, are present in patients with COVID-19, especially those with severe pneumonia[44,45]. This can lead to immune-mediated liver injury *via* activation of intrahepatic CD4+ and CD8+ cells, T cells, Kupffer cells, and a dysregulated innate immune response[46,47]. This phenomenon has also been described in infections caused by herpes viruses (Epstein-Barr virus, cytomegalovirus, and herpes simplex virus), parvovirus, adenovirus, and SARS-CoV[47]. Moreover, COVID-19 patients with increased AST also have elevated IL-6, ferritin, lactate dehydrogenase, and C-reactive protein compared to patients with normal AST[48].

In the course of infection by SARS-CoV-2, hepatic ischemia and hypoxia with impaired tissue perfusion can develop as a consequence of pneumonia-associated hypoxemia, circulatory failure, respiratory distress syndrome, and multiple organ failure[49]. Hepatic congestion secondary to high positive end-respiratory pressure in mechanically-ventilated patients may also enhance the degree of hypoxic damage in hepatocytes[32,46].

Liver injury associated with COVID-19 may also occur secondary to the potentially hepatotoxic effects of many drugs used for its treatment, such as acetaminophen, antivirals, antibiotics, corticosteroids, and immune modulators, among others. The presence of microvesicular steatosis and liver inflammation in liver biopsies of patients with SARS-CoV-2 infection could also be drug-related[37]. The drug-cytochrome P-450 interaction could explain some of the liver toxicity secondary to such drugs as azithromycin, lopinavir/ritonavir, hydroxychloroquine, and acetaminophen[50]. Additionally, patients with underlying NAFLD might be more susceptible to DILI because the cytokine monocyte chemoattractant protein-1 (*i.e.*, MCP-1) is often elevated in COVID-19 patients and could exacerbate steatohepatitis[51]. In a systematic review which included 107 articles ($n = 20874$ patients), the pooled incidence of DILI in COVID-19 patients was 25.4%[21]. A more detailed description of the drugs to treat SARS-CoV-2 infection and their potential risk of liver damage is discussed later.

SARS-CoV-2 RNA has been detected in feces, and it appears plausible that virus and inflammatory mediators present within the gut lumen could reach the liver through the portal circulation. Kupffer cells could attempt to clear the viral particles, consequently increasing the inflammatory response[39,50].

Other causes that are not necessarily associated with direct hepatocyte injury may explain the abnormal liver biochemical indicators in patients with SARS-CoV-2 infection. Transaminitis could originate from myositis rather than liver damage[52]. Muscular injury [defined as the presence of myalgias and creatinine kinase (CK) > 200 U/L] has been documented in 10% of hospitalized patients by COVID-19 and some studies have reported increased levels of myoglobin of CK in association with COVID-19 severity[46,53,54]. Hypoalbuminemia could be explained by decreased hepatic synthesis, malnutrition, increased catabolism, and albumin extravasation because of increased capillary permeability[55,56]; we must recall that hypoalbuminemia is also an acute phase reactant. Alkaline phosphatase and GGT are considered as cholangiocyte-related enzymes, but the higher prevalence of abnormal GGT may be attributed to acute inflammatory stress because the GGT is recognized as a surrogate marker for increased oxidative stress and inflammation[57].

Management

The recommendations by the American Gastroenterology Association and the World Gastroenterology Organization regarding the general approach to patients with SARS-CoV-2 infection and liver injury are as follows[58,59]: (1) In patients with abnormal liver function test results in the context of suspected or known COVID-19, evaluate for

alternative etiologies, including proof of viral hepatitis, particularly in developing countries; (2) Routine outpatient testing of liver biochemistries is not recommended; (3) In in-patients with COVID-19, obtain baseline liver indicators at the time of admission and consider its monitoring throughout the hospitalization; and (4) Avoid routine liver imaging, unless it will alter management.

FATTY LIVER DISEASE

General implications and epidemiology

The presence of metabolic dysfunction-associated fatty liver disease (MAFLD; previously known as NAFLD)[60] in the patients with infection by SARS-CoV-2 (*i.e.*, COVID-19) is important given that specific metabolic and cardiovascular comorbidities intrinsically related to MAFLD, like hypertension, diabetes, obesity, coronary artery disease, and cerebrovascular disease, were identified as independent risk factors associated with increased risk of infection by SARS-CoV-2[61,62], especially hypertension[52], diabetes[63,64], and obesity [body mass index (BMI) > 30 kg/m²][65]; furthermore, morbid obesity (BMI > 40 kg/m²) is a strong risk predictor of hospitalization in patients with COVID-19[66].

MAFLD has been associated with an increased risk for mortality in patients with community-acquired pneumonia, which is further enhanced in patients with advanced liver fibrosis[67]. Also, MAFLD has been associated with an increased risk for bacterial infections, independent of the presence of metabolic syndrome and especially among patients with vitamin D deficiency[68]. The relevance of this is the recognition of MAFLD as a risk factor for severe infections.

MAFLD is an independent risk factor for progression of COVID-19 respiratory disease (OR: 6.4, 95%CI: 1.5-31.2), and this risk is heightened in patients with associated liver fibrosis[38,69,70]. In addition, MAFLD is associated with a higher likelihood of abnormal levels of aminotransferases at time of discharge as well as increased duration of virus shedding, which renders the individual infectious for 5 d longer[38,59]. The increased risk for viral infection in patients with MAFLD may be related to the pre-existent intrinsic up-regulation of ACE2 receptors that occurs in this disease, as well as in liver injury; in addition, the ACE2 receptors have been identified as the cellular point of entry of SARS-CoV-2[59].

A multicenter study of COVID-19 patients in the United States found a significant association between MAFLD and ICU admissions (OR: 2.30, 95%CI: 1.27-4.17, $P = 0.03$) as well as need for mechanical ventilation (OR: 2.15, 95%CI: 1.18-3.91, $P = 0.02$) but did not find a correlation with increased mortality[71]. A cohort study in the United Kingdom (Forlano *et al*[72]) showed that patients with MAFLD were younger than their counterparts without MAFLD. MAFLD *per se* had no direct correlation with increased mortality; however, among those who died in hospital, the risk was associated with male sex (71% *vs* survivors: 50%, $P = 0.01$), elevated ferritin (2076 µg/L *vs* survivors: 688 µg/L, $P = 0.003$), and early weaning score ($n = 7$ *vs* survivors: 3, $P = 0.047$). A recent systematic review of eight studies, including 8142 patients with COVID-19 and 833 of those with MAFLD, found that MAFLD by itself conferred an increased risk for severe COVID-19 of 2-fold (OR: 2.358, 95%CI: 1.902-2.923, $P < 0.001$) [73]. Finally, a meta-analysis of six studies ($n = 1293$) found an increase in the risk of COVID-19 disease severity of almost 3-fold (OR: 2.93, 95%CI: 1.87-4.60, $I^2 = 34.3\%$, $P = 0.166$) among patients with MAFLD[74].

The comorbidities and increased inflammatory state in patients with MAFLD confer a hypothetical increased risk for DILI and, hence, careful monitoring of liver function is warranted in these patients, as are efforts to minimize exposure to polypharmacy [75].

Age and MAFLD

A cohort study in the United Kingdom found that most patients with COVID-19 and MAFLD were younger than 60 years old, as compared with patients with no MAFLD [72]. Among younger patients (age < 60 years old), the risk of severe COVID-19 is increased by 4-fold among those with concomitant NAFLD (OR: 4.07, 95%CI: 1.20-13.79, $P = 0.02$)[76,77].

Histopathologic changes in COVID and MAFLD

Although the severity of hepatic visceral fat correlates with the risk of COVID-19 infection[78], in general, the histopathologic findings in the liver in patients with SARS-CoV-2 infection have been presumed to be related mostly to the underlying liver

disease (*e.g.*, MAFLD) or other comorbidities (*e.g.*, drug toxicity and ICU care) rather than to a direct effect of the viral infection[79]. However, Nardo *et al*[80] described several mechanisms in which there is increased liver steatosis as a consequence of the viral infection; these include impaired mitochondrial dysfunction, endoplasmic reticulum stress-induced lipogenesis, and inflammation (including cytokine storm) with increased IL-6 and hyperstimulation of the mammalian target of rapamycin (*i.e.*, mTOR). The mTOR is also activated by glucose and insulin, and insulin resistance is also intrinsically associated with MAFLD; therefore, not only is there already an underlying inflammatory state but it can also be enhanced further by direct viral cytopathic effect[80].

Obesity and MAFLD

When considering the correlation of obesity and metabolic disease with the increased risk of COVID-19 as well as of severity of clinical presentation, one of the most accepted hypotheses is the presence of underlying chronic inflammatory state in these patients enhancing oxidative stress and increasing atherosclerosis and cardiovascular disease[81,82]. In addition, it is well evidenced that obesity confers an impaired immune response to viruses, with associated prolonged viral shedding as well as emergence of virulent minor variants[83]. If the readers would like to explore more intricate descriptions of the pathophysiology of inflammation in MAFLD and obesity, they are referred to the excellent manuscript by Portincasa *et al*[84].

In a study conducted in a Chinese population by Gao *et al*[65], the presence of obesity was found to increase the risk of severe COVID-19 by almost 3-fold (OR: 2.91, 95%CI: 1.31-6.47); furthermore, this risk was incrementally raised by 12% per unit of increase in BMI (OR: 1.12, 95%CI: 1.01-1.23). A prospective study of 5279 patients admitted to a hospital in New York, United States found that BMI > 40 kg/m² increased the risk of hospitalization by more than 2-fold (OR: 2.5, 95%CI: 1.8-3.4) and the risk of critical illness by 50% (OR: 1.5, 95%CI: 1.0-2.2)[66]. A very important epidemiological risk factor was reported by Kass *et al*[85], who identified a negative correlation of increased BMI and age among patients with severe COVID-19 infection, which showcases its impact in young patients. The co-existence of obesity and MAFLD has also been associated with an almost 6-fold increase in the risk of severe COVID-19 infection[38,86]. Furthermore, the severity of steatosis also correlates with the risk of infection as demonstrated by Roca-Fernández *et al*[78], who reported that among obese patients (BMI > 30 kg/m²) with liver fat > 10%, the risk of symptomatic COVID-19 infection was increased almost 3-fold (OR: 2.96, 95%CI: 1.12-7.78, *P* = 0.02).

Management of patients with MAFLD in the era of COVID-19

The World Gastroenterology Organization recently published its recommendations for management of patients with MAFLD in the COVID-19 era, which essentially recommends to[59]: (1) Recognize the presence of MAFLD in patients with underlying metabolic disease, formally identifying its stage and grade; (2) Recognize that obesity and diabetes mellitus increase the risk of mortality from respiratory illnesses, including COVID-19; (3) Recognize that the risk of respiratory disease progression is higher in patients with MAFLD; and (4) Encourage patients with MAFLD to make lifestyle changes that will mitigate risk factors (*e.g.*, obesity) that can worsen the prognosis of COVID-19.

SARS-COV-2 INFECTION IN LIVER TRANSPLANT PATIENTS

In this section, we will focus on the assessment and management of patients with a transplanted liver who present with infection by SARS-CoV-2 (COVID-19).

Liver transplant patients are frail and have many risk factors for COVID-19 infection, including immunosuppression, in addition to other underlying comorbidities[87]. The symptomatology among patients with solid organ transplant who are infected with COVID-19 is similar to that among the general population; however, the severity and outcomes are worse, especially as both are impacted by their comorbidities[88,89].

Epidemiology

Imam *et al*[87] reported a review of ten studies from all over the world that included 22 patients with orthotopic liver transplant, among which 72% experienced clinical recovery from COVID-19, with a median duration of illness of 17 d. ICU admission was required in 28.6% of patients and the mortality rate in the cohort was 13.6%. On

the other hand, a European liver transplant cohort study of 57 patients with COVID-19 (70% male; median age of 65 years) found no significant impact of decreasing immunosuppression (37% of patients). The rate of hospitalization was 72%, and acute respiratory distress syndrome was present in 19% of cases. The overall mortality in the cohort was 12%, which increased to 17% among hospitalized patients. Among those who died, a history of cancer was common (5 out of 7 patients)[90]. An international multicenter cohort study of 151 adult liver transplant recipients from 18 countries (68% male; median age of 60 years) performed a comparison with 627 patients without a history of liver transplant (52% male; median age of 73 years). The liver transplant cohort had more frequent rates of ICU admission (28% *vs* 8%, $P < 0.0001$) and invasive ventilation (20% *vs* 5%, $P < 0.0001$). The mortality rate was 19% in the liver transplant cohort *vs* 27% in the comparison cohort ($P = 0.046$). After adjusting for comorbidities (age, sex, creatinine concentration, obesity, hypertension, diabetes, and ethnicity), liver transplantation was not associated with a significant increase in the risk of mortality in patients with COVID-19; however, multivariable logistic regression analysis demonstrated that the mortality increase in liver transplant patients was associated with age [(OR: 1.06, 95%CI: 1.01-1.11) per 1 year increase], serum creatinine [(OR: 1.57, 95%CI: 1.05-2.36) per 1 mg/dL increase], and cancer (OR: 18.30, 95%CI: 1.96-170.75) [91].

Recommendations for management of liver transplant patients with COVID-19

Multiple guidelines and reviews have been published with the aim of outlining the management of patients with COVID-19 who are either liver transplant candidates or have post-liver transplant status[92-98]. Most have very similar recommendations to the ones by the American Association for the Study of Liver Diseases (AASLD)[99] and Asian-Pacific Association for the Study of the Liver (APASL)[100] summarized below.

The AASLD published an Expert Panel Consensus Statement for Management of Liver Transplant During the COVID-19 Pandemic[99].

Recommendations that apply to the patient post-transplant status: (1) Given the associated high risk for severe COVID-19, these patients must be prioritized for testing; (2) In patients with COVID-19 and elevated aminotransferases, other etiologies unrelated to COVID-19 should be considered, such as viral hepatitis, myositis (especially if AST > ALT), cytokine release syndrome, and ischemia; (3) Ancillary studies should be minimized (*e.g.*, ultrasound and magnetic resonance imaging) to avoid the risk of healthcare personnel exposure, unless it will change management (*e.g.*, venous thrombosis and biliary obstruction); and (4) In the post-transplant time, which includes concerns for acute cellular rejection, a formal histopathologic confirmation with biopsy is necessary.

In patients who are candidates for transplantation: (1) The pandemic may affect the waiting time to transplant. Care teams must consider the evaluation of patients with a high model for end-stage liver disease score or hepatocellular carcinoma with severe disease (upper levels of Milan criteria), who would have a higher priority; (2) Screening for COVID-19 must be done on both the donor and the recipient. At this time, donors who are positive for SARS-CoV-2 are not considered eligible for organ donation. In the same tenure, transplantation is not recommended for COVID-19-positive patients; (3) Care teams should aim to select donor livers with a low risk of delayed graft function, in order to avoid complications and duration of postoperative hospitalization; and (4) Care teams may consider postponing a liver donor program during the pandemic.

In post-transplant patients with COVID-19 infection: (1) It is adequate to consider decreasing the dosage of high-dose prednisone. Although, a dosage that is sufficient to avoid adrenal insufficiency must be maintained; and (2) Reduction of azathioprine, mycophenolate, or daily calcineurin inhibitor dosages can be considered, especially in the setting of lymphopenia, fever, or worsening pneumonia attributed to COVID-19.

Very similar recommendations have been published by the APASL[100]. In addition, they recommend immunization of all patients with liver transplant against pneumococcus and influenza. Other recommendations include avoiding drugs that would have a significant impact on the tacrolimus levels, such as would occur in any other clinical setting[98].

One of the considerations to keep in mind for patients with liver transplant who become infected with COVID-19 is their public health impact, given their risk to be long-term carriers not only due to the slower clearance of the virus but also as they can be asymptomatic carriers[96]. This increases their risk for viral spread in the community, as well as nosocomially as they may have prolonged hospitalizations due

to their medical complexity[96].

Conclusions

Patients with liver transplant must be managed with similar protocols as non-transplanted patients; yet, clinicians must be mindful of the impact of immunosuppression on these patients' viral shedding and carrier status, as well as of medication interaction.

COVID-19 AND LIVER CIRRHOSIS

General considerations and epidemiology

The current evidence that describes the overall impact of COVID-19 in patients with liver cirrhosis, either compensated or decompensated, is scant. However, extrapolating from the current knowledge of the physiopathology of both diseases, the expected morbidity and mortality are more severe when compared to other groups. Many factors must be considered in the interaction of COVID-19 and the liver; for instance, most of the drugs used in the treatment of COVID-19, including biologic agents, can have either a direct hepatotoxic effect or reactivate chronic viral diseases, such as hepatitis B virus[14]. Other studies have detected the presence of SARS-CoV-2 in the liver tissues of patients who had died from COVID-19[101], suggesting viral replication at this level. In patients with liver cirrhosis, both effects have a critical impact as they may worsen the course of the disease by damaging the remaining liver parenchyma[96,102]. Otherwise, there are studies with findings suggesting that if the liver damage induced by COVID-19 is immunologically driven, then the immunocompromised status of cirrhotic patients might be more protective than harmful[103]. However, due to the limited number of patients with chronic liver disease within individual studies on COVID-19 to date, the true impact of underlying liver disease on viral progression and outcomes is unknown.

Existing evidence about outcomes of COVID-19 infection in patients with chronic liver disease is contradictory. A pooled analysis of six studies estimating the impact of chronic liver disease in COVID-19 patients suggested that chronic liver disease and cirrhosis seem to play a minor role in determining patient progression towards the severe forms of the disease; in that study, there was no correlation found between chronic liver disease and increased odds of the severe form of COVID-19 (OR: 0.96, 95%CI: 0.36-2.52) nor with increased odds of mortality (OR: 2.33, 95%CI: 0.77-7.04)[104]. Similar data were reported by Bangash *et al*[46]; specifically, a mortality rate of 0 to 2% was shown by COVID-19 patients with liver cirrhosis. A study of 22 patients with chronic liver disease, among which only three had liver cirrhosis, found that the only significant difference between patients with chronic liver diseases *vs* those without was the risk of progression to severe forms of COVID-19 ($P < 0.001$); however, there were no statistical differences in other variables, such as in-hospital days, death/discharge, or significant changes in liver enzyme values[69]. Finally, a meta-analysis found that the pooled prevalence of chronic liver disease among studies reporting on severity of COVID-19 was 2.64% (95%CI: 1.73-4.00), with 3.03% (95%CI: 1.97-4.64) among severe and 2.20% (95%CI: 1.16 - 4.15) among non-severe COVID-19. The relative risk of chronic liver disease in severe *vs* non-severe patients was 1.69 (95%CI: 1.05-2.73)[105].

The controversy in the data involves evidence generated by another meta-analysis which demonstrated that patients with a pre-existing chronic liver disease have an increased risk for severe COVID-19 (53.33%) and higher mortality (17.65%)[106]. This outcome is likely related to coexistent thrombocytopenia and lymphopenia[32,107] as well as cirrhosis-associated immune dysfunction[108]; therefore, precautions against SARS-CoV-2 infection are warranted among patients with cirrhosis. In addition, stress and sepsis related to over-imposed bacterial infections in COVID-19 are particularly risky and problematic in patients with decompensated liver cirrhosis, given the associated risk of developing acute-on-chronic liver failure, increasing the underlying risk of death from 26.2% to 63.2%; however, most of the studies have shown the cause of death in most liver cirrhosis patients with COVID-19 not to be due to progressive liver disease but rather to pulmonary disease[107,109]. Nonetheless, recent studies have found a higher 30-d mortality rate among patients with cirrhosis and COVID-19 [110], and the presence of cirrhosis has even been proposed as an independent predictor of mortality[71].

Treatment recommendations

The current available evidence suggests that COVID-19 patients with liver cirrhosis have worse outcomes and disease progression than those without. Thus, the treatment recommendations by most international associations are as follows: (1) Minimal exposure to medical staff, ideally leveraging telemedicine as the preferred method; (2) Listing for liver transplantation being restricted to patients with acute liver failure or poor short-term prognosis; (3) Prophylaxis regimens for spontaneous bacterial peritonitis and hepatic encephalopathy being strictly followed at home, to prevent decompensation and the need for hospital admissions; (4) Testing for SARS-CoV-2 for every patient with cirrhosis and acute decompensation or acute-on-chronic liver failure[95]; (5) In-person new patient visits being restricted to only those with significant liver diseases, such as jaundice, elevated transaminases > 500 U/L, or recent decompensation; (6) Rescheduling elective procedures, such as screening for varices and hepatocellular carcinoma; and (7) Urgent procedures, such as paracentesis, being performed using a COVID-19-free path in either the hospital or home care[111-113].

The data regarding vaccination against SARS-CoV-2 in patients with liver cirrhosis is scarce. Despite the inclusion of nearly 100000 participants in all the vaccination trials, data for patients with liver disease are extremely limited. For example, in the Pfizer vaccination study, 217 (0.6%) of 37706 participants had liver disease and only three (< 0.1%) had moderate to severe liver disease. Similar numbers can be seen in the Moderna trial. Importantly, criteria used to classify liver disease and its severity in each study were not specified. Therefore, the real SARS-CoV-2 vaccine safety profile and its immunological response in patients with liver cirrhosis will almost completely come from post-licensing, real-world data[114].

We must not forget the underlying deficiencies in innate and humoral immunity, termed cirrhosis-associated immune dysfunction, that are present in patients with advanced liver disease. It can be hypothesized that this may confer an attenuated immune response to vaccination, but this remains to be verified[115]. Nonetheless, taking into account the risk of COVID-19 progression in these patients (as described above) and considering that there are no absolute contraindications to SARS-CoV-2 vaccination in cirrhosis, it is fundamental to prioritize immunization in this subgroup. AASLD recommendations establish that, when the supply of COVID-19 vaccine is limited, it is reasonable to prioritize patients with higher model for end-stage liver disease and Child-Turcotte-Pugh scores for vaccination together with those who are anticipated to undergo imminent liver transplantation; ideally, however, all chronic liver disease patients should be vaccinated whenever possible[114,116,117].

MISCELLANEOUS

Autoimmune hepatitis

Treatment of autoimmune hepatitis (AIH) has posed a challenge during this COVID-19 pandemic. One of the main challenges is the management with immunosuppressive drugs, since these medications are associated with an increased risk of severe viral infections[118]. COVID-19 has been hypothesized to decompensate or increase the risk of an unfavorable course of liver disease[99]. In a small cohort in northern Italy of ten AIH patients on immunosuppressive treatment who became infected with COVID-19, five developed COVID-19 pneumonia, with only one patient dying (who had decompensated cirrhosis previously), while the rest of the patients fully recovered. Regarding the impact of the COVID-19 on AIH, only one patient presented relapse associated with the interruption of immunosuppressive treatment; it was concluded that patients with AIH under immunosuppressive and COVID-19 treatment have no increased risk of severity or complications of COVID-19 disease when compared to the general population[119]. A multicenter study that included 70 AIH patients with COVID-19, where 58 patients were on immunosuppressant therapy, and of whom 52% received combined immunosuppressant therapy, found that 65 (93%) patients reported clinical symptoms, mainly respiratory (74%) and gastrointestinal (26%), and 15% were asymptomatic. Mortality occurred in 16 (22.8%) patients; among those who died, the causes were attributed to a pulmonary etiology in nine (56%), liver etiology in five (31%), and cardiac etiology in two (13%). The factors associated with death in AIH patients were age (OR: 2.01 per 10 years, 95%CI: 1.07-3.81, $P = 0.031$), Child-Pugh B score (OR: 42.48, 95%CI: 4.41-409.53, $P = 0.001$), and Child Pugh C score (OR: 69.30, 95%CI: 2.83-1694.50, $P = 0.009$) unrelated to immunosuppressant use and death[120]. When comparing this group of patients with a cohort of patients with liver disease

without AIH, the authors did not find a statistical difference among groups, concluding that AIH patients on immunosuppressive therapy are not associated with an increased risk or severity of SARS-CoV-2 infection; therefore, the recommendation is not to decrease or discontinue immunosuppressive treatment in patients with AIH and COVID-19, due to the risk of decompensation of liver disease.

Viral hepatitis

Hepatitis B (HB) and hepatitis C (HC) represent major global public health problems [121,122]. The coinfection of SARS-CoV-2 and HB and/or HC depends on local prevalence. For example, a Chinese study of a cohort of 1099 cases of COVID-19 patients demonstrated that 23 (2.1%) had pre-existing HB; in contrast, in the northeastern United States, a series of 5700 patients hospitalized with COVID-19 showed a prevalence of 0.1% HB and < 0.1% HC [29,52].

The impact on the evolution of COVID-19 and HB superinfection is uncertain. The first reports of the cohort in Wuhan, China found that 2.1% (23/1099) of patients with HB accounted for 0.6% of severe cases [52]. Another report from different hospitals in China involving a cohort of 571 patients showed that 15 (2.63%) patients had underlying HB; the incidence of admission to ICU and death in the HB group was 0% and 6.47% (36/556), respectively, in the non-HB group [123]. Contradictory data stem from other studies. A retrospective study of 70 patients with COVID-19 and HB documented a higher susceptibility of acquiring COVID-19, as well as higher rates of hepatic damage and coagulation disorders and severity of the disease, without having an impact on hospital stay or mortality [124]. A retrospective study of 123 patients with COVID-19, found that HB was present in 15 (12.2%) patients, among who 11 (73.3%) evolved favorably and were discharged from the hospital uneventfully; out of the four who remained in the hospital, two (13.3%) died from digestive bleeding. In comparison, the mortality rate was lower in the group of 108 patients with COVID-19 without HB, among which only eight (5.6%) remained in the hospital and three (2.8%) died due to respiratory failure [125]. Theoretically, this association of poor clinical forecast is due to the common lymphopenia caused in patients with COVID-19, which generates a loss of immune tolerance over HB, which itself can cause viral reactivation [126]. However, there is one study showing that COVID-19 was not associated with reactivation or seroconversion in chronic HB patients, despite using immunomodulatory treatment in a short course for severe COVID-19 [127].

The current data are controversial and contradictory; therefore, it is necessary to take into account the number of patients and the heterogeneity of the population studied based on HB activity, the presence of cirrhosis, and stage of the liver disease. A recent systematic review and meta-analysis concluded that the association of coinfection of HB and SARS-CoV-2 does not have a serious adverse impact in patients hospitalized with COVID-19 [128].

In regards to the treatment of COVID-19 in patients with chronic HB, we must be cautious as the use of corticosteroids or tocilizumab may reactivate HB [129]; although, as previously mentioned, this has not been shown to happen [127]. Finally, the evolution of patients with COVID-19 and HB superinfection is not clear, as the studies have yielded contradictory results and prospective studies with large numbers of patients and control of variables such as presence of other comorbidities, viral replication, cirrhosis, and stage of the liver disease are required. In the case of patients with COVID-19 and recently diagnosed HC, the HC treatment should be postponed until the remission of COVID-19; however, if treatment has already been ongoing, it is necessary to monitor the interactions of HC and COVID-19 treatments [99].

Drug-induced damage

Since the onset of the COVID-19 pandemic, multiple medications have been used as potential treatments, including antimalarials, antiparasitics, antivirals, monoclonal antibodies, *etc.* Some of these medications have hepatotoxic effects, which can be reviewed on the website <http://www.livertox.nih.gov>, where updated data of all drugs are available (Table 2) [58,99,130]. Of similar relevance is the consideration of drug interactions, as some treatments are experimental. Interactions can be reviewed at: <https://www.covid19-druginteractions.org> of Liverpool University.

Most of the data collected have come from case reports, particularly of serious cases and cohorts, for which there may be uncontrolled variables, with patients having pre-existing liver disease, interaction with unreported medicines, and use of traditional medicine, herbal products, or substances. Heightened awareness of both hepatotoxicity and drug interactions in patients with COVID-19 must continue, as should further research efforts regarding these interactions.

Table 2 Therapeutic management of patients with coronavirus disease 2019 and hepatotoxicity

Medication	Hepatotoxicity	Action mechanism	Currently recommended use for COVID-19
Hydroxychloroquine	Likelihood score: D (possible). Rare cause of clinically-apparent liver injury	Altered metabolism of other medications	Not recommended
Azithromycin	Likelihood score: A (well-known). Transient and asymptomatic elevation in serum aminotransferases; Typical cholestatic hepatitis	Unknown	Not recommended
Ivermectin	Likelihood score: D (possible). Mild elevation of serum aminotransferases; Reports of acute liver failure	Unknown	Not recommended
Dexamethasone	Likelihood score: A (well-known). Long-term use effects; Symptoms usually represent the worsening or triggering of an underlying liver disease	Drug-associated fatty liver disease	Recommended as emergency use
Remdesivir	Likelihood score: D (possible). Mild to moderate transient elevation of serum aminotransferases	Inhibition of mitochondrial RNA polymerase or idiosyncratic injury	Recommended as emergency use
Lopinavir/ritonavir	Likelihood score: D (possible). Moderate to severe elevation of serum aminotransferases (pattern hepatocellular to cholestatic or mixed); Duration 1-2 mo; Reports of acute liver failure; Caution in patients with co-infection by hepatitis B virus-hepatitis C virus-human immunodeficiency virus	Inhibits both of the isoforms of CYP3A del P450, which may result in production of a toxic intermediate	Not recommended
Baricitinib	Likelihood score: E (unlikely). Moderate transient elevation of serum aminotransferases (17% of patients); Hepatitis B reactivation	Unknown	Recommended as emergency use
Tocilizumab	Likelihood score: C (probably). Mild to moderate transient elevation of serum aminotransferases; Duration 8 wk	Unknown	Recommended as emergency use

COVID-19: Coronavirus disease 2019.

Vaccination controversies

Chronic hepatic disease (CHD) is considered a state of immunosuppression due to a multifactorial state of systemic immunological diffusion[131], which predisposes to infections and a cause of decompensation and mortality in cirrhotic patients[132]. Immunization is, therefore, recommended in patients with cirrhosis and pre-transplantation and post-transplanted patients, with specifications for the different types of vaccines[133]. Inactivated vaccines (*e.g.*, influenza, pneumococcal, viral hepatitis A, viral HB, diphtheria, tetanus, poliomyelitis, and acellular pertussis) are preferred over live attenuated vaccines (*e.g.*, tuberculosis vaccine, measles, mumps, rubella, varicella zoster virus, and Herpes zoster)[132,133].

The development of the SARS-CoV-2 vaccine has evolved favorably with phase 3 trials, offering effectiveness and safety. Currently, 53 vaccines have been authorized by the United States’ Federal Drug Administration, including those from Pfizer/BioNTech, Moderna, Oxford/AstraZeneca/Sputnik V, and Janssen. Due to the haste of the trials, very strict inclusion and exclusion criteria have been applied to avoid adverse effects. Patients with CHD are preferably not included. In the Pfizer vaccination study, 217 (0.6%) of 37706 participants had liver disease, and only three (< 0.1%) had moderate to severe liver disease. In the Moderna trial, 196 (0.6%) of 30351 participants had liver disease; the Oxford/AstraZeneca, Sputnik V, and Janssen trials completely excluded patients with pre-existent CHD. On the other hand, trials of the 53 vaccines excluded patients with systemic immunosuppression which involves post-transplant liver patients and AIH patients[114,134,135].

As mentioned, CHD patients are a susceptible and high-risk population for COVID-19 complications, and should be classified as a vulnerable population. It is paramount to define the effectiveness and safety of immunization against SARS-CoV-2. As the development and trial of new vaccines occur and vaccination programs are started, information will be generated in different subgroups of populations, including patients with hepatic disease.

FUTURE RESEARCH DIRECTIONS

After a year of pandemic, the information that has emerged regarding SARS-CoV-2

infection and liver injury in patients without or with pre-existing liver disease has opened the course of new lines of research that should be addressed in future studies. The pathophysiology of COVID-19-induced liver injury is complex and more research is necessary to determine the degree of relevance of each of the described mechanisms. Abnormal liver biochemical parameters have been associated with a more serious course and a worse prognosis in patients with SARS-CoV-2 infection, so the usefulness of such measurements in the identification and staging of those patients with related alterations should be evaluated in depth in prospective studies. It is necessary to investigate the impact of SARS-CoV-2 infection in the clinical course of pre-existing liver disease (*e.g.*, fatty liver disease, viral or AIH, and cirrhosis). Long-term follow-up in liver transplant patients suffering from COVID-19 should be investigated to determine if the infection alters graft viability. It is necessary to include patients with liver diseases in the vaccination protocols, to determine the related effectiveness and safety.

CONCLUSION

Liver injury in patients with infection due to SARS-CoV-2 is a frequent extrapulmonary manifestation, particularly in hospitalized patients, and its presence has been associated with an increased risk of complications, including death. The pathophysiology of liver damage in COVID-19 patients is multifactorial and various mechanisms interact. On the other hand, SARS-CoV-2 infection in patients with pre-existing liver disease (*i.e.*, fatty liver disease, cirrhosis, autoimmune or viral hepatitis, and liver transplant patients) presents an increased risk of an ominous course of the disease. Therefore, the presence of liver damage (both acute onset or as a pre-existing condition) requires close monitoring and individualized management according to the individual conditions of the patients. Further research is required to have a better understanding of the SARS-CoV-2 and liver interaction that can improve the therapeutic approach for patients.

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