Effect of COVID-19 on Liver

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The gastrointestinal tract plays an important role in the pathogenesis of COVID-19. Most patients present with gastrointestinal symptoms and/or abnormal liver function tests, both of which have been associated with adverse outcomes. The mechanisms of liver damage are currently under investigation, but the damage is usually transient and nonsevere. Liver transplantation is the only definitive treatment for acute liver failure and end-stage liver disease, and unfortunately, because of the need for ventilators during the COVID-19 pandemic, most liver transplant programs were temporarily suspended.

Keywords: COVID-19 ; SARS-CoV-2 ; Liver

1. Proposed Mechanisms of Liver Injury

The liver is the only organ with double blood supply (arterial and portal) and harvests the largest reserve of macrophages, playing a crucial role in the immune response to SARS-CoV-2 through hepatic stellar cells. In addition, endothelial cells in liver sinusoids register and activate the immune response through Toll-like receptors [1].

The interaction between SARS-CoV-2 and the liver is under active investigation because ACE2 receptors are not expressed in Kupffer cells, hepatocytes, or endothelium of the hepatic sinusoids [2]. By contrast, ACE2 receptors are expressed in vascular endothelium and in cholangiocytes, almost in the same proportion as in the type II pneumocytes [3]. The endothelium of bile ducts is more susceptible to SARS-CoV-2, therefore the upregulation of ACE2 receptors favors internalization of the virus and results in liver damage due to compensatory proliferation of hepatocytes [4]. Interestingly, the expression of ACE2 receptors has been reported in fatty liver animal models [5] and in regeneration nodules in liver cirrhosis [1], giving rise to the possibility of greater susceptibility to liver damage in such patients.

Currently, there is no consensus on the exact mechanism of liver damage in COVID-19. However, several hypotheses have been postulated: (1) direct cytopathic damage, (2) systemic inflammatory response with immune-mediated collateral damage, (3) hypoxia and liver ischemia, as in hypoxic hepatitis, (4) acute-on-chronic liver failure, and (5) drug-induced and/or herbal-induced liver injury [6].

Direct cytopathic damage has not been demonstrated and in a study of postmortem liver biopsies, only moderate lymphocytic lobular infiltrate and centrilobular sinusoidal dilatation were reported, findings that the scholars attributed to the patient's previous comorbidities [7]. In another postmortem study, no viral inclusions were found in the liver parenchyma [8].

The terms "cytokine release syndrome" and "cytokine storm" have been described in the medical literature since 1992 and refer to the role of a devastating effect of immune dysregulation, characterized by constitutional symptoms, systemic inflammation, and multiorgan dysfunction that can lead to multiorgan failure and death [9]. The cytokine storm in COVID-19 is characterized by high circulating levels of interleukin-1β, interferon-γ, and monocyte chemoattractant protein-1 [1], which upregulates the expression of ACE2 and TMPRSS2 receptors [10].

Hypoxic hepatitis refers to the massive, rapid rise in serum aminotransferases as a result of reduced oxygen delivery to the liver, which most common in cardiac failure, septic shock, and respiratory failure, but may occur in the absence of hypotension or a shock state in about 50% of cases [11]. In COVID-19, hypoxic hepatitis may be secondary to septic shock, COVID-related myocarditis (as cardiogenic shock), and ventilator complications [12]. In a series of 40 patients who died of complications of COVID-19, congestion and centrilobular ischemic necrosis were found in 78% and 40% of cases, respectively [13]. Hypoxic hepatitis may be considered among the differential diagnoses of liver injury in patients with COVID-19.

Acute-on-chronic liver failure (ACLF) refers to an acute decompensation in patients with chronic liver disease that is associated with a high risk of short-term mortality [14]. This syndrome is characterized by intense systemic inflammation, a close precipitating event, and single or multiple organ failure [15]. The mortality burden of ACLF in wait-listed patients is high, with prompt liver transplantation required in survivors. It has been hypothesized that patients with cirrhosis and ACLF have an increased risk of developing severe COVID-19 because of immune dysregulation (or immune paralysis). In cirrhosis, immune dysregulation is responsible for 30% of the mortality and is characterized by increases in anti-inflammatory cytokines, suppression of proinflammatory cytokines, increased gut permeability, reduced intestinal transit, and altered intestinal microbiota, which increases the risk of bacterial translocation and endotoxemia [16]. In a study that included 2460 patients, 35% met the definition of ACLF from the European Association for the Study of the Liver (EASL)-Chronic Liver Failure Consortium and exhibited prolonged hospital stay (14.7 ± 17.3 days vs. 5.4 ± 5.3 days, $p = 0.004$), severe COVID-19 (25% vs. 3%, $p = 0.03$), need for intensive care unit (45% vs. 11%, $p = 0.003$), and higher mortality (30% vs. 5%, $p = 0.01$) than patients without ACLF [17].

Drug-induced liver injury (DILI) and herb-induced liver injury (HILI) are defined as liver dysfunction and/or abnormalities in liver function tests secondary to the use of medications, herbs, or xenobiotics within the reasonable exclusion of other etiologies [18]. Many drugs have been used to treat patients with COVID-19, including antiviral agents (e.g., lopinavir, ritonavir, remdesivir, darunavir, umifenovir, and favipiravir), antibiotics (e.g., azithromycin), antimalarials (e.g., chloroquine and hydroxychloroquine), monoclonal antibodies (e.g., tocilizumab), JAK inhibitors (e.g., baricitinib), tyrosin kinase inhibitors (e.g., imatinib) [19][20], complementary alternative medicine (e.g., chlorine dioxide and Ayurvedic Kadha), and home remedies (*Allium sativum*) [21], many of which have been associated with hepatotoxicity alone or in combination as compassionate treatment. In this context, the Réseau d'Étude Francophone de l'Hépatotoxicité des Produits de Santé, a European study network focused on DILI, reported four cases of lopinavir/ritonavir suspected hepatotoxicity [22]. In clinical practice, polypharmacy is not uncommon, and physicians must be aware of DILI and HILI as potential causes of liver injury in patients with COVID-19. The same work-up and recommendations for patients without COVID-19 should be started upon suspicion of polypharmacy and DILI, especially discontinuation of the offending drug.

The exact mechanism of liver damage in COVID-19 is complex, challenging, and multifactorial in nature.

2. Implications in Fatty Liver Disease

Information concerning the association of hepatic steatosis and fibrosis with COVID-19 outcomes is limited. A more severe illness and worse outcomes are expected because a higher expression of ACE2 receptors has been found in hepatocytes of animal models of fatty liver [5].

A retrospective study that included 202 patients with fatty liver assessed by a hepatic steatosis index (HSI) > 36 points and/or confirmation by liver ultrasound reported a higher risk of progression of COVID-19 (6.6% vs. 44.7%, $p < 0.00001$) and longer shedding time (17.5 days vs. 12.1 days, $p < 0.00001$) in comparison with patients without fatty liver disease [23].

Obesity and metabolic syndrome are common risk factors for metabolic associated fatty liver disease (MAFLD) and in many cases coexist with COVID-19 in an alarming way. A prospective study of 214 patients with COVID-19 reported a 30.8% prevalence of MAFLD, of whom 68.2% had obesity associated with greater severity of disease (OR 6.32; 95% CI 1.16–34.54, $p = 0.033$) [24].

Establishing the risk of MAFLD through noninvasive predictive models at the time of hospitalization for COVID-19 may result in an overestimation of the prevalence of MAFLD because biomarkers (e.g., transaminases) used in the models (e.g., HSI, NAFLD-FS) may be altered by COVID-19. In addition, imaging techniques such as ultrasound have an overall sensitivity of 84.8% (95% CI 79.5–88.9) and a specificity of 93.6% (95% CI 87.2–97.0) for the detection of moderate to severe fatty liver [25], which could be considered as a reliable bedside diagnostic tool for fatty liver and for excluding other causes of abnormal liver tests.

3. Implications in Liver Cirrhosis

Liver cirrhosis is estimated to affect 4.5–9% of the world's population [26], and a high proportion of patients with cirrhosis are expected to be infected with COVID-19. A multicenter study of 160 patients reported a prevalence of advanced fibrosis of 28.1% assessed with FIB-4 ≥ 2.67, which was associated with a higher risk for requiring intensive care (OR 3.41; 95% CI 1.30–8.92) [27].

The two most important international registries of patients with chronic liver disease and COVID-19 are COVID-Hep.net (University of Oxford and EASL) and SECURE-Cirrhosis Registry (University of North Carolina at Chapel Hill). In the first report, which included 745 patients (386 with cirrhosis and 359 controls), a mortality of 32% was found in patients with cirrhosis, which increased according to liver disease severity to 35% (OR 4.14; 95% CI 1.03–3.52) in Child–Pugh B and 51% (OR 9.32; 95% CI 4.80–18.08) in Child–Pugh C. Acute decompensation was observed in 46% of cases, of which 21% had no respiratory symptoms and 50% presented as ACLF [28].

An additional concern during the COVID-19 pandemic is the role of immunosuppression in patients with autoimmune liver diseases due to the increased risk of respiratory tract infections. However, a greater severity of infection has not yet been demonstrated in this group of patients. In this regard, recommendations for the approach to this group of patients are summarized in **Table 1** [29].

Table 1. Recommendations for patients with autoimmune liver disease and COVID-19 (adapted from Lleo [29]).

Summary of Recommendations
• Organize independent access to health services to avoid contact with COVID-19-positive patients.
• Limit invasive screening procedures to only emergency interventions (e.g., endoscopy).
• Initiate immunosuppressive treatment at standard doses for the treatment of exacerbation of autoimmune hepatitis.
• Coordinate care with the transplant committee in case of acute liver failure.
• Reduce immunosuppression in case of infection, especially antimetabolites in patients with lymphopenia.

4. Implications in Liver Transplantation

Since 1980, transplant programs around the world have responded to the pandemics of HIV, SARS-CoV, East Nile Virus, Influenza A/H1N1, Zika, and Ebola, maintaining their operation with the evaluation of the transmission to the donor, the severity of the disease in the recipient, and the risk of transmission to health personnel [30]. Unlike other solid organ transplant programs where alternatives or bridging therapies exist, such as hemodialysis, cardiac assist devices, and extracorporeal membrane oxygenation, in the case of patients with acute liver failure or end-stage liver disease, liver transplantation is the only treatment alternative. Currently, liver transplantation programs are among the most vulnerable around the world.

During the COVID-19 pandemic, the availability of intensive care beds has been vital, and this need is shared by transplant programs whose patients require specialized postoperative care. Therefore, a staggered-phase approach has been proposed with a decrease in the activity of transplant programs according to the tolerance of transplant risk, hospital capacity, and pandemic activity in the locality [30]. In a health system completely overwhelmed by the care of COVID-19 patients, the transplant program must be reduced by 100%.

Early experience at the beginning of the COVID-19 pandemic has been reported in a prospective nationwide study containing 111 liver transplant patients with COVID-19. At a median of 23 days, up to 86.5% of patients were hospitalized, 19.8% required intubation, 10.88% were admitted to the intensive care unit, and 18% died [31]. Currently, there is no consensus regarding the time of liver transplant in patients with COVID-19. Even so, successful liver transplants have been reported in patients with asymptomatic COVID-19 [32].

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