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Editorial

COVID-19 and Liver Disease: A panorama that is being clarified

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The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has become a significant burden on economies and health systems worldwide. The disease course of COVID-19 ranges from asymptomatic —identified by antigen detection or rapid tests, polymerase chain reaction (PCR), molecular tests, and antibodies (before vaccination)— to multiorgan dysfunction and high mortality[1,2]. Perhaps rarely have we seen how research by multidisciplinary groups achieved results so rapidly in diagnosing, managing, and developing a highly effective vaccine to prevent severe manifestations of a disease. As of December 2021, all-cause mortality reports collected in more than 74 countries accounted for 6 million deaths, mainly in India (4.07 million), the USA (1.13 million), Russia (1.07 million), Mexico (798,000), Brazil (792,000), Indonesia (736,000), and Pakistan (664,000)[3].

The coronavirus (CoV) family displays a corona-like structure on its surface that is visible through electron microscopy. In humans, at least 7 types of this family result in disease, 4 of which are self-limiting, and 3 additional species (SARS-CoV-MERS-CoV and SARS-CoV-2) are highly pathogenic, causing severe respiratory disease. The SARS-CoV-2 is a single-stranded (positive polarity) RNA enveloped virus composed of a 30 kbp (kilobase pairs) genome, encoding 16 non-structural proteins and 4 structural proteins. The structural proteins of the surface include envelope (E), nucleocapsid (N), membrane (M), and *spike* (S), the main protein responsible for interacting with the host's primary receptor (ACE2), its co-receptor (neuropilin-1) and a transmembrane serine protease 2 (TMPRSS2). After the adhesion of the receptors, the virus envelope contacts the infected cell cytoplasm, generating endosomes (early or delayed) or endolysosomes. Then, the viral genome is released in the direction of the endoplasmic reticulum as a template (strand) for the translation of proteins. The assembly of the synthesized proteins occurs in the Golgi apparatus, where the virus is released, infecting other cells[4-6].

Risk factors associated with the severity of COVID-19 have been described, including age, metabolic comorbidities, heart disease, cancer, and immunosuppression. Multiple organ involvement is most evident during the acute phases of the disease. The most common manifestations include systemic, respiratory, gastrointestinal, cardiovascular, and neurological conditions. The severity of acute COVID-19 is associated with the post-COVID-19 syndrome, symptoms that persist for more than 6 months. Some of the most common manifestations include fatigue, brain fogginess, sleep problems, chronic headache, palpitations, muscle pain, nausea, and laboratory abnormalities: neutrophilia, anemia, thrombocytosis, and low albumin levels[7,8]. In addition, genetic predisposi-

tion to infection and to develop severe forms of the disease may exist. Genome-wide association studies (GWAS) have identified at least 13 genetic loci accounting for the response to infection[9].

Although the respiratory system represents the main entry point of the virus, the digestive tract represents a significant angiotensin-converting enzyme receptor 2 (ACE2) expression, mainly in the small intestine and colon. The SARS-CoV-2 mRNA has been detected primarily in the esophagus, stomach, duodenum, and rectum. As many as 64% of patients may remain positive for RNA in stool for several weeks by reverse transcription-polymerase chain reaction (RT-PCR) after negative nasopharyngeal tests. In patients with severe disease, histopathological findings show endothelial inflammation of the submucosal vessels of the intestinal wall, including interstitial edema, lymphocyte, and plasma cell infiltrate in the lamina propria of the stomach, duodenum, and rectum[10].

A study including 2036 hospitalized patients with COVID-19 showed that gastrointestinal symptoms occur in 59.7%. Some significant symptoms included nausea, diarrhea, loose stool, and emergencies. In addition, nausea can persist even after infection resolution[11].

In a healthy liver, the ACE2 receptors are expressed at low levels, mainly in cholangiocytes, liver sinusoidal endothelial cells (LSECs), and less frequently in hepatocytes. However, in patients with cirrhosis, ACE2 mRNA levels are 34-fold up-regulated, expressed by immunostaining in 80% of hepatocytes, which explains the high susceptibility to infection of this organ[12].

Liver involvement during COVID-19 has been associated with increased disease severity, prolonged hospital stays, ventilatory support, and mortality. Studies in hospitalized patients report a 3-5-fold elevation of aminotransferases in 20%-67% at entry and 61%-83% during hospitalization. Aspartate aminotransferase (AST) is generally higher than alanine aminotransferase (ALT), highlighting microvascular damage in COVID-19. Alkaline phosphatase and total bilirubin elevations occur in 20%–30% and 4%–16%, respectively, and cholestasis is described in an average of 15% of hospitalized patients, establishing a pattern of hepatocellular injury. It is unclear whether these changes occur before infection, are caused by the virus, or are related to events within the disease[13,14].

Alcohol etiology alone influences the outcome severity to date, and its consumption increased significantly during the pandemic[15,16]. No clear pattern has been demonstrated in patients with metabolic dysfunction associated with fatty liver disease (MAFLD) (where risk factors such as obesity and diabetes dominate), viral hepatitis, autoimmune hepatitis, or cholestatic diseases. Antiviral therapies may begin and continue, given the risk of reactivation with immunosuppressive drugs[17-19].

For patients with autoimmune hepatitis, the course of the disease is not at risk of a worse outcome, and immunosuppression is not associated with increased severity, so maintenance is recommended. The main predictor of complications in these patients is the presence of cirrhosis[20].

Nonetheless, given the previously described abnormalities, more studies are needed to define the short- and long-term consequences of SARS-CoV-2 infection in patients with underlying chronic liver disease[21].

Few case series have been published regarding histopathological changes in the liver during COVID-19. Changes range from fatty liver disease (55%), sinusoidal dilatation and congestion (34.7%), micro thrombosis (29.4%), fibrosis (20%), portal inflammatory infiltrate (13.2%), and invasive lobular carcinoma (11.6%). SARS-CoV-2 RNA has been detected in liver tissue *postmortem* studies in up to 55% of cases. At the same time, electron microscopy shows viral particles, mitochondrial edema, endoplasmic reticulum dilation, and apoptosis[22].

The mechanism by which liver injury occurs may be related to a direct cytopathic effect of the virus (currently unlikely), immune-mediated damage associated with the cytokine storm triggered by virus recognition due to innate immunity. Furthermore, it may be linked to hypoxic brain injury in patients with severe hemodynamic instability. Ultimately, drug-induced liver injury (azithromycin, hydroxychloroquine, non-steroidal anti-inflammatory drugs [NSAIDs], lopinavir/ritonavir, remdesivir, tocilizumab, tofacitinib, and dexamethasone) can cause it too[23,24]. Reactivation of preexisting diseases with the use of immunosuppressants (hepatitis B) is also a possibility. Also, the relationship between autoimmune hepatitis *de novo* and the different approved vaccines has been described[25]. Additionally, cholangiocyte injury in the form of cholangiopathy associated with the SARS-CoV2, a type of secondary sclerosing cholangitis (SSC), is possible[26].

An alternative mechanism to the described liver injury could be endothelial injury mediated by inflammation and thrombosis, caused by an inflammatory response to the virus and expressed by an increase in D-dimer, fibrinogen, von Willebrand factor(VWF), thrombomodulin and factor VIII. In addition, acute decompensation, associated with multiple organ failures and high short-term mortality, may occur in cirrhotic patients, leading to acute, chronic liver failure[27].

Cirrhosis is a risk factor for mortality. The Child-Pugh score system is the most prognosis assessment determinant for cirrhosis. Mortality in non-cirrhotic chronic liver disease patients was 8% at hospitalization, 20% in the intensive care unit (ICU), and 21% with mechanical ventilation. Child-Pugh A class was 22%, 40%, and 52%; Child-Pugh B was

39%, 62%, and 74%; Child-Pugh C was 54%, 79%, and 90%, respectively[28]. A collaborative study including 8941 cirrhotic patients with SARS-CoV-2 infection confirmed a mortality risk with a *Hazard Ratio* (HR) of 3.31 to 30 days[29]. The largest cohort of hospitalized COVID-19 patients in Latin America, which included 1611 patients, showed an alteration of the liver analysis at admission in 45.2%, with higher mortality of 18% versus 12% (< 0.001) compared to those with a normal profile[30]. An important aspect to highlight is the late diagnosis of hepatocarcinoma in cirrhosis, given the decrease in face-to-face consultations during the pandemic, hindering protocols for monitoring and detecting new cases[31]. Changes in screening schedules were reported in reference centers in 80%, and therapies were modified or canceled in 65% of cases[32].

Liver transplants were affected globally due to a significant decrease in donors[33]. The course of the COVID-19 disease is not different in transplant recipients, and no changes in immunosuppression should be made[34]. A recent European multicenter study evaluating the outcome in 243 patients transplanted with COVID-19 showed 25% mortality. The risk was more significant in those over 70 with comorbidities such as diabetes and chronic renal failure. The use of tacrolimus was associated with more prolonged survival. Therefore, maintaining the usual doses is recommended. No recommendations were made regarding other immunosuppressants such as mycophenolate mofetil[35].

The rapid production and clinical development of highly effective vaccines to prevent severe forms of COVID-19 reflect decades of research in immunology and biology. Vaccine safety represents one of the most critical challenges, particularly in special groups not included in approval trials. Another important aspect is the humoral response to vaccination in immunocompromised patients concerning immunocompetent ones. Due to their safety profile and high effectiveness, the mRNA (Pfizer, Moderna) and adenovirus vector (AstraZeneca, Johnson & Johnson) vaccines have gained more popularity[36]. The Centers for Disease Control and Prevention (CDC) recommendations prioritized patients with chronic liver disease and patients on the transplant list (even with one dose, a second dose should be transplanted at 6 weeks)[37].

Seroconversion in patients on the waiting list in one study reached 94.4%. No serious adverse events were observed, and no disease was documented in the first two months[38]. Similarly, the humoral response to mRNA vaccines in solid organ transplant recipients is slightly lower than in immunocompetent patients[39]. Protection is manifested by a 64% decrease in infection, 58% in symptomatic COVID-19, and 87% in mortality[40]. The recommendations point to vaccine boosts to achieve similar immunity.

As for antiviral drugs for COVID-19, there is little experience in patients with cirrhosis, given the possibility of drug-induced damage, becoming evident with toxicity from lopinavir/ritonavir and remdesivir[41].

A significant advance applicable during the pandemic refers to the Baveno VII guidelines. These guidelines recommend deferring endoscopy in cirrhotic patients with transient elastography <20 kPa and more than 150,000 platelets and initiating carvedilol administration in patients with a result >25 kPa, given the correlation with the presence of clinically significant portal hypertension (hepatic venous pressure gradient [GPVH] >10 mm Hg). Care in endoscopy units should be maintained due to the risk of transmission by micro-droplets of aerosols suspended in the environment[42].

Despite being based on an outpatient retrospective cohort, the study published in this issue of the journal provides essential insights into the epidemiology, behavior of the chronic liver disease, and abnormal liver tests, confirming, in this group, a low mortality rate. However, given their low number, these results do not apply to the population of cirrhotic and transplanted patients. Therefore, vaccination and monitoring complications such as hepatocarcinoma remain vital.

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