



## Opinions

## The growing need to monitor the liver function after SARS-CoV-2 infection in the Mexican population with obesity



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The current Coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has become a major public health problem over the last two years. It has reached 418,650,474 confirmed cases of COVID-19, including 5,856,224 deaths, until February 2022, according to the World Health Organization [1]. Unfortunately, Mexico was already dealing with obesity, another public health problem. In Mexico, the reported 2018 prevalence of obesity in adults was 36.1% [2]. Obesity, along with its underlying comorbidities, such as hypertension, diabetes, non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease are major factors predicting poor COVID-19 outcomes. In this sense, the pre-pandemic prevalence of obesity and chronic and metabolic diseases in Mexico may be related to the high COVID-19 associated lethality rate in the region [3].

Much has been speculated about the possible consequences and long-term effects for those who have been infected by SARS-CoV-2. While the most recognized sequelae are cardiac, sensitive, and respiratory conditions; an organ that also has cells with entry pathway receptors for SARS-CoV-2 has been left out. Angiotensin-converting enzyme 2 receptors are the main viral entry point for SARS-CoV-2 [4], and they are highly expressed in the lung and kidney, but are also expressed in gastrointestinal tract, vascular endothelium and cholangiocytes of the liver [5, 6], which is relevant because it positions the liver as a potential target for SARS-CoV-2.

In this sense, the term “COVID-19 associated liver injury” has emerged to define any liver damage that occurs during illness and treatment of patients with COVID-19, with or without pre-existing liver disease [7]. COVID-19 affects multiple organs, including anomalies in liver function [8]. Even though studies that determine liver

function biomarkers in Mexican patients with COVID-19 are scarce, they coincide in the detection of abnormal values of hepatic transaminases, whose elevated levels reflect liver damage are common in patients with COVID-19, both for those with and without chronic liver disease (CLD). A recent study in which the majority of its population had overweight and obesity investigated the effects of the SARS-CoV-2 virus on liver function and its association with the severity of acute respiratory distress syndrome in Mexican population found a high frequency of patients who have alterations in liver function tests (LFTs), especially aspartate aminotransferase (AST) and gamma glutamyl Transferase (GGT) [9]. Another study reported that higher levels of alanine aminotransferase (ALT) are associated with higher in-hospital mortality risk in Mexican patients admitted with COVID-19 [2]. Abnormal LFTs on admission have been given the role of diagnostic biomarkers, for manifesting within the first 7 days of infection, and for their prognostic value during the disease [10]; even they have been associated, both independently and together with obesity, with mortality and severe COVID-19 in hospitalized patients with SARS-CoV-2 infection and its use as a surrogate marker of inflammation has been suggested [11].

On the one hand, the diagnostic and predictive value of liver markers during COVID-19 is undeniable; on the other hand, it is still unknown the long-term effects of the COVID-19 associated liver injury, for both obese and non-obese patients. However, a possible bridge between obesity, COVID-19 and LFTs alterations could be NAFLD, since NAFLD is the most frequently liver disease associated with obesity, and recently is predicted to be present in the majority of COVID-19 patients with pre-existing CLD worldwide [12]. Evidence indicates that SARS-CoV-2 can infect the liver and cause conspicuous hepatic cytopathic injury. Microvesicular and macrovesicular steatosis have been observed in liver autopsies of COVID-19 patients who presented SARS-CoV-2 infection as the only risk factor for liver injury. A recent prospective cohort evaluated the histopathological

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evolution during COVID-19, and observed prominent dilation of the sinusoids in all liver biopsies, regardless of the stage of the disease, while the presence of lobular inflammation was limited to patients with mild or moderate COVID-19 [13]. Other histopathological findings in SARS-CoV-2-infected livers include mild lobular and portal activity, massive apoptosis, and binuclear hepatocytes with notable mitochondrial inflammation, endoplasmic reticulum dilation [14]. In this sense, it has been suggested that one of the cytopathic effects of SARS-CoV-2 is through the deregulation of the host lipid metabolism and mitochondrial activity. Other possible pathological mechanism involve the viral S protein, which could be capable of inducing stress in endoplasmic reticulum, and this in turn induce *de novo* lipogenesis, which could contribute to the development of steatosis in patients with COVID-19 [7]. This is relevant because NAFLD is an important cause of more severe pathologies such as liver cirrhosis and hepatocellular carcinoma. However, there is a great need for studies that confirm these hypotheses; as long-term follow-up studies are also required to explore potential sequelae of SARS-CoV-2 infection.

Even though the mechanism by which COVID-19 causes liver injury and dysfunction has not yet been clarified, the most prominent explanations are (a) immune-mediated damage due to the severe inflammatory response following infection, (b) direct cytopathic effect of SARS-CoV-2 in hepatic tissue, and (c) drug-induced liver injury [12]. At this point, it is important to note that certain medications commonly used during hospitalization, including corticoids, antiretroviral agents, and methotrexate, contribute to abnormal liver function test results of COVID-19 patients [15] and might trigger the transition of simple fatty liver to non-alcoholic steatohepatitis or worsen pre-existing steatosis, necroinflammation, and fibrosis [12]. Although it is not yet clear whether SARS-CoV-2 directly or the medication used for its treatment is the main cause of liver damage during and after COVID-19; it should be taken into account when providing treatment for these patients, prioritizing the use of drugs that are capable of inhibiting the inflammatory response while protecting liver function [8].

Finally, LFTs should be routinely ordered to assess relative liver injury in patients diagnosed with COVID-19. The general recommendation for all patients in the mild category with associated comorbidity or patients in moderate category at hospital admission includes LFTs along with a complete blood count, C-reactive protein, and serum creatinine. If any of these markers are abnormal, further investigations for patients in severe category may be considered [10]. In Mexico, the need to monitor liver function should be added to the recommendation for those who have survived the mild and severe COVID-19 disease, especially those with metabolic disorders, also for cases of people who have been reinfected by the virus, due to the possibility of presenting liver disorders after infection; as well as for those people who have pre-existing CLD during COVID-19, to determine the aggravation by SARS-CoV-2. The effects of COVID-19 on underlying CLD require detailed evaluation and further research is warranted in this area.

## Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; COVID-19, coronavirus disease 2019; LFTs, liver function tests; NAFLD, Nonalcoholic fatty liver disease; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; WHO, World Health Organization.

## Declaration of Competing Interest

The authors have not conflicts of interest

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