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COVID-19 Liver Manifestations. What should we know? A Literature Review

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19), caused by the coronavirus of severe acute respiratory syndrome, has become a threat to global health due to the high rates of morbidity and mortality. Predominantly, the infection is related to respiratory symptoms, but gastrointestinal manifestations, including hepatic, have also been reported.

Objectives: This literature review addresses the new coronavirus pathogenic mechanism in the liver and its consequences. The repercussions of liver damage are mild to moderate elevations in serum levels of transaminases, gamma-glutamyl transferase, alkaline phosphatase and hypoalbuminemia.

Design and Setting: In this literature review we searched PubMed for studies published between March, 2020 and June, 2020.

Methods: The search terms included "COVID 19", "Gastrointestinal", "Liver". The eligible studies were those that focused on liver manifestations caused by the new coronavirus and infected patients who already had liver comorbidities.

Results: The liver damages result both from the direct virus aggression in the cells, as well as secondary to the patient's evolution and possible pre-existing morbidities, explaining the alterations in liver enzymes.

Conclusions: This literature review helps to understand the hepatic involvement, although further studies are needed to elucidate the course and prognosis of the disease. The most severe enzymatic changes are strongly related to a worse prognosis. Therefore, doctors must pay attention to the evolution of the infection.

Keywords

SARS-CoV-2, Hypertransaminasemia, Hepatology, Multi-organ failure and immunopathology.

Introduction

In December 2019, a virus from the Coronaviridae family, who received the official name SARS-Cov-2, began to spread in Wuhan, Hubei province, China. Two other viruses from the Coronaviridae family were already known to cause infections in humans, the Severe Acute Respiratory Syndrome Coronavirus (SARS-Cov)

and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Although all of them are serious and potentially lethal, only SARS-Cov-2 has spread worldwide.

The disease caused by this pathogen was officially called Coronavirus Disease 2019 (COVID 19) on February 11, 2020 by the World Health Organization (WHO) and, a month later, on March 11 of the same year, it was classified as a pandemic.

This current pandemic cause consists of a spherical virus that has

four distinct proteins that form its structure [1] - a nucleocapsid layer formed by its positive-sense single-stranded ribonucleic acid (RNA) associated with proteins, a protein membrane, an envelope and several spicules composed of glycoprotein S trimers (spike protein) that give it the crown aspect and are responsible for its adhesion to host cells [2].

It appears that its transmission occurs mainly through respiratory droplets disseminated by air. However, recent studies also point to a possible fecal-oral transmission due to the viral RNA presence in infected people stool samples [3].

The main symptoms are fever, tiredness and dry cough. However, some patients also report nasal congestion, anosmia, ageusia, and sore throat, shortness of breath and body aches.

Beyond respiratory symptoms, gastrointestinal tract commitment was reported in 15% of patients, including nausea, vomiting and diarrhea. In this context, there is evidence that patients with gastrointestinal tract involvement have a more severe clinical condition when compared to those without digestive symptoms. In 19% of patients, liver damage was also reported, pointing to the liver as a possible target organ for infection. It was evidenced by changes in alanine aminotransferase serum levels (ALT) and aspartate aminotransferase (AST), in addition to other laboratory changes [4].

Also, it is important to note that SARS-Cov-2 shares 79% of its genome with SARS-Cov and 50% with MERS-Cov, viruses in which the relationship with liver failure is already known, being reported in up to 60 % of SARS patients [5,6].

Methods
In this literature review, we searched the PubMed database for studies published between March, 2020 and June, 2020. The combined keywords "COVID 19", "Gastrointestinal" and "Liver" were used to identify the articles on the subject. Adding all the databases, 70 articles were found.

After reading the articles' titles, it was noted that some did not meet the criteria of this study. The eligible studies were those that focused on liver manifestations caused by the new coronavirus and infected patients who already had liver comorbidities. Then, 23 articles were selected to read the abstract and those that did not focus on liver manifestations were excluded, leaving 12 articles for the study. From there, the full text was reviewed and we extracted only the relevant information to build this literature review.

The final selection included articles on literature review, systematic review, meta-analysis, mini-review and letter to editor. Some studies were excluded because the information available was limited and unsatisfactory for the analysis that we needed.

Results
Many reports identifying liver changes in hospitalized COVID 19 patients motivated further studies in this perspective. Based on these discoveries, a cohort study led by the First Affiliated Hospital of Guangzhou Medical University, which included 1099 patients from 552 hospitals in 31 provinces or provincial municipalities, found that patients with the new coronavirus who developed more severe infections, showed greater hepatic repercussions [7].

This cohort in association with a study by the First Hospital of Lanzhou University, which included 7 hospitals, found that 6.2% to 22.2% of patients had increased AST levels and 21.3% to 28.1% ALT levels in serum [8].

Besides, high ALT, AST and bilirubin serum levels are possibly a worse prognosis indicative. A study pointed out that ALT levels > 40Ul / L are more related to hospital mortality and that elevated AST and bilirubin levels are more associated with the risk of progression to respiratory failure and death [9].

Other studies have shown changes in gamma-glutamyl transferase serum levels (GGT), a cholangiocyte lesion biomarker, more significant when compared with alkaline phosphatase. Higher bilirubin levels were also observed in about 11% of patients, being more prevalent in cases admitted to the ICU [8]. There is also a reported decrease in albumin levels (around 26.3 to 30.9 g / L) [4].

Although more studies are needed to determine epidemiological data about gender and age group, a series of cases indicate that infected men are more likely to develop liver dysfunction, as they have higher serum AST levels compared to infected women. Regarding the age group, there were no serum changes in children, whereas, in adults (35 to 56 years), abnormalities in liver enzyme levels were noticed. Thus, it is possible to conclude that liver damage is more associated with old age [8].

Discussion
All of these observed changes are indicatives of liver tissue damage and can significantly contribute to indicate the infection severity. The lesions occur both by virus direct aggression, as well as secondary to drug use, intestinal translocation and hypoxia.

Primary aggression mechanism
It is known that the pathogenesis mechanism of the new coronavirus begins when its S protein, through the receptor-binding domain (RBD), recognizes the angiotensin-converting enzyme 2 receptor (ACE2) and makes its binding. Then, the viral membrane fuses with the host cell membrane. Its internalization that makes viral replication viable uses the cellular machinery [10]. For this reason, ACE2 receptors are considered responsible for the virus entrance into host cells via plasma membrane or via endocytosis, through proteases release [11]. These receptors are expressed in the lungs, kidneys and gastrointestinal tract, being more present in the liver and bile duct when considering the last one.

According to results obtained by two independent cohorts, ACE 2 is expressed in 59.7% of cholangiocytes and 2.6% of hepatocytes [12]. This data linked to hepatic and biliary enzyme abnormalities strongly suggests a viral cytopathic effect.

Serious patients can develop liver damage due to an inflammatory storm, also called Systemic Inflammatory Response Syndrome (SIRS) caused by the immune system activation. Furthermore, this storm has a great impact on the patient's prognosis, as it can cause multiple organ failure and even lead to death.

After the virus endocytosis, innate and cellular immunity are activated. It occurs through toll-like receptors (TLRs) and T lymphocytes activation. Both TCD4 + lymphocytes and TCD8 + lymphocytes are of great importance to the immune response caused by SARS-Cov-2.

When attacking infected cells, activated CD8+ T lymphocytes lead them to apoptosis and necrosis until they are depleted, configuring the typical lymphopenia during SARS-CoV-2 infection. As consequence, with the decrease of T lymphocytes, it is not possible to control viral and bacterial infections anymore, being the inflammatory signaling pathway induced by NF-kB an alternative used, activating cytokines and chemokines even more [12].

In association with cytotoxic TCD8+ lymphocytes, the TCD4+ lymphocyte has a convergent action by producing the granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6) [12].

The inflammatory monocytes CD14 and CD16, activated by GM-CSF, induce a production increase of interleukin 6 (IL-6) 8 and other inflammatory factors such as IL-10, IL-2 and IFN- α [12].

IL-6 has an important role in regulating liver regeneration. When its level increases, regeneration gets disorganized, leading to a larger production of pro-inflammatory cytokines by hepatocytes [13].

As a result, a succession of activation of sometimes macrophages, sometimes inflammatory cytokines, characterizes a cycle responsible for not only liver but also pulmonary, cardiac and renal injuries.

Moreover, it is important to highlight those two subgroups of TCD4 lymphocytes can be identified by the type of cytokine produced. Research has shown that, depending on the antigen molecular weight, different responses can be triggered. For this reason, proteins with more than 70kD, such as S proteins, are related to the Th1 response (pro-inflammatory), and proteins with less than 70kD, such as nucleocapsid, membrane and envelope proteins, are related with the Th2 response (anti-inflammatory). In the case of SARS-Cov-2 infection, the levels of pro-inflammatory cytokines such as IFN-γ, IFN-α, IL-6 are high, configuring a higher Th1 response [11].

However, due to the increase in viral fragments with less than 70 kD released by apoptosis, a higher B cell stimulation occurs and leads to a condition called activated-induced cell death (AICD). This condition stimulates, even more, the release of pro-inflammatory cytokines and apoptosis, resulting in the lymphopenia already described. As a result, IL-10 is released and an imbalance occurs, leading to a Th2 response stronger than it should be and causing greater suppression of the immune system. Furthermore, it was found that patients with higher levels of the Th2 response need more intensive care than patients who did not have this imbalance. For this reason, it is worth mentioning that patients who need more care are the same ones with more hepatic vulnerability [11].

Liver damage can also be related to gut-liver and gut-pulmonary axes breakage. The presence of SARS-Cov-2 RNA in stool samples suggests a connection with a more intense intestine lumen translocation. It occurs in consequence of the gut vascular barrier (GVB) breakdown due to the vulnerability to infectious agents [13]. Sepsis occurrence is also associated with the altered barrier permeability [11].

Secondary aggression mechanisms
Liver alterations during the new coronavirus infection are not uncommon. Therefore, studies carried out from a necropsy identified moderate microvesicular steatosis and mild lobular and portal inflammatory activity [13]. All these changes were induced by oxygen reduction and lipid accumulation in hepatocytes due to shock and hypoxia. Besides that, all of them can trigger cell death [8]. It has been proven from an experimental data that through in vivo and in vitro models, liver cell death and inflammatory infiltration are caused by the induced hypoxia by COVID-19 complications [8].

These studies results are strongly related to hypoxia associated with pneumonia, being one of the main factors of secondary liver damage. However, research has failed to distinguish whether the data is directly related to infection or drug toxicity [13].

The drugs used to manage COVID19 (antiviral drugs, antimalarial drugs, antibiotics, steroids) are frequently associated with hepatotoxicity [13]. According to Zhang et al's study, liver function can change during and after SARS-Cov-2 infection, using the hypothesis of residual effect on the liver, since it is where all these drugs are metabolized [5]. Also, doctors must observe the evolutionary line of the patient's liver function before and during treatment through laboratory tests [9].

Another factor that can trigger liver damage is mechanical ventilation. This happens due to the high levels of positive end-expiratory pressure (PEEP) that patients are subjected to. This process is explained by the significant increase in right atrial pressure that compromises the venous return of the inferior vena cava - from the liver. Thereby, congested blood contributes to liver damage [13].

Liver dysfunction in patients with comorbidities
It is known that patients with comorbidities such as diabetes, cardiovascular disease, hypertension and liver disease (cirrhosis, hepatitis and liver cancer) have increased susceptibility to liver dysfunction.

A study combined data from 103 patients with cirrhosis and 49 with chronic non-cirrhotic liver disease from 21 countries on 4 continents, with 59.9% being male, the average age of 61 years and the following etiologies: 22.4% non-alcoholic fatty liver disease, 19.7% alcohol, 11.8% hepatitis B, 10.5% hepatitis C, 35.6% others/combination. As a conclusion, 23.3% of patients with cirrhosis were admitted to the Intensive Care Unit (ICU), 17.5% needed supportive invasive ventilation, 18.6% non-invasive ventilation, 4.9% therapy renal replacement and 39.8% died [14].

Regarding patients with hepatitis (HBV, HBC) who have had SARS-Cov-2 co-infection, it is worth mentioning that they are more predisposed to develop severe hepatitis. These complications occur due to the increased hepatitis virus replication during the co-infection [12]. For this reason, patients with pre-existing liver diseases are more vulnerable because of their systemic immunocompromise.

Conclusion

The pandemic triggered by the new coronavirus, highly associated with comorbidities and damage to various organs, has already killed thousands of people around the world. In this literature review, it was shown that hepatic manifestations in SARS-COv-2 infection are not uncommon. For this reason, it's important to evaluate liver enzymes evolutionarily, mainly because patients with pre-existing comorbidities have a worse course disease due to the immunocompromise already presented.

Thereby, doctors must know the liver's function since the beginning of the infection, because in addition to having a better perspective on the patient's prognosis, they will know which therapeutical measures should be prioritized. As a consequence, the outcome of people with COVID19 may be better and liver sequelae reduced. Although changes in the liver are notorious due to SARS-CoV-2, new data must be collected to enable studies to differentiate which is the main etiology responsible for the liver dysfunctions that are occurring.

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