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REVIEW ARTICLE

Liver Changes Caused by Sars-CoV-2

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Abstract: With the Sars-CoV-2 virus endemic, many individuals with preexisting liver diseases such as liver cirrhosis and chronic liver diseases have become exposed to decompensation due to the virulence of exposure and individual susceptibility to the new coronavirus infection. The direct cytotoxicity of the Sars-CoV-2 virus occurs through its replication in liver cells, given by the binding of the agent to the target cells by the expression of the angiotensin-converting enzyme 2 (ACE2), which is the main mediator of viral replication in infected patients. by Covid-19. As a consequence, pro-inflammatory cytokines increase and can cause hypoxia and systemic ischemia. In association with lymphopenia and a decrease in CD4+ T-cell levels, patients may progress to decompensation or worsening of the infectious condition, with chronic liver failure worsening since the first week and, thus, a decrease in survival. Patients pre-diagnosed with cirrhosis and infected with the Covid-19 virus have greater liver involvement and worse prognosis and, therefore, deserve special monitoring, being carefully evaluated in order to enable the reduction of liver damage caused by the infection.

Descriptors: Sars-CoV-2; Covid-19; Hepatocytes; Pandemics; Cytokine release syndrome; Hepatic cirrhosis; hypoxia.

INTRODUCTION

Covid-19 is a highly contagious infection that emerged as an endemic in December 2019 with its first cases in the Chinese province of Wuhan and then evolved into a pandemic.[1] Covid-19 is a highly contagious infection that emerged as an endemic in December 2019 with its first cases in the Chinese province of Wuhan and then evolved into a pandemic.[2,3]

With SARS-CoV-2 contagion, the single-stranded RNA virus initiates pathogenicity in the individual. The process of viral invasion occurs through the high affinity binding of the S protein present in the virus with the angiotensin-converting enzyme 2 (ACE2), which is highly present in the airways. This binding enables penetration into alveolar target cells through the process of clathrin-dependent endocytosis, thus enabling viral fusion and replication within alveolar cells and their propagation to other lung segments and other systems that express ACE2.[4,5] The systemic involvement caused by infection by Sars-CoV-2 was observed in cardiac, renal, neurological and hepatic cells, the latter being verified in several studies by altering tests of proteins that are markers of liver injury.[6-12]

The clinical picture of viral infection is versatile, ranging from asymptomatic to classic symptomatic cases, such as fever, dry cough, fatigue, expectoration, dyspnea, sore throat, headache, myalgia or arthralgia, nasal congestion, diarrhea, hemoptysis, and conjunctival congestion.[13] The severity of the infection varies according to the

virulence of exposure and the susceptibility of the affected individual. The classification of risk factors for more severe cases of the new coronavirus are: advanced age, obesity, diabetes mellitus, systemic arterial hypertension, chronic respiratory diseases, cardiovascular diseases and neoplasms, highlighting the importance of comorbidities in patients.[14]

Liver injury is an important marker of worsening infection in individuals affected by the new coronavirus infection, in addition to being characterized as a comorbidity in patients who already have preexisting liver diseases, such as decompensated liver cirrhosis and chronic liver diseases.[15-17] This directly reflects not only the damage caused to the liver at the time of infection, but also the long-term follow-up of patients, as demonstrated by the APCOLIS study.[18] In this study on the evolution of preexisting liver disease in patients with SARS-CoV-2 infection, acceleration of liver damage was observed in patients with cirrhosis when compared to individuals without comorbidities.[18]

This study performs a non-systematic review of the mechanisms of liver injury caused by Sars-CoV-2 and its association with the pre-diagnosis of liver cirrhosis, seeking to analyze the worsening of pre-existing liver injury, possible laboratory investigation methods and prognoses of these patients in post-infection by Covid-19.

MECHANISMS OF HEPATIC INJURY BY SARS-COV-2

In order to understand how Covid-19 can affect the liver, a cohort study was carried out comparing several laboratory tests among infected patients who did not have liver complications.[19] Although the mechanism of liver injury by Covid-19 has not been fully understood, the pathological investigation of an infected patient demonstrated the presence of moderate steatosis, leukocyte infiltration in the lobular and portal areas, focal necrosis and sinusoidal congestion.[19]

Direct viral cytotoxicity to the liver

Direct cytotoxicity due to virus replication in liver cells is due to the binding of Sars-CoV-2 to target cells, demonstrated by the expression of ACE2, which is the main mediator of viral replication in patients infected with Sars-CoV-2.[20]

A study carried out by the University Medical Center of Groningen, in the Netherlands, analyzed the distribution of ACE2 in body tissues, detecting the presence of these proteins in hepatocytes.[21] Recently, in 2020, there was the publication of a cohort study that revealed a significant enrichment of ACE2 expression in the liver, mainly in the cells that make up the bile ducts (cholangiocytes), observing an average 20 times higher in relation to the expression level in hepatocytes, while in Kupffer cells ACE2 was not detected.[22] Reinforcing this proposal, biopsy samples collected from patients with Covid-19 show moderate microvesicular steatosis and mild lobular and portal activity.[23]

Patients infected with the virus during hospitalization in Wuhan demonstrated elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) levels, suggesting an injury linked to the progression of Sars-CoV-2.[24]

Immune-mediated liver injury by the body's systemic response

Among the possible explanations for such processes is the immune-mediated injury by the systemic inflammatory response, according to the report of a study that showed increased pro-inflammatory cytokines mainly in severe cases of Covid-19, which could cause hypoxia and systemic ischemia.[25]

The exacerbated increase in inflammatory cytokines has been described as a cytokine storm, and together, lymphopenia and decreased levels of CD4+ T cells, common findings in patients infected with Sars-CoV-2, may be associated with the intensity of the disease and mortality.[26]

One of the cohort studies characterized, in inflammatory cytokines, the presence of kinetic alterations, including IL-6, IL-2, IL-4, IFN-γ and TNF-α in the participants' serum. Thus, it was observed that in patients with characteristics of mild Sars-CoV-2 infection, fluctuations in the serum levels of these cytokines were considerably smaller than in critically ill patients, who had significant fluctuations.[27]

With the exception of IL-6, all other cytokines reached their peak in serum between three and six days after the onset of the disease, however the levels of IL-6 and IL-10 showed a sustained increase in the group with a more severe condition if compared to the other with a milder infection. In this logic, it was seen that the decrease in T cells in Covid-19 can result in worsening inflammatory responses, while the normalization of the number of these cells can decrease inflammatory responses. Reinforcing this hypothesis, the T cell count pointed to an inversely proportional correlation between its values compared to the levels of cytokines in the peripheral blood of critically ill patients, because when the T cells were at the lowest levels, the peak in the serum levels of IL- 10, IL-2, IL-4, TNF-α and IFN-γ, approximately between the fourth and sixth day.[27]

In view of the research, a possible protagonist role of IL-6 in the process is observed: 30.39% of participants with mild infection by Sars-CoV-2 had IL-6 values higher than normal, while in the group with severe infection 76.19% of the patients had their value increased. Although not completely clarified, it is considered possible that such a process occurs due to the inhibition of Th2 cells participating in humoral immunity in the earliest stage of Covid-19.[28]

Effects of severe hypoxemia on the liver

There are three main risk factors that generate severe hypoxemia in patients who progress to liver involvement: heart failure, severe sepsis, and respiratory failure.[29,30] Under these circumstances, a cytokine storm impairs the proper functioning of the liver, hindering transduction for cell survival, and causes significant accumulation of lipids, as well as increased consumption of glycogen and depletion of adenosine triphosphate from hepatocytes. Such associated factors cause oxidative stress and an increase in pro-inflammatory factors.[27,31,32]

As a consequence, patients develop a circulatory disorder resulting from passive congestion and decreased hepatic perfusion, which leads to hypoxia and ischemia.[33] With liver damage installed, intracellular swelling of the organelle will be present. To reduce such negative effects, Kupffer cells increase the production of cytokines for leukocyte activation, which promotes increased levels of transaminase and lactate dehydrogenase (LDH), generating the need for oxygen support.[3]

Fig. 1 demonstrates the simultaneous action of the mechanisms of liver injury with the invasion of Sars-Cov-2 in hepatocytes and cholangiocytes, causing irreversible dysfunctions, with consequent cell death.

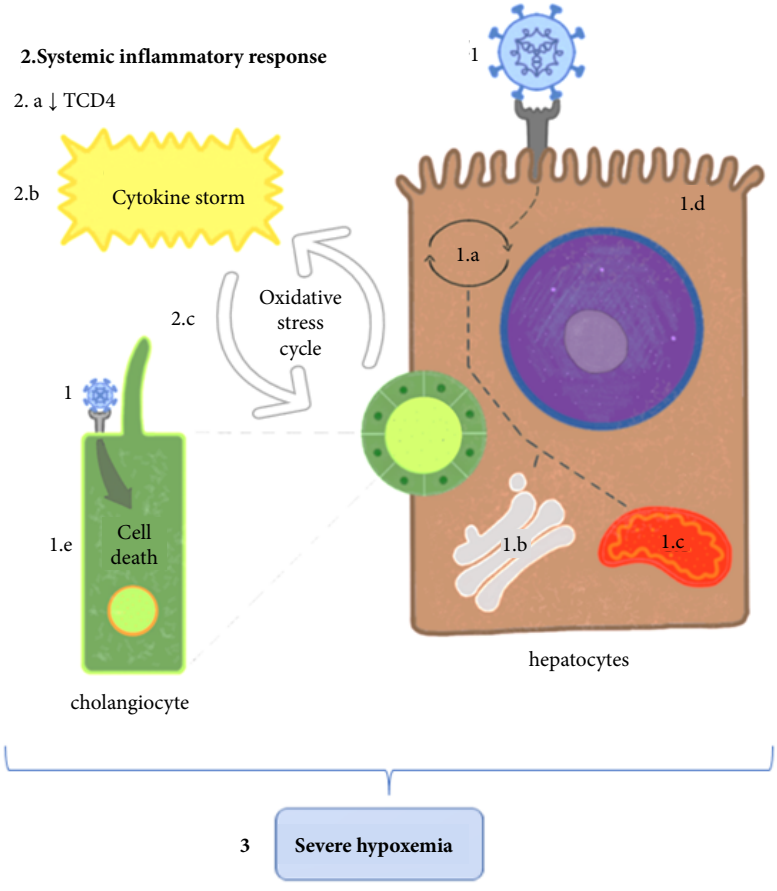

Figure 1. (1) The Sars-CoV-2 virus enters the cell by binding to the angiotensin-converting enzyme 2 (ACE2) expressed on the surface of hepatocytes and cholangiocytes. (1.a) Viral replication. (1.b) Endoplasmic reticulum stress. (1.c) Mitochondrial edema. (1.d) Cell membrane injury. (1.e) Cell death due to irreversible damage to organelles. (2) Systemic inflammatory response. (2.a) Lymphopenia characterized by a fall in the TCD4 lymphocyte count. (2.b) Exacerbated increase in inflammatory cytokines. (2.c) Oxidative stress cycle: the pro-inflammatory environment created by cytokines hinders the process of cellular respiration, thus damaging the liver cell. As a result, there is a further increase in pro-inflammatory factors. (3) Severe hypoxemia, as a result of circulatory disturbance caused by the inflammatory environment and dysfunctional cells.

Evolution and prognosis

Patients with severe Covid-19 without preexisting liver comorbidities take about three weeks to start developing liver damage. However, previously cirrhotic patients in a compensated state who are affected by the infection have an accelerated progression of liver damage, and decompensation or evolution of the injury may be noticeable with acute chronic liver failure since the first week.[34,35]

In these patients, it is possible to observe an increase in pro-inflammatory cytokines, associated with the presence of inflammatory markers of liver injury, weighted by the increase in the level of gamma-glutamyltransferase, ALT and AST proteins in the bloodstream. These proteins were measured as markers in studies with cirrhotic patients with Sars-CoV-2, in addition to the presence of leukopenia, lymphopenia and thrombocytopenia in laboratory tests.[35-37]

As a result of the liver involvement caused by the Covid-19 virus, the controlled cirrhotic patient can progress to a decompensation condition. In this way, there is greater damage to the patient's liver and the chances of survival are reduced.[38] A study was carried out based on cadaveric examinations of patients who died from decompensated cirrhosis and found that the invasion of liver cells by the Covid-19 virus, associated with mitochondrial edema and cell membrane damage, therefore causes apoptosis of the hepatocytes, significant focal lobular inflammation and important lymphocyte infiltrate.[39]

The association of liver cirrhosis with the new coronavirus was related to higher positions of liver severity in the international assessment represented by the Child-Pugh system, with 1/3 of patients being reclassified into more severe categories.[40] Assessment systems for patients with chronic liver disease are directly proportional to mortality from Sars-CoV-2. That is, patients classified as high Child-Pugh are more likely to die.[41-43]

In this way, it is validated that patients pre-diagnosed with cirrhosis and infected with the Covid-19 virus have greater liver involvement and worse prognosis.[37,38,40,41,43,46]

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Nascimento FBM; Fabris GM; Souza FG; Castro MS; Oliveira MEC; Silva VS and Buri R; **Conception and design:** Nascimento FBM; Fabris GM; Souza FG; Castro MS; Oliveira MEC; Silva VS and Buri R; **Analysis and interpretation of data:** Silva VCB; Castro MS; Lima MKZ; Zattar AK; Jesus VN; Oliveira MEC; Silva VS; Rodrigues LO and Buri R; **Manuscript writing:** Nascimento FBM; Fabris GM; Silva VCB; Castro MS; Lima MKZ; Zattar AK; Jesus VN; Oliveira MEC; Silva VS; Rodrigues LO and Buri R; **Final approval:** Nascimento FBM; Castro MS; Zattar AK; Oliveira MEC; Silva VS and Buri R.

AVAILABILITY OF RESEARCH DATA

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CONCLUSION

Liver findings are common in Covid-19 infection, caused by direct cytotoxicity, immune-mediated injury, hypoxemic effects, and also by the use of drugs for treatment, but there was no precise confirmation as to the direct effects on the death of patients infected by Sars-CoV-2 demonstrated in autopsy exams.[23] Patients with preexisting liver diseases deserve special monitoring, since the clinical

changes in the liver are more intense than normal, representing a worse prognosis and increased mortality in decompensated liver disease patients.[40] Based on the information collected, the management and treatment of Covid-19 in patients should be carefully evaluated in order to reduce the liver damage caused by Sars-CoV-2.

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