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## CLINICAL ASPECTS OF LIVER DAMAGE IN COVID-19

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**Abstract.** COVID-19 poses a serious threat to global public health. Currently, COVID-19 is considered as a systemic disease with impaired immune system function, affecting primarily the lungs, but also the heart, kidneys, intestines, liver and spleen. Liver damage occurs mainly in severe COVID-19. Today, it is not entirely clear whether changes in liver laboratory parameters in patients with COVID-19 are related to previously diagnosed liver disease, or whether they reflect liver damage in COVID-19. The article presents works devoted to the study of liver lesions during the period of COVID-19 disease in patients without previous pathology or with pre-existing liver pathology.

**Keywords.** COVID-19, liver, SARS-CoV-2, chronic liver disease

**Introduction.** The liver is a vital organ that performs many functions in the body and is involved in the reactions of the immune system that determine the overall level of the body's resistance to infections and is responsible for the production of antibodies to fight viruses and bacteria. The state of the liver affects both the course of infectious diseases and the inflammatory processes caused by them, and the speed of recovery. Chronic liver diseases are among the most common in the world. In an epidemic, effective monitoring and continued treatment of patients with these pathologies is especially important to maintain health, as well as to reduce the burden on healthcare and reduce the total number of people affected by coronavirus infection. To date, scientific evidence has confirmed that at risk, with an increased likelihood of infection and severe course of coronavirus infection, are elderly patients and patients with chronic cardiovascular diseases such as hypertension, coronary heart disease and diabetes mellitus. Less is known about the impact of other chronic diseases, and in particular liver disease. However, it is already clear that patients with severe fibrosis and cirrhosis of the liver, patients after liver transplantation also represent a vulnerable group with an increased risk of infection and a severe course of COVID-19. Therefore, they are strictly ordered to self-isolate and reduce social contacts. The international medical community analyzed the available data on the impact of SARS-CoV-2 coronavirus infection on the course of chronic liver diseases and made preliminary conclusions.

### **Direct effects of SARS-CoV-2 on the liver**

The mechanisms of the direct effect of the SARS-CoV-2 virus on the liver (direct cytotoxicity due to the active replication of the virus in the liver cells) are not well

understood. In earlier studies associated with infection with coronaviruses of the Betacoronavirus genus (SARS-CoV (2002–2003) and MERS-CoV (2012)), liver damage was quite common and was associated with the severity of the disease [14, 15]. As is known, SARS-CoV, as well as SARS-CoV-2, use ACE2 as receptors for entry into the cell, which are widely distributed in the cells of the heart, kidneys, blood vessels, especially alveolar epithelial cells, as well as the liver, pancreas, intestinal epithelium, which ensures systemic damage [16]. However, it is not entirely clear whether liver damage can be caused directly by the SARS-CoV-2 coronavirus. Previous RNA-seq sequencing data in the Human Protein Atlas Database confirms ACE2 expression in the liver of SARS-CoV [17]. At the same time, a low frequency of ACE2 expression is observed only in cholangiocytes, but not in hepatocytes, Kupffer cells, or endothelial cells. In addition, SARS-CoV, through a specific protein 7a, is able to induce apoptosis in cell lines of various organs (including lungs, kidneys, and liver) in a caspase-dependent manner. This indicates the possibility of a direct impact of SARS-CoV on liver tissue. During autopsy of patients with SARS-CoV by RT-PCR, the SARS-CoV genome was found not only in the lungs, but also in parenchymal cells, including hepatocytes, vascular endothelium of various organs. A liver biopsy in SARS-CoV patients with SARS revealed pronounced mitoses, acidophilic bodies, Kupffer cells, and balloon-like hepatocytes. This suggested that SARS-CoV induces apoptosis of liver cells and thereby contributes to its damage [14]. Critically ill COVID-19 patients often show signs of liver dysfunction, according to Chinese doctors. Therefore, patients with cirrhosis and COVID-19 are at higher risk of decompensation and liver failure.

In addition, scientists have found that the SARS-CoV-2 virus can directly infect liver cells and cells lining the intra- and extrahepatic bile ducts (cholangiocytes), since they contain, although in low concentrations, a special enzyme (angiotensin-converting 2), which the SARS virus- CoV-2 uses to enter the cell. This may explain the detection of the virus in faeces. The same enzyme is found in the cell membranes of the intestines, kidneys, and lungs, which may play a key role in the risk of developing severe respiratory distress (acute respiratory syndrome of the lungs)

### **Drug-induced liver injury**

The most common cause of liver damage in COVID-19 is associated with drug-induced liver damage, which is a consequence of the use of etiotropic treatment of SARS-CoV-2 infection and pathogenetic therapy of COVID-19 [19, 20]. During the pandemic, initial clinical guidelines recommended drugs for the treatment of SARS-Cov-2 infection, and some of them, including lopinavir/ritonavir, hydroxychloroquine, azithromycin, umifenovir, famipiravir, recombinant interferon beta-1b, have potential hepatotoxicity [26]. The hepatotoxicity of hydroxychloroquine has been described in isolated clinical observations in the

treatment of patients with systemic lupus erythematosus, cutaneous porphyria tarda, rheumatoid arthritis, and malaria. According to the LiverTox registry, hydroxychloroquine is category C and is likely to cause idiosyncratic liver injury [34]. Probably, in addition to direct drug-induced hepatotoxicity, the possibility of developing idiosyncratic (immune-mediated) liver damage, the most common cause of which is antibiotics, should be singled out separately [35]. Accordingly, all patients receiving etiologic and pathogenetic therapy for COVID-19 need to monitor liver parameters to prevent severe drug-induced hepatitis at the stage of both inpatient treatment and subsequent outpatient follow-up. It should be noted that all patients with already established liver cirrhosis (LC) for any reason of decompensation are at high risk of morbidity and mortality, regardless of the viral epidemic. Patients with cirrhosis may be more susceptible to infections due to systemic immunodeficiency, so avoiding SARS-CoV-2 infection is paramount. So, Y. Xiao et al. noted cirrhosis decompensation in 17% of patients with COVID-19 who did not comply with preventive measures [38]. There is no evidence that patients with autoimmune liver disease (AILD) are at higher risk of becoming infected or developing severe COVID-19. Preliminary experience (Bergamo, Lombardy) shows that patients with stable AILD on long-term maintenance immunosuppressive therapy have a low risk of complications and/or progression [40]. However, it is possible that exacerbation of autoimmune hepatitis may require a higher dose of corticosteroids, and therefore potentially increase the risk of infection.

### **Impact of COVID 19 virus infection on the course of chronic liver disease.**

Patients with chronic liver diseases require increased attention of doctors during the epidemic, as the exacerbation of their disease increases not only the risk of contracting the COVID 19 virus infection, but also its more severe course.

In patients with severe fibrosis and cirrhosis of the liver, a high risk of infection is due to the state of immune deficiency. The same is true for liver transplant patients and for patients with autoimmune liver disease who are receiving immunosuppressive therapy. There is no strong evidence that people living with viral hepatitis B or hepatitis C are at greater risk of contracting COVID-19, but the infection is much more severe and contributes to the progression of liver disease. Patients with hepatocellular insufficiency and after liver transplantation are at very high risk and are at significant risk of contracting COVID-19 infection and its more severe course.

### **Summary and Conclusion**

COVID-19 is a systemic disease that affects the immune system, primarily affecting the lungs, but also the heart, kidneys, intestines, liver, and spleen. The mechanisms of liver damage that occur during SARS-CoV-2 infection are not well understood.

Among the main pathogenetic effects on the liver are:

- immune activation and inflammation caused by circulating cytokines with the initiation of a cytokine storm and multiple organ failure;
- direct cytotoxicity due to active replication of the virus in liver cells with the participation of ACE2 as receptors for introduction into the cell;
- severe hypoxia, which leads to increased inflammation, oxidative stress, hypoxemia, hypoxia, the development of symptoms of acute respiratory distress syndrome and multiple organ oxygen deficiency;
- drug-induced liver injury in terms of direct drug hepatotoxicity and idiosyncratic (immune-mediated) injury. Timely anti-inflammatory therapy for COVID-19, careful clinical monitoring are crucial and should be individualized, taking into account comorbidity and immune status, to achieve the most favorable results.

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