Coronavirus Infection - A Trigger Factor of Liver Damage

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ABSTRACT

There are quite a few options for the harmful effects of coronavirus infection on the liver. It is no secret that SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE-2) as a receptor to enter the intracellular environment. It was found that ACE-2 is expressed to a greater extent on cholangiocytes , which makes the liver a possible target for the virus. A liver biopsy from SARS- CoV patients in 2002 showed a multiple increase in mitotic cells with eosinophilic bodies and balloon-like hepatocytes, suggesting that SARS- CoV may induce hepatocyte apoptosis and cause liver damage. Many studies have presented that SARS- CoV , through a specific protein 7a, can induce apoptosis at subcellular levels of various organs (including lungs, kidneys, and liver) in a caspase - dependent manner, proving the possibility that SARSCoV can directly act on hepatic tissue. First of all, at an early stage of SARS- CoV infection in patients, abnormal serum thresholds of cytokines and chemokines were found: serum levels of IL-1, IL-6 and IL-10 in patients with chronic diffuse liver diseases were higher than in patients with normal or slightly reduced liver function, calculating a tolerable correlation between liver damage and inflammatory reactions caused by coronovirus infection. In addition, SARS patients with HBV/HCV infection were more resistant to reversal of liver injury and severe hepatitis is usually associated with an increase in hepatitis virus replicatio n during SARS- CoV infection. Despite the fact that equal data on SARS-CoV-2 has not been achieved, chronic viral hepatitis probably does not increase the likelihood of a severe prognosis of COVID-19. CHB, which is more common in China than in Europe, does not appear to affect the outcome of COVID-19. Based on this, there is no credible argument to suggest that immunosuppression may even provide a kind of complex safety against immunopathological processes that contribute to lung damage in cases with more dangerous expressions of the disease. Most likely, this is due to the macrophage activation syndrome in pro-inflammatory syndrome, which qualifies as a cytokine storm and multiple organ failure. Systemic viral infections are partly associated with transient increases in transaminases, which may reflect generalized immune activation or inflammation caused by circulating cytokines without liver dysfunction, the so-called "bystander hepatitis" phenomenon - hepatitis not involved in the process.

Liver damage with Covid -19 occurs in full due to hypoxia (oxygen depletion), which develops against the background of pulmonary insufficiency. Hypoxemia associated with severe pneumonia causes ischemic liver damage in patients with coronavirus infection. A decrease in the oxygen content in the body during hypoxic conditions can lead to the death of liver cells.

Keywords: Covid-19 pandemics, chronic diffuse liver diseases, ACE receptors, liver enzymes, cytokine storm, antiviral drugs.

Introduction. At the end of 2019, the world community is still in a difficult situation due to the Covid -19 pandemic. Virus of the Coronaviridae family , The genus Betacoronavirus threatens the entire global health community with high prevalence and lethality. SARS-CoV-2 is an ingenious weapon of mass destruction of the whole organism. When infected, a number of pathological changes begin to occur in the body. But in some infected people, the course of the disease is milder, while in others, it can lead to death. 2020 will forever be remembered for how our lives have changed due to the pandemic, as this virus is known to have greatly impacted the safety of patients and their caregivers. This directly affected people with liver disease, dramatically changing the practice of hepatology , hepato-oncology , and liver transplantation.

Although the main route of transmission, morbidity and mortality from COVID-19 is associated with the respiratory system and the local and systemic immune response to infection, direct and indirect effects on the liver and survival of patients with liver disease from COVID-19 have been observed. We focused on clinical, instrumental, biochemical changes associated with liver damage and inflammation due to COVID-19 and their impact on patient outcomes. Similarly, it indirectly affected the monitoring and surveillance of patients with chronic diffuse liver disease.

Purpose: Determination of the frequency of hepatic lesions and the study of the role of provoking factors of liver damage in CDLD, against the background of C OVID - 19;

Materials and methods: Synthesis and collection of research literature published in regular publications.

Results: As with SARS- CoV , angiotensin-converting enzyme 2 (ACE2) appears to be a sensitive receptor for SARS-CoV-2 and is expressed in more than 80% of lung alveolar cells. *In* vitro during the SARS epidemic, ACE was identified as the host receptor for virus entry.

Immunohistochemical studies of human tissues during the SARS pandemic showed a high expression of the ACE2 receptor protein in the vascular endothelium of small and large arteries and veins. In the lungs, ACE2 is highly expressed in type 2 alveolar cells. Interestingly, fibrosed lungs had much higher ACE2 staining, while bronchial epithelial cells showed weaker expression. A recent study showed that SARS-CoV-2 has a 10-20 times higher binding affinity for receptors. [4]

Immunohistochemical studies revealed higher expression of ACE receptors in the gastrointestinal tract. ACE expression is high in the basal layer of the squamous epithelium . from the mucous membranes of the nose, oral cavity and nasopharynx. Smooth muscles of the gastric and colonic mucosa also express ACE. In addition, ACE is abundantly expressed in enterocytes of the duodenum, jejunum, and ileum.

ACE is the host cell receptor for SARS-CoV-2; it is present in type 2 alveolar cells, the gastrointestinal tract, and the liver. [8]

The hepatic distribution of ACE is peculiar. It is highly expressed in the endothelial layer of small blood vessels, but not in the sinusoidal endothelium. Chai and colleagues found that the cell surface receptor ACE was more expressed in cholangiocytes (59.7%) than in hepatocytes (2.6%). The level of ACE expression in cholangiocytes was similar to that in lung alveolar type 2 cells, indicating that the liver may be a potential target for SARS-CoV - immunohistochemical stains for ACE were negative on Kupffer cells , as well as T- and B-lymphocytes . [10]

A recent study in Wuhan found that Asian men had higher ACE expression, indicating the possibility of a higher susceptibility to COVID-19 in this population. [5]

SARS-CoV-2 has spread as a zoonotic infection; however, the disease was rapidly transmitted from person to person by airborne droplets, especially among close contacts. SARS-CoV-2 is resistant and can remain viable from 2 hours to 14 days depending on weather conditions.

The transmission potential of an infection in a community is based on its base reproduction rate, which is commonly referred to as the disease transmission rate. This represents the number of secondary cases resulting from an index case in a susceptible COVID-19 population of 2.2. [7]

Previous studies have shown that between 19.6% and 73% of SARS patients had gastrointestinal symptoms. [2]

With limited therapeutic options, prevention through social distancing appears to be the cornerstone of COVID-19 treatment. Transmission of the virus can be reduced by various methods described in the WHO protocol. [3]

Liver damage in COVID-19 may be due to direct cytopathic effects of the virus, an uncontrolled immune response, sepsis, or drug-induced liver injury. Given the higher expression of ACE receptors in cholangiocytes , the liver is a potential target for SARS-CoV-2. In addition, COVID-19 may cause worsening of underlying chronic diffuse liver disease, leading to hepatic decompensation and acute chronic liver failure with higher mortality. [1]

Overall, 4–16% of patients with COVID-19 were diagnosed with chronic diffuse liver disease, and 14–53% of patients with COVID-19 developed liver dysfunction, especially in those with severe disease. Hepatic dysfunction was significantly higher in critically ill patients and was associated with poor outcome. [18]

In a recent study from Wuhan written by Wang and colleagues, 4 patients (2.9%) with COVID-19 had comorbid chronic diffuse liver disease. Again, one study from China showed that 23 (2.1%) patients were positive for HBsAg , of which only one had severe COVID-19. Interestingly, a study conducted by Xu and colleagues outside of Wuhan identified 26 patients with COVID-19, 11% of whom had chronic liver disease. In another study, a comparison of 113 non-survivors and 161 survivors showed that 4% of them had chronic hepatitis B. [19]

Cases of acute lesions in patients with chronic diffuse liver diseases were observed in 13 (5%) of 274 patients, of which 10 (76.9%) died. Based on the available data, it is clear that elevated liver enzymes occur predominantly in severe and critical cases of COVID-19. An increase in AST was noted in 8/13 (62%) patients in the ICU compared with 7/28 (25%) in the non-ICU setting.

Reported peak levels of alanine aminotransferase (ALT) and AST were 7590 U /L and 1445 U/L, respectively, in severe COVID-19. [4]

Curiously, patients treated with lopinavir / ritonavir showed a higher proportion of enzyme elevations (56.1% vs 25%). [7]

It was not clear whether the elevated liver enzymes were due to disease per se or drug-induced liver injury in this population. Possible effect of liver damage due to inflammatory cytokine storm in severe COVID-19. It has been reported that 14–53% of patients with COVID-19 develop some form of liver dysfunction. [9]

Interestingly, despite the presence of ACE in cholangiocytes , more patients developed elevated transaminase levels . Unpublished data from Wuhan, China provided by Xu et al . showed elevated levels of gamma-glutamyltransferase (GGT) in severe cases of COVID-19. Whether COVID-19 exacerbates cholestasis in patients with primary biliary cholangitis and primary sclerosing cholangitis requires further analysis. [10]

It may be that liver dysfunction may be the result of a cytokine storm rather than a direct cytopathic effect of viral particles. More data is needed to establish the nature and extent of liver damage in patients with COVID-19.

Unlike SARS- CoV and SARS-CoV-2, MERS- CoV uses dipeptidyl peptidase-4 (DPP-4), which is abundant in the liver, as a cell entry receptor. [16]

Low albumin has been found to be an independent predictor of severe MERS- CoV infection . Biopsy of patients suffering from chronic diffuse liver disease with MERS showed lobular lymphocytic infiltration and moderate hydropic dystrophy of hepatocytes .

Among patients with MERS, non-survivors had a higher incidence of liver injury than survivors (91.3% vs. 77.9%, respectively). Mortality was higher in patients with comorbidities. [12]

A case fatality rate of 3.6–15% was reported in 4292 Chinese patients. Mortality was higher in

men (3.25:1), over the age of 75 years and with concomitant diseases (diabetes mellitus, arterial hypertension and cardiovascular diseases). These comorbidities were noted in 48% of patients in a study by Zhou and colleagues reporting 191 patients with COVID-19: 54 died (28.2% mortality), of which 36 (66.6%) had an underlying chronic disease. [eleven]

In a meta-analysis of 8 studies including 46,248 patients that analyzed the prevalence of comorbidities in COVID-19, the most common comorbidities were hypertension (14–22%), followed by diabetes mellitus (6–11%), cardiovascular disease . diseases (4–7%) and respiratory diseases (1–3%). [12]

Mortality was higher in patients with hypertension (48%), followed by 21% in diabetics, 14% in patients with cardiovascular disease, 10% in patients with chronic lung disease, and 4% each in patients with malignant neoplasms, chronic diseases kidney and cerebrovascular diseases . would be cold. However, the mortality rate in patients with comorbid chronic liver disease was 0–2%.

There is some evidence that a possible mechanism for the development of hepatic coagulopathy in coronavirus infection may consist of :

- decreased synthesis of coagulation factors (pathological fibrinogen), impaired synthesis of vitamin K
- thrombocytopenia (hypersplenism with platelet sequestration, decreased production of thrombopoietin)
- reduced degradation of activated coagulation factors (DIC) and increased activation of the fibrinolytic system - hyperfibrinolysis

In this analysis, hypertension (48% vs 24%), diabetes (21% vs 14%), and cardiovascular disease (14% vs 4%) were more common in nonsurvivors . Fatty liver disease is likely considered part of the metabolic syndrome in this group of patients, which may complicate the issue. [14]

Another study from Wuhan reported characteristic features of deceased patients (n = 113). Levels of AST, ALT, alkaline phosphatase, GGT, and bilirubin were significantly higher in non- survivors than in survivors. An elevated AST level (>40 U /L) was observed in 59 (52%) deceased and 25 (16%) recovered patients, and an elevated ALT level (>41 U/L) was found in 30 (27%) deceased and 30 (19%). %) of recovered patients. Similarly, hypoalbuminemia (<32 g/L) was found in 74 (65%) patients who died compared to 22 (14%) patients who recovered. Serum bilirubin was 12.6 μmol and 8.4 μmol in the dead and recovered, respectively. In a recent report by Chen *et al* . , 13 (5%) patients with COVID-19 developed acute liver injury during the course of the disease, of which 10 (76.9%) died. Although the numbers are small, it provides important information about patients with COVID-19 and liver dysfunction. [9]

Liver dysfunction was significantly more common in critically ill patients and was associated with poor outcome.

Although the evidence is less clear, current treatment recommendations include antivirals, antibiotics, intravenous fluids, and corticosteroids. Oseltamivir was used in 89.9% of patients in the Wuhan series. Although remdisivir was initially promising, a recent randomized control trial has shown no clinical benefit in COVID-19, other than a marginally faster clinical recovery. Moreover, liver damage was observed in 10-13% of the remdisivir group . [18]

broad-spectrum ribavirin would be expected to work; unfortunately, during the SARS outbreak, ribavirin was associated with significant toxicity, including severe hemolysis. Curiously, Omrani and colleagues found that interferon alfa-2A in combination with ribavirin improved survival at day 14 (70% vs. 17%, p = 0.004), but not at day 28 (30% vs. 17% , p = 0.054) during the outbreak of the Middle East respiratory syndrome coronavirus . [17]

Lopinavir / ritonavir , approved for the treatment of HIV infection, has shown activity *in vitro* against SARS- CoV and was effective against MERS- CoV .

These drugs are being tested for COVID-19. Lopinavir , a protease inhibitor, has been

shown to be effective against SARS- CoV . Ritonavir was added to increase lopinavir trough levels by inhibiting the hepatic CYP450 enzyme. A recently published open -label randomized controlled trial in 199 patients with severe COVID-19 showed no benefit from lopinavir and ritonavir (99 patients). Current recommendations for the treatment of COVID-19 include corticosteroids, antivirals, antibiotics, and intravenous fluids. [15]

In this study, 20.5% and 41% of patients had elevated AST and ALT, respectively, before randomization; however, the presence of liver cirrhosis, ALT, or AST was more than 5 times the upper limit of normal in this study. An increase in bilirubin and an increase in AST levels were noted in 3.2% and 2.1% of patients in the treatment group, respectively.

Importantly, the use of ritonavir to inhibit CYP450 will increase trough levels of calcineurin inhibitors , the most commonly used immunosuppressive agents in solid organ transplant recipients, which could lead to potential drug toxicity. [18]

Antibiotics such as fluoroquinolones and third-generation cephalosporins have been used to reduce secondary infection. Corticosteroids (methylprednisolone) have been used in COVID-19 patients to control inflammation, and dexamethasone has recently been found to reduce mortality. Their use may lead to reactivation of chronic hepatitis B. Thus, HBsAg -positive patients should receive antiviral therapy, and we recommend that the status of the main antibodies to hepatitis B be checked and, if positive, treat patients with antiviral drugs for the duration of steroid therapy. [7]

Recently Chen *et al* . built a three-dimensional model of the crystal structure of SARS-CoV-2 proteases. Virtual screening of the active viral site has demonstrated that NS5A hepatitis C inhibitors may be effective against SARS-CoV-2. Ledipasvir and velpatasvir readily inhibited SARS- CoV proteases in their model. However, more evidence is needed. [19]

Discussion and conclusion. In patients with COVID-19, liver damage is often detected, which is probably caused by the effect of viral particles on the cells of the bile ducts, in other words, a functional disorder caused by the use of antiviral drugs. Still, there are results of histopathological examinations of patients with COVID-19, showing a slight steatosis of microvessels and inflammation in the vena zone . portae , thus, according to the results of autopsy, no real detrimental effect of viral particles on hepatocytes was revealed . Great interest should be given to the status of liver function of patients on the background of COVID-19. First , it is necessary to look at liver changes in the presence of central liver disease, increasing monitoring and evaluation of hepatocyte function in patients with complicated COVID-19. Secondly, it is necessary to scrupulously detect the sources of liver damage in combination with pathophysiological modifications caused by COVID-19. As a result of active treatment of the central link, it is appropriate to prescribe treatment to strengthen the protective properties of hepatocytes that reduce liver damage.

Conclusion

COVID-19 is currently a pandemic with an overall mortality rate of 12% to 26% for infected patients, which increases with age and comorbidities. COVID-19 causes acute respiratory failure, and invariably liver dysfunction occurs in severe cases and is associated with death. Cases of severe acute liver injury with higher mortality have been reported. Larger studies with long-term follow-up are needed to characterize the extent and cause of liver damage in COVID-19. The impact of COVID-19 on underlying chronic liver disease needs to be assessed in detail, and further research is needed in this area.

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