Coronavirus Infection - A Trigger Factor in Liver Damage

Babanazarov Umid Turobkulovich Bukhara State Medical Institute

Kayimov Mehriddin Tuymurodovich Bukhara State Medical Institute

ABSTRACT

There are a fair number of options for the detrimental effect of coronavirus infection on the liver. It is no secret that SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE-2) into receptor hypostases for penetration into the intracellular environment. It has been revealed that ACE-2 is more expressed on cholangiocytes, which makes the liver a possible object for the virus. Liver biopsy in patients with SARS-CoV in 2002 indicated a large increase in mitotic cells with eosinophilic bodies and balloon-like hepatocytes, suggesting that SARS-CoV may cause hepatocyte apoptosis and cause liver damage. Many studies have presented that SARS-CoV via a specific protein 7a can induce apoptosis in the subcellularlevels of various organs (including the lungs, kidneys and liver) in a caspase-dependent way, proving the possibility that SARSCoV can directly First of all, at the early stage of SARS-CoV infection , abnormal serum thresholds of cytokines and chemokines were found in patients: serum IL-1, IL-6 and IL-10 levels in patients with chronic diffuse liver disease were higher than in patients with normal or slightly reduced liver function, calculating an acceptable correlation between liver damage and inflammatory responses caused by coronavirus infection. In addition, patients with SARS with HBV/HCV infection were more resistant to altered liver damage and severe hepatitis usually are associated with increased replication of the hepatitis virus during SARS-CoV infection. Although no equal information on SARS-CoV-2 has been achieved, chronic viral hepatitis probably does not increase the likelihood of a severe prognosis for COVID-19. HBV, 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 for suggesting this, immunosuppression may even provide a kind of comprehensive safety from immunopathological diseases. Processes that contribute to lung damage in cases with more dangerous expressions of the disease. Most likely this is due to the syndrome of activation of macrophages in the pro inflammatory syndrome, which qualifies as cytokine storm and multiple organ failure. Systemic viral infections are partly combined with transient increases in transaminases, which can display allthe overall immune activation or inflammation caused by circulating cytokines without impairing liver function, the so-called phenomenon of "bystander hepatitis" - hepatitis, not participating in the process.

Liver damage in Covid-19 occurs entirely due to hypoxia (oxygen depletion) that develops against the background of pulmonary insufficiency. Hypoxemia that occurs with aggravated pneumonia causes ischemic liver damage in patients with coronavirus infection. A decrease in the oxygen content in the body in 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. The world community at the end of 2019 and to this day is in a difficult situation due to the Covid-19 pandemic. The virus of the coronaviridae family, the genus Betacoronavirus, threatens the entire world health community with high prevalence and lethality. SARS-CoV-2 is an ingenious weapon of mass destruction of the whole organism as a whole. When infected, a number of pathological changes begin to occur in the body. But in some infected people, the course of the disease is easier, and in others up to a lethal case. The year 2020 will forever remain in our memory of how our lives have changed due to the pandemic, as you know, this virus has greatly affected 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 primary route of transmission, morbidity, and mortality from COVID-19 are related to the respiratory system and the local and systemic immune response to infection, there have been direct and indirect effects on the liver and survival of patients with liver disease in COVID-19. We focused on the clinical, instrumental, biochemical changes associated with liver damage and inflammation due to COVID-19 and their impact on patient outcomes. Similarly, this indirectly affected the monitoring and surveillance of patients with chronic diffuse liver disease.

Objective: To determine the frequency of hepatic lesions and to study the role of provoking factors of liver damage in CDDP, against the background of COVID - 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 alveolar lung cells. *In* a test tube during the SARS epidemic, ACE was identified as a host receptor for the penetration of the virus.

Immunohistochemical studies of human tissues during the SARS pandemic showed high expression of the APF 2 receptor protein in the vascular endothelium of small and large arteries and veins. In the lungs, APF2 is strongly expressed in type 2 alveolar cells. Interestingly, fibrosed lungs had a much higher staining of APF 2, whereas bronchial epithelial cells showed weaker expression. A recent study showed that SARS-CoV-2 has a 10-20 times higher affinity for binding to receptors. [4]

Immunohistochemical studies have revealed higher expression of ACE receptors in the gastrointestinal tract. ACE expression is high in the basal layer of the squamous epithelium. mucous membranes of the nose, oral cavity and nasopharynx. Smooth muscles of the gastric mucosa and colon also express ACE. In addition, ACE is abundantly expressed in the 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 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. Tea and colleagues found that the cell surface receptor of ACE was more pronounced in cholangiocytes (59.7%) than in hepatocytes (2.6%). The level of expression of ACE in cholangiocytes was similar to that in alveolar cells of the lungs of type 2, indicating that the liver may be potent. The target for SARS-CoV immunohistochemical stains on ACE were negative on Kupffer cells as well as on T and B lymphocytes. [10]

A recent study conducted 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 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 stable and can remain viable from 2 hours to 14 days depending on weather conditions.

The potential for transmission in a community is based on its baseline reproductive rate, which is commonly referred to as theefficient of disease transmission. This represents the number of secondary cases resulting from the index ratein a susceptible population of COVID-19 is 2.2. [7]

Previous studies have shown that between 19.6% and 73% of PATIENTS with SARS 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 the direct cytopathic effects of the virus, an uncontrolled immune response, sepsis, or drug-induced liver damage. Given the higher expression of ACE receptors in cholangiocytes, the liver is a potential target for SARS-CoV-2. In addition, COVID-19 can cause a worsening of the 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 developed liver dysfunction against the background of COVID-19, especially those with severe form. Hepatic dysfunction was significantly higher in critically ill patients and was associated with an unfavorable outcome. [18]

In a recent study from Wuhan written by Wang and colleagues, 4 patients (2.9%) with COVID-19 had concomitant chronic diffuse liver disease. Again, from onestudy from China, 23 (2.1%) patients were positive for HBsAg, of which only one had a severe form of COVID-19. Interestingly, a study conducted by Xu and colleagues outside 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 found that 4% of them had chronic hepatitis B. [19]

Cases of acute lesions in patients with chronic diffuse liver disease were noted in 13 (5%) of 274 patients, of whom 10 (76.9%) died. Based on the available data, it becomes clear that elevated liver enzyme levels are observed mainly in severe and critical cases of COVID-19. An increase in AST was observed in 8/13 (62%) patients in ICU compared to 7/28 (25%) in conditions outside ICU.

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

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

It was unclear whether the elevated liver enzymes were caused by disease per se or by drug-induced liver damage in this population. Liver damage may have an effect due to an inflammatory cytokine storm in severe COVID-19. It is 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-glutamyl transferase (GGT) in severe cases of COVID-19. The question of whether COVID-19 exacerbates cholestasis in patients with primary biliary cholangitis and primary sclerosing cholangitis requires further analysis. [10]

Maybe the liver dysfunction may be the result of a cytokine storm rather than the direct cytopathic action of virusparticles. More data is needed to establish the nature and extent of liver damage in COVID-19 patients.

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 levels have 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, the incidence of liver damage was higher in non-survivors than in 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 the patients in the study by Zhou and colleagues, with reports of 191 COVID-19 patients: 54 died (mortality rate 28.2%), of which 36 (66.6%) had underlying chronic disease. [11]

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

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

There is some evidence in thepossible mechanism of development of hepatic coagulopathy in coronavirus infection can 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 syndrome) 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 non-survivors. Fatty liver disease is likely seen as part of metabolic syndrome in this group of patients, which may complicate the problem. [14]

Another study from Wuhan reported on the characteristics of deceased patients (n = 113). Levels of AST, ALT, alkaline phosphatase, GGT, and bilirubin were significantly higher in non-survivors than in survivors. Elevated AST levels (>40 U/L) were observed in 59 (52%) deceased and 25 (16%) recovered patients, and elevated ALT levels (>41 IU/L) were found in 30 (27%) of the deceased and 30 (19%). %) of recovered patients. Similarly, hypoalbuminemia (<32 g/L) was found in 74 (65%) deceased patients compared to 22 (14%) recovered patients. Serum bilirubin was 12.6 μmol and 8.4 μmol in the deceased and recovered, respectively. In a recent report by Chen *et al.* , 13 (5%) covid-19 patients developed acute liver damage 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 much more common in critically ill patients and was associated with an adverse outcome.

Although the evidence is less clear, current treatment recommendations include antiviral drugs, 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 showed no clinical benefit in COVID-19, except for a smaller, faster clinical recovery. Moreover, liver damage was observed in 10-13% of the group receiving remdisivir. [18]

Since this is an RNA virus, one would expect broad-spectrum ribavirin to work; unfortunately, during the SARS outbreak, ribavirin was associated with significant toxicity, including severe hemolysis. Curiously, Omrani and his colleagues found that interferon alfa-2A combined with ribavirin improved survival on day 14 (70% vs. 17%, p = 0.004), but not on day 28 (30% vs. 17%, p = 0.054) during an outbreak of Middle East respiratory syndrome a koronavirus. [17]

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

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

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

In this study, 20.5% and 41% of patients prior to randomization had elevated AST and ALT, respectively; however, the presence of cirrhosis of the liver, ALT or AST was more than 5 times higher than the upper limit of the norm 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.

It is important to note that the use of ritonavir to inhibit CYP450 will increase minimal levels of calcineurin inhibitors, the most commonly used immunosuppression agents in transplanted parenchymal organ recipients, which can 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 relieve inflammation, and it has recently been found that dexamethasone reduces mortality. Their use can lead to reactivation of chronic hepatitis B. Thus, HBsAg-positive patients should receive antiviral therapy, and we recommend checking the status of the main antibodies to hepatitis B and, in case of a positive result, treating 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 the SARS-CoV-2 proteases. Virtual screening of the active viral site demonstrated that hepatitis C inhibitors NS5A can be effective in the fight against SARS-CoV-2. Ledipasvir and velpatasvir easily 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 found, which is likely to becaused by the effect of virus particles on the cells of the biliary procurrents in other words, a functional disorder due to the use of antiviral drugs. Still, there are results of histopathological examinations of patients with COVID-19 showing a slight degree of microvessel atosis and inflammation in the v ena portae zone, so the results of the autopsy did not reveal a significant detrimental effect. virusparticles on hepatocytes. Major interest should be given to the status of liver function of patients against the background of COVID-19. First, it is necessary to takea look at liver modifications in the presenceof central liver disease, increasingthe monitoring and evaluation of hepatocyte function in patients with a complicated course of COVID-19. Secondly, it is necessary to scrupulously detect the sources of damage to the furnace in combination with the 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 protectiveproperties of hepatocytes that reduce liver damage.

Inference

COVID-19 is now a pandemic with an overall mortality rate of infected patients of 12 to 26%, which increases with age and comorbidities. COVID-19 causes acute respiratory failure, and liver dysfunction is severe and fatal. Cases of severe acute liver damage with higher mortality have been reported. Larger, long-term studies are needed to characterize the extent and cause of liver damage in COVID-19. The impact of COVID-19 on the underlying chronic liver disease requires a detailed assessment and further research is needed in this area.

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