Liver During The Coronavirus Epidemic

Babanazarov Umid Turobkulovich.

Bukhara State Medical Institute

ABSTRACT

There are numerous ways in which coronavirus infection can adversely affect the liver. One notable aspect is the virus's use of the angiotensin-converting enzyme 2 (ACE-2) receptor to infiltrate cells, particularly cholangiocytes, indicating the liver as a potential target. Research from the 2002 SARS outbreak revealed liver abnormalities such as increased mitotic cells and hepatocyte damage, suggesting virus-induced apoptosis and liver injury.

Early-stage SARS-CoV infections were associated with abnormal levels of cytokines and chemokines, notably elevated IL-1, IL-6, and IL-10, indicating a correlation between liver damage and inflammatory responses. Patients with chronic liver diseases exhibited higher cytokine levels, potentially exacerbating liver injury during coronavirus infection. Moreover, patients co-infected with hepatitis B or C viruses demonstrated increased hepatitis virus replication and resistance to liver injury reversal.

While data on SARS-CoV-2 remains limited, evidence suggests that chronic viral hepatitis may not significantly impact COVID-19 prognosis. For instance, chronic hepatitis B (CHB), more prevalent in China, does not seem to affect COVID-19 outcomes. Liver damage in COVID-19 primarily results from hypoxia due to pulmonary insufficiency. Severe pneumonia-induced hypoxemia can lead to ischemic liver injury, as decreased oxygen levels in the body contribute to liver cell death.

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. A virus of the Coronaviridae family, genus Betacoronavirus, threatens the entire global healthcare community with high prevalence and lethality. SARS-CoV-2 is an ingenious weapon of mass destruction of the entire 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, while in others it can even lead to death. The year 2020 will forever be remembered for how our lives have changed due to the pandemic, as we know, this virus has greatly impacted the safety of patients and their caregivers. This has had a direct impact on people with liver disease, dramatically changing the practice of hepatology, hepato-oncology, and liver transplantation.

Purpose: To determine the frequency of liver damage and study the role of provoking factors of liver damage in HDLD, 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 lung alveolar cells. In vitro, during the SARS epidemic, ACE was identified as a host receptor for viral entry.

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

Immunohistochemical studies revealed higher expression of ACE receptors in the gastrointestinal tract. ACE expression is high in the basal layer of squamous epithelium. mucous membranes of the nose, oral cavity and nasopharynx. Smooth muscle of the gastric and colonic mucosa also expresses 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 et al found that the cell surface ACE receptor was more expressed in cholangiocytes (59.7%) than in hepatocytes (2.6%). The level of ACE expression in cholangiocytes was similar to that in type 2 lung alveolar cells, indicating that the liver may be a potential target for SARS-CoV - immunohistochemical stains for ACE were negative on Kupffer cells and on T and B lymphocytes . [10]

A recent study from Wuhan found that Asian men had higher ACE expression, suggesting the possibility of 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 persistent and can remain viable for 2 hours to 14 days depending on weather conditions.

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

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

With limited therapeutic options, prevention through social distancing appears to be the cornerstone of treatment for COVID-19. 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 reaction, 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 by Wang and colleagues, 4 patients (2.9%) with COVID-19 had underlying chronic diffuse liver disease. Again, one study from China showed that 23 (2.1%) patients were HBsAg positive, 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 found that 4% had chronic hepatitis B.[19]

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

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

Interestingly, patients receiving lopinavir/ritonavir therapy had a higher proportion of enzyme elevations (56.1% vs. 25%). [7]

It was unclear whether elevated liver enzymes were caused by the disease itself or drug-induced liver injury in this population. Possible effect of liver damage due to 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 gamma glutamyl transferase (GGT) levels in severe cases of COVID-19. Whether COVID-19 worsens 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 are 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 levels were found to be an independent predictor of severe MERS-CoV infection. A biopsy of patients suffering from chronic diffuse liver diseases with MERS showed lobular lymphocytic infiltration and moderate hydropic degeneration of hepatocytes.

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

A case fatality rate of 3.6–15% was reported in 4292 Chinese patients. Mortality was higher in men (3.25:1), those over 75 years of age, and those with comorbidities (diabetes mellitus, hypertension, and cardiovascular disease). These comorbidities were noted in 48% of patients in a study by Zhou and colleagues reporting 191 patients with COVID-19: 54 died (mortality rate 28.2%), of whom 36 (66.6%) had an underlying chronic disease. [eleven]

According to 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 (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 malignancy, chronic disease kidney and cerebrovascular diseases. diseases. However, the mortality rate in patients with underlying chronic liver disease was 0–2%.

There is some evidence of a possible mechanism for the development of hepatic coagulopathy during coronavirus infection, which may consist of:

- decreased synthesis of coagulation factors (pathological fibrinogen), impaired synthesis of vitamin K
- thrombocytopenia (hypersplenism with platelet sequestration, decreased thrombopoietin production)
- 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 nonsurvivors. Fatty liver disease is likely considered part of the metabolic syndrome in

this group of patients, which may complicate the problem. [14]

Another study from Wuhan reported the characteristics of deceased patients (n = 113). Levels of AST, ALT, alkaline phosphatase, GGT, and bilirubin were significantly higher in nonsurvivors 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 U/L) were 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 with 22 (14%) patients who recovered. Serum bilirubin was 12.6 μmol and 8.4 μmol in deceased and recovered patients, 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 whom 10 (76.9%) died. Although the numbers are small, this 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 showed no clinical benefit in COVID-19 other than a modest faster clinical recovery. Moreover, liver damage was observed in 10-13% of the remdisivir group. [18]

Since it is an RNA virus, broad-spectrum ribavirin would be expected to work; unfortunately, during the SARS outbreak, ribavirin was associated with significant toxicity, including severe hemolysis. Interestingly, 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 Middle East respiratory syndrome coronavirus outbreak. [17]

Lopinavir/ritonavir, approved for the treatment of HIV infection, demonstrated in vitro activity 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 of 199 patients with severe COVID-19 showed no benefit from lopinavir and ritonavir (99 patients). Current treatment recommendations for 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. Increased bilirubin and increased AST levels were observed in 3.2% and 2.1% of patients in the treatment group, respectively.

It is important to note that using ritonavir to inhibit CYP450 will increase trough levels of calcineurin inhibitors, the most commonly used immunosuppressive agents in solid organ transplant recipients, leading to potential drug toxicity. [18]

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

Recently, Chen et al. built a three-dimensional model of the crystal structure of SARS-CoV-2 proteases. Virtual active site screening demonstrated that hepatitis C NS5A 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 influence 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 slight microvascular steatosis and inflammation in the vena portae area, so the autopsy results did not reveal a real detrimental effect of viral particles on hepatocytes. Great interest should be paid to the liver function status of patients with COVID-19. Firstly, it is necessary to look at liver modifications in the presence of central liver disease, increasing monitoring and assessment of hepatocyte function in patients with complicated COVID-19. Secondly, it is necessary to scrupulously detect the sources of liver damage in combination with the pathophysiological modifications caused by COVID-19. As a result of active central treatment, it is appropriate to prescribe treatment to strengthen the protective properties of hepatocytes, which reduce liver damage.

Conclusion

COVID-19 is currently a pandemic with an overall mortality of infected patients ranging from 12 to 26%, which increases with age and comorbidities. COVID-19 causes acute respiratory failure, and 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 requires detailed assessment and further research is needed in this area.

СПИСОК ЛИТЕРАТУРЫ:

1. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: evidence for virus evolution. J Med Virol 2020;92(4):455–459.

2. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–273.

3. Babanazarov, U. T., & Barnoyev, S. S. (2023). Clinical Characteristics of Patients with Chronic Diffuse Liver Disease Against the Background of Covid-19. Genius Repository, 26, 49-55.

4. Urokov Sh.T., Babanazarov U.T., Eshonov O.Sh. PECULIARITIES OF THE STATE OF THE LIVER IN PATIENTS WITH POST-COVID-19 //New Day in Medicine 2(40)2022 298-301 https://cutt.ly/zAFkdPw

5. Zhu N, Zhang D,WangW, Li X, Yang B, Song J, et al. China novel coronavirus investigating and research team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727–733.

6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.

7. Мусаева Д.М., Самадов Б.Ш., Дубинина Н.В., Бабаназаров У.Т., Озодов Ж.Х.У., Шарипова Д.Ш., Озодова Н.Х. Антиокссидантная коррекция фармакометаболизирующей функции печени при эксперементальном токсическом гепатите вестник науки и образования .2020. №14-1(92). С. 63-70.

8. Turobkulovich, B. U., & Tuymurodovich, K. M. (2022). Coronavirus Infection-A Trigger Factor in Liver Damage. Eurasian Research Bulletin, 15, 52-58.

9. Бабаназаров, У. Т., Уроков, Ш. Т., & Бахронов, Д. Г. (2022). ХРОНИЧЕСКИЕ ДИФФУЗНЫЕ ЗАБОЛЕВАНИЯ ПЕЧЕНИ ВО ВРЕМЯ ПАНДЕМИИ COVID-19. PEDAGOGS jurnali, 11(3), 26-44.

10. Dinesh Jothimani, Radhika Venugopal, Mohammed Forhad, Abedin Ilankumaran, Kaliamoorthy Mohamed Rela COVID-19 and the liver. Journal of Hepatology June 15, 2020 DOI:https://doi.org/10.1016/j.jhep.2020.06.006

11. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A. Specific АПФ expression in cholangiocytes may cause liver damage after 2019-nCoV infection. Bio-Rxiv 2020. https://doi.org/10.1101/2020.02.03.931766.

12. Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a

data-driven analysis in the early phase of the outbreak. Int J Infect Dis 2020;92:214–217.
13. Turobkulovich, B. U., & Tuymurodovich, K. M. (2023). Coronavirus Infection-A Trigger Factor of Liver Damage. Eurasian Research Bulletin, 18, 156–162.
14. Бабаназаров, У. Т., & Хайитов, Д. Х. (2024). БОЛЬШЕ, ЧЕМ МИНИМАЛЬНОЕ СОЗНАНИЕ: АПАЛЛИЧЕСКИЙ СИНДРОМ. European Journal of Interdisciplinary Research and Development, 23, 109-112.
15. Leung WK, To KF, Chan PK, Chan HL, Wu AK, Lee N, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus.
16. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–1069.
17. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–1720.
18. Babanazarov, U. T., & Qayimov, M. T. (2023). Epidemiology, Etiology, Clinical Description, and Prevention of Postoperative Cognitive Dysfunction. Eurasian Research Bulletin, 19, 38–46.
19. Бабаназаров, У. Т., & Кайимов, М. Т. (2023). ДВОЙНОЙ УДАР: ПЕЧЕНЬ И COVID-19. European Journal of Interdisciplinary Research and Development, 11, 141-148.