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The Relationship of Hepatobiliary System Dysfunction with Covid-19

Sobirova G. N., Bafoeva Z. O.
Tashkent Medical Academy

Uzakov J. K.
Republican Specialized Scientific and Practical Medical Center for Therapy and Medical Rehabilitation, Uzbekistan

Annotation: The World Health Organization has repeatedly stated that coronavirus mainly affects the lower respiratory tract, but did not deny that in severe cases of the disease, multisystem damage may occur. However, patients began to develop a variety of symptoms of this infection: from asymptomatic to severe clinical symptoms, critical conditions, symptoms of acute distress, acute respiratory failure, multiple organ failure and, ultimately, death [52]. In patients infected with the virus, the clinical manifestations were different, there were many extrapulmonary symptoms, including liver damage [58]. According to a group of articles by hepatologists, when evaluating a systematic meta-analysis in patients, the level of liver damage is associated with a severe or mild course of the disease [53].

Keywords: Covid-19, multiple organ failure, hepatobiliary system, damage, liver.

Currently, Covid-19 is considered as a systemic disease and the basis of immune system dysfunction. The lungs are affected first, followed by the heart, kidneys and intestines. In severe forms of the disease, hyperimmune inflammation, imbalance of the renin-angiotensin-aldosterone system, endothelial dysfunction and a certain type of vasculopathy (thrombotic microangiopathy and intravascular coagulopathy) predominate. A group of scientists gave this process another name - thromboinflammatory process or coagulopathy associated with Covid-19 [12,37]. The disease caused by the Covid-19 pathogen proceeds unnoticed, its characteristic symptoms are fever, cough, episodic diarrhea, severe headache, heart damage, and in some patients, liver damage is considered one of the most common symptoms among adults [19]. Patients with hematological and cardiovascular diseases have the worst prognosis for coronavirus [18]. Based on the above, it can be said that this infection is classified as a complex, poorly understood disease. Liver dysfunction in Covid-19 remains elusive, and some scientists believe that it is associated with long-term hospitalization of patients [51].

Factors affecting the severity of Covid-19 include age (over 65 years) and comorbidities [7; 13], as well as cardiovascular diseases, arterial hypertension, diabetes mellitus, chronic lung diseases, tumors, chronic kidney diseases, obesity, smoking, immunodeficiency states, chronic liver diseases [1; 27].

Patients with chronic gastrointestinal or liver diseases may be more susceptible to coronavirus transmission and have a higher risk of a more severe course. The high susceptibility of the gastrointestinal tract to this infection is due to the presence of the ACE2 enzyme, which is converted to angiotensin in the intestine. It is well known that the SARS-Cov-2 receptor is APF2. Symptoms from the digestive system are associated with a direct attack of SARS-Cov-2 infection, tissue damage is the result of an immune response [4]. The nucleocapsid protein of the virus is found in the cytoplasm of epithelial cells of the stomach, duodenum and rectum. The pathogenesis of viral damage to the digestive organs is known, but the pathogenesis of chronic diseases is unknown. It is known from a number of scientific studies that the incidence of liver damage as a result of coronavirus ranges from 14 to 53% [56]. Cases of liver damage by coronavirus are considered by a group of scientists [6; 39; 41, 47, 58]. The direct impact of SARS-Cov-2 on the liver has not yet been fully studied. Many years ago, SARS-cov (2002-2003) and MERS-cov (2012), which belong to the betacoronavirus family,

showed greater liver damage in those infected with the coronavirus, and such patients had a severe course of the disease [2; 23].

SARS-Cov and SARS-Cov-2 use APF2 as a receptor for cell entry, APF2 is present in the heart, kidney, blood vessels, alveolar epithelial cells, liver, MRD, intestine, which in turn causes systemic inflammation [8]. It has not yet been definitively proven that SARS-Cov can damage the liver. APF 2 is expressed in liver cells during SARS-Cov when the Human Cell Atlas database was studied [49]. Only low-frequency expression of APF 2 is observed in cholangiocytes, but not in hepatocytes, Kupffer cells or endothelial cells. In addition, SARS-Cov can penetrate cells of various organs (lungs, kidneys, liver) through a special protein 7A, causing apoptosis. This does not deny that it can directly damage liver cells. Based on RNA sequencing data, it has been suggested that a novel coronavirus receptor, APF2, is expressed in liver cells. Based on RNA sequencing data from healthy liver cells, two unrelated groups showed that specific expression of APF2 is present in cholangitis and to a lesser extent in hepatocytes. The results showed that the virus may bind to cholangocytes via APF2 and not necessarily to hepatocytes. APF2 is more highly expressed in bile ducts than in hepatocytes, and since this binding method is the second most common among alveoli, the liver remains a target organ [8].

Therefore, based on the data presented, changes in biochemical tests in patients infected with coronavirus may be due not to hepatocyte damage, but to cholangiocyte dysfunction and a number of other reasons. That is, hepatotoxic drugs, systemic inflammation can damage the liver [20]. In the blood of patients with Covid-19, aminotransferase activity is increased, but not alkaline phosphatase [22].

SARS-Cov was detected during autopsy by RT-PCR not only in lung cells, parenchymal organ cells, vascular endothelium of various organs and liver hepatocytes. In a liver biopsy of a patient with atypical pneumonia caused by SARS-Cov, mitosis, acidophilic bodies, Kupffer cells and balloon-shaped hepatocytes were found. This confirms that SARS-Cov damages liver cells by inducing apoptosis in liver cells [23]. Biopsy of the deceased showed normal microvesicular steatosis, lobular and portal hypertension. This does not exclude the possibility of liver damage by the virus, but it does not exclude the possibility of damage from drugs, such consequences can also be caused by hypoxia. Autopsy revealed hepatomegaly, hepatocyte dystrophy, focal necrosis, neutrophilic, lymphocytic and monocyte infiltrate, sinusoidal dilation, microthrombi. Histological data did not prove that liver damage is the cause of liver failure and biliary tract damage [32; 34; 53]. Liver damage as a result of immune system protection is associated with macrophage hyperactivity syndrome. Hyperinflammation syndrome, cytokine storm, coagulopathy and multiple organ failure are among the factors that determine the severe course of Covid-19 [24; 50]. If Covid-19 infects patients who already have liver pathology, the liver damage will be more severe. Among such patients, the fatality rate is 58.1-78% [3].

In most cases, systemic viral infections are accompanied by a temporary increase in transaminase levels, which causes an increase in general immunity, and circulating cytokines resulting from hyperalgesia do not affect liver function. This phenomenon is called bystander hepatitis [26;].

Characteristic signs of a cytokine storm are a large release of inflammatory biomarkers, which are manifested by a decrease in FRO, ferritin, LDH, D-dimer, IL 1beta, 6,2, tumor necrosis factor alpha, and T-lymphocyte blood chemokines [35, 38]. Recent studies have shown that SARS-Cov 2 infection first damages T-lymphocytes, mainly SD 4+ and SD 8+, which are important cells for protecting the body [9].

The development of lymphopenia in sick people means the destruction of the innate immune system, which means the body is vulnerable to infection, and in this case, the inflammation deepens. Autopsy revealed secondary damage to the lymphoid tissue, i.e., damage to the spleen, resulting in a decrease in the number of lymphocytes. Examination of the spleen revealed cellular dystrophy, focal hemorrhagic necrosis, macrophage proliferation, and phagocytosis. Atrophy and necrosis were found in the lymph nodes. Immunohistochemical examination revealed a sharp decrease in the number of SD4+ and SD8+ cells in the spleen and lymph nodes [42].

Systemic inflammatory syndrome and sepsis are among the serious complications of coronavirus, sepsis is an uncontrolled response of the body to infection, which in turn leads to multiple organ dysfunction [31]. In sepsis, the liver plays an important role in immune defense and metabolic adaptation to inflammation. In this case, the liver serves as a target organ for multiple organ failure caused by sepsis. Pathophysiologists associate liver damage with hypoxia in shock and ischemia, cholestasis with changes in bile metabolism, and hepatocellular damage with drug toxins [46]. The combination of sepsis and Covid-19 is one of the causes of liver damage and provokes a severe course of Covid-19.

A characteristic symptom of Covid-19 is shortness of breath. In severe cases, hypoxic hepatitis often develops as a result of anoxia. Severe hypoxia, anoxia and hypovolemia are the main causes of liver damage in acute respiratory failure or shock in Covid-19. This damage leads to metabolic acidosis in the liver, increased permeability of calcium and mitochondrial membranes, which leads to cytolysis [33]. It can also be said that non-structural oxygen of SARS-Cov 2 has the property of changing the shape of hemoglobin and red blood cells, which, in turn, leads to oxygen transport, iron dissociation, porphyrin formation and an increase in ferritin. This effect increases the inflammatory process in the lungs, causes hypoxia, hypoxemia and multiple organ failure [36]. One of the factors causing many liver lesions is a combination of drugs used in the etiotropic and pathogenetic treatment of the virus [22, 32].

During the pandemic, hospitals were offered a group of drugs for the treatment of SARS-Cov 2 for the first time, including lopinavir, rinotavir, hydroxychloride, azithromycin, umifenovir, famipirovir, recombinant beta1b, which are included in the group of potentially hepatotoxic drugs [26]. The hepatotoxic effect of hydroxychloride has been noted in many clinical observations, that is, its effect was clearly manifested in the treatment of systemic lupus erythematosus, cutaneous porphyria, rheumatoid arthritis, myalaria. Lopinavir / ritonavir belongs to a group of antiviral drugs. Its interaction with drugs, especially with immunosuppressants, has been well studied. It cannot be used together with a motor inhibitor (sirolimus, everolimus). Lopinavir levels should be monitored when used concomitantly with a calcineurin inhibitor. There are data on its use in patients with liver cirrhosis. Low hepatotoxicity in chronic liver failure has also been studied. It is not recommended for use in the decompensated stage of liver cirrhosis [11].

If they do not cause direct damage, this group of drugs can be a mediator, that is, when used together with antibiotics, liver damage can occur. When treating Covid-19, it is recommended to use the "drug interaction database" in Liverpool to identify drug interactions in patients with comorbidities [48].

Therefore, each patient who is treated for coronavirus should have liver parameters monitored in inpatient and outpatient settings, otherwise severe drug-induced hepatitis may occur.

Various chronic liver diseases are common in the world, these are non-alcoholic fatty liver diseases, metabolic syndromes (obesity, diabetes mellitus), cirrhosis of the liver, hepatitis B, C, which can cause liver damage in coronavirus. With SARS-Cov2, patients with CKD are more often infected. But this has not yet been proven. According to a number of scientific observations, 2-11% of patients belong to this group [55, 58]. Patients with CKD have a high tendency to a severe course of the disease, which is caused by hypoxia, hypoxemia as a result of pneumonia or cytokine storm [9, 10, 42].

It is worth noting that the high level of infection and mortality among patients with cirrhosis and liver decompensation is not associated with the virus epidemic. The reason for this is systemic immunodeficiency, in the observations of some authors it was found that 17% of patients are in the stage of decompensation of JT, and almost all of them are those who neglected preventive measures [52].

Patients with chronic hepatitis B (CH) and CHC against the background of the coronavirus (SARS-Cov2) have not yet developed liver failure. But during SARS-Cov, that is, atypical pneumonia, in 2002, such patients developed severe liver failure, which scientists associate with the replication of the hepatitis virus [25].

The association of liver damage with coronavirus, whether during the progression of Covid-19, treatment, pre-existing disease or burden, is considered liver damage. Currently, an increase in the level of liver enzymes ALT, AST and a slight increase in bilirubin are observed in 14-56% of patients [5]. People with elevated levels of enzymes are mainly men and people with severe disease [45]. An increase in AST is often observed. A decrease in the amount of albumin indicates an exacerbation of the disease. A number of clinical researchers around the world have conducted clinical observations among people infected with large-scale coronavirus.

In a large clinical study of 5771 cases in China, 81 (1.4%) had pre-existing liver disease, and liver dysfunction was associated with coronavirus mortality [17]. AST increased by 39.4%, ALT increased by 28.1%, and AST increased in deceased patients [15, 29]. From February to April 2020, 655 patients were clinically observed at the University of Instruk in Austria. 96 of them, i.e. 15%, were hospitalized with Covid-19, 15 of them required intensive care. Enzymes, IF, bilirubin, GGT, IL-6, FRO, ferritin, LDH were determined in the blood plasma of all patients. The results showed an increase in AST by 42%. In all patients with increased AST, IF, bilirubin, GGT, IL-6, SRO, ferritin, LDH, AST was higher than in normal patients. It has been proven that liver damage is even higher in intensive care patients.

In laboratory conditions, liver parameters were studied in 2541 patients. The following were found: ALT/AST in 25%, LDH in 20%, bilirubin in 3% and ALT in all cases within the norm [89]. Among 5700 patients, AST was elevated in 58.4%, ALT - in 39% [43]. In a retrospective study of 3428 patients, liver parameters increased as the disease progressed in patients [40]. Some scientists believe that these parameters did not change in patients with mild disease as well as in patients with severe disease [3, 21], a meta-analysis associated this condition with death [93], some with deepening of the process in the lungs [52], with patients requiring intensive care [50], some associate it with a long stay in the hospital [16]. It has been established that liver indices increase in 58.06-78% of patients who died from coronavirus [54, 57].

Conclusions. Based on the above, it can be said that this infection is classified as a complex, poorly understood disease. Based on the information provided, coronavirus is considered a virus with multi-organ properties and does not bypass the liver and bile ducts. A large number of patients have changes specific to liver damage. It is possible that this is due to various causes, such as the action of drugs, the influence of the virus, latent liver diseases, metabolic changes. Liver dysfunction in Covid-19 remains elusive, and some scientists believe that it is associated with long-term hospitalization of patients [51]. Based on clinical observations and the above, we see that this virus affects the hepatobiliary system. Determining the mechanisms of damage will help health care workers develop a specific treatment strategy. This, in turn, still requires a lot of research.

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