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# MODERN ASPECTS OF DIAGNOSTICS OF POST-COVID LIVER COMPLICATIONS

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**Summary.** The COVID-19 pandemic has quickly spread around the world, becoming a challenge to the healthcare system. The spread of this disease on a global scale is due to its high contagiousness and tendency to rapid mutations, which could lead to high mortality. According to the (World Health Society) WHO, the number of patients with COVID-19 in the world has reached 676,570,149, of which 6,881,802 have died, in our country it has reached 248,222 cases, more than 1650 deaths. (COVID-19 17th Epidemiological Update, 2022). This pandemic affected not only the respiratory system, but also other organs like the liver. At the moment, after recovery from this disease, post-covid syndrome develops over time, which is caused in many cases by a complication of the liver, since it is also the target organ of coronavirus infection.

**Key words:** post-COVID syndrome, coronavirus infection, liver, pathology.

**Relevance.** At that time, COVID-19 became a pandemic, covering almost the entire world, unfortunately, continued to increase the socio-economic burden in all countries of the world. The pandemic nature of the COVID-19 epidemic has significantly changed the work of medical institutions around the world, creating a significant burden on diagnostic and laboratory services and placing a huge burden on the healthcare system [2,6,11].

**Comorbidity of coronavirus disease and liver pathology.** Coronavirus infection is characterized by multimorbidity, affecting, in particular, the respiratory, cardiovascular, urinary, muscular, and hepatobiliary-pancreatic systems. According to the literature, comorbidity is defined as a condition in which a patient has two or more pathogenetically related chronic diseases occurring simultaneously or sequentially. Diagnosis and management of comorbid conditions in COVID-19 is very relevant today. The most common comorbid conditions in COVID-19 patients are hypertension, diabetes mellitus, coronary heart disease, kidney disease, and, less frequently, gastrointestinal and rheumatic diseases. There is no single classification of comorbid conditions. According to OganovR.G. and other comorbid conditions can be divided into three types: transindromic, transnosological and chronological. As the research team emphasizes, transsyndromic and transnosological are the coexistence of two or more syndromes or diseases in one patient, achronological require their temporal coincidence or temporal order [3,9].Feinstein A.R. first introduced the concept of comorbidity in 1970. According to him, "comorbidity is any existing separate condition that can manifest itself or be complicated by the clinical course of the corresponding disease in a patient. One disease is assigned a leading role, while the other is secondary, since the latter may or may not affect the course and treatment of the underlying disease".

Numerous studies highlight the importance and necessity of considering comorbidities in patients with COVID-19 at the individual and population levels to predict survival and maximize treatment efficacy. At that time, COVID-19 acquired the character of a pandemic and covered almost the entire world, and, unfortunately, continues to increase the social and economic burden on all countries of the world. It should be taken into account that the pandemic nature of the spread of COVID-19 has significantly changed the system of functioning of medical institutions around the world, putting a huge burden on diagnostic and laboratory services [2,6]. The disease is caused by a new strain of coronaviruses, Severe Acute Respiratory Syndrome, Coronavirus-2 (SARS-CoV-2).

**Risk factors in the development of post-covid syndrome.** A condition in which symptoms characteristic of COVID-19 develop for more than 12 weeks after infection with COVID-19 and are not explained by an alternative diagnosis is called post-COVID syndrome, i.e. the acute phase of the disease has ended, but the patient has not yet recovered. Postcovid syndrome manifests itself in the form of respiratory, cardiac, gastrointestinal, renal, endocrine, neurological, psychopathological, rheumatic, dermatological variants and nutritional deficiency. The gastrointestinal variant can occur with dyspepsia, diarrhea, impaired liver function (cytolysis, intrahepatic cholestasis). Studies have shown that patients had varying degrees of liver dysfunction - the frequency ranged from 1% to 53% - mainly indicated by abnormal levels of ALT and AST concentrations, accompanied by a slight increase in bilirubin concentration [4,8].

Liver damage can be caused not only by viruses or hepatotropic toxins, but also by many drugs. As a rule, this occurs in individuals with hypersensitivity to these drugs, and is due to the individual genetic characteristics of a person. Acute damage can occur in the parenchyma of an organ due to a cytotoxic or cytolytic effect on hepatocytes, in the elements of the biliary system (cholestatic lesions) or is of a combined nature. According to various data, no more than 5% of cases of clinically detected jaundice are associated with taking medications. However, when examining patients with chronic hepatitis of unclear etiology, in 10% of cases, changes in laboratory parameters can be associated with medication. Among patients over the age of 50, this figure is 40%. As a rule, the diagnosis of drug-induced liver injury is established by clinical and anamnestic data. Intravital morphological examination of the liver in such patients is rare, therefore, data on the structural features of the liver tissue in lesions are not systematized and scattered. Which, in turn, requires refinement and further research in the health care system. In modern science, many new diseases and their effect on the body are revealed through experimental studies on animals, which are similar to the internal organs of a person. At which, assessing healthy tissues, one can compare their condition and draw a conclusion about the real disease [7].

Since the liver is the most important organ in which more than 500 processes occur, the pathology of this organ can affect many other organs and systems of the body. One of them is the transformation of many drugs (PM). The liver is a target for the manifestation of the toxicity of a number of drugs, since it is in this organ that the complex metabolism of xenobiotics occurs. The biotransformation of drugs consists in the processes of conjugation of metabolites, while the end products are excreted in the bile or urine. Hepatotoxicity often manifests itself as a rather dangerous side effect of drug therapy. For modern medicine, drug-induced liver injury (DILI) is a complex clinical problem due to a wide range of clinical forms and the lack of developed clear principles of therapy, except for drug withdrawal. In DILI, the pathological process usually involves hepatocytes, cholangiocytes, stellate (Ito cells) and endothelial cells, which causes a wide variety of clinical and morphological variants of liver damage. Toxic (drug) lesions of the liver include the following pathomorphological processes: necrosis in zones III and I of the hepatic acinus, fatty degeneration, fibrosis. Necrosis of hepatocytes in zone III of the hepatic acinus can occur when exposed to isoniazid, paracetamol, carbon tetrachloride, toluene, ethylene trichloride, etc., which is caused by an excessively high concentration of enzymes that metabolize drugs and other xenobiotics, while the oxygen pressure in the blood is a sinusoid minimal . The severity of zone III necrosis may increase with an increased dose of the drug taken. Under these conditions, in the hepatocytes of the III zone of the hepatic acinus, hydropic dystrophy is detected in the form of a transparent cytoplasm with a pycnotic nucleus, an inflammatory process can be observed, and a slight infiltration of the portal tracts by polymorphonuclear leukocytes.

When taking large doses of preparations containing iron, as well as organophosphorus compounds, necrosis of hepatocytes of the I zone of the hepatic acinus occurs. Microscopic examination of liver cells shows necrosis in zone III of the hepatic acinus, and severe periportal fibrosis can also be detected. A wide range of hepatotoxic effects have drugs that have an immunosuppressive effect. Some drugs, when used in high doses, disrupt the synthesis of guanosine nucleotides, inhibiting inosine monophosphate dehydrogenase, which ultimately leads to inhibition of the proliferation of T- and B-lymphocytes and the production of antibodies, thereby exerting a cytostatic effect that is more pronounced on lymphocytes than on other cells, since proliferation T- and B-lymphocytes are highly dependent on de novo purine synthesis, while other cell types may switch to bypass metabolic pathways.

Subsequently, prolonged exposure leads from the beginning to damage, and then to inflammation and apoptosis of the liver cell. In the occurrence of post-COVID syndrome, complicated by liver pathology, it is caused in the first place by the negative influence of the SARS-CoV-2 virus, and subsequently, multiple drugs are added that were used in patients as a result of a short-term study to relieve symptoms in high doses [6].

**Pathogenesis of the development of hepatic pathology in COVID-19.** Angiotensin-2 converting enzyme (ACE-2) is the receptor pathway for intracellular entry of SARS-CoV-2. ACE-2 is expressed in many tissues such as lungs, testicles, heart and liver, it is important to fight the virus and maintain the integrity of organs with appropriate and targeted therapy. Angiotensin-2 converting enzyme (ACE-2) is the receptor pathway for intracellular entry of SARS-CoV-2. ACE-2 is expressed in many tissues such as the lungs, testicles, heart, and liver. it is important to fight the virus as well as maintain the integrity of the organs with appropriate and targeted therapy. Angiotensin-2 converting enzyme (ACE-2) is the receptor pathway for intracellular entry of SARS-CoV-2. ACE-2 is expressed in many tissues such as the lungs, testicles, heart, and liver. Studies have shown that the concentration of ACE-2 varies at different stages of infection, especially in the most severe phase, its decrease is shown. Some data have shown that the cell surface ACE-2 receptor is expressed in liver tissue, being more expressed in cholangiocytes (59.7%) than in hepatocytes (2.6%). In particular, the data show that the level of expression of ACE-2 in cholangiocytes was similar to that in type 2 pneumocytes, indicating that the liver is a potential target organ for SARS-CoV-2. Instead, it appears that ACE-2 is poorly expressed by Kupffer cells [1,8]. In view of the above, the liver is a potential target for SARS-CoV-2 entry. The involvement of liver damage from COVID-19 may be due to several factors. These include direct viral injury via ACE-2 to enter the liver tissue, an uncontrolled inflammatory/immune response causing fibrosis and liver dysfunction, or liver damage caused by COVID-19 drug therapy.

In most cases, viruses have a direct cytopathic effect on hepatocytes and cholangiocytes. The proposed mechanism of virus entry is via host angiotensin-converting enzyme 2 receptors expressed in the gastrointestinal tract, vascular endothelium, and hepatic cholangiocytes. In addition, approximately 10% of patients with COVID-19 have diarrhea, and SARS-CoV-2 RNA has been detected in stool and blood samples. Gamma-glutamyltransferase (GGT), released by damaged cholangiocytes, indicates the likelihood of viral exposure to the liver. GGT levels were found to be elevated in 30 (54%) of 56 patients with COVID-19 during hospitalization.

Additional evidence for direct cytopathic damage to the liver by SARS-CoV comes from autopsy studies in which SARS-CoV was detected in 41% of liver tissue samples with a maximum viral load of 1.6×10 6 copies/g. COVID-19 revealed microvesicular steatosis and inflammation in the lobular and portal region. However, this is not specific to COVID-19, and histological damage can also be seen in sepsis or various DI. COVID-19 can also lead directly to acute hepatitis.

Activation of the immune system and dysregulation of the innate immune response may occur in the context of liver damage during COVID-19 infection. Hypoxia associated with pneumonia can also contribute to ischemic liver disease, which often develops in critically ill patients with COVID-19 infection. In patients with COVID-19, marked activation of C-reactive protein, lymphocytes, neutrophils, and cytokines, in particular interleukin-6, was often observed. Not many clinical studies have examined the release of cytokines from the gastrointestinal mucosa in patients with COVID-19, but it is possible that liver dysfunction may be the result of a cytokine storm and not just a direct cytopathic effect of the virus. If this is the case, controlling cytokine dysregulation at an early stage will help to contain the progression of the disease.

**Diagnosis of liver damage in COVID-19.** Clinical signs of liver damage include detectable abnormal liver function and changes in liver imaging. Symptoms of liver dysfunction may include fever, fatigue, anorexia, nausea, vomiting, diarrhea, abdominal pain, dark urine, and jaundice. However, with the exception of tea-colored urine and jaundice, most symptoms are nonspecific. The manifestations of COVID-19 range from no symptoms to severe illness and death. Most manifestations of COVID-19 are respiratory and systemic, such as fever (65.9%), cough (23.5%), malaise (23.5%), and sore throat (12.9%). The most common digestive manifestations are loss of appetite (98%), nausea (73%), vomiting (65%) and diarrhea (37%). Although liver dysfunction has been reported in many studies,

symptoms/signs of liver-related complications such as jaundice or dark urine with COVID-19 are rarely reported.

Liver function tests, computed tomography, and ultrasound can help evaluate liver damage. Liver damage mainly manifests as abnormal liver function tests (ACEF). Changes in biomarkers of hepatocyte injury (HRH), such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (AP), and gamma-glutamyl transferase (GGT), are commonly used to assess COVID-19-related liver injury. Elevated lactate dehydrogenase (LDH), hypoproteinemia, prolonged prothrombin time, total bilirubin (TB), and direct bilirubin (RB) have also been used in some cases to assess liver function in patients with COVID-19.

Some blood tests are designed to evaluate the degree of liver fibrosis. For example, FibroTestTM (FibroTest), known as FibroSure® in the US, includes several parameters. Another such test, the aspartate aminotransferase to platelet ratio (APRI), uses these 2 routine laboratory tests. These blood tests are often used in conjunction with ultrasound or vibration-controlled transient elastography to assess liver fibrosis, especially in patients with chronic hepatitis C and non-alcoholic fatty liver disease (NAFLD), with duration ranging from 3 weeks to 3 weeks. up to 6 months and more from the onset of the disease. Initially, this condition was regarded as a post-covid syndrome; publications appeared that studied the frequency of occurrence of certain symptoms after an acute period of infection after 2 months. and more.

Changes in liver function are predictors of severity and mortality in patients with COVID-19. Abnormal liver biochemical parameters are strongly associated with an increased risk of mortality in critically ill patients with COVID-19. The levels of ALT, AST, GGT, LDH, OB and BP in severe patients were significantly higher than in patients with mild and moderate severity. Conversely, severe patients had significantly lower albumin levels than non-severe patients. In a US study in Arkansas, more than 1,027 hospitalized patients who were primarily examined for 5 parameters of liver injury, ALT, AST, OB, PB, and indirect bilirubin, were identified as important prognostic factors, while total protein, albumin, ALP, GGT and total bile acid were less important for the prognosis of the patient's condition.

**Treatment.** Treatment of post-COVID syndrome includes relief of symptoms of COVID-19 and hepatic pathology, as well as restoration of liver cells with essential phospholipids, artichoke extracts, and other complex measures. All therapeutic measures will have to be carried out under liver monitoring. In addition, taking into account dysbiotic changes in the intestine, it is necessary to include probiotic preparations in the treatment regimens for long-term coronavirus syndrome. In order to have a cytoprotective effect on the mucous membrane of the esophagus, stomach and intestines, as well as to correct the increased permeability of the mucous membrane of the gastrointestinal tract for the prevention and infection of COVID-19, it is recommended to take the drug rebamipide. Trimebutin (Trimedat®) is recommended for use as an anti-inflammatory, antispasmodic agent for functional gastrointestinal diseases. Therapy for liver damage in COVID-19 should be carried out in a standard regimen, using hepatoprotective, anti-inflammatory and detoxifying agents. As part of the correction of liver damage associated with COVID-19, and especially with prolonged persistence of the virus in the body (“longkovid”), the use of hepatoprotectors, antioxidants and antihypoxants should be considered. Ursodeoxycholic acid (UDCA) preparations are recommended for the development of cholestatic syndrome in patients with COVID-19, including drug-induced liver injury. The drug is also approved for use in patients with chronic liver disease during the period of infection with COVID-19.

**Conclusion.** Based on the above thoughts, it can be argued that more in-depth studies with long-term follow-up are needed to characterize the extent and cause of liver damage in COVID-19 and its clinical consequences.

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