# HEPATIC DYSFUNCTION AND COVID-19: A REVIEW OF THE LITERATURE AND AN ASSESSMENT OF THE PROBLEM

**D.Sh. Adylova**
Tashkent State Medical University

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***Abstract.*** *This article analyzes research studies on the clinical manifestations, pathogenesis and effective treatment of extrathoracic lesions of coronavirus infection. Recent studies have shown that the pathogenetic mechanisms of liver damage in COVID-19 may include various factors, including direct viral damage, a severe systemic inflammatory response, hypoxia, drug-induced toxic injury, and activation of preexisting liver disease. The degree of liver dysfunction can vary from asymptomatic elevations of serum transaminases and/or bilirubin to severe hepatocellular failure. Inflammatory and toxic damage can develop both in the acute phase and in the post-infection phase during the rehabilitation period.*

***Keywords:*** *coronavirus Disease 2019, enzyme-linked immunosorbent assay, non-alcoholic fatty liver disease, Post-COVID-19 Functional Status, liver dysfunction.*

**Introduction.** It has long been recognized that the clinical significance and long-term consequences of COVID-19-associated liver injury are not fully understood. Therefore, determining the severity of structural and functional liver damage in patients who have recovered from COVID-19 and developing methods for its correction are pressing issues in modern medicine. It should be noted that from 2019 to 2022, extensive work was undertaken in our country to improve the healthcare system and refine diagnostic, treatment, and prevention methods for somatic diseases. To advance healthcare services to a new level, important tasks have been identified "...aimed at improving the efficiency, quality, and accessibility of medical care, supporting a healthy lifestyle, and disease prevention, including through the development of a medical standardization system, the implementation of high-tech diagnostic and treatment methods, and effective models of home care and medical examination.". In this regard, in recent years, as healthcare has reached a new level, the diagnosis of post-COVID syndrome, COVID-19-associated liver injury, and the development of medical treatment principles have become particularly important, improving quality of life, and reducing disability and mortality.

According to international studies in recent years, COVID-19 viruses affect not only the respiratory system but also parenchymal organs (Jin X et al, 2020; Huang C, et al, 2020). In a systematic review, "Coronavirus disease (COVID-19) and the liver," published in September 2020, the cumulative prevalence of acute liver injury was 23.7 cases (16.1-33.1) per 100 COVID-19 patients (Kumar-M P. et al, 2020). In another meta-analysis, the incidence of liver injury ranged from 19% to 53%. Moreover, the incidence of liver damage is higher in patients with severe disease (74.4%) compared to patients with moderate infection (43.0%), and elevated levels of ALT, AST, and bilirubin are associated with a long period of hospitalization (Fan J-G., 2020; Wang D. et al., 2019). A number of studies have shown that liver damage is more prevalent in patients with severe infection compared to moderate infection (Jiehao C. et al., 2020, Li L. et al., 2020). Epidemiological studies have demonstrated that increased levels of ALT, gamma-glutamyl aminotransferase (GGT), and bilirubin

associated with COVID-19 are more pronounced in men compared to women (Cai Q. et al., 2020) and in young patients compared to older ones (Phipps MM. et al., 2020). In children, hyperenzymemia is less common than in adults, as are pulmonary involvement and severe cases of the disease (Xu Y. et al., 2020).

Research studies on the pathophysiology of COVID-19-associated liver injury have shown that COVID-19 has both direct and indirect effects on the hepatobiliary system. Liver biopsy revealed the detection of viral RNA in the parenchyma, confirming direct viral liver injury (Gu J, Han B, Wang J. 2020). Viral liver injury is characterized by hepatomegaly with dark red ballooning of hepatocytes, lobular necrosis, infiltration of neutrophils, lymphocytes, and monocytes in the portal system, sinusoidal dilation, and vascular congestion with microthrombosis (Zhang C., et al., 2020; Li J, Fan JG., 2020). A group of researchers (Zhou Z., et al, 2020; Zhong P, Xu J. et al, 2020; Wrapp D. et al, 2020) demonstrated that SARS-CoV2 infection depends on the lock-and-key binding of the viral S protein and the ACE receptor type 2, where the S protein acts as the key, and that the SARS-CoV2 S protein has a 10-20-fold higher affinity for the membrane ACE receptor type 2 compared to SARS-CoV.

The presence of angiotensin-converting enzyme 2 (ACE) receptors in cholangiocytes, which act as a key receptor for SARS-CoV2 particles, confirms the retrograde model of liver parenchyma injury after biliary tree invasion (Galanopoulos M. et al, 2020; Tan Y-J et al, 2004). Scientists have found that the expression of ACE-2 receptors in cholangiocytes is 20 times higher than in hepatocytes (Chai X. et al, 2020; Guo A-X. et al, 2020; Hamming I et al, 2004). SARS-CoV2 infection disrupts the barrier and transport function (bile acid transport) of cholangiocytes, leading to toxic damage to cholangiocytes by bile acids (Zhao B. et al, 2020). A number of studies have shown that liver damage in the context of COVID-19 involves a systemic inflammatory response, viral replication, and drug-induced injury. A direct association has been demonstrated between systemic inflammation involving ferritin, IL-2, and C-reactive protein (CRP), liver injury, and hepatotoxicity (Banks RE et al, 2020; Gauldie J. et al, 2021), as well as a strong association between the level of IL-6, acute-phase mediators of inflammation, and AST activity in peripheral blood serum (Drexler JF. et al, 2021).

It is well established that scientific and clinical studies on the timely diagnosis of liver damage in coronavirus infection emphasize the importance of determining blood biomarkers such as albumin concentration in peripheral blood, ALT, AST, GGT, LDH, and others (Chai X, Hu L et al, 2020; Gholizadeh P et al, 2020). A retrospective study conducted in the United States and including more than 1800 patients with COVID-19 revealed an increase in ALT, AST, and alkaline phosphatase (ALP) upon admission in 41.6%, 66.9%, and 13.5% of patients, and in the middle of hospitalization in 61.6%, 83.4%, and 80% of patients, respectively (Hundt MA et al, 2020). According to some researchers, bilirubin concentration in patients with COVID-19 can increase to 2 times the normal value, but jaundice is a rare symptom (Cai Q. et al, 2020; El Ouali S, Romero-Marrero C et al, 2020; Jaza L. et al, 2020). It has been established that the severity of COVID-19 correlates with an increase in the activity of ALT, AST, and alkaline phosphatase in the peripheral blood serum and a decrease in albumin concentration (Cai Q, Huang D. et al, 2020; Hundt MA, Deng Y. et al, 2020; Mantovani A, Beatrice G. et al, 2020).

In recent years, Karimov M.M., Muminov D.K., Daminov B.T., Alyavi A.L., and Gadaev A.G. have been conducting research in Uzbekistan aimed at early diagnosis and optimization of therapy for patients with various clinical variants of post-COVID syndrome. An analysis of the current state of the problem revealed that impaired structural and functional liver function in COVID-19 patients is widespread and potentially detrimental in the late post-infection period.

Further study of the severity of these abnormalities, identification of factors that contribute to liver damage progression, and development of methods for their correction are urgent issues.

**Aim of research:** To analyze contemporary research articles to examine the functional and structural state of the liver in patients who have recovered from COVID-19.

**Research methods:** The study included research articles using databases such as PubMed, ResNet, eLibrary, Scopus, and Web of Science. The search was conducted using the English keywords "Coronavirus Disease 2019" and "Liver dysfunction," which identified relevant studies on this issue.

**Epidemiology of COVID-19-associated liver injury.** COVID-19, which has caused a pandemic that has spread worldwide over the past 3 years, is also associated with infection by the SARS-CoV2 virus [1, 2; pp. 250-256]. Early symptoms of COVID-19 include fever, cough, myalgia, and general weakness. Severe infection, observed in 15-20% of patients, is characterized by shortness of breath and can progress to acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF) [3; pp. 497-506]. In addition to respiratory syndromes, SARS-CoV2 can cause liver damage, accompanied by manifestations of cytolytic and cholestatic syndromes. Pathogenetic mechanisms of liver damage in COVID-19 can be various factors - direct viral damage, severe systemic inflammatory response, hypoxia, drug-induced toxic damage, as well as activation of pre-existing liver pathology [4; pp. 1278-1281, 5; pp. 18-24]. The degree of liver dysfunction can vary from an asymptomatic increase in serum transaminases and/or bilirubin to severe hepatocellular failure [6; pp. 1231-1240].

If liver damage persists, there is a high risk of chronicity of the pathology and progression of hepatobiliary dysfunction in the future, after recovery from COVID-19. In sepsis, the liver is one of the most important organs regulating metabolic processes and the activity of the systemic inflammatory response. It is believed that metabolic liver dysfunction against the background of sepsis is associated with the progression of pathology to MOF [7; p.335-337]. Patients with metabolic liver dysfunctions, especially with autoimmune lesions or against the background of post-transplant immunosuppression, demonstrate an increased risk of infection due to disruption of the normal functioning of the immune system. Patients with liver cirrhosis have a high risk of decompensation against the background of systemic bacterial, fungal or viral infection [8; pp.220-245]. Hepatobiliary symptoms in patients with COVID-19 can be observed against the background of respiratory symptoms or without them. Hepatobiliary symptoms are associated with a worse clinical prognosis and an increased risk of mortality [9; pp.521-523]. Clinical and biochemical manifestations of liver damage should be carefully monitored taking into account the previous functional state of the organ and the therapy used for the infection [10,26].

In a systematic review published in September 2020, the cumulative prevalence of acute liver injury was 23.7 cases (16.1-33.1) per 100 COVID-19 patients [11; pp. 711-722]. In another meta-analysis, the incidence of liver injury was 19% (1-53%). Hypoalbuminemia (26.3-30.9 g/L) was more common in patients with severe infection (6%). The incidence of elevated serum alanine, aspartame aminotransferase (ALT and AST) and bilirubin levels was 18% (13-25%), 21% (14-29%) and 6% (3-11%), respectively [12; pp. 667-678]. Elevated levels of ALT, AST and bilirubin are associated with a prolonged period of hospitalization. Liver damage is more prevalent in patients with severe compared to moderate infection [13]. In fatal COVID-19 cases, the incidence of clinically evident liver dysfunction is 58%-78% [27,28].

**Conclusion**

It is generally recognized that increased levels of ALT, gamma-glutamyl aminotransferase (GGT), and bilirubin associated with COVID-19 are more pronounced in men compared to women [12,26] and in younger patients compared to older ones [13; pp. 807-817]. Hyperfermentemia is less common in children than in adults, as are lung damage and severe cases of the disease. Moreover, this also applies to children with pre-existing liver pathology [14; pp. 1547-1551, 15; pp. 1663-1665, 16; pp. 689-696]. Children under 18 years of age are less likely to show signs of liver damage compared to adults: 10% [17; p. 1561, 18] versus 18% [19; pp. 1518-1519, 20, 21, 22, 23, 24], although the difference is not statistically significant [25; pp. 667-678].

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