DRUG-INDUCED HEPATOTOXICITY AND ITS COMORBIDITY WITH SARS-CoV-2 INFECTION

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Abstract. *This article presents an analysis of scientific research focused on the clinical manifestations, pathogenesis, and effective treatment of extrapulmonary complications of coronavirus infection. Recent studies have demonstrated that the pathogenetic mechanisms of liver injury in COVID-19 involve multiple factors, including direct viral damage, a pronounced systemic inflammatory response, hypoxia, drug-induced toxic injury, as well as the activation of pre-existing liver diseases.*

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

Introduction

At present, the clinical significance and long-term consequences of COVID-19–associated liver injury remain unclear. Therefore, determining the severity of structural and functional liver disorders in patients who have recovered from COVID-19 and developing methods for their correction represents a relevant issue in modern medicine. Patients with COVID-19 demonstrate a wide spectrum of liver injuries, which may be associated with pre-existing pathology, direct viral damage, inflammatory injury, or the effects of pharmacological agents. Approximately 50% of patients show signs of impaired structural and functional liver status upon hospital admission. During hospitalization, up to 90% of patients exhibit a moderate increase (up to two times the upper limit of normal) in aminotransferase activity in peripheral blood, while in 25% of patients' enzyme levels exceed three times the upper limit of normal [1,2; pp. 727–733]. The most frequently observed symptom is hypoalbuminemia. One of the causes of hepatopathy may be drug-related effects. Responsible agents include antiviral drugs such as umifenovir (arbidol), favipiravir, remdesivir, as well as steroid hormones and anti-inflammatory drugs, including acetaminophen and other nonsteroidal anti-inflammatory drugs [3; pp. 420–422; 4; pp. 475–481].

Drug-induced liver injury is confirmed by the detection of microvesicular steatosis and mild inflammatory changes in the hepatic parenchyma [3; pp. 420–422]. At least 10% of patients demonstrate drug-induced hepatopathy [5; pp. 566–574]. In a meta-analysis by Kulkarni et al., drug-induced liver injury was diagnosed in 25.4% of more than 20,000 patients [6; pp. 584–599]. Antiviral drugs prescribed to patients with severe and critical COVID-19, as well as to those with moderate and mild disease but at risk of viral persistence and adverse outcomes, are all metabolized in the liver and utilize the cytochrome P450 system, the activity of which is reduced in COVID-19 [7; pp. 17, 38].

Favipiravir is an antiviral drug approved in Japan for the treatment of influenza. It is a prodrug whose active metabolite, favipiravir ribofuranosyl-5′-triphosphate, is formed through intracellular phosphorylation. This compound is a purine nucleotide that inhibits RNA-dependent RNA polymerase. The drug is effective against Ebola virus, West Nile fever virus, yellow fever virus, and Lassa fever virus [8; pp. 446–454]. Adverse effects of favipiravir include hyperuricemia

and diarrhea, observed in approximately 20% of patients, while psychiatric disorders, neutropenia, and elevated transaminase levels occur in about 2% of patients. Overall, the drug has an excellent safety profile [9; pp. 45–51]. Another study reports that the use of lopinavir/ritonavir, with or without ribavirin, interferon beta, and/or corticosteroids, is associated with increased transaminase levels in patients with COVID-19 [10; pp. 733–742].

Lopinavir is a protease inhibitor used in the treatment of HIV infection in combination with low doses of ritonavir, another protease inhibitor that prolongs the half-life of lopinavir [11; pp. 1787–1799]. The use of high doses of lopinavir (1200 mg/day, once daily) is associated with pronounced adverse effects, including hepatotoxicity. Therefore, the drug is administered at lower doses (200–400 mg) to enhance the effectiveness of other antiviral agents [12; pp. 2277–2284]. Studies have shown that hospitalized patients receiving lopinavir/ritonavir exhibit elevated levels of gamma-glutamyl transferase (GGT) and bilirubin; thus, this antiviral combination should be used with extreme caution in patients with a history of metabolic liver disease [12; pp. 2277–2284, 39].

Studies indicate that antiviral drugs used in the treatment of COVID-19 play a key role in the development of hepatic dysfunction. In particular, the use of lopinavir/ritonavir is associated with hepatocyte injury and impaired liver function in patients with a non-critical course of infection [13; p. 347]. In 11% of patients, alanine aminotransferase (ALT) levels increased more than threefold, while in 12% of patients' gamma-glutamyl transferase (GGT) levels increased more than threefold. Moreover, the use of this drug combination increases the risk of liver failure fourfold [14; pp. 727–733].

Cytochrome P450 (CYP450) is a superfamily of monooxygenases that mediate clinically significant interactions in various pathological conditions [15; pp. 1267–1293]. There is a hypothesis that the metabolic activity of CYP450 is impaired—predominantly reduced—during COVID-19, leading to decreased clearance of substances and corresponding alterations in the pharmacokinetics of antiviral agents. In addition, liver involvement in the infectious process contributes to an increased risk of complications. In May 2020, remdesivir, previously approved for the treatment of Ebola virus disease, received emergency authorization for use in patients with COVID-19. Remdesivir is also metabolized by cytochrome P450 enzymes, particularly CYP3A4. Other potential therapeutic candidates for COVID-19 include chloroquine [16; pp. 72–73] and colchicine [17; pp. 42–45], which are likewise metabolized by hepatic enzymatic systems. Understanding the interactions between drug molecules and hepatic enzyme systems is essential for predicting both therapeutic efficacy and toxic effects [18; p. 110033]. These patterns necessitate cautious use of anti-cytokine agents and the incorporation of measures aimed at normalizing hepatic metabolic activity into immunomodulatory treatment strategies.

Remdesivir has been shown to reduce the duration of hospitalization in patients with COVID-19 [19; pp. 1813–1826]. Among patients treated with remdesivir, a reversible increase in serum ALT and AST activity has been observed without the development of other pathological changes in liver or kidney function. A significant elevation in ALT and AST levels is diagnosed in 6% of patients, including life-threatening liver dysfunction in 2%, which has led to recommendations to shorten the duration of remdesivir therapy [20; pp. 1827–1837]. Conversely, moderate hepatic dysfunction manifested by an increase in ALT/AST activity up to two times the upper limit of normal in patients without pre-existing liver disease does not tend to progress to acute liver failure. In patients with prior liver pathology, remdesivir therapy should be administered under strict monitoring of liver function [21; pp. 881–883].

A recent placebo-controlled study evaluated the protective effect of intravenous remdesivir in hospitalized patients with severe COVID-19. It was found that patients receiving remdesivir discontinued treatment more frequently than those in the placebo group due to increased transaminase activity and/or elevated bilirubin levels in peripheral blood. Given the frequent association of COVID-19 with hepatic dysfunction, a higher incidence of liver injury was observed in patients treated with remdesivir compared with other therapeutic strategies. Although the drug remains approved for the treatment of COVID-19, its use requires careful and continuous monitoring of liver function [22; pp. 2835–2836].

Other antiviral drugs used in the treatment of patients with severe COVID-19 (used in approximately 50% of cases) include oseltamivir, umifenovir (arbidol), lopinavir, and ritonavir [23; pp. 475–481]. All of these drugs are capable of causing impaired liver function. In addition, ribavirin-induced hemolysis leads to tissue hypoxia, which may also result in increased transaminase activity in peripheral blood. Pre-existing chronic liver diseases (hepatitis B, C, etc.), regardless of whether blood enzyme levels are elevated or not, also predispose patients to the development of drug-induced hepatotoxicity [24; pp. 4753–4762]. Furthermore, in patients with pre-existing liver diseases, the use of nonsteroidal and steroidal anti-inflammatory drugs, traditional (“folk”) remedies, and antibiotics should be undertaken with caution, taking into account and monitoring liver function.

Doxycycline is a broad-spectrum tetracycline antibiotic that chelates zinc used by inflammatory matrix metalloproteinases and also inhibits the activity of SARS-CoV-2 RNA polymerase and the penetration of viral particles into cells. Doxycycline is an inhibitor of viral serine protease and demonstrates high antiviral activity. In addition, doxycycline exhibits anti-inflammatory effects by reducing the activity of nuclear factor kappa B in activated B lymphocytes, which leads to decreased secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and by inducing apoptosis of mast cells [25; pp. 487–488]. Hepatotoxicity has been observed during doxycycline therapy; however, it occurs less frequently than with tetracycline use. Doxycycline is an effective and generally safe drug; nevertheless, it may cause damage to the biliary tract. Moreover, isolated cases of acute liver injury and liver failure have been reported in patients receiving potentially hepatotoxic drugs in combination with doxycycline [26; pp. 483–487].

Azithromycin also exerts toxic effects on the hepatobiliary system, including symptoms and signs of cholestatic hepatitis, such as fever, weakness, jaundice, pruritus, and eosinophilia. There are sporadic case reports of acute liver failure requiring liver transplantation associated with bile duct injury during azithromycin therapy [27; pp. 1171–1178; 28; pp. 683–686].

Tocilizumab is a drug approved for the treatment of rheumatoid arthritis and juvenile rheumatoid arthritis. Although it is not a specific antiviral agent, some researchers have proposed the use of tocilizumab for the management of hyperactivation of the systemic inflammatory response and cytokine storm in patients with COVID-19 [29]. Tocilizumab is a recombinant monoclonal antibody directed against interleukin-6 (IL-6) receptors, blocking the pathogenetic signaling pathway mediated by this cytokine. The most common adverse effects associated with tocilizumab therapy include headache and arterial hypertension. Hepatotoxicity may also occur during tocilizumab treatment, ranging from moderate elevations in liver enzymes to severe drug-induced liver injury [30; pp. 1901–1905].

There is evidence supporting the effectiveness of tocilizumab in patients with COVID-19 in terms of controlling the systemic inflammatory response, even in the presence of a fivefold increase in transaminase levels above the upper limit of normal and a tenfold increase in gamma-glutamyl transferase (GGT) activity. In patients with pre-existing liver disease, liver biopsy is

recommended prior to initiating tocilizumab therapy in order to assess the structural and functional state of the hepatic parenchyma and to reduce the risk of acute liver failure. Some studies have demonstrated the possibility of liver injury associated with a systemic inflammatory response triggered by the administration of antiviral and antibacterial drugs [31; pp. 11–12]. Further studies are required to evaluate the safety and feasibility of using tocilizumab in patients with chronic liver diseases [32; pp. 727–733].

When treating patients with COVID-19, it is necessary to consider the potential for viral and immune-mediated liver injury, the risk of hepatotoxicity associated with administered medications, and the presence of pre-existing liver pathology. For all patients with COVID-19, especially hospitalized and elderly individuals, regular monitoring of serum transaminase activity, bilirubin and albumin concentrations, and coagulation parameters is recommended. If increased levels of lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) are detected in the absence of alanine aminotransferase (ALT) elevation, possible skeletal or cardiac muscle injury should be considered. In patients with previously diagnosed viral hepatitis B or C, discontinuation of antiviral therapy is not recommended in order to avoid viral reactivation during treatment with anti-inflammatory agents and corticosteroids.

Pharmacological agents used in the treatment of COVID-19 and their potential hepatotoxic and hepatoprotective properties are presented in Table 1.1. In the presence of signs of severe hepatic parenchymal injury in a patient with COVID-19, thorough evaluation is required to identify underlying liver disease, exposure to hepatotoxic agents, the severity of hypoxic liver injury, and the degree of liver failure. In cases of hypoxic liver injury, circulatory and respiratory support is recommended [33; pp. 217–231].

To reduce the severity of hepatic encephalopathy and decrease ammonia levels in systemic circulation, L-ornithine L-aspartate is used. However, this agent is palliative in nature, as it does not correct hepatic dysfunction but rather masks its manifestations. In the presence of impaired liver function, intestinal dysbiosis and “leaky gut” syndrome may develop, leading to increased endotoxemia and ammonia production. To restore normal intestinal microbiota, the use of pro- and prebiotics is recommended [34]. Administration of silymarin at a dose of 420 mg/day and ursodeoxycholic acid (UDCA) at a dose of 500 mg/day may prevent hepatic dysfunction, particularly in patients with elevated transaminase and bilirubin levels associated with severe COVID-19 [35].

Table 1.1.

Characteristics of drugs used in the treatment of COVID-19 in terms of their hepatotropic effects and evidence base

Drug	**Pharmacological activity**	**Mechanism of action**	**Molecular effects (liver)**	**Molecular effects (lungs)**

Tocilizumab	IL-6 receptor blocker	Decreased expression of TNF-α and IL-10, reduced inflammasome activity, inhibition of monocyte phagocytic activity, suppression of cytokine storm	Moderate elevation of transaminases; drug-induced liver injury	Reduction of inflammatory activity in lung tissue
Remdesivir	Antiviral agent	Inhibitor of RNA-dependent RNA polymerase (adenosine analog)	Increased transaminases and bilirubin	Reduces viral load in lungs, decreases risk of pulmonary hemorrhage, improves lung function
Oseltamivir	Antiviral agent	Neuraminidase inhibitor; inhibits release of viral progeny from infected cells	Elevated transaminases and bilirubin (rare)	Decreased IL-1β, TNF-α, IL-4, interferon-γ
Umifenovir (Arbidol)	Antiviral agent	Inhibits binding of spike protein to ACE2 receptors; blocks viral entry; stimulates immune response	Increased transaminases	Reduced viral attachment to ACE2 receptors
Lopinavir/ Ritonavir	Antiviral agent	Protease inhibitors; impairment of viral entry	Golgi apparatus fragmentation; activation of organelle stress response	Activation of DNA damage response
Bicyclol	Candidate antiviral agent	Direct damage to viral membranes; reduction of host inflammatory response	Decreased transaminases; reduced hepatic triglycerides	Reduced severity of acute lipopolysaccharide-induced lung injury
Ribavirin (+ interferon)	Antiviral agent	Inhibition of viral RNA-dependent RNA polymerase (guanine analog)	Reduced transaminases; decreased histological liver injury; reduced hepatic inflammation	Improved survival in MERS-CoV infection
Favipiravir	Antiviral agent	RNA-dependent RNA polymerase inhibitor	Increased transaminases	Reduced viral load and inflammation in lung tissue

Chloroquine and Hydroxychloroquine	Antimalarial agents	Inhibition of viral binding and entry into cells	Reduced IL-6, TNF-α, NF-κB expression; reduced hepatocyte apoptosis and hepatic inflammation	Reduced lung inflammation, oxidative stress, and pulmonary fibrosis
Probiotics	Live normal microbiota	Preventive effect against bacterial and viral infections	Reduced hepatic inflammation and transaminases; decreased TNF-α; restoration of liver function and parenchyma	Reduced lung inflammation; preventive effect against respiratory infections
N-acetylcysteine	Antioxidant	Precursor of reduced glutathione; mucolytic agent	Reduced lactic acid in liver; improved liver function	ACE inhibition; reduced viral replication and lung inflammation
Glycyrrhizic acid	Natural triterpenoid saponin	Anti-inflammatory, antioxidant, antiviral effects	Reduced oxidative stress; decreased hepatocyte apoptosis	Inhibition of coronavirus replication and cell entry; reduced IL-33
Vitamin E	Fat-soluble vitamin (α-tocopherol)	Antioxidant and immunomodulator	Reduced free radicals; increased glutathione; inhibition of NF-κB; reduced inflammation, fibrosis, and transaminases	Reduced oxidative stress; decreased NO and cyclooxygenase activity; increased T-cell proliferation
Vitamin A	Fat-soluble vitamin (retinol)	Antioxidant and immunomodulator	Reduced transaminases; increased IL-10; inhibition of NF-κB and TNF-α	Reduced IL-1β; decreased oxidative stress; improved lung function

Vitamin D	Fat-soluble secosteroid (cholecalciferol)	Reduces viral entry, replication, and inflammation	Modulation of hepatic inflammation and fibrogenesis	Reduced TNF-α and interferon-γ; increased glutathione
Vitamin C	Water-soluble vitamin (ascorbic acid)	Enzymatic cofactor; antioxidant	Reduced transaminases; increased superoxide dismutase and glutathione; reduced oxidative stress and TNF-α	Reduced TNF-α, IL-1β, IL-8; inhibition of NF-κB; reduced inflammation
Zinc	Dietary trace element	Anti-inflammatory and antioxidant effects	Reduced pro-inflammatory cytokine production; reduced oxidative stress and hepatocyte apoptosis	Reduced lung inflammation; decreased TNF-α, IL-6, IL-1β; increased IL-2
Magnesium	Dietary trace element	Anti-inflammatory and antioxidant effects	Reduced hepatic fibrosis; decreased IL-6 and TNF-α; inhibition of NF-κB pathway; reduced transaminases	Reduced IL-6 and IL-1β; inhibition of NF-κB; decreased COX-2 activity, prostaglandin E2, and oxidative stress
Copper	Dietary trace element	Antiviral activity via viral envelope damage and genome destruction	Increased ceruloplasmin; reduced inflammation and IL-6; increased oxidative stress	Reduced viral replication, release, and cellular entry

Dexamethasone	Corticosteroid hormone	Suppression of excessive inflammatory response	Increased VLDL and HDL; reduced IL-1β, IL-2, TNF-α, interferon-γ; reduced prostaglandin production; prevention of hepatic fibrosis	Reduced inflammation; inhibition of NF-κB; decreased oxidative markers; reduced pulmonary fibrosis and mortality in severe COVID-19

A study evaluating the use of N-acetylcysteine (NAC) [36] demonstrated that this agent reduces the risk of bronchial obstruction and may be safely used in patients with COVID-19 who have glucose-6-phosphate dehydrogenase deficiency. The administration of NAC is associated with an improvement in clinical condition and a reduction in C-reactive protein (CRP) and ferritin concentrations. Upon discontinuation of the drug, inflammatory marker levels return to baseline values.

The use of NAC also reduces the duration of mechanical ventilation and length of hospital stay. In addition, NAC inhibits hemolysis and prevents elevations in liver enzyme levels in patients with glucose-6-phosphate dehydrogenase deficiency. The mechanism of action of NAC includes inhibition of viral infection and attenuation of the cytokine storm. Patients who have undergone liver transplantation, due to their immunosuppressed status, may remain viral carriers for a prolonged period. Moreover, they are predisposed to bacterial superinfection, sepsis, and multiple organ failure, with a high risk of mortality [37,38].

Conclusion. Thus, a review of the available literature indicates that the use of corticosteroids in patients with significant liver injury—whether due to pre-existing liver disease or COVID-19–associated damage—should take into account the underlying pathogenetic mechanisms of hepatic injury. Hormonal therapy is justified in cases of inflammatory liver damage but may be hazardous in the presence of viral-mediated liver injury.

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