УДК 616.98:578.834.1]-036.21-06:616.36-002.17-02
https://doi.org/10.20538/1682-0363-2023-2-134-144

Factors affecting the development of liver fibrosis in patients who experienced COVID-19

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ABSTRACT

The aim of the review is to highlight the main factors affecting the development of liver fibrosis and possible mechanisms of liver damage in patients who have experienced COVID-19. A search was carried out using keywords in the Scopus, Web of Science, and PubMed databases in literary sources of the last three years on factors associated with fibrogenesis in novel coronavirus infection.

The review presents the main mechanisms of liver damage in COVID-19: direct effects on hepatocytes and cholangiocytes, hypoxia, and immune-mediated and drug-induced damage. We analyzed the significance of factors affecting fibrosis development in patients with COVID-19: chronic diffuse liver diseases, against which COVID-19 occurs, such as non-alcoholic fatty liver disease, alcohol-associated liver disease, chronic hepatitis B, C, and cirrhosis of the liver.

Damage to the liver in coronavirus infection develops by several mechanisms. The development of COVID-19 against the background of diffuse liver pathology of various genesis is associated with progression of these diseases (increased fibrogenesis) and a poorer prognosis.

Keywords: factors, liver fibrosis, COVID-19

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Source of financing. The study was carried pit within the topic of the state assignment “Epidemiological monitoring of the population health and study of molecular genetic and biological mechanisms of development of common internal diseases in Siberia to improve their diagnosis, prevention, and treatment” (No. 122031700094-5).

For citation: Kruchinina M.V., Pershina N.E., Svetlova I.O., Kruchinina E.V. Factors affecting the development of liver fibrosis in patients who experienced COVID-19. *Bulletin of Siberian Medicine.* 2023;22(2):134–144. https://doi.org/10.20538/1682-0363-2023-2-134-144.

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Факторы, влияющие на развитие фиброза печени, у пациентов, перенесших COVID-19

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РЕЗЮМЕ

Цель обзора – осветить основные факторы, влияющие на развитие фиброза печени, и возможные механизмы повреждения печени у пациентов, перенесших COVID-19. Проведен поиск с использованием ключевых слов в текстовых базах данных Scopus, Web of Science, PubMed по литературным источникам последних 3 лет о факторах, ассоциированных с фиброгенезом, при коронавирусной инфекции.

Представлены основные механизмы повреждения печени при COVID-19: прямое воздействие на гепатоциты, холангиоциты, гипоксическое, иммуноопосредованное, лекарственно-индуцированное повреждение. Проведен анализ значимости факторов развития фиброза у пациентов, перенесших коронавирусную инфекцию: хронические диффузные заболевания печени, на фоне которых протекает COVID-19: неалкогольная жировая болезнь печени, алкоголь-ассоциированная болезнь печени, хронические вирусные гепатиты B, C, цирроз печени.

Поражение печени при коронавирусной инфекции развивается по нескольким механизмам. Развитие COVID-19 на фоне диффузной патологии печени различного генеза ассоциировано с прогрессированием этих заболеваний (усиление фиброгенеза), худшим прогнозом.

Ключевые слова: факторы, фиброз печени, COVID-19

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Работа выполнена в рамках темы госзадания «Эпидемиологический мониторинг состояния здоровья населения и изучение молекулярно-генетических и молекулярно-биологических механизмов развития распространенных терапевтических заболеваний в Сибири для совершенствования подходов к их диагностике, профилактике и лечению» (№ 122031700094-5).

Для цитирования: Кручинина М.В., Першина Н.Е., Светлова И.О., Кручинина Э.В. Факторы, влияющие на развитие фиброза печени, у пациентов, перенесших COVID-19. *Бюллетень сибирской медицины.* 2023;22(2):134–144. https://doi.org/10.20538/1682-0363-2023-2-134-144.

INTRODUCTION

A new coronavirus outbreak with an epicentre in the City of Wuhan, Hubei province, is known to have occurred in the People's Republic of China (PRC) in late 2019. On February 11 2020, the World Health Organization (WHO) defined the official name of the infection caused by the new coronavirus – COVID-19 (Coronavirus disease 2019) [1]. Within several months the coronavirus infection swept the globe, and it continues to spread. According to the available data as of March 2022, 436,520,897 cases were registered worldwide, of which 16,398,036 cases were confirmed in the Russian Federation.

People of all ages and with any health condition are at risk of contracting SARS-CoV-2. Risk factors for severe disease and mortality have been identified. They include old age, coexisting chronic pathologies, such as diabetes mellitus, cancer, obesity, cardiopulmonary disease, and chronic kidney disease, as well as features of the living conditions (e.g. residents of long-term care facilities) [2].

SARS-CoV-2 is an enveloped virus with a positive-sense single-stranded RNA belonging to the Coronaviridae family, *Betacoronavirus* genus, *Sarbecovirus* subgenus. This name is associated with the structure of the virus: large thorny spikes in the form of a mace, which resemble a crown, exit the supercapsid. The nucleocapsid is a flexible spiral consisting of a positive strand of RNA and a large number of nucleoprotein N molecules. The supercapsid contains spike (S) glycoprotein, membrane (M) protein, small envelope (E) protein, and hemagglutinin esterase (HEs) (Fig. 1) [1, 3].

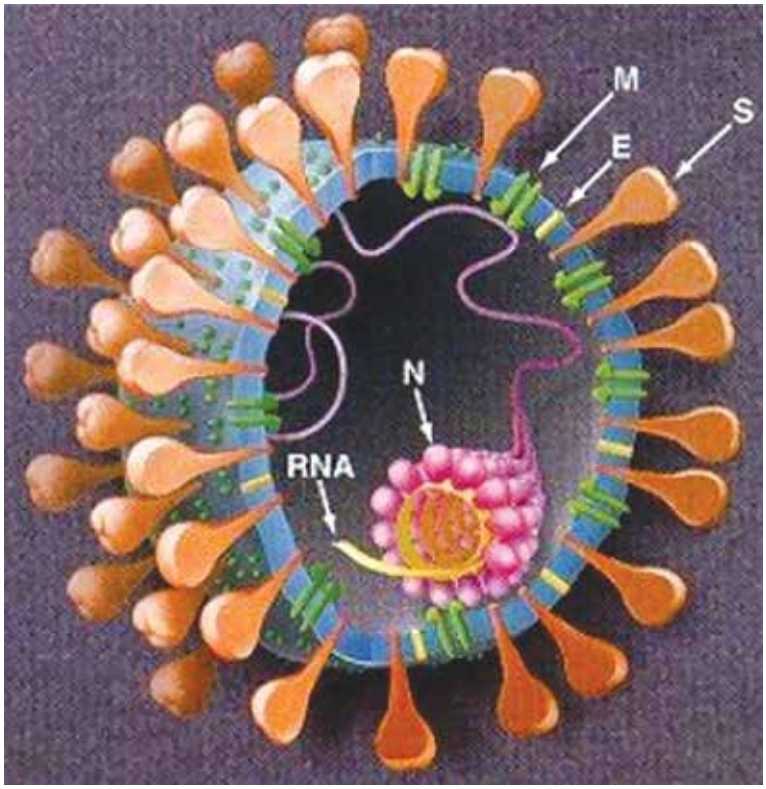

Fig. 1. A model of the coronavirus structure, showing the location of spikes (S), membrane glycoproteins (M), and the envelope (E). The RNA is protected by a spiral capsid of protein (N) monomers [4]

The entry gateway of infection is the epithelium of the upper respiratory tract and epithelial cells of the stomach and intestines [1]. The clinical presentation includes fever and symptoms of acute respiratory infections (nasal congestion, sore throat, dry cough, anosmia, myalgia), as well as cardiovascular and hemostatic disorders, and damage to the gastrointestinal tract (decreased appetite, vomiting, nausea, diarrhoea) [5].

The assessment of the course of the disease in 74 patients with COVID-19 who had gastrointestinal complaints showed that severe and critical infections occurred significantly more frequently (22.97 and 31.08%, respectively) than in individuals without such symptoms (8.14 and 20.45%, respectively) [6].

The liver is the second most frequently affected internal organ in COVID-19 after the lungs [7]. With increasing numbers of cases and further studies, biochemical parameters, such as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP), have been shown to be significantly elevated in many patients with COVID-19, indicating hepatocellular and cholangiocellular damage [8].

Although hepatic disease does not appear to occur in the absence of pre-existing liver disease, liver damage in COVID-19 may correlate with the overall disease severity and serve as a prognostic factor for the development of acute respiratory distress syndrome (ARDS) [9].

The aim of the review was to highlight the main factors affecting the development of liver fibrosis and possible mechanisms of liver damage in patients who have experienced COVID-19.

COVID-19 INVASION PROCESS

According to W. Tai et al. (2020), the key virulence factor is the interaction of the receptor-binding domain of protein S located on the outer membrane of SARS-CoV-2 with the receptor of angiotensin-converting enzyme 2 (ACE2) activated by human transmembrane serine proteases (TMPRSS2) [10]. The ACE2 receptor, an important part of the renin – angiotensin – aldosterone system, is the entry gateway for the penetration of SARS-CoV-2 into host cells. ACE2 is located in the cytoplasmic membrane of many types of human cells, including alveolar type II epithelial cells in the lungs, enterocytes in the small intestine, endothelial cells in arteries and veins, smooth muscle cells in arteries, and macrophages. ACE2 and TMPRSS2 have been found in the tissue cells of the respiratory organs, esophagus, intestines, heart, adrenal glands, bladder, brain, etc. [1].

As airborne transmission is the main transmission route for the infection, the respiratory tract is most often affected. Therefore, with a large amount of replication of SARS-CoV-2 and accumulation of various proinflammatory cytokines and chemokines, alveolar epithelial cells can be damaged, and the integrity of the air – blood barrier can be compromised. The virus diffuses from damaged alveoli into capillaries and spreads to organs and tissues [11]. Since the liver has dual blood supply, it can be easily exposed to COVID-19. Another way of SARS-CoV-2 penetrating into the liver is also possible. After penetration of SARS-CoV-2 into the intestinal tract, it can damage the intestinal epithelium and the vascular barrier and enter the liver through the portal vein. Then SARS-CoV-2 can enter the bile via bile capillaries after the virus infects hepatocytes [8].

The mechanism of liver damage in COVID-19. Several mechanisms for the damaging effects of the novel coronavirus infection on the liver are being currently considered, such as the direct effect of SARS-CoV-2 on the liver (direct cytotoxicity due to active viral replication in liver cells), immune-mediated liver injury in the light of hyperinflammatory syndrome with cytokine storm, hypoxia (associated with lung damage), multiple organ failure, use of hepatotoxic drugs, vascular changes due to coagulopathy, endotheliitis or right ventricular heart failure, and exacerbation of the underlying liver disease, although the ultimate cause is likely to be multifactorial [9].

Hepatic damage in COVID-19 manifests itself as a moderate increase in serum AST and ALT levels, accompanied by a moderate increase in total bilirubin [10, 12, 13]. Having analyzed 79 medical histories of patients who died of coronavirus infection, J.B. Ibrayeva et al. found that a 4-fold increase in ALT and AST levels was revealed in 28 and 16% of cases, respectively. The total bilirubin level in 96.0% of patients remained within the normal range [14].

Direct effects of COVID-19 on the liver. X. Chai et al. found low expression of ACE2 in hepatocytes (2.6%), with an average expression level being 20 times lower than that in cholangiocytes [15]. Although the level of ACE2 expression in the liver is very low, the distribution of the ACE2 receptor does not correspond to the level of infection of the organ [8]. It has been shown that the virus can bind directly to ACE2-positive cholangiocytes, but not necessarily to hepatocytes [15].

Y. Wang et al. performed a liver biopsy in two deceased COVID-19 patients with elevated transaminase levels. Using transmission electron microscopy, immunohistochemistry, and postmortem studies, they found large numbers of SARS-CoV-2 particles in the cytoplasm of the liver cells in these patients [16]. The authors suggested that liver injury caused by SARS-CoV-2 is more associated with the biliary system, and to a lesser extent – with the impact of the virus on ACE2 hepatocytes. The post-mortem biopsies also revealed massive hepatic apoptosis and binuclear hepatocytes in the histologic sections, mitochondrial swelling, and dilation of the endoplasmic reticulum on transmission electron microscopy [2]. These findings suggest that liver injury in patients with SARS-CoV-2 and SARS pneumonia may be due to cholangiocyte dysfunction and other causes, such as drug-induced injury and systemic inflammation [15].

Hypoxic damage. The liver has high metabolic activity and active blood supply, which makes it particularly vulnerable to circulatory disorders [17]. The liver is sufficiently protected against ischemic damage by the dual circulatory system (almost 25% of the cardiac output that the liver receives is distributed between the portal vein and the hepatic artery). It has highly permeable sinusoids (which allows for increased diffusion of oxygen to hepatocytes) and is also able to respond to decreased cardiac blood flow by releasing adenosine and dilating the hepatic vasculature to increase hepatic blood flow [18].

As is known, COVID-19 most commonly affects the lungs; therefore, it can cause the development of respiratory failure (RF). Hypoxemia is the main hemodynamic factor in the development of hypoxic hep-

atitis in RF. Associated with RF, a very low level of oxygen partial pressure can be noted. Cardiac output and hepatic blood flow in this condition are within the normal range or even increased [19]. In addition to hypoxia, coronavirus infection can cause a number of complications, such as systemic inflammatory response syndrome and multiple organ dysfunction, which can lead to reperfusion injury [19, 20]. These two processes lead to a decrease in the oxygen content and accumulation of lipids in hepatocytes [21], which results in cell death. A subsequent increase in reactive oxygen species (ROS) and their peroxidation products can act as a secondary mediator, further enhancing the release of multiple proinflammatory factors and liver injury [17].

In addition, there is evidence that SARS-CoV-2 is capable of secreting non-structural proteins orf1ab, ORF10, and ORF3a, which easily penetrate the erythrocyte cell membrane and displace a divalent Fe atom from the porphyrin nucleus of the beta chain in hemoglobin molecules. One Fe atom is capable of transporting four oxygen molecules. Thus, hemoglobin is destroyed inside the erythrocyte. The released iron ion contributes to further oxidation of organic molecules. Hemolytic and microhemolytic anemia occurs. The authors attribute the occurrence of respiratory failure primarily to the resulting hemoglobin deficiency and the oxidative damage initiated by iron ions and haemolysis [22]. Such exposure can lead to increased inflammatory processes in the lungs, development of oxidative stress, hypoxemia, hypoxia, symptoms of acute respiratory distress syndrome, and multiple organ failure due to oxygen deficiency [23].

Immune-mediated liver injury. The spectrum of potential pathophysiological mechanisms of liver damage in COVID-19 is extensive, including immune-mediated liver damage due to a severe inflammatory response [9]. The occurrence of multiple organ failure in critically ill COVID-19 patients is mainly associated with the sudden onset of an inflammatory storm.

The so-called inflammatory (cytokine) storm, or systemic inflammatory response syndrome (SIRS), is closely linked to the activation of both humoral and cellular immunity triggered by COVID-19 infection. [12] The term “cytokine storm” refers to an immunopathological condition characterized by elevated levels of proinflammatory cytokines in the blood, such as tumour necrosis factor (TNF) , interleukin (IL)-2, IL-6, IL-7, IL-18, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)γ, and ferritin, as well as by impaired immune defence mechanisms, and development of life-threatening systemic reactions [17, 24].

SARS-CoV-2 binds to lung epithelial cells and induces multiple proinflammatory signals via Toll-like receptors (TLRs), as well as activation of cytotoxic T cells. After infection with SARS-CoV-2, cytotoxic T cells are rapidly activated, producing GM-CSF, IL-6, and other proinflammatory cytokines. Later, GM-CSF activates CD14+ / CD16+ inflammatory monocytes, which produce more IL-6 and other proinflammatory cytokines. Activated T lymphocytes attack infected cells of the body, leading to their apoptosis and necrosis, until the T lymphocytes are shrivelled [7].

Drug-induced liver injury. Liver injury that occurs in some patients with coronavirus infection depends on age, geographical region, severity of COVID-19 in general, and a number of other circumstances. The liver is the main organ serving as a metabolic and detoxification tool; thus, maintaining healthy liver function is crucial for the efficacy and tolerability of different COVID-19 treatment regimens [25].

Many medicines have been tested to fight against the novel coronavirus infection. Some pharmaceuticals or their combinations can cause exacerbations of chronic liver disease (CLD) and drug-induced hepatotoxicity and can interact with other medicines to increase their toxic effects on the liver.

Earlier clinical guidelines recommended the use of lopinavir / ritonavir, ribavirin, chloroquine, and hydroxychloroquine for etiotropic drug therapy for COVID-19. Currently, it is recommended to prescribe such drugs as favipiravir, molnupiravir, remdesivir, umifenovir, and interferon alpha. In addition to antiviral drugs, antipyretics, antibiotics, glucocorticoids, and genetically-engineered biological drugs (GEBD) are used [1].

It was shown that the increase in serum enzyme levels during treatment with hydroxychloroquine was low and similar to that in patients receiving placebo or reference listed drugs [26]. But in one of the cases described, a patient with severe COVID-19 pneumonia, who received hydroxychloroquine, was shown to have a 10-fold increase in the transaminase levels; these levels quickly regressed after withdrawal of this drug [27]. Tocilizumab may be the cause of the elevated transaminase level and acute liver damage in patients with COVID-19 [28]. The mechanism of drug-induced hepatotoxicity mainly includes mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, lipodystrophy, and insulin resistance [8, 29].

Favipiravir is a synthetic antiviral l drug, a selective RNA polymerase inhibitor, which acts against RNA-containing viruses. In a study including 200 men and women with COVID-19 aged 18–80 years, L.A. Balykova et al. investigated the hepatotoxicity of favipiravir. The favipiravir group included 53 (50.96%) men and 51 (49.04%) women, and the standard therapy group encompassed 47 (49.02%) men and 55 (50.98%) women. Both groups showed an increase in both ALT (17.3 and 18.6% for the experimental and control groups, respectively) and AST (12.5 and 12.7%, respectively). Thus, favipiravir itself does not lead to an increase in the level of transaminases, and their increase is most likely due to other factors [1, 30].

Lopinavir / ritonavir is a combination antiviral medication, a protease inhibitor of human immunodeficiency virus. This drug is mainly metabolized in the liver, first of all through cytochrome P450 (CYP). This pathway produces a toxic intermediate product that can cause drug-induced liver injuries. [29] Moderate to severe elevation of serum aminotransferase levels can be found (> 5 times higher than the upper limit of the normal range) in 3–10% of patients taking lopinavir / ritonavir [12]. Remdesivir (RDV), originally used to treat Ebola disease, also shows antiviral activity against SARS-CoV-2. Studies have shown that the use of RDV is associated with an increase in the AST and ALT levels [29]. In most cases, the increase in enzymes did not reflect severe liver damage. [31]. However, cases of acute liver failure, presumably caused by the use of RDV, have been reported. Two patients have been described who had a significant increase in transaminase levels between days 3 and 10 of RDV therapy, accompanied by coagulopathy and encephalopathy [31]. Therefore, hepatotoxic drugs should be used with caution in patients with reduced liver function.

S. Gao et al. performed a retrospective, multicenter study that included 4,010 patients treated for coronavirus infection between December 19, 2019 and April 26, 2020. 395 patients (9.85%) developed acute liver failure during hospitalization. Acute liver failure was diagnosed with an increase in ALT or AST ≥ 3 × upper limit of normal (ULN), alkaline phosphatase or total bilirubin ≥ 2 × ULN. Drug therapy for hospitalized patients with COVID-19 mainly included antiviral drugs, antibacterial, antifungal drugs, hydroxychloroquine / chloroquine, corticosteroids, traditional Chinese medicine (TCM), immunotherapy, and diet therapy. Among the patients who developed acute liver failure, 293 (12.71%) patients were treated with antibiotics and 25 (35.71%) patients received antifungal medicines. Regarding antiviral drugs, 52 (18.18%), 200 (19.92%), 252 (7.23%), 88 (23.78%), and 80 (19.42%) patients were treated with ribavirin, corticosteroids, TCM drugs, parenteral nutrition (PN), and enteral nutrition (EN), respectively. There was a significant difference in the incidence of drug-induced hepatotoxicity between the patients who used and those who did not use these drugs ($p < 0.05$). Patients who received hydroxychloroquine / chloroquine (362 (95.26%)) and TCM drugs (3,234 (92.77%)) were less likely to develop acute liver failure [25].

DEFINITION AND PATHOGENESIS OF LIVER FIBROSIS

Liver fibrosis (LF) is accumulation of major extracellular matrix components (collagen, non-collagenous glycoproteins, glycosaminoglycans, proteoglycans, and elastin) in the liver tissue. Development of septal and perisinusoidal fibrosis is a universal mechanism of progression of chronic hepatitis and cirrhosis of the liver [32].

Hepatitis B and hepatitis C viruses, immune and metabolic disorders in the liver, oxidative stress accompanied by activation of free radical lipid peroxidation, various hepatotoxins, and hypoxia act as triggers for the development of liver fibrosis [32]. Fibrotic changes in the liver also occur in diseases, such as primary sclerosing cholangitis, hereditary hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease, primary biliary cholangitis, and chronic heart failure [33].

In the era of the coronavirus pandemic, triggers for the development and progression of liver fibrosis can be hypoxia, cytokine storm, the effects of medications, as well as the direct effect of SARS-CoV-2 on hepatocytes. This, in turn, leads to damage to hepatocytes, which begin to release various substances, including peroxides and proteases. As a result, these biologically active substances (BAS) activate macrophages. Activated macrophages, in turn, begin to secrete BAS, causing activation of stellate cells. The main inducers of their activity include proinflammatory cytokines (IL-1), TNFα, peroxides, nitric oxide, endothelin, but the main role in stellate cell activation is attributed to the platelet-derived growth factor (PDGF), plasminogen activator, and transforming growth factor beta 1 (TGFβ1). Under their influence, stellate cells come out of a state of rest and undergo a number of transformations. Along with this, the number of cytokine

receptors stimulating proliferation and fibrogenesis increases [34].

In the first step, the resting stellate cell, under the influence of the macrophage and endothelial cell products listed above, loses its retinoid depot and starts secreting TGFβ1, which plays a key role in the development of subsequent stellate cell autoactivation. Under its influence, stellate cells not only continue to activate themselves, but also acquire the ability to migrate to areas of inflammation.

The next stage is accompanied by transformation of stellate cells into myofibroblasts, which are elongated cells containing alpha actins (which gives them some ability to contract). These cells continue to secrete TGFß1 and are also capable of producing the hepatic extracellular matrix. Myofibroblasts acquire the ability to actively divide in areas of inflammation. Liver fibrosis is a reversible process, but only if the etiological and / or pathogenetic factor is timely removed [34].

CHRONIC LIVER DISEASES AND CORONAVIRUS INFECTION

Individuals with chronic liver diseases, especially those having cirrhosis of the liver, are more susceptible to the novel coronavirus infection due to weakened immunity [35]. Therefore, it is likely that they are more susceptible to a more severe course of COVID-19 with a potential for liver fibrosis progression. The most common diseases are non-alcoholic fatty liver disease (NAFLD), alcohol-related liver disease (ARLD), chronic viral hepatitis B and C (CHB, CHC), and the outcome of these diseases is the cirrhosis of the liver.

Non-alcoholic fatty liver disease. Non–alcoholic fatty liver disease (NAFLD) is a chronic liver disease of metabolic genesis in individuals with no exogenous factors of toxic damage caused by accumulation of lipids in the cellular elements that make up the liver lobule. According to histologic signs, steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis of the liver are distinguished as the outcome of NAFLD. The prevalence of NAFLD in the general population worldwide ranges from 6.3 to 33.0%. The disease affects all age groups but is significantly more frequent in obese individuals (up to 62–93%) [36].

The level of ACE2 expression in the adipose tissue is higher than in the lung tissue. This conclusion may explain vulnerability of the adipose tissue to COVID-19 invasion [37]. A retrospective study conducted by M.F. Fondevila et al. showed that in the liver of obese patients, SARS-CoV-2 penetration factors depend differently on type 2 diabetes and NAFLD. At the same time, in obese women suffering from type 2 diabetes, the levels of ACE2 and TMPRSS2 are unexpectedly lower than in obese women with normoglycaemia, whereas in obese patients with steatohepatitis, the expression of these genes is noticeably higher. Consequently, late stages of NAFLD may predispose to COVID-19 [38].

It is worth noting that the risk of developing severe COVID-19 is significantly higher in patients with NAFLD who have been diagnosed with liver steatosis by computed tomography (CT) (odds ratio (OR) 4.32; 95% confidence interval (CI) 1.94–9.59) or in individuals with intermediate-risk and high-risk of fibrosis according to the FIB-4 scoring system (OR 5.73; 95% CI 1.84–17.9), regardless of metabolic comorbidities, compared to patients with NAFLD with a low FIB-4 index or persons without NAFLD [39].

However, a two-sample Mendelian Randomisation Study (TSMR) showed that NAFLD (OR 0.97, p = 0.61), the ALT level (OR 1.03, p = 0.47), the degree of steatosis (OR 1.08, p = 0.41), the degree of NAFLD intensity (OR 1.02, p = 0.39), and fibrosis stage (OR 1.01, p = 0.87) were not associated with severe COVID-19. Among all the associated NAFLD factors, the risk of severe COVID-19 was associated only with body mass index (BMI) (OR 1.73, $p = 7.65 \times 10^{-9}$), waist circumference (WC) (OR 1.76, $p = 2.58 \times 10^{-5}$), and hip circumference (HC) (OR 1.33, $p = 7.26 \times 10^{-3}$).

Currently, it seems likely that general obesity (indexed by BMI, WC, and HC), rather than NAFLD, plays a causal role in the development of severe COVID-19 symptoms. The potential mechanism underlying the increased risk of developing severe COVID-19 with an increase in BMI remains unclear. Preliminary hypotheses explaining this phenomenon included lower cardiopulmonary reserve and immune dysregulation in patients with high BMI, which exacerbate the symptoms of COVID-19. In general, weight control may be the most important modifiable risk factor for preventing the development of severe COVID-19 [40].

Alcohol-related liver disease. Alcohol consumption is one of the leading risk factors for the development of pathology of internal organs. Alcohol-related diseases are associated with almost 10% of deaths in the world among the population aged 15–49 years [41]. According to the National Research Center of Narcology in Moscow, alcohol consumption has increased in the context of the COVID-19 pandemic.

Alcohol-related liver disease (ARLD) is independently associated with a 1.8-fold increased risk of mortality in patients with COVID-19 [39].

There are many reasons why alcohol consumption can predispose to worsening of COVID-19 outcomes. Firstly, alcohol consumption and concomitant liver disease disrupt the innate and adaptive immunity, affecting the functioning of immune cells important for protection against viral infections [42].

Secondly, chronic alcohol consumption is associated with increased susceptibility to acute respiratory distress syndrome [43]. This may be due to the direct effect of alcohol on immune function in addition to the dysfunction of the alveolar epithelium and a decrease in the concentration of pulmonary antioxidants in people with chronic alcohol abuse [43].

Thirdly, patients with excessive alcohol consumption often have other concomitant diseases, including metabolic syndrome, chronic kidney disease, and tobacco smoking, which were independently associated with severe outcomes of COVID-19 [43].

Coinfection of SARS-CoV-2 and viral hepatitis B. Currently, hepatitis B virus (HBV) remains the main cause of cirrhosis of the liver, liver failure, and hepatocellular carcinoma [44]. L. Chen et al. showed in their study that among 326 confirmed COVID-19 patients, of whom 20 (6.1%) were coinfected with HBV, there was no difference in the length of hospital stay between the two groups. According to the authors, HBV coinfection did not affect the course and prognosis of COVID-19 [45].

Yu. Rentao et al. observed 67 patients who were divided into HBsAg+ (n = 7) and HBsAg- (n = 60) groups with an assessment of the levels of AST and HBV markers (HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, and HBV-DNA) at admission and discharge. There were no significant differences between the groups of patients with positive and negative HBsAg. The authors suggested that SARS-CoV-2 infection was not associated with HBV reactivation in the examined patients. On the other hand, the presence of HBV also did not affect the severity of SARS-CoV-2 [46].

From a virological point of view, coinfection with HBV did not increase the cycle of virus spread or the incubation period of SARS-CoV-2 infection. From a clinical point of view, HBV coinfection did not intensify the severity of diseases or the duration of hospitalization in patients with COVID-19 [46]. HBV can also cause immunological exhaustion, in which stimulated T cells cannot produce such a strong cytokine response to SARS-COV2 infection, resulting in a less severe course of the disease [2].

For patients with severe COVID-19 and HBV coinfection, there is a risk of HBV reactivation. This is usually associated with immunosuppressive therapy, such as treatment with IL-6 receptor antagonists (tocilizumab and siltuximab), IL-1 receptor antagonists (anakinra), and high doses of corticosteroids. These drugs are used to control cytokine storm, thereby reducing immune-mediated multiple organ dysfunction [44].

J. Liu et al. observed 21 patients with SARS-CoV-2 and HBV coinfection in a retrospective study. 19 patients were tested for HBV DNA viral load at least twice during hospitalization. Three of the 19 patients developed HBV reactivation, which manifested itself by a rapid increase in the viral load of HBV DNA. These three patients were negative for the hepatitis B antigen and had not received any treatment against HBV prior to hospitalization. During hospitalization, two out of three patients received methylprednisolone, which may explain the reactivation, and one patient did not receive corticosteroids [47].

Coinfection of SARS-CoV-2 and hepatitis C virus. Chronic hepatitis C virus (HCV) is a chronic inflammatory disease lasting more than 6 months with predominant lesion of the liver tissue due to infection with HCV. Globally, an estimated 1% of the population (about 71 million people) have HCV antibodies (anti-HCV), of whom 2/3 are chronically infected and 1/3 have recovered or have been cured [48].

B. Cerbu et al. conducted a study that included 1,057 patients infected with HCV, in 126 (11.9%) individuals COVID-19 was verified. Of these, 95 patients (75.4%) were treated according to the SOF / VEL regimen or achieved a stable virological response, while the remaining 31 (24.6%) patients showed active HCV replication. The proportion of severe COVID-19 cases in the active HCV group was significantly higher compared to the inactive HCV group (32.2 vs. 7.3%, $p < 0.001$). It was also shown that the length of stay in the hospital and intensive care unit for COVID-19 was significantly greater in patients with active HCV infection [49]. Currently, data on the effect of coronavirus infection on the course of HCV, as well as its prognosis, are insufficient.

Cirrhosis of the liver. Cirrhosis is a late stage of liver fibrosis caused mainly by NAFLD / NASH, ARLD, and chronic viral hepatitis [39]. In a study conducted in New York, only 0.4% of patients with a novel coronavirus infection had pre-existing cirrhosis.

The effect of cirrhosis on the course of COVID-19 is not fully known yet. Liver cirrhosis has been found to be associated with increased mortality in patients with acute respiratory distress syndrome [50]. ACE2 levels are known to increase (a 97-fold increase in the parenchyma) in cirrhosis [51]. Therefore, patients with cirrhosis may be more vulnerable to SARS-CoV2 infection.

CONCLUSION

COVID-19 is a multisystem disorder. Damage to the liver can occur in several ways: via direct impact of SARS-CoV-2 on hepatocytes, immune-mediated damage due to a severe inflammatory response, hypoxia, and drug use.

Particular attention is paid to diffuse chronic liver diseases, such as NAFLD, ARLD, viral hepatitis, and cirrhosis of the liver. Coronavirus infection, apparently, can contribute to the progression of these diseases, as well as have a worse outcome in these conditions.

Data on the follow-up of patients with chronic liver disease who have experienced SARS-CoV-2 are currently insufficient for definite conclusions, and this situation requires further research.

REFERENCES

1. Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). Temporary guidelines. Version 15 (22.02.2022). Moscow: Ministry of Health of the Russian Federation, 2022 (in Russ.). URL: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/059/392/original/BMP_COVID-19_V15.pdf (date of access: 10.06.2022).
2. Driggers K.E., Sadowski B.W., Shagla E., Kwok R.M. Care of the hepatology patient in the COVID-19 era. *Current Hepatology Reports*. 2022;21(2):9–20. DOI: 10.1007/s11901-021-00581-x.
3. Nikiforov V.V., Suranova T.G., Mironov A.Yu., Zaboz-laev F.G. Novel coronavirus infection (COVID-19): etiology, epidemiology, clinical presentation, diagnosis, treatment, and prevention. M., 2020: 48 (in Russ.).
4. Holmes K.V., Enjuanes L. The SARS coronavirus: a post-genomic era. *Science*. 2003;300(5624):1377–1378. DOI: 10.1126/science.1086418.
5. Mnatsakanyan M.G., Pogromov A.P., Lishuta A.S., Fomin V.V., Tashchyan O.V., Kuprina I.V. et al. Liver and COVID-19: possible mechanisms of damage. *Therapeutic Archives.* 2021;93(4):427–430 (in Russ.). DOI: 10.26442/00403660.2021.04.200733.
6. Jin X., Lian J.S., Hu J.H., Gao J., Zheng L., Zhang Y.M. et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020;69(6):1002–1009. DOI: 10.1136/gutjnl-2020-320926.
7. Idalsoaga F., Ayares G., Arab J.P., Díaz L.A. COVID-19 and indirect liver injury: a narrative synthesis of the evidence. *J. Clin. Transl. Hepatol*. 2021;9(5):760–768. DOI: 10.14218/JCTH.2020.00140.
8. Zhang X.T., Yu Y., Zhang C. Wang H., Zhao L., Wang H. et al. Mechanism of SARS-CoV-2 invasion into the liver and hepatic injury in patients with COVID-19. *Mediterr. J. Hematol. Infect. Dis.* 2022;14(1):e2022003. DOI: 10.4084/MJHID.2022.003.
9. Nardo A.D., Schneeweiss-Gleixner M., Bakail M., Dixon E.D., Lax S.F., Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. *Liver Int.* 2021;41(1):20–32. DOI: 10.1111/liv.14730.
10. Sabirov I.S., Murkamilov I.T., Fomin V.V. Hepatobiliary system and novel coronavirus infection (COVID-19). *The Scientific Heritage.* 2020;49:49–58 (in Russ.).
11. Xiaohong Y., Tingyuan L., Zhicheng H., Yifang P., Huawen L., Shicang Y. et al. A pathological report of three COVID-19 cases by minimal invasive autopsies. *Chinese Journal of Pathology.* 2020;49(5):411–417. DOI: 10.3760/cma.j.cn112151-20200312-00193.
12. Vinokurov A.S., Nikiforova M.V., Oganesyan A.A., Vinokurova O.O., Yudin A.L., Yumatova E.A. COVID-19. Liver damage – visualization features and possible causes. *Medical Imaging*. 2020;24(3):26–36 (in Russ.). DOI: 10.24835/1607-0763-2020-3-26-36.
13. Il'chenko L.Yu., Nikitin I.G., Fedorov I.G. COVID-19 and liver damage. *Archives of Internal Medicine.* 2020;10(3):188–197 (in Russ.). DOI: 10.20514/2226-6704-2020-10-3-188-197.
14. Ibraeva Zh.B., Aitkuluev N.S., Makembaeva Zh.I., Suranbaeva G.S., Murzakulova A.B., Anarbaeva A.A. et al. COVID-19 and liver damage. *International Journal of Applied and Basic Research*. 2021;9:17–21 (in Russ.). DOI: 10.17513/mjpfi.13266.
15. Chai X., Hu L., Zhang Y., Han W., Lu Z., Ke A. et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *BioRxiv.* 2020. DOI: 10.1101/2020.02.03.931766.
16. Wang Y., Liu S., Liu H., Li W., Lin F., Jiang L. et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *Journal of Hepatology*. 2020;73:807–816. DOI: 10.1016/j.jhep.2020.05.002.
17. Surkova E.Yu., Mosina L.M., Esina M.V. To the question about some pathogenetic features of liver damage in COVID-19. *Modern Problems of Science and Education*. 2021;3 (in Russ.). DOI: 10.17513/spno.30880.
18. Waseemand N., Chen P.H. Hypoxic Hepatitis: A Review and Clinical Update. *J. Clin. Transl. Hepatol*. 2016;4(3):263–268. DOI: 10.14218/JCTH.2016.00022.
19. Storozhakov G.I, Oskanova R.S., Il'chenko L.Yu., Kosyura S.D., Fedorov I.G. Hypoxic hepatitis. *Archives of Internal Medicine.* 2014;6(20):42–47 (in Russ.). DOI: 10.20514/2226-6704-2014-0-6-42-47.
20. Petrov V.I., Ponomareva A.V., Ivakhnenko I.V., Razvalyaeva O.V., Meshrki B.A., Statsenko V.I. Etiopathogenetic aspects of liver injury in patients with COVID-19. *Bulletin of VolgGMU*. 2020;4(76):9–15 (in Russ.). DOI: 10.19163/1994-9480-2020-4(76)-9-15.
21. Feng G., Zheng K.I., Yan Q.Q., Rios R.S., Targher G., Byrne C.D. et al. COVID-19 and liver dysfunction: Current

insights and emergent therapeutic strategies. *J. Clin. Transl. Hepatol.* 2020;8(1):18–24. DOI: 10.14218/JCTH.2020.00018.
22. Wenzhong L., Hualan L. COVID-19: Attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. *ChemRxiv.* 2020. DOI: 10.26434/chemrxiv.11938173.v5.
23. Sandler Yu.G., Vinnitska E.V., Khaimenova T.Yu., Bordin D.S. Clinical aspects of liver damage in COVID-19. *Effective Pharmacotherapy*. 2020;16(15):18–23 (in Russ.). DOI: 10.33978/2307-3586-2020-16-15-18-23.
24. Potapnev M.P. Cytokine storm: causes and consequences. *Immunology.* 2021;42(2):175–188 (in Russ.). DOI: 10.33029/0206-4952-2021-42-2-175-188.
25. Gao S., Yang Q., Wang X., Hu W., Lu Y., Yang K. et al. Association between drug treatments and the incidence of liver injury in hospitalized patients with COVID-19. *Front Pharmacol*. 2022;13:799338. DOI: 10.3389/fphar.2022.799338.
26. LiverTox: Clinical and research information on druginduced liver injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–Hydroxychloroquine. URL: https://www.ncbi.nlm.nih.gov/books/ (date of access: 15.04. 2021).
27. Falcao M.B., Pamplona de Goes Cavalcanti L., Filgueiras Filho N.M., Antunes de Brito C.A. Case Report: Hepatotoxicity Associated with the Use of Hydroxychloroquine in a Patient with COVID-19. *Am. J. Trop. Med. Hyg*. 2020;102(6):1214–1216. DOI: 10.4269/ajtmh.20-0276.
28. Muhovic D., Bojovic J., Bulatovic A., Vukcevic B., Ratkovic M., Lazovic R. et al. First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19. *Liver International*. 2020;40(8):1901–1905. DOI: 10.1111/liv.14516.
29. Satsangi S., Gupta N., Kodan P. Current and new drugs for COVID-19 treatment and its effects on the liver. *J. Clin. Transl. Hepatol.* 2021;9(3):436–446. DOI: 10.14218/JCTH.2020.00174.
30. Balykova L.A., Granovskaya M.V., Zaslavskaya K.Ya., Simakina E.N., Agaf'ina A.S., Ivanova A.Yu. et al. New possibilities for targeted antiviral therapy for COVID-19. Results of a multicenter clinical study of the efficacy and safety of the drug Areplivir. *Infectious Diseases: News, Opinions, Training.* 2020;9(3):16–29 (in Russ.). DOI: 10.33029/2305-3496-2020-9-3-16-29.
31. Carothers C., Birrer K., Vo M. Acetylcysteine for the treatment of suspected remdesivir-associated acute liver failure in COVID-19: A case series. *Pharmacotherapy*. 2020;40(11):1166–1171. DOI: 10.1002/phar.2464.
32. Tsimmerman Ya.S. Liver fibrosis: pathogenesis, diagnosis, and treatment. *Clinical Pharmacology and Therapy*. 2017;26(1):54–58 (in Russ.).
33. Pavlov Ch.S., Shul'pekova Yu.O., Zolotarevskii V.B., Ivashkin V.T. Current views on the pathogenesis, diagnosis, and treatment of liver fibrosis. *Russian Journal of Gastroenterology, Hepatology, Coloproctology.* 2005;2:13–20 (in Russ.).
34. Gubergrits N.B., Lukashevich G.M., Fomenko P.G., Belyaeva N.V. Liver fibrosis: from fatalism to optimism. Moscow: Prima Print, 2015: 48 (in Russ.).
35. Vranić L., Radovan A., Poropat G., Mikolašević I., Milić S. Non-alcoholic fatty liver disease and COVID-19-two pandemics hitting at the same time. *Medicina (Kaunas).* 2021;57(10):1057. DOI: 10.3390/medicina57101057.
36. Lazebnik L.B., Golovanova E.V., Turkina S.V., Raikhel'son K.L., Okovityi S.V., Drapkina O.M. et al. Non-alcoholic fatty liver disease in adults: clinical presentation, diagnosis, and treatment. Guidelines for therapists, third version. *Experimental and Clinical Gastroenterology*. 2021;185(1):4–52 (in Russ.). DOI: 10.31146/1682-8658-ecg-185-1-4-52.
37. Metawea M.I., Yousif W.I., Moheb I. COVID 19 and liver: An A–Z literature review. *J. Digestive and Liver Disease.* 2021;53(2): 46–152. DOI: 10.1016/j.dld.2020.09.010.
38. Fondevila M.F., Mercado-Gomez M., Rodriguez A., Gonzalez-Rellan M.J., Iruzubieta P., Valentí V. et al. Obese patients with NASH have increased hepatic expression of SARS-CoV-2 critical entry points. *Journal of Hepatology*. 2021;74(2):469–471. DOI: 10.1016/j.jhep.2020.09.027.
39. Martinez M.A., Franco S. Impact of COVID-19 in liver disease progression. *Hepatology Communications.* 2021;5(7):1138–1150. DOI: 10.1002/hep4.1745.
40. Li J., Tian A., Zhu H., Chen L., Wen J., Liu W. et al. Mendelian randomization analysis reveals no causal relationship between nonalcoholic fatty liver disease and severe COVID-19. *Clin. Gastroenterol. Hepatol.* 2022;20(7):1553–1560.e78. DOI: 10.1016/j.cgh.2022.01.045.
41. Lazebnik L.B., Golovanova E.V., Tarasova L.V., Krivosheev A.B., Sas E.I., Eremina E.Yu. et al. Adult alcoholi-related liver disease. *Experimental and Clinical Gastroenterology*. 2020;174(2):4–28 (in Russ.). DOI: 10.31146/1682-8658-ecg-174-2-4-28.
42. Szabo G., Saha B. Alcohol's effect on host Defense. *Alcohol Res.* 2015;37(2):159–170.
43. Moon M., Curtis B., Mandrekar P., Ashwani K, Singal A.K., Verna E.C. et al. Alcohol-associated liver disease before and after COVID-19 – an overview and call for ongoing investigation. *Hepatol. Commun*. 2021;5(9):1616–1621. DOI: 10.1002/hep4.1747.
44. Xiang T.D., Zheng X. Interaction between hepatitis B virus and SARS-CoV-2 infections. *World J. Gastroenterol.* 2021;27(9):782–793. DOI: 10.3748/wjg.v27.i9.782.
45. Chen L., Huang S., Yang J., Cheng X., Shang Z., Lu H. et al. . Clinical characteristics in patients with SARS-CoV-2/HBV co-infection. *J. Viral Hepat.* 2020;27(12):1504–1507. DOI: 10.1111/jvh.13362.
46. Yu R., Tan S., Dan Y., Lu Y., Zhang J., Tan Z. et al. Effect of SARS-CoV-2 coinfection was not apparent on the dynamics of chronic hepatitis B infection. *Virology*. 2021;553:131–134. DOI: 10.1016/j.virol.2020.11.012.
47. Liu J., Wang T., Cai Q., Sun L., Huang D., Zhou G. et al. Longitudinal changes of liver function and hepatitis B reactivation in COVID 19 patients with preexisting chronic hepatitis B virus infection. *Hepatology Research*. 2020;50 (11):1211–1221. DOI: 10.1111/hepr.13553.
48. Chronic viral hepatitis C. Clinical guidelines. M.: Ministry of Health of the Russian Federation, 2021 (in Russ.). URL: https://cr.minzdrav.gov.ru/schema/516_2 (date of access: 10.06.2022).

49 Cerbu B., Pantea S., Bratosin F. Vidican, I.. Turaiche M., Frent S. et al. Liver Impairment and Hematological Changes in Patients with Chronic Hepatitis C and COVID-19: A Retrospective Study after One Year of Pandemic. *Medicina.* 2021;57(6):597. DOI: 10.3390/medicina57060597.

50. Pinchuk T.V., Orlova N.V., Suranova T.G., Bonkalo T.I. Mechanisms of liver damage in COVID-19. *Medical Alphabet*. 2020;19:39–46 (in Russ.). DOI: 10.33667/2078-5631-2020-19-39-46.

51. Lizardo-Thiebaud M., Cervantes-Alvarez E., Limon-de la Rosa N., Tejeda-Dominguez F., Palacios-Jimenez M., Méndez-Guerrero O. et al. Direct or collateral liver damage in SARS-CoV-2–Infected patients. *Semin. Liver Dis*. 2020;40(3):321–330. DOI: 10.1055/s-0040-1715108.

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Received 20.07.2022;
approved after peer review 05.09.2022;
accepted 08.12.2022