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COVID-19 and Liver Damage

Abstract

An outbreak of unknown pneumonia, caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2), was reported in China at the end of December 2019. On February 11, 2020, the World Health Organization officially named SARS-CoV-2 infection COVID-19 (Coronavirus Disease 2019). The most common clinical manifestation of COVID-19 is pneumonia. However, with the spread of the COVID-19 pandemic and analysis of clinical data, symptoms that are not characteristic of "atypical" pneumonia have been identified in patients. Neurological symptoms, skin and eye damage, etc., are described. The extrapulmonary presence of SARS-CoV-2 was also detected in cholangiocytes. Virus-induced effects, systemic inflammation ("cytokine storm"), hypoxia, hypovolemia, hypotension in shock, drug-induced hepatotoxicity, etc., are considered possible factors of liver damage. In 14–53 % of COVID-19 patients, changes in biochemical parameters, which usually do not require drug therapy, can be recorded. Acute hepatitis is very rare. However, special attention should be given to COVID-19 patients at risk: after liver transplantation; receiving immunosuppressants and antiviral drugs; and in cases of decompensated cirrhosis, acute-on-chronic liver failure, and hepatocellular carcinoma. Constant data sharing and open access to research data, new technologies, and up-to-date guidelines are required.

Key words: *Coronaviruses that cause respiratory syndrome; novel coronavirus disease; liver damage*

ALT — alanine aminotransferase, ACE2 — angiotensin-converting enzyme type 2, AST — aspartate aminotransferase, WHO — World Health Organization, GGTP — gamma-glutamyltransferase, IL — interleukin, ARDS — acute respiratory distress syndrome, LDH — lactate dehydrogenase, RNA — ribonucleic acid, CRP — C-reactive protein, CLD — chronic liver disease, ALP — alkaline phosphatase; COVID-2019 — Coronavirus Disease 2019, MERS-CoV — Middle East respiratory syndrome coronavirus, RBD — receptor-binding domain, SARS-CoV — severe acute respiratory syndrome coronavirus, SARS-CoV-2 — novel coronavirus COVID-19; TMPRSS2 — Transmembrane protease, serine 2

Introduction

Coronaviruses are widespread and usually cause the common cold (up to 25%). Most of them cause mild viral infection, but some, such as SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus), lead to severe respiratory syndrome with high mortality rate [1, 2].

Many species of bats are natural hosts of coronaviruses. By evolving due to mutations and preadaptation processes, they sometimes cause epidemics in human populations. The outbreak of unknown pneumonia reported in China at the end of December 2019 led to a public health emergency, which subsequently led to the pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) [2, 3]. On February 11, 2020,

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the World Health Organization (WHO) officially named the SARS-CoV-2-infection COVID-19 ("Coronavirus Disease 2019"). SARS-CoV-2 has a mortality rate of 0.5–3% [4].

SARS-CoV-2 and Possible COVID-19 Pathogenesis Factors

Novel coronavirus is a single-stranded RNA virus of the family *Coronaviridae*, genus Betacoronavirus. SARS-CoV-2 is a zoonotic virus: phylogenetic analysis showed its closest connection with the SARS-like bat coronavirus BM48-31/BGR/2008 isolate (96% identity). Bats appear to be a reservoir of SARS-CoV-2, while other small mammals (in particular, pangolins) are intermediate hosts, which possibly infected the "patient zero" [1]. Also, the phylogenetic analysis of SARS-CoV-2 yielded data indicating 88% sequence identity with SARS-CoV and about 50% with MERS-CoV [1, 5]. The structure of respiratory syndrome coronaviruses is very similar (Fig. 1).

Among structural proteins, SARS-CoV-2 secrete S-proteins or "spike proteins", membrane protein, coat protein and nucleocapsid. S-protein plays an important role in the attachment, fusion and penetration of the virus into cells, which means it can be considered as a possible target for antibodies and the vaccine.

The pathogenesis of novel coronavirus infection has not been sufficiently studied [6, 7]. The key factor of virulence is the interaction of the receptor-binding domain (RBD) of the S-protein, located on the outer membrane of SARS-CoV-2, with the angiotensin-converting enzyme 2 receptor (ACE2), which is activated by human transmembrane serine proteases (TMPRSS2 — Transmembrane protease, serine 2) [8]. ACE2 is expressed in surfactant, which is secreted in type 2 alveolocytes from plasma components. Surfactant is a surface-active monomolecular film, which is located at the air-water interface of alveoli, alveolar ducts and respiratory bronchioles of the 1st–3rd order. It prevents the collapse of the alveolar walls when breathing. ACE2 expression protects the lungs from damage but decreases due to its binding to the SARS-CoV S-protein, which increases the risk of infection. At the same time, the experiment showed that increased ACE2 expression does not prevent increased binding to SARS-CoV. Up to three viruses can attach to one target. ACE2 and TMPRSS2 are unevenly distributed among patients of European and Asian descent, which can also affect the intensity of infection.

It has been suggested that non-structural proteins of SARS-CoV can modify the structure of hemoglobin in the red blood cell, which disrupts oxygen transport, causes iron dissociation, the formation of porphyrin, and increase in the ferritin level. This effect can intensify inflammation in the lungs and cause oxidative stress, hypoxemia, hypoxia, with the development of symptoms of acute respiratory distress syndrome (ARDS) and multiple organ failure due to hypoxia [9]. However, this hypothesis was based on a biotransformational model built without experimental and clinical studies.

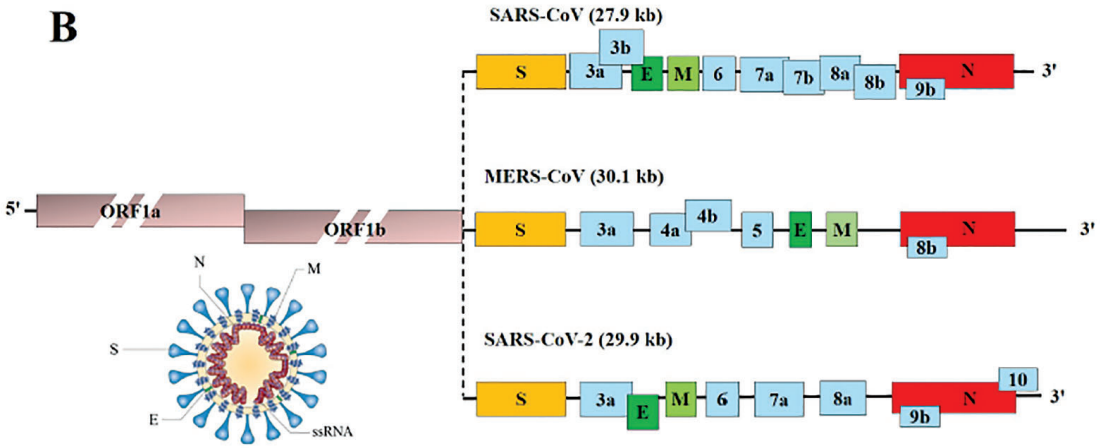

Figure 1. *Structure of SARS-CoV, MERS-CoV, and SARS-CoV (Adapted from Li X., et al., 2020)*

SARS-CoV-2 has an affinity to goblet cells contained in the mucous membrane of the respiratory tract, intestines, eye conjunctiva, pancreatic and parotid gland ducts. Active replication of the virus significantly reduces the protective functions of goblet cells (mucus formation), which also aids the penetration of the virus into the human body.

In response to the coronavirus replication, hyperimmune response — the so-called "cytokine storm" — is triggered, which characterized by the synthesis of a significant (abnormal) amount of pro-inflammatory cytokines (IL-1β, IL-6, tumor necrosis factor, etc.) and chemokines, while reducing the content of T-lymphocytes in the blood [10]. Furthermore, while infecting the blood vessel endothelium, SARS-CoV-2 interacts with ACE2 in the endothelium, causing endothelial dysfunction, hyperpermeability, impairment of microcirculation, thrombophilia, and thrombosis [11].

The progression of COVID-19 is determined by diffuse alveolar damage, with the formation of hyaline membranes and the development of pulmonary edema. The post-mortem histopathological pattern of the lung tissue is characterized by the organization of alveolar exudates and interstitial fibrosis, the formation of hyaline membranes, interstitial mononuclear inflammatory infiltrates, numerous fibrin microthrombi, severe edema, hyperplasia and focal desquamation of type 2 alveolocytes, and significant content of macrophages with viral inclusions in the alveolar exudate. Hemorrhage, necrosis, and hemorrhagic infarct are detected in the most severely affected areas [12, 13].

Clinical Presentation and Diagnosis of COVID-19

Human SARS-CoV-2 infection occurs in the last days of the incubation period and peaks in the first three days of the disease. The overwhelming majority of infections occur due to contact with a COVID-19 patient in cases of clinical manifestation of the disease (in up to 75–85% of cases, the contact is with infected relatives within the family). It should be emphasized that viral shedding usually lasts up to 12 days in mild/moderate cases and more than 14 days in severe cases. However, in patients who have recovered from COVID-19, novel coronavirus RNA may be positive even after the disappearance of clinical symptoms. A patient with COVID-19 can infect 3–5 people around him/her, while a person with flu can only infect 1–2 people [14–16].

Epidemiological data indicate that patients with cardiovascular diseases, hypertension, diabetes mellitus, and cancer are the most susceptible to SARS-CoV-2. The incubation period is 2–14 days (5–6 days on average). SARS-CoV-2 is transmitted via airborne droplets (coughing, sneezing, conversation), air-dust (with dust particles in the air), contact (through handshakes, household items) and fecal-oral routes [17].

Clinical Course of COVID-19 [18]:

- *Mild* (with damage to only the upper respiratory tract)
- *Moderate* (pneumonia without respiratory failure)
- *Severe* (pneumonia with signs of respiratory failure, or the appearance of "ground-glass opacity" pattern in the lungs, occupying more than 50% of the lungs within 24–48 hours)
- *Very severe/critical* (pneumonia, ARDS, sepsis, septic shock, multiple organ failure)

The proportion of asymptomatic (latent) course of COVID-19 is not clear. However, even with an asymptomatic course, in the absence of complaints and clinical signs, the "ground-glass opacity" pattern can be observed on CT scans, which is more clearly recorded at the peak of inspiration, which enables to diagnose pneumonia.

The report of the WHO-China joint mission on the novel coronavirus disease identified typical signs and symptoms of the disease (Table 1).

However, with the spread of the COVID-19 pandemic and analysis of clinical data, symptoms that are not characteristic of "atypical" pneumonia have been found [19]. In the absence of respiratory disorder, doctors of various specialties have been diagnosing COVID-19 based on the identification of "atypical" signs and the subsequent use of molecular genetic methods.

Clinical observations of patients with a positive SARS-CoV-2 RNA test and the presence of neurological signs in the form of anosmia (loss of the sense of smell), dysgeusia (loss of the sense of taste), which is apparently associated with intranasal infection and damage to neurovasal structures, have been described [20, 21]. In cases of severe

Table 1. *The main symptoms of COVID-19 [18]*

Symptoms	%	Symptoms	%
Fever	87.9%	Myalgia or arthralgia	14.8%
Cough	67.7%	Chills	11.4%
Fatigue	38.1%	Nausea and/or vomiting	5.0%
Sputum production	33.4%	Nasal congestion	4.8%
Dyspnea	18.6%	Diarrhea	3.7%
Sore throat	13.9%	Hemoptysis	0.9%
Headache	13.6%	Subconjunctival hemorrhage	0.8%

course, the infection was complicated by the development of transient ischemic attack, epilepsy, and cerebral infarction [22, 23].

In the Russian population, there have been cases of patients seeking medical attention for hemorrhages and pain in the eyes, and lacrimation, followed by dryness. A positive test for SARS-CoV-2 confirmed the viral nature of the disease in several observations. In the absence of other clinical signs, the latent course of COVID-19 was diagnosed, which manifested only as conjunctivitis (Fig. 2, authors' personal clinical experience). Foreign colleagues [24] described similar observations.

Other possible causes of conjunctivitis should also be considered. In this regard, it seems important to identify viral and bacterial antigens in SARS-CoV-2-positive patients.

A Stanford University (Stanford University, USA) study conducted in 2020 confirmed the presence of co-infection in case of COVID-19. In 20.7% of cases, various combinations of markers of influenza and type 1–4 parainfluenza viruses, respiratory syncytial virus, adenovirus, rhinovirus, enterovirus, Chlamydia pneumoniae and Mycoplasma pneumoniae were detected [25].

Atypical signs of COVID-19 were also recorded in dermatological practice. S. Recalcati, 2000 [26], described various skin changes (erythematous or vesicular rash, common urticaria) in 18 (20.4%) of 88 patients; and in 4 cases, the changes were noted at the onset of the disease and were accompanied by mild itching [26].

The nature of skin manifestations differed in various age groups. In a Spanish study conducted among 375 COVID-19 patients, 6% of elderly patients developed livedo reticularis and necrosis [27].

The dermatology community is also discussing another COVID-19 symptom never observed before [28]. The symptom is associated with damage to the fingers and toes with a characteristic purple color, hence its name "coronavirus fingers" (Fig. 3). Burning sensation and pain in the fingers are apparently due to microcirculation disorder and/or the development of microthrombosis, which is possibly a local manifestation of SARS-CoV-2 exposure.

According to the authors, the analysis of atypical signs of COVID-19 generally points to endothelial dysfunction and, to a certain extent, the possibility of local or systemic vasculitis.

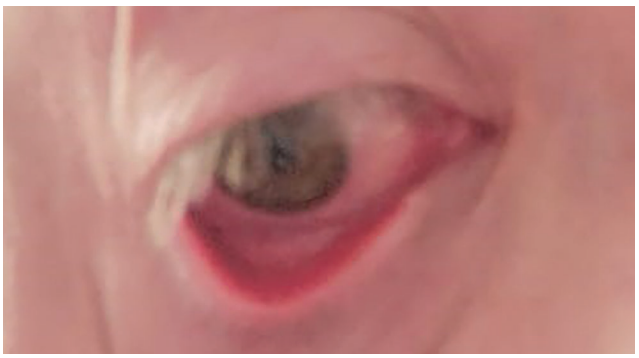

Figure 2. *COVID-19. Conjunctivitis (personal clinical experience of the authors)*

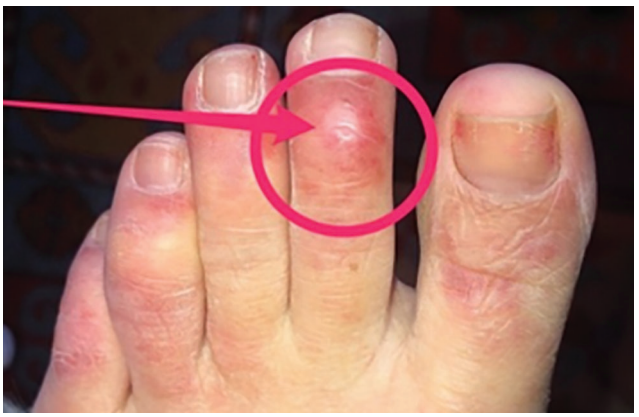

Figure 3. *«Red fingers»*

Diagnosis of COVID-19

The most common clinical manifestation of COVID-19 is pneumonia. The diagnosis of pneumonia in COVID-19 is based on epidemiological history and clinical examination, laboratory test results, and other investigations. Chest X-ray and computed tomography reveal changes in the form of «ground-glass opacity», infiltrates in different lobes, and interstitial changes [29]. Positive SARS-CoV-2 RNA and the appearance of antibodies confirm the diagnosis of COVID-19.

Leukopenia, lymphopenia, thrombocytopenia, increased C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH) activity, as well as D-dimer, are usually detected with this infection. The increase in the D-dimer level may indicate deep vein thrombosis, pulmonary embolism, and is an unfavorable prognostic factor [30].

Extrapulmonary presence of ACE2 and TMPRSS2 is found in glandular cells of the gastric epithelium, entero- and colonocytes, podocytes, proximal tubule cells of the kidneys, and cholangiocytes. These cells should be considered as probable targets of SARS-CoV-2 [8].

COVID-19-Related Liver Damage

Previous studies have shown that SARS-CoV and MERS-CoV cause liver damage in infected patients [31]. With COVID-19, abnormalities in the functional state of the liver were also detected. These abnormalities were associated with the progression and severity of the infection process [32, 33].

Mechanisms of COVID-2019-related liver damage are poorly understood. Virus-induced effects, systemic inflammation («cytokine storm»), hypoxia, hypovolemia, hypotension in shock, drug-induced hepatotoxicity, etc., are considered possible factors of liver damage.

It was shown that ACE2 expression in cholangiocytes is much higher than in hepatocytes and is comparable with ACE2 expression in type 2 alveolocytes [33]. With COVID-19, liver damage may be determined primarily by damage to cholangiocytes. In this regard, there are a number of issues that need to be addressed.

1. Does SARS-CoV-2 have a direct cytopathic effect on hepatocytes?
2. Does SARS-CoV-2 affect the course and outcome of chronic liver disease (CLD)?
3. What is the role of drug hepatotoxicity and drug interactions in COVID-19?

Articles analyzing the state of the liver in COVID-19 patients in Wuhan (People's Republic of China) described biochemical changes in 14–53% of said patients [31, 33, 34], and showed that in 2–11% cases, the infection developed in the presence of CLD [31]. The increase in ALT/AST (alanine and aspartate aminotransferases) activity, as a rule, did not exceed 1.5–2 times the normal from the upper limit of normal and was accompanied by a slight increase in the total bilirubin content.

Similar data were obtained in the study conducted by Cholankeril G. et al. (2020) in California. The analyzed group consisted of 116 patients with COVID-19; men (53.4%) of middle age (50 years) predominated, and half of them were Caucasian (50.9%). In two cases, CLD was previously diagnosed. The most common signs of infection were cough (94.8%), fever (76.7%), dyspnea (58%), and myalgia (52.2%). The average duration of symptoms was 5 days. In 31.9% of patients, gastrointestinal symptoms atypical for COVID-19 were observed at the onset of the disease: loss of appetite (22.3%), nausea/vomiting (12%), and diarrhea (12.0%). In 26/65 cases, changes in biochemical parameters that did not require drug therapy were revealed (Table 2).

The proportion of liver damage in patients with severe COVID-19 was significantly higher than in patients with a mild course. However, fatal liver failure was not observed even in critical conditions and fatal outcomes [32, 33, 35]. However, in several cases, protein synthesis impairment was noted: the albumin level decreased to 30.9–26.3 g/l [36].

In the post-mortem examination of COVID-19 patients, the liver is dark red, enlarged; the gallbladder is enlarged. Microscopic examination reveals microvesicular steatosis, focal necrosis of hepatocytes, the predominance of neutrophils in lobular and portal infiltrates, and microthrombi in sinusoids [13]. To a greater extent, the described histopathological changes may be due to drug-induced damage, rather than SARS-CoV-2 [31].

Molecular genetic methods detected the SARS-CoV gene not only in lung tissue, but also in

Table 2. *Biochemical parameters of liver function in patients infected with SARS-CoV-2 [35]*

Parameters	Patients tested for biochemical parameters (n = 65)	Patients with altered biochemical parameters (n = 26)
AST, U/l	35 (22–58)	64 (24–76)
ALT, U/l	32 (22–48)	59 (22–76)
ALP, U/l	67 (53–85)	75 (53–89)
Total bilirubin, mg/dl	0.4 (0.3–0.7)	0.5 (0.3–0.7)

Note: AST — aspartate aminotransferase; ALT — alanine aminotransferase; ALP — alkaline phosphatase. Mean values are presented as median and interquartile range (25–75% percentiles)

parenchymal cells, and vascular endothelium of other organs, including hepatocytes [33]. SARS-CoV RNA was detected in feces, which explains the appearance of gastrointestinal symptoms during virus transmission via the fecal-oral route [37]. However, its long-term detection in feces after clinical recovery (up to 11 days) [38] does not exclude a possible recurrence of the disease [39, 40]. The reasons, as well as the possible role of virulence and variability of the virus in cases of ongoing SARS-CoV replication, remain unclear.

Acute Hepatitis in COVID-19 Patients

Rare cases of acute hepatitis are described. Wander P. et al. (2020) observed a 59-year-old female patient with HIV infection and metabolic syndrome, for which she received etiopathogenetic therapy with a good effect. No deviations were detected shortly before the study of biochemical parameters. Epidemiological history was unremarkable. The patient was hospitalized for examination as an HIV-infected patient with a single complaint of dark urine. No changes were detected during physical examination. A laboratory study revealed significant hyperenzymemia (ALT — 697 IU/l; AST-1230 IU/l) with normal bilirubin level, hyperferritinemia (6606 ng/ml), and a decrease in albumin (up to 31 g/l). No markers of hepatitis A, B, C, Epstein—Barr viruses, cytomegalovirus, and respiratory viruses were detected. On the second day of hospitalization, the patient developed fever (39 °C), decreased saturation (94%), and bilateral interstitial pneumonia was diagnosed via X-ray examination. Oxygen therapy was started, and from the 4th day of hospitalization, a 5-day course of hydroxychloroquine at a dose of 200 mg was prescribed without stopping the use of previously taken drugs. Nasopharyngeal swabs revealed SARS-CoV RNA. On the 8th day, the patient was discharged in a satisfactory condition (AST — 114 IU/l, ALT — 227 IU/l, ALP — 259 IU/l, albumin — 28 g/l). Since all other causes of acute anicteric hepatitis were excluded, it seems very likely that it was caused by SARS-CoV (Fig. 4).

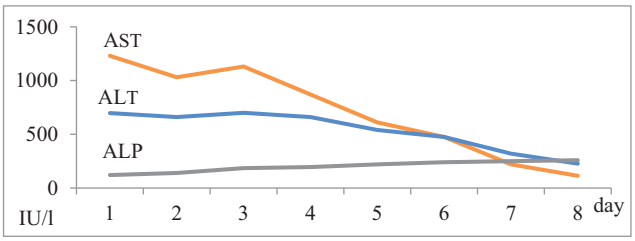

Figure 4. *Biochemical parameters pattern in acute anicteric hepatitis in a patient with COVID-19*

AST — aspartate aminotransferase; ALT — alanine aminotransferase; ALP — alkaline phosphatase

Chronic Liver Disease and COVID-19

Analysis of the clinical pattern of COVID-19 showed no significant effect of SARS-CoV on CLD. Patients with viral etiology of CLD were more likely to develop liver damage, which is probably associated with increased replication of hepatitis B and C viruses in the presence of SARS-CoV infection [42].

Immunosuppressive drugs used in autoimmune liver diseases can apparently have some protective effect and prevent immunopathological processes that cause lung damage in cases of severe COVID-19 [43].

Patients with non-alcoholic steatohepatitis (NASH) associated with concomitant diseases (diabetes, hypertension, cardiovascular disorders) are

at high risk of SARS-CoV infection and severe COVID-19 [44].

Also, patients that have undergone liver transplantation, patients receiving immunosuppressants and antiviral drugs, and patients with liver cirrhosis, acute-on-chronic liver failure, and hepatocellular carcinoma are at risk [42, 45, 46].

International and Russian scientific communities are developing and constantly updating guidelines for the treatment of COVID-19 [15, 16, 47]. The fight against the global pandemic should include sharing and open access to research data and new technologies. Recently, the European Association for the Study of the Liver actively supported the COVID-Hep project, which was launched by Oxford University and is intended to create a registry to collect data on patients with liver disease at any stage or liver transplants who develop COVID-19 (information on the registry can be found at: **http://covid-hep.net**).

Drug Hepatotoxicity and Drug Interactions in COVID-19

One of the important functions of the liver is detoxification. The treatment methods used, including hydroxychloroquine, antibiotics, and antiviral drugs can increase liver damage due to potential hepatotoxicity.

A report from Brazil, prepared by Falcão M. B. et al. (2020), describes a patient with pneumonia caused by SARS-CoV. After two doses (800 mg) of hydroxychloroquine, a 10-fold increase in the activity of aminotransferases and their decrease to normal levels after discontinuation of the drug were noted. The authors suggested that in COVID-19, the use of higher doses of hydroxychloroquine can lead to drug-induced liver damage.

Hydroxychloroquine-induced hepatotoxicity is rare. Cases of liver damage have been described when therapeutic doses of hydroxychloroquine are administered to patients with systemic lupus erythematosus, porphyria cutanea tarda, and Still disease [49, 50].

The mechanisms of hydroxychloroquine-related liver damage are not well understood. Hepatotoxicity may be due to the action of metabolites, oxidative stress, toxic or synergistic effects associated with inflammatory processes [51].

Furthermore, under the influence of hydroxychloroquine, the QT interval in COVID-19 patients may be prolonged due to the blocking of potassium channels, which is aggravated when combined with antibiotics (in particular, azithromycin) [52]. The identified unfavorable signs require the monitoring of liver function and electrocardiogram, especially among risk groups: patients with CLD and cardiac repolarization disorders.

The scale of the use of experimental treatment methods for COVID-19 is unprecedented. However, there is still no evidence of their effectiveness. In light of this, drug-drug interaction remains a critical issue for clinical practice. The website of the University of Liverpool (UK) (**www.covid19-druginteractions.org**) lists the main experimental drugs that are currently used in COVID-19 therapy, with a description of their mechanisms of action; an assessment of their combined use with other drugs is also given, taking into account the risks and benefits, duration of use, the patient's condition, and drugs indicated for previously diagnosed diseases [53].

Conclusion

At the time of this writing, more than 3.5 million cases of COVID-19 with more than 250,000 deaths had been reported worldwide [54].

Unfortunately, there are currently no effective specific methods of treating COVID-19 [55]. Numerous clinical randomized trials of various drugs are being carried out.

So far, there is no evidence that patients who recovered from COVID-19 are safe from reinfection [56]. Individuals with anti-SARS-CoV-2 antibodies require follow-up in comparison with individuals without said antibodies, with an assessment of the incidence of SARS-CoV-2 infection and the development of COVID-19 over a long period (at least one year).

However, the first experimental use of IgG-containing plasma of patients who had recovered from COVID-19 showed encouraging results [57].

Patients who have recovered from COVID-19 and asymptomatic individuals, who secrete the virus with feces, can be considered as a possible source of infection. Also, since SARS-CoV-2 RNA has been detected in wastewater samples, the issue of virus

viability in ambient conditions, through which the fecal-oral route can also be realized, remains unresolved [58]. The question of a possible second outbreak, reactivation, or a new wave of SARS-CoV-2 infection remains open.

Vaccine development has begun in earnest since the declaration of the pandemic. There have been reports of 115 potential vaccines, 78 of which are at different stages of clinical trials [59].

Restrictive measures are still required to contain the spread of SARS-CoV-2 and COVID-19. The pandemic has far-reaching medical, social, and economic consequences («coronacrisis») for all countries worldwide. Today, professional and personal actions of each of us should be aimed at combating this threat.

Author Contribution

All authors made a significant contribution to the preparation of the article, read and approved the final version before publication.

L.Yu. Ilchenko (ORCID ID: https://orcid.org/0000-0001-6029-1864): writing and editing the paper

I.G. Nikitin (ORCID ID: https://orcid.org/0000-0003-1699-0881): design and approval of the final version of the article

I.G. Fedorov (ORCID ID: https://orcid.org/0000-0003-1003-539X): search for literature and editing the paper.

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