LIVER DAMAGE IN PATIENTS WITH COVID-19

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The clinical spectrum of SARS-CoV-2 infection continues to expand, raising important fundamental issues regarding the SARS-CoV-2 cellular tropism and pathogenic mechanisms. Liver damage is observed in patients with all forms of COVID-19, especially severe and critical forms, which could be due to the direct viral damage, immune dysregulation (systemic inflammatory response and cytokine storm), hypoxia-ischemia, drug-induced hepatotoxicity, and concomitant chronic disorders. Liver damage, defined primarily by elevated transaminase levels, is often observed in patients with COVID-19 and correlates with clinical outcomes, including mortality. Diagnostic criteria, pathogenesis, clinical characteristics, treatment, and prognosis of liver injury in COVID-19 should be clarified in further clinical trials. Currently, there is a critical shortage of proven treatment options for patients with COVID-19, resulting in an urgent need to study the multiple organ failure and liver damage pathogenesis in patients with this disease. The review provides information about the pathophysiological mechanisms of the SARS-CoV-2-induced liver damage and the development of liver failure in COVID-19. Information sources were searched in the PubMed database using the keywords "liver damage in COVID-19" and "immune liver damage in COVID-19".

Keywords: coronavirus SARS-CoV-2, COVID-19, liver damage, csystemic hepatotoxicity, immune liver damage, drug-induced hepatotoxicity, concomitant chronic liver disease

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ПОРАЖЕНИЕ ПЕЧЕНИ У БОЛЬНЫХ COVID-19

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Спектр клинических проявлений инфекции SARS-CoV-2 продолжает расширяться, возникают важные фундаментальные вопросы, касающиеся ее клеточного тропизма и патогенетических механизмов. Повреждение печени происходит при всех формах COVID-19, особенно при тяжелых и крайне тяжелых, что может быть связано с прямым вирусным поражением, иммунной дисрегуляцией (системным воспалительным ответом и цитокиновым штормом), гипоксическим/ишемическим повреждением, лекарственной гепатотоксичностью и сопутствующими хроническими заболеваниями. Повреждение печени, определяемое в основном по повышению уровней трансаминаз, часто обнаруживают у пациентов с COVID-19, и оно коррелирует с клиническими исходами, включая смертность. Диагностические критерии, патогенез, клинические характеристики, лечение и прогноз поражения печени при COVID-19 должны быть уточнены в дальнейших клинических исследованиях. В настоящее время критически не хватает проверенных вариантов лечения пациентов с COVID-19, что приводит к неотложной необходимости изучения патогенеза полиорганной недостаточности и повреждения печени при этом заболевании. В обзоре представлена информация о патофизиологических механизмах повреждения печени коронавирусом SARS-CoV-2 и развитии печеночной недостаточности при COVID-19. Поиск источников информации проведен в базе данных PubMed по ключевым словам «liver damage in COVID-19» и «immune liver damage in COVID-19».

Ключевые слова: коронавирус SARS-CoV-2, COVID-19, повреждение печени, системная гепатотоксичность, иммунное повреждение печени, лекарственная гепатотоксичность, сопутствующее хроническое заболевание печени.

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SARS-CoV-2 coronavirus is a respiratory pathogen causing COVID-19. Complications of COVID-19 affect almost all organs, including liver. Direct virus cytotoxicity, dysregulated immune responses, microcirculatory disorders and thrombosis contribute to the systemic toxicity in COVID-19. The diversity of the COVID-19 manifestations is associated with the broad organotropism of SARS-CoV-2.

SARS-CoV-2 infects cells by means of the multifunctional cellular receptor, ACE2 (angiotensin-converting enzyme-2), which is found on the cell membranes in all organs, including liver, and makes the tissue vulnerable to the coronavirus invasion. Cellular serine protease TMPRSS2 (transmembrane protease serine 2) is involved in the SARS-CoV-2 invasion, contributing to the virus internalization into target cells [1]. ACE2 and TMPRSS2 are expressed in the cells of many tissues, including gastric glandular cells, enterocytes, hepatocytes, cholangiocytes, and endothelial cells [2, 3]. Elevated ACE2 expression in hepatocytes has been revealed in patients with liver fibrosis/cirrhosis [2, 4]. This finding is very important: concomitant liver disease may increase the SARS-CoV-2 liver tropism.

Hepatic dysfunction may influence the multisystem manifestations of COVID-19, such as acute respiratory distress syndrome (ARDS), coagulopathy, and multiple organ failure. Liver is the main human organ involved in metabolism and detoxification, that is why even a moderate decline in liver

function can alter the safety profiles and therapeutic efficacy of antiviral drugs metabolized in the liver [4].

Epidemiological data on liver injury in patients with COVID-19

The prevalence of liver injury in patients with severe COVID-19 (74.4%) is higher than in patients with the mild course of the disease (43.0%). Patients with severe COVID-19 admitted to an intensive care unit (ICU) had a more severe hepatic disfunction compared to patients with the milder disease. The prevalence of elevated hepatic transaminase plasma levels in patients with COVID-19, which are particularly high in severe cases, reached 53% in survivors [5, 6] and 78% in the deceased [5]. Elevated serum levels of aspartate transaminase (AST) were observed in almost 18% of patients with mild COVID-19 and 56% of patients with severe disease; elevated levels of alanine aminotransferase (ALT) were found in almost 20% of patients with mild COVID-19 and 28% of patients with the severe disease. Elevated levels of cholestatic enzymes, alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT), were observed in 6.1 and 21.1% of patients with COVID-19, respectively [7].

Elevated levels of transaminases and bilirubin and the reduced albumin concentration in patients with COVID-19 correlate with the length of hospital stay, risk of admission to ICU and 30-day mortality. In the majority of patients, transaminase levels are back to normal after recovery. The patients with persistently elevated transaminase levels are severely ill or have a chronic liver disease (CLD). Elevated levels of GGT and ALP in patients with COVID-19 are indicative of damage to the bile duct cells in the liver. Liver injury could be secondary to the bile duct cell damage, since there are no viral inclusions in the biopsy specimens taken from some patients, and the pathological changes manifest themselves in the form of microvascular steatosis and moderate lobular and portal inflammation. Furthermore, the extent of liver injury positively correlates with the infection severity [8].

According to systematic review with meta-analysis of 11 studies (793 patients), abnormally low serum albumin levels were found in 79% (40–99%) of patients [9]. When performing meta-analysis, only the baseline laboratory data obtained at admission were taken into account.

In general, hepatic dysfunction is typical for 76.3% of patients, and liver injury is typical for 21.5% of patients [10].

Mechanisms underlying liver damage in COVID-19

Pathogenesis of liver injury caused by COVID-19 have not been properly clarified, since the available data are scarce and contradictory. The mechanisms of hepatocellular injury are multifactorial and include direct viral damage, immune-mediated injury, hypoxia-ischemia, thrombosis, and drug-induced hepatotoxicity [8, 10].

Direct viral damage to the liver

Infection of hepatocytes with SARS-CoV-2, mediated by the ACE2 cellular receptor, results in the acute cytopathic liver injury and is associated with the high mortality [3]. Foci of periportal and centrilobular necrosis without significant inflammation are reported [11].

In addition to hepatocellular pattern of the liver enzyme level elevation, COVID-19-associated liver injury can manifest itself in the form of cholestatic pattern. ACE2 expression on the biliary epithelial cells results in the direct viral infection. Swelling of endothelium of the hepatic artery branches in the portal tract together with luminal narrowing are observed, endophlebitis of the portal vein, endotheliitis, and blood clots in the branches of the portal vein emerge [12].

ACE2 expression on the majority of cholangiocytes (59.7% of cells) and a relatively weak expression on hepatocytes (2.6%; the average expression levels are 20 times lower than in cholangiocytes) suggest that SARS-CoV-2 contributes to liver injury, causing cholangiocyte dysfunction. SARS-CoV-2 infection decreased cell-cell tight junction between cholangiocytes and reduces their barrier function. Assessment of liver biopsy specimens in fatal cases has revealed coronavirus in the cytoplasm of hepatocytes. Considerable hepatocyte apoptosis in combination with the presence of the CD4 and CD8 T cells in the lobular and portal tracts is indicative of the direct liver infection with SARS-CoV-2. These data demonstrate the SARS-CoV-2 ability to infect hepatocytes, despite low ACE2 expression [10].

Immune-mediated liver injury

In the course of the SARS-CoV-2 infection, 80% of immune cells entering liver are represented by CD8 T cells. CD4 T cell infiltration correlates with B cell activation, and the levels of neutralizing antibodies against SARS-CoV-2 and pro-inflammatory cytokines (IL1β, IL6 and TNFα), as well as the SARS-CoV-2 hepatic clearance [8]. IL6 is a factor of acute liver injury in patients with COVID-19, which induces liver sinusoidal endotheliopathy with neutrophil infiltration and a hypercoagulable phenotype [13]. The hypercoagulable and inflammatory phenotypes of the liver sinusoidal endothelial cells are considered the marker of endothelial damage and mortality predictor in patients with liver cirrhosis and COVID-19 [14].

Sudden deterioration of liver function at the advanced stage of the disease is associated with systemic inflammatory response, which can damage multiple organs, including liver. Moreover, patients with lymphocytopenia more often suffer from liver dysfunction [15]. Inflammatory changes, such as hepatocyte swelling and steatosis, liver sinus cell proliferation, Kupffer cell hyperplasia, and immune cell infiltration are found in liver cells of patients with severe COVID-19 [16].

Post-mortem examination of some patients with COVID-19 revealed cholestatic features, such as bile duct proliferation, portal inflammatory infiltrates, and, in a number of cases, canalicular/ductular bile plugs [17]. Cytokine storm typical for the SARS-CoV-2-associated viral sepsis could be the main contributing factor, since inflammatory cytokines IL6, TNFα and IL1β could cause hepatocellular cholestasis. Persistent systemic IL6 signaling induced by the SARS-CoV-2 infection inhibits albumin synthesis. Hypoalbuminemia associated with the cytokine storm and cholestasis resulting from inhibition of hepatobiliary excretion could be considered part of the COVID-19 acute phase. IL6 provides strong mitogenic stimulation of cholangiocytes, which induce proliferative and pro-inflammatory phenotypes [4].

In those infected with SARS-CoV-2, elevated C-reactive protein (CRP) levels and lymphopenia are considered independent risk factors for liver injury [18]. Taking into account the fact that histopathological examination has revealed no signs of severe inflammatory liver injury [19], alterations in the levels of hepatic enzymes in patients with SARS-CoV-2 could be due to hepatitis being the secondary response to the SARS-CoV-2-induced systemic inflammation [10].

Hypoxic hepatitis

Hepatic sinus endothelial cells contribute to perfusion disorders, responding to inflammatory signals. Ischemia–reperfusion injury

in the liver could result in inflammation due to activation of Kupffer cells, neutrophils, and platelets. In the conditions of ischemia and hypoxia, inhibition of the cell survival signaling pathway in hepatocytes results in hepatocyte necrosis. In patients with ARDS, hypoxia induces oxidative stress, persistent elevation of the levels of reactive oxygen species, and secretion of pro-inflammatory substances that cause hepatocyte damage and necrosis [8].

Hypoxia is a typical sign of severe COVID-19 and the main regulator of hepatocellular ACE2 expression. This may explain the fact that extrapulmonary dissemination of SARS-CoV-2 is observed mainly in patients with ARDS and other hypoxic conditions. Gene expression analysis has shown that primary hepatocytes infected with SARS-CoV-2 are characterized by overexpression of pro-inflammatory cytokines together with inhibition of key metabolic processes. These data illustrate the comprehensive nature of liver injury in patients with COVID-19 and the mutual influence of multiple SARS-CoV-2-activated molecular pathways involved. Biliary ducts of patients with COVID-19 are subject to hypoxia due to respiratory failure (exacerbated by the peribiliary arterial plexus obliteration resulting from vasculitis/thrombogenesis). Thus, poor blood circulation and hypoxia, as well as continuous inflammatory stimulation, are the main triggers of damage to the bile duct epithelium in patients with severe COVID-19 [4].

Coagulation and thrombosis

Elevated levels of hypercoagulability markers, D-dimer, fibrinogen and factor FVIII, were found in 100, 74 and 100% of patients with the extremely severe COVID-19. Microvascular thrombosis may result in the end-stage liver disease. Autopsy has revealed infiltration of lymphocytes and monocytes in the portal area with sinus thrombosis and congestion; hepatocyte degeneration and lobular necrosis have been found in the liver [16]. These data show that in patients with COVID-19 hypercoagulation is one of the causes of liver damage.

Coronavirus therapy-induced hepatotoxicity

Drug-induced liver injury results in varying degree liver damage, observed in patients with COVID-19. Antiviral drugs (oseltamivir, abidor, lopinavir, and ritonavir), antibiotics, steroids and hormones which have side effects, including liver damage, are widely used in treatment of COVID-19. In particular, the use of lopinavir/ritonavir increases the likelyhood of liver injury by 4 times. Liver metabolizes the majority of drugs for SARS-CoV-2. Elevated levels of ALT, ALP, bilirubin, and GGT, were observed in individuals infected with SARS-CoV-2, who were treated with lopinavir, ritonavir, and remdesivir [20].

Liver damage was more likely in patients who received medications of several types, and high-dose hormones. Liver injury disrupts metabolism and drug excretion and increases the antiviral drug toxicity. That is why great importance should be attached to the liver function monitoring, although in the majority of COVID-19 cases mild liver injury is observed, which is of a temporary nature and returns to normal without any specific treatment. Patients with severe liver injury need targeted hepatoprotective therapy. Treatment of the COVID-19-associated liver damage is based on inhibition of inflammation and correction of hypoxemia aimed at preventing the multiple organ dysfunction syndrome, as well as on one or two hepatoprotective drugs depending on the patient's liver dysfunction [15].

Hepatotoxic therapeutic agents include antiviral drugs that target the virus itself (remdesivir), IL6 and its effector signaling pathways (tocilizumab and baricitinib), and systemic inflammation (dexamethasone) together with antibiotics and steroids.

The randomized clinical trials have shown that the combination of remdesivir, the antiviral drug used in treatment of SARS-CoV-2 infection, with baricitinib, the JAK protein kinase inhibitor, improve the COVID-19 outcomes compared with the use of remdesivir only [21].

Coformulated drug lopinavir/ritonavir can cause liver necrosis and suppress hepatocyte proliferation. The drug induces inflammation and exacerbates liver injury due to increased oxidative stress. Lopinavir/ritonavir administration results in 7-fold increase in the hepatic enzyme levels [20].

Dexamethasone reduces the levels of biomarkers of endothelial damage (angiopoietin-2, intercellular adhesion molecules ICAM-1 and sRAGE) and inflammation (CRP) [22].

The use of endogenous cytokines, interferons, released by cells in response to viral infection (including SARS-CoV-2), in treatment of COVID-19 in order to inhibit replication of the pathogen resulted in leukopenia, lymphopenia, hepatocyte injury, autoimmune hepatitis, and other severe side effects [8].

Baricitinib, the JAK-STAT signaling pathway inhibitor, affects hyperinflammatory status arising from the SARS-CoV-2 infection, and is capable of preventing endocytosis and viral infection. However, the drug increases the risk of thrombosis and leads to liver injury. The increasing number of the reported cases of liver damage, cholestasis and hepatitis developing in the considerable number of patients who received JAK inhibitors to treat COVID-19, attracts attention [23].

Tocilizumab, anti-IL-6 receptor monoclonal antibody, is used as part of combination therapy in severe COVID-19 cases. Tocilizumab therapy must be discontinued if the levels of hepatic enzymes exceed the upper limit of normal more than three times [8].

These data indicate that it is necessary to regularly monitor the hepatic enzyme levels during treatment of patients with COVID-19 in order to minimize the risk of complications [24].

Taking into account the increased risk of death from COVID-19 in patients with CLD, European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), and Belgian Liver and Intestine Advisory Committee (BeLIAC) have recommended to give priority to vaccination against COVID-19 to patients with CLD and liver transplant recipients [25].

COVID-19-associated liver damage in patients with no concomitant chronic liver disease

Liver injury (predominantly hepatocellular rather than cholestatic) observed at admission correlates with clinical outcomes (ICU admission, mechanical ventilation, death). Patients having normal AST levels at admission and patients with abnormal levels of AST, ALT and ALP at peak hospitalization are at higher risk of mechanical ventilation [26]. Analysis of biopsy specimens has shown that the coronavirus-induced liver damage is the main cause of liver dysfunction in COVID-19 patients with no CLD. SARS-CoV-2 causes hepatic cytopathy with massive apoptosis and the presence of binuclear (less mature) hepatocytes being the predominant histological features [18, 27].

Among 900 COVID-19 patients, 28% had elevated levels of at least one hepatic enzyme [24]. Liver examination in patients with COVID-19 revealed endotheliitis [28] and fibrin microthrombi in hepatic sinusoids [29]. Liver study performed during autopsy revealed the dilated portal vein

and the increased number of the portal vein branches, partial thrombosis or complete obstruction of the portal and sinusoidal vessels, portal tract fibrosis, and microthrombi in hepatic sinusoids. None of these patients had CLD before or at admission to hospital. All liver specimens showed minimum signs of inflammation. Histopathological findings indicate a secondary nature of intrahepatic vasculature abnormalities to systemic changes caused by the virus [30].

Microvesicular steatosis is considered the main COVID-19-associated hepatocellular alteration. However, signs of liver damage, such as ground glass hepatocytes, fibrin aggregates in the sinusoidal lumen, sinusoidal dilatation and hepatocyte atrophy, dilated Disse spaces, and intrasinusoidal deposition of fibrin and red blood cells are also found in patients with no steatosis. Sinusoidal dilatation and Kupffer cell activation are the signs of thrombotic sinusoiditis. Intrahepatic vasculature abnormalities, including sinusoidal microthrombi, were found in the liver of 15% of patients who died from COVID-19: this was a marker of liver desease caused by SARS-CoV-2. A body of observations allows us to consider severe thrombotic sinusoiditis as a negative prognostic factor in patients with COVID-19 [17]. Liver injury can be also associated with the interaction between the intrahepatic cytotoxic T cells and Kupffer cells. Hypoxia and shock can cause ARDS, hypoxia/reperfusion-induced dysfunction, and hepatic ishemia. Indirect damage to the liver sinusoidal endothelium could result from systemic inflammation or iatrogenic causes (mechanic ventilation) [4].

Autopsy of the deceased COVID-19 patients' liver also revealed portal fibrosis accompanied by considerable pericyte activation. Liver autopsy performed in patients with COVID-19 revealed SARS-CoV-2 RNA in blood vessel lumens and endothelial cells of portal veins [30]. Inflammation mediated by endothelium is a possible mechanism of sustained liver injury, since endotheliopathy persists in patients with long COVID-19 [31].

Micro- and macrovesicular steatosis was observed when performing liver autopsy in patients with COVID-19, for whom SARS-CoV-2 infection was the only factor of liver damage. Microvesicular steatosis usually results from the genetic or acquired disorders of mitochondrial β-oxidation. In patients with COVID-19, SARS-CoV-2 affects mitochondrial activity and causes mitochondrial cristae abnormalities, thus worsening the liver metabolic status [18].

COVID-19-associated ARDS could be accompanied by the right ventricular dysfunction resulting in congestive hepatopathy due to elevated central venous pressure. In cases of sustained hemodynamic and/or respiratory failure hypoxia leads to hepatocyte death, defined as the centrilobular necrosis when performing histopatological examination. Furthermore, acute right-sided heart failure and the resulting hepatic congestion in patients with COVID-19 could be caused by hypercoagulation [4]. However, in the majority of cases, SARS-CoV-2-associated liver injury was mild and failed to meet the diagnostic criteria for hypoxic hepatitis even in patients admitted to ICU [7].

Coagulopathy characterized by elevated levels of D-dimer and fibrinogen is one of the features of COVID-19. Elevated levels of D-dimer are associated with severe COVID-19 and high mortality. High levels of D-dimer were found in almost all patients (96%) who died from severe COVID-19; elevated ALT levels were found in the majority of patients (62%), which pointed to the link between liver injury, hepatic vein thrombosis and coagulopathy. None of the patients had a history of CLD or portal hypertension [30]. Autopsy revealed the platelet-fibrin microthrombi in hepatic sinusoids and platelet aggregation in the portal vein in at least 50% of patients [30, 32].

In 86% of cases, autopsy of patients who died from severe COVID-19-associated pneumonia revealed moderate centrilobular necrosis associated with minimum portal or lobular inflammation; steatosis and cholestasis were found in 57% of cases, and in 36% of cases discrete proliferation of bile ducts was observed. Although most of patients were treated with drugs having low hepatotoxicity, hypoxia resulting from severe lung injury could reduce the tolerance of hepatocytes to toxic damage. The combination of hypoxia caused by severe pneumonia and drug toxicity was the most likely cause of liver injury in the deceased patients with COVID-19 [19].

The correlation between liver injury and COVID-19 severity has been confirmed [33]. Abnormal liver function test results at admission to hospital increase the risk of severe COVID-19-associated pneumonia [20]. The COVID-19 severity correlates with the AST and ALT levels, particularly in patients admitted to ICU [24]. In patients admitted with liver diseases, the risk of death correlates with the grade of liver damage: the risk is 1.4 times higher in patients with grade I liver injury, and 2.8 times higher in patients with grade II liver damage [34]. Thus, liver damage is an independent prognostic factor of mortality in patients infected with SARS-CoV-2.

COVID-19 in patients with concomitant liver disease

According to meta-analysis of epidemiological studies, the overall prevalence of CLD in patients with COVID-19 is 3%. SARS-CoV2 infection in patients with CLD is associated with higher mortality compared to other etiologies [13]. In case of liver disease diagnosed before the COVID-19 infection, coronavirus affects the emergence, severity, prognosis of COVID-19, as well as the treatment success [8]. Individuals with CLD are more likely to be infected with SARS-CoV-2 due to weak immune response. Half of the patients with abnormal liver function test results have CLD, including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, and chronic hepatitis B [20]. NAFLD is the most common dysmetabolic liver disease in the world being an independent risk factor of the COVID-19 progression (OR 6.4). The disorder is associated with the higher risk of liver dysfunction and the longer viral clearance period. Moreover, it increases the risk of severe COVID-19 progression related to metabolic dysfunction [35].

The study of patients within the Yale-New Haven Health System (USA) confirmed that the patients with abnormal liver tests were at high risk of severe disease. Liver injury was predominantly hepatocellular rather than cholestatic. In these patients, liver abnormalities increased at peak hospitalization. Multivariate analysis made it possible to reveal the relationship between the liver function indicators and clinical outcomes (admission to ICU, mechanical ventilation, and death) [26]. In COVID-19 with elevated serum transaminase levels, it is necessary to take into account the SARS-CoV-2-associated reactivation of the existing liver diseases, including autoimmune disorders.

Pro-inflammatory environment occurring in patients with hepatocellular and cholangiocellular COVID-19-associated injury contributes to activation of hepatic stellate cells, and, as a result, to fibrosis induction in patients with CLD [4]. Activation and proliferation of Kupffer cells resulting from systemic inflammation are often observed, particularly in the liver specimens obtained from the deceased patients with COVID-19 [8].

Chronic liver damage determines immunosuppression, which signficantly increases patient mortality, as it has been shown in the observational study of 17,425,445 patients with COVID-19 [36].

Patients with liver cancer are also at high risk of coronavirus infection, especially those undergoing chemotherapy or immunotherapy in the hospital [37]. Cancer patients infected with SARS-CoV-2 have a poorer prognosis compared to COVID-19 patients having no cancer; in such patients, mortality reaches 20% [38].

Liver transplant

The risk of infection and severe course of COVID-19 during the perioperative and the early post-transplant period is higher because of the high levels of immunosuppression [39]. At the same time, hyperactive response of innate immunity can cause liver damage and multiple organ failure; immunosuppression reduces the risk of hyperinflammation and cytokine storm in the liver transplant recipients [15].

The registry of patients with COVID-19 and CLD contains the data of 1588 patients with CLD and no cirrhosis, 772 patients with cirrhosis, and 280 liver transplant recipients [40]. Acute hepatic decompensation occurred in 46% of patients with cirrhosis, while 21% of them had no respiratory symptoms. In patients with acutely decompensated liver disease, mortality is two times higher than in patients with compensated cirrhosis (44% vs. 22%; $p < 0.001$) [41].

Pathogenic gut–liver axis in COVID–19

Since the beginning of the pandemic, gastrointestinal (GI) symptoms were reported as the distinctive features of COVID-19 along with the respiratory and hepatic symptoms. According to meta-analysis of 60 studies involving 4,243 patients with COVID-19, the prevalence of GI symptoms is 17.6% [42]. GI symptoms can appear before or even in the absence of respiratory symptoms [43].

SARS-CoV-2 identification in fecal samples and the combination of GI and liver symptoms are indicative of the gut–liver axis dysregulation in these patients. High expression of ACE2 receptor in the gastrointestinal epithelium (100 times higher than on hepatocytes) allows SARS-CoV2 to enter the cells of biliary ducts and suppress liver function [8]. The COVID-19-induced bowel infection can disrupt the intestinal epithelial barrier and gut vascular barrier leading to the viral translocation into liver through the portal vein. Subsequently, SARS-CoV-2 virions released by the infected hepatocytes, enter the bile [44]. Biliary tract provides the direct link between the liver and the gut, that is why SARS-CoV-2 can reach the gut and infect the gut through bile, causing reinfection. Thus, the prospective hepatobiliary mechanism can create a vicious cycle explaining the worst outcome in patients with the symptoms of liver disease and GI symptoms [4, 45].

When comparing the deceased patients with the critically ill survivors, immunomodulatory and tissue proteins associated with the COVID-19 survival were identified in blood plasma [46]. Comparison of the organ-specific "death signitures" revealed the significant correlation between the liver signature and the levels of ALT and AST. Proteins associated with the COVID-19 severity included THBS2 (thrombospondin 2), ACTA2 (actin alpha 2), HGF (hepatocyte growth factor), PDGFRA (platelet-derived growth factor receptor A) of Kupffer cells, TACSTD2 (tumor-associated calcium signal transducer 2) of cholangiocytes, CA2 (carbonic anhydrase 2), and BLVRB (biliverdin reductase B) of erythroid cells of the liver. Thus, blood plasma proteome could be used as the liquid biopsy for studying the potential therapeutic targets, and the diagnosis and stratification of patients at high risk being the candidates for personalized therapy [46].

CONCLUSION

SARS-CoV-2 coronavirus mainly affects respiratory tract. However, it shows tropism to the liver and bile ducts. That is why hepatologists are increasingly involved in combating the novel coronavirus infection. Medical practitioners predict the increasing prevalence of liver diseases in the months and years ahead, since SARS-CoV-2 is capable of directly infecting and causing damage to the liver tissue.

The course and outcome of COVID-19 depend largely on the patient's health and concomitant diseases. NAFLD, hepatitis B and C, liver cirrhosis, hepatic cancer, and taking immunosuppressants after the liver transplant result in immunodeficiency. Complications occur earlier and to a greater extent in patients with systemic immunodeficiency.

With the spread of the pandemic and publishing the new data on the effects of coronaviruses on the infected body it has become possible to define the risk factors for hepatic complications in patients infected with SARS-CoV-2. Studying the clinical data of patients with COVID-19 and liver diseases is important for identification of hepatic complications, prediction of the response to treatment, creation of the hepatic complication risk models, and development of the guidelines for patients with liver diseases and coronavirus infection.

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