Analysis Of Immunometabolic Changes in Patients With Chronic Liver Disease With Covid-19

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ABSTRACT

Scientific research data on Covid-19 shows that 14-53% of patients have signs of mild-to-moderate liver damage: increased levels of aminotransferases, hypoproteinemia, increased prothrombin time. Severity of Covid-19 cases are correlated with extensity of liver damage. On the other hand, prior to infection, active liver disease increased the severity of the infection. SARS-Cov-2 has a feature of direct damage of the hepatocytes which is explained by presence of angiotensin converting enzyme 2 receptors in the cholangiocytes. Patients with chronic diffuse and advanced liver diseases are at higher risk of infection due to cirrhosis affect on immune mechanisms.

Keywords: chronic hepatitis, Covid-19, damage, inflammation

The direct effect of SARS-CoV-2 on liver cells is associated with the expression of ACE2 receptors in cholangiocytes. Patients suffering from chronic diffuse liver diseases for a long time are at a higher risk of infection due to impaired immune system. Like other systemic viral infections, COVID-19 is associated with elevated transaminases, and these changes are not dependent on the liver itself, but rather reflect systemic immune changes that indicate the activity of circulating cytokines in the serum. This condition is called bystander hepatitis. An increase in the amount of transaminases was observed in 43-57% of patients with the disease of COVID-19 (usually the amount of transaminases increased by 2 times compared to the norm). Also, transaminase elevations were observed in patients receiving lopinavir and ritonavir, and these changes normalized when the drug was discontinued [1,2]. In such cases, reactive hepatitis is also possible. Increased alanine aminotransferase, decreased platelet count, and decreased albumin were associated with increased mortality in patients. Studies have shown increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ranging from 14% to 53%, indicating liver damage.

In addition to the above-mentioned inflammatory mechanisms of the liver in the case of COVID-19, respiratory distress syndrome and polyorgan failure can cause ischemia and reperfusion dysfunction of the liver, causing hypoxia and shock. As a result of biopsies previously conducted by scientists, it was found that in shock and hypoxia, the decrease in the amount of oxygen in the hepatocytes and the increase in the amount of lipids lead to fatty dystrophy and the death of hepatocytes. Then the increase of active forms of oxygen, the increase of lipid peroxidation products is a secondary cause, which can indirectly cause the increase of inflammatory factors, antigens, interleukin-6 and liver damage [3].

Patients with chronic liver diseases are insufficiently informed about the infection with SARS-CoV-2 and the course of the disease. Therefore, many questions remain open. For example, there are reports that chronic hepatitis V (this disease is more common in China than in Europe) does not affect the course of the disease of COVID-19 [4]. Also, there are unconfirmed assumptions that immunosuppression may protect against immunopathological conditions that are important in lung damage even in advanced cases [5].

These changes may be associated with hyperinflammation syndrome, "cytokine storm" and polyorgan failure associated with activation of macrophages. While the majority of patients have a mild illness, 20% of patients have a severe or critical illness from the second week of the illness. Some of these patients develop respiratory failure. As a result of laboratory tests, the amount of IL-1, IL-6, TNF, and C-reactive protein, which causes a "cytokine storm", is observed in some patients, such as changes observed in atypical pneumonia, Middle East respiratory syndrome, or liver microcirculation in influenza.

As a result of hypoxia, hepatocytes become prone to damage, and immune inflammatory processes increase this phenomenon. As a result, hepatocytes are damaged and their function is lost. Decreased perfusion due to heart failure in some patients who do not have COVID-19, such as hypoxic liver damage, also leads to this condition. This condition occurs in elderly patients with chronic heart failure, which lasts for a long time and is accompanied by a decrease in cardiac output.

Chronic liver diseases such as viral hepatitis, alcoholic and non-alcoholic liver disease, autoimmune hepatitis and liver cirrhosis are common, so it is very important to identify these diseases during the pandemic of the COVID-19 disease, and to provide timely and accurate assessment of organ damage. Singh S. and co-authors found that the mortality rate was higher in the group of patients with chronic liver disease than in the group without liver disease. This rate was especially high in patients with liver cirrhosis. 1099 patients participated in the cohort study, 552 of them received inpatient treatment, 261 (23.7%) had chronic liver disease. Of these patients, 23 (2.1%) had hepatitis V.

The severe course of coronavirus infection in these patients confirms the existence of a correlation between these diseases [6]. There is a correlation between lymphocytopenia and increased activity of hepatitis V disease in severe cases of coronavirus infection, which is explained by the reduced immunotolerance status in viral hepatitis. Patients with COVID-19 who stop taking antiviral drugs or take glucocorticoids can also reactivate hepatitis V and cause liver damage. The effect of the SARS-CoV-2 virus on patients with cirrhosis of the liver is particularly significant. Systemic inflammation, hypoxia, and circulatory failure caused by the virus can cause secondary infection, decompensation of liver function, and increased risk of bleeding. Also, this condition can cause a 40-63% increase in the mortality rate according to the International Registry of Patients with Chronic Liver Diseases and Liver Cirrhosis. According to Qiu H. and co-authors, alcoholic cirrhosis patients infected with SARS-CoV-2 had decompensated chronic liver failure. Patients with non-alcoholic fatty liver disease also experience worsening of the disease, as this disease is part of the metabolic syndrome and is a very common disease. Metabolic inflammation is controlled by macrophages, different from bacterial inflammation, and has a stimulating role in the pathogenesis of nonalcoholic fatty liver disease.

This inflammation is weak, aseptic and persistent. For this reason, third-degree fibrosis develops in most patients. SARS-CoV-2 infection and associated immune changes may be an additional “hit” that exacerbates steatohepatitis and inflammation in nonalcoholic fatty liver disease. By analyzing these changes, it can be concluded that the disease of COVID-19 increases the development of non-alcoholic fatty liver disease. In addition, because non-alcoholic fatty liver disease is associated with increased levels of cytokines, these patients are prone to developing a "cytokine storm" in the disease of COVID-19 and to a severe course of the disease.

Such changes have been observed in a number of retrospective studies. For example, a follow-up study of 202 patients with COVID-19 in China who had fatty liver disease showed a higher prevalence of disease (44.7% (34/76) vs. 6.6% (5/126)) compared to healthy controls and patients with COVID-19. <0.0001), liver failure from the day of admission to the day of hospital discharge (70% (53/76) versus 11.1% (14/126)), long-term detection of the virus (17.5±5.2) days (12.1±4.4) compared to the day; r<0.0001). Patients who developed the disease were older, had a higher body mass index, and had more comorbidities. Thus, the presence of chronic liver diseases is a prognostic risk indicator in coronavirus infection, and patients belonging to this group require vigilance and long-term follow-up. Thus, the mechanism of hepatotropism of the SARS-CoV-2 virus and the effect of autoimmune changes have not been sufficiently studied. All patients infected with the disease of COVID-19 should be continuously monitored, taking into account the effect of the virus on the liver.

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