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The role of coronavirus infection Covid -19 in causing liver damage

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Annotation: Post covid syndrome can develop in all patients who have had COVID-19, regardless of the severity of the disease. The clinical picture of post covid syndrome is very diverse, but the most common are asthenic disorders, anxiety-depressive disorders (TDD) and cognitive impairment (CN).

Keywords: COVID-19; post covid syndrome; cognitive impairment; depression; SARS-CoV-2, indicators.

Introduction

In December 2019, a new pathogen, the coronavirus, was identified in Wuhan City (Hubei Province, China) , causing an outbreak of pneumonia. The World Health Organization (WHO) designated it as "2019-nCoV" in March 2020. Based on phylogenetic features, taxonomy, on February 11, 2020, a new virus was identified as a virus that causes severe acute respiratory syndrome and named SARS - CoV - 2 (severe acute respiratory syndrome coronavirus-2) [1]. Within 3 months, SARS-CoV-2 spread from the city of Wuhan throughout China, and then to more than 181 countries across four continents. The epidemiological situation is still not stable enough, because, despite the increase in the rate of vaccination, both infected patients and deaths continue to be recorded daily [2].

Transmission of SARS-CoV-2 from person to person occurs by airborne droplets, and the fecal-oral route of transmission is also possible [3]. In a short period of time, the SARS-CoV-2 infection and the associated incidence of COVID-19 led to significant losses in the planet's population, health and serious socio-economic damage, which significantly destabilized the existing healthcare system and the economy around the world [4].

SARS-CoV-2 infection can occur both asymptomatically and asymptomatically , and clinically pronounced (for a severe course, pulmonary edema, acute respiratory distress syndrome and increasing multiple organ failure are characteristic, leading to death in cases of severe and super-severe disease) [4] . Studies have shown that the worst prognosis in patients with COVID-19 is associated with male gender, age over 60 years and comorbidities (cardiovascular disease, primarily arterial hypertension; diabetes mellitus, chronic lung disease; obesity; immunodeficiency states; chronic kidney disease ; chronic liver diseases, etc.) [5–7].

Inflammatory biomarkers such as C-reactive protein (CRP), serum ferritin , lactate dehydrogenase (LDH), D-dimer , interleukin (IL)-6, IL-2 are significantly elevated in severe patients with COVID-19 [8, 9].

Clinical symptoms in most patients include signs of lower respiratory tract involvement with fever, dry cough, and shortness of breath [5, 6]. Myalgia, fatigue, and headache are often noted. The presence of neurological symptoms in a number of patients with COVID-19 indicates the tropism of the virus to the cells of the nervous tissue [10].

In addition, a number of authors have described the manifestation of gastrointestinal and liver disorders in patients with COVID-19, in addition to one of the possible comorbid conditions that increase the severity of COVID-19 infection [6, 11].

To date, it is known that angiotensin -converting enzyme type 2 (ACE2) is a key enzyme in the pathogenesis of the disease, since the ACE2 receptor is the receptor for entry into the SARS-CoV-2 cell [12]. Due to the distribution of this viral entry receptor in many organs, SARS-CoV-2 is characterized by a systemic lesion involving not only alveolar epithelial cells, but also the heart, pancreas, kidneys, and the hepatobiliary system [12, 13].

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Liver damage in patients with COVID-19

There is increasing evidence of liver damage in patients with COVID-19, which, as a rule, manifests itself as a transient increase in serum aminotransferases , less often laboratory signs of hepatocellular insufficiency, intrahepatic cholestasis phenomena . The pathogenesis of liver injury in cases of COVID-19 likely includes hypoxia, systemic inflammatory response, drug toxicity, and progression of pre-existing liver disease [2]. COVID-19-associated liver injury is defined as any liver injury occurring during the progression and treatment of COVID-19 in patients with or without pre-existing liver disease. It was found that almost half of patients with moderate and severe disease had elevated levels of hepatic aminotransferases [14]. The incidence of abnormal liver function tests (LFTs) in hospitalized patients with COVID-19, due to aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin, ranges from 14% to 53% [15-17], while hepatic aminotransferases and bilirubin significantly higher in the blood
in patients with severe disease [18, 19].

At autopsy in the liver of patients, signs of moderate microvesicular steatosis , lobular and portal inflammation [20]. It is assumed that the reason for the increase in aminotransferases lies not only in liver pathology, their increase may be a consequence of myositis, similar to that observed in severe influenza [21].

However, some research groups have concluded that the direct cytotoxic effect of the virus due to its active replication in liver cells is due to the fact that SARS-CoV-2 binds to target cells through ACE2 receptors [8, 12]. Since ACE2 receptors are highly expressed in hepatocytes and cholangocytes , the liver and biliary system are potential targets for infection [8]. In 90% of patients infected with SARS-CoV-2, lymphopenia was detected , 25% had diarrhea, and 66% had an increase in liver enzymes [9]. Another study demonstrated a slightly different percentage: at an early stage of SARS-CoV-2 infection, 2–10% of COVID-19 patients had SARS-CoV-2 RNA in stool and blood samples, which was accompanied by symptoms of involvement in the pathological process of the gastrointestinal tract. intestinal tract (GIT), such as diarrhea, abdominal pain, nausea and vomiting [22].

TN Chau et al. demonstrated in their study that liver biopsy specimens from patients with COVID-19 showed a significant increase in mitotic cells, as well as eosinophils and balloon -like cells of the liver, indicating that SARS induces apoptosis of liver cells and thus leads to liver damage [23]. A study by YJ Tan et al . showed that SARS-CoV- specific protein 7a can induce cell apoptosis in various organs (including lungs, kidneys, and liver) through a caspase-dependent pathway, further confirming the possibility that SARS-CoV can directly affect liver tissue and cause damage [24]. Given the expression of the ACE2 receptor in cholangiocytes , it remains unclear whether SARS-CoV-2 infection causes cholestasis in patients and whether it can lead to an increase in alkaline phosphatase (AP) and gamma-glutamyl transpeptidase (GGTP) levels. There are research results showing that the biomarker of cholangiocyte damage GGTP is several times increased in patients with severe COVID-19-associated disease [25].

In severe cases of the disease, often there is liver damage associated with hypoxia, the so-called hypoxic hepatitis (“ischemic hepatitis”, “shock liver”), which is characterized by a transient increase in serum aminotransferases caused by hypoxic necrosis of centrilobular liver cells [26].

Materials and methods of research

Case histories of 79 patients who died from COVID-19 caused by SARS-CoV-2 were used as material for the study. Of these, 28 patients with liver damage were selected for analysis. SARS-CoV-2 infection was reliably identified in all patients using polymerase chain reaction (PCR). The criterion for inclusion in the study was the presence of liver damage in patients with characteristic symptoms of coronavirus infection and the presence of SARS-CoV-2, determined by PCR.

Research results and discussion

During the study, we found that with an unfavorable outcome of the disease from COVID-19, 35.4% of the total number of patients had liver damage. At the same time, the number of men among patients with liver damage was 57.1%. The age structure of patients is shown in fig. one. From fig . 1 shows that the main group of patients aged 41 to 70 years are male patients. In women in the sample, the maximum values of indicators prevailed in the age group of 70 years and older (33.3–33.4%).

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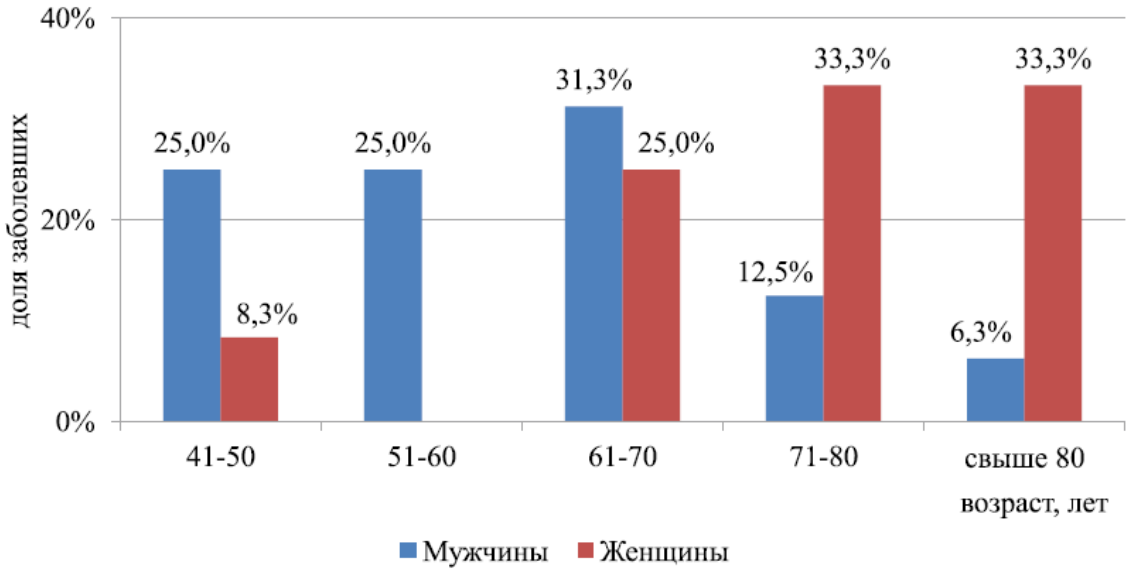
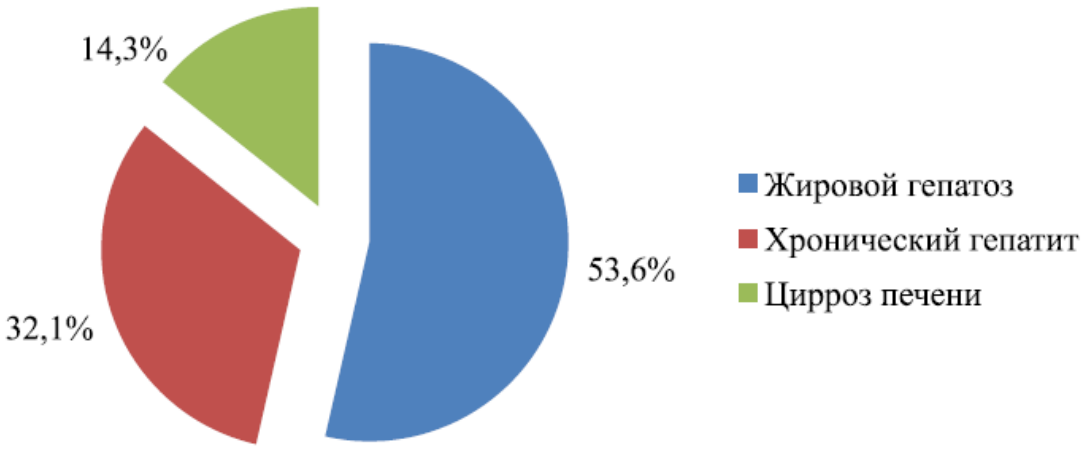


Pic. 1. *Age structure patients with lesions liver with COVID-19, n = 28*

It is interesting to note the absence of liver disease in women in the 51-60 age group. It can also be seen that the trends in men and women associated with liver disease are directly opposite. So, in men, the indicator first increases (25.0–31.3%), then decreases (12.5% in the range of 71–80 years) and then to 6.3% - over 80 years . In women, on the contrary, in the age dynamics, the indicator increases all the time (8.3–25.0%, in the range of 41–70 years), then stabilizes in the range of 71–80 years and above . __ The liver diseases we have identified in patients with COVID-19 are shown in Fig. 2. It is noteworthy that the largest number of patients with COVID-19 is occupied by patients with fatty liver - fatty hepatosis (53.6%). Chronic hepatitis is observed in 32.1%, cirrhosis liver in 14.3% of the total number of cases. All these liver diseases mainly occurred against the background of cardiovascular pathologies and diabetes mellitus.



Pic. 2. *Structure diseases liver with COVID-19, n = 28*

In previous studies of the coronavirus situation, various authors have found that SARS-CoV and MERS-CoV cause direct liver damage in infected patients. With COVID-19, significant deviations in the functional state of the liver were also found, which correlated with the progression and severity of the infectious process [12].

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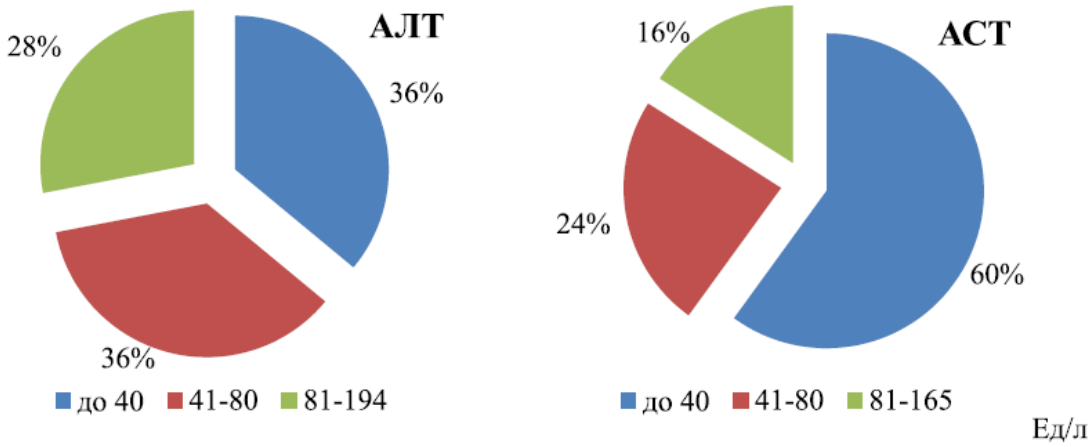
Our studies also confirm the presence of deviations in the functional state of the liver and patterns in the progression of its disease with the severity of the infectious process. Published papers analyzing the liver status of Chinese patients with COVID-19 from Wuhan, People's Republic of China showed that 14-53% of them had changes in biochemical parameters. And in 2–11% of the total number of cases, the infection developed against the background of chronic liver diseases. Increased activity of ALT / AST (alanine and aspartic aminotransferase), as a rule, did not exceed 1.5–2 norms from the upper limit of the norm and was accompanied by a slight increase in the concentration of total bilirubin in the blood [7]. An increase in the level of transaminases , a decrease in the concentration of platelets, as well as a low level of albumin in the blood , at the time of admission to the hospital, correlate with higher rates of mortality in patients.

In the course of a retrospective study of patients with liver lesions, we have shown that the majority of patients with COVID-19 had deviations in laboratory parameters of the liver status from the norm associated with its cytolytic damage. There is also a slight increase in the level of activity of ALT and AST (Fig. 3).



Pic 3. *Indicators of ALT and AST in the blood with COVID-19, n = 25*

Normally, ALT for men over 18 years of age is less than 41 U / l, for women it is less than 33 U / l. In chronic hepatitis, ALT activity is characterized by the usual excess of more than 4 times the norm . On the fig . 3, such an indicator was noted in 28% of cases (81–194 U / l), i.e. several higher than 4 times . _
For AST - the norm for men over 18 years of age, less than 40 U / l, for women - less than 32 U / l. Exceeding the norm of AST by 4 times is observed in a group consisting of 16% of patients. Such indicators are higher than noted in the work of Shu-Yuan Xiao [7]. Such groups in which the indicators exceed the norm by 4 or more times (81-194 U / l for ALT and 81-165 U / l for AST) can be attributed to high-risk groups. A fourfold or more excess of the norm indicates the presence of an acute viral infection in patients, aggravating the severity of liver damage.

Indicators, within the normal range, of ALT and AST activity are noted in 36% and 60%, respectively. Indicators up to 1.5–2 times higher than the norm (41–80 U / l) are noted in 36% and 24% , respectively , for ALT and AST.

Icteric staining of tissues (sclera, skin) and tissue fluid, which occurs due to an increase in the total level of bilirubin in the blood serum, was not observed in a significant proportion of patients. Only 4% of patients had a slight excess of total bilirubin (21–35 µmol /l), normally from 0.5 to 20.5 µmol /l. There was also a simultaneous decrease in the concentration in the blood general protein , in 54.2% of patients (44–63 g/l) and albumin in 60% (22–34 g/l).

A kidney function study showed that creatinine and urea levels were above normal in 20% of patients with COVID-19.

Also noteworthy is the decrease in the number of platelets in 33.3% of patients (below 180 x10**9/l), at a rate of 180–320 x10**9/l.

The level of the prothrombin index in 96.4% of patients remained within the normal range, and only one patient had a decrease in this indicator below the norm.

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Conclusion

Pathological changes with an unfavorable outcome from COVID-19 in the liver occurred in our study in 35.4% of patients. The largest number of patients with COVID-19 infection is occupied by patients with fatty liver - fatty hepatosis (53.6%). Chronic hepatitis is observed in 32.1%, liver cirrhosis in 14.3% of general numbers cases .

The main clinical and biochemical indicators of these changes include a slight increase in the level of liver enzymes (ALT, AST). Indicators of activity of transaminases ALT and AST, exceeding the norm by 4 times, in our study were observed in 28% and 16% , respectively .

The level of total bilirubin in 96.0% of patients remained within the normal range . Also, in patients with COVID-19 with liver damage, a decrease in total protein, albumin, platelets, and prothrombin index was recorded. All patients with liver pathology infected with COVID-19, in our opinion, need further careful monitoring in order to timely assess the possible consequences and improve the quality of treatment. The nature of liver damage directly in COVID-19 is not well understood and requires further clarification.

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